POCKET NOTEBOOK

POCKET PRIMARY CARE

Second Edition

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A Massachusetts General Hospital Handbook

Wolters Kluwer

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EVIDENCE-BASED MEDICINE

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

		Disease	
		+	–
Test of exposure	+	A	B
	–	C	D

- **Incidence:** (New cases of a disease)/(pop at risk) in a given period of time (e.g., 1 case of flu/10,000 elderly in February 2018)
- **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 of the disease will be detected by ⊕ test (↑ sens desirable for screening); **A/(A+C)**
- **Specificity (True-negative rate):** *Among pts w/o disease,* probability of the disease will be excluded by ⊖ test (↑ spec desirable for confirming dx); **D/(B+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 (OR):** (Odds of exposure in disease group)/(odds of exposure in control group) = A/C divided by B/D = **AD/BC;** approximates relative risk
- **Relative risk (RR):** (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

- **Risk difference (reduction in RCTs):** (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
- **Number needed to treat/harm:** No. of pts that must be treated to prevent/cause 1 pt to have the measured outcome; 1/(risk difference), e.g., 5% reduction in MI with drug X, 1/(0.05) → NNT of 20

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

- **Observational Studies:** often only practical/ethical way to look for association (exposure & outcome are somehow linked)
  - *Case-control:* using groups characterized by *outcome,* goal is to identify differences in *risk factors/exposures;* e.g., using groups of pts w/ & w/o lung cancer & comparing smoking exposure; assoc measured w/ odds ratio
  - *Cohort***:** using groups characterized by *exposure/risk factor,* goal is to identify differences in *outcome;* e.g., using groups of patients who do & don't smoke & following them over time to compare lung cancer incidence; assoc measured w/ relative risk (RR)
  - *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 participants randomly assigned to intervention groups (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
  - *Single-blinded:* study participants unaware of group assignment (e.g., placebo pill vs. active study drug)
  - *Double-blinded:* both study participants & investigators unaware of group assignment
- **Meta-analysis:** Analysis that 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

- **Internal Validity:** Can I believe these results? Does study accurately answer its question?
- **Bias/study design:** Depending on nature of bias, can minimize **or** exaggerate true association; intrinsic to study itself
  - *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?" & thus not to have their events counted?
  - *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)
- **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., hormone replacement therapy 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)
- **External Validity:** Do these results apply outside the context of this study? Was study population drawn from community it is meant to represent (e.g., people willing to enroll in weight-loss study may be more willing to start exercise program than random sampling from general population)? Who was excluded from the study? How pragmatic was the intervention (e.g., were participants called weekly to ensure adherence?)
- **Applicability:** How closely do study subjects resemble my pt?
- **Generalizability:** Can the results of this study be replicated elsewhere?

HEALTH LITERACY

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

- **Definition:** Set of skills/abilities needed to gain access to, understand, & use health-related info; interaction between individual skills & health system demands
- **Numeracy:** Related concept; the math skills needed for timing, scheduling, dosing medications & understanding math concepts (arithmetic, percentages, probability) to understand & apply provider recommendations
- **Epidemiology:** 33% of US adults read at <5th grade level; 55% have difficulty w/ basic calculations; **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)
- **Role in health disparities:** Poor health literacy is more strongly assoc w/ poor health than race or education level (↓ med adherence, ↓ f/u, ↓ DM control, ↑ costs, ↑ morbidity, ↑ mortality; may mediate some health care disparities
- **Simpler communication improves outcomes:** 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

- **Screening:** Either 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 problems learning about your medical condition because of difficulty understanding written information?"

  Many recommend "universal precautions" w/ all pts; okay to ↑complexity/speed/terminology of explanation as indicated by

pt responses & questions

Management (ahrq.gov)

Health Literacy Universal Precautions	
• **Slow down** • **Use plain language; avoid confusing terms (e.g., "positive test")** • **Show/draw pictures**	• **Limit info provided to most important** • **Use "teach-back" method (below)** • **Encourage questions (below)**

- **Teach-back:** Have 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 partner about this?"
- **Encourage questions:** Pts who don't have questions often have not fully understood; ask "*What* questions or concerns do you have?" rather than "*Do* you have any questions?"
- **Medication review:** Ask pts to bring in their meds to appts & describe how they take them; can help w/ clarifying pt understanding & med adherence
- **Medication adherence:** Provide pill boxes, simplify refills (90-day supply, 3 ref), use medication charts (https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/quality-patient-safety/quality-resources/tools/literacy-toolkit/healthlittoolkit2_tool16.pdf)
- **Discussing risk** (*BMJ* 2003;327:745)
  - Frequency is easier to understand than percentages, i.e., "Two in 10 people will have a side-effect" is better understood than "a 20 percent chance of side-effect"
  - Framing influences pts, i.e., "If 100 pts are treated with drug A, 94 will experience no side effects" vs. "Six of 100 patients 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

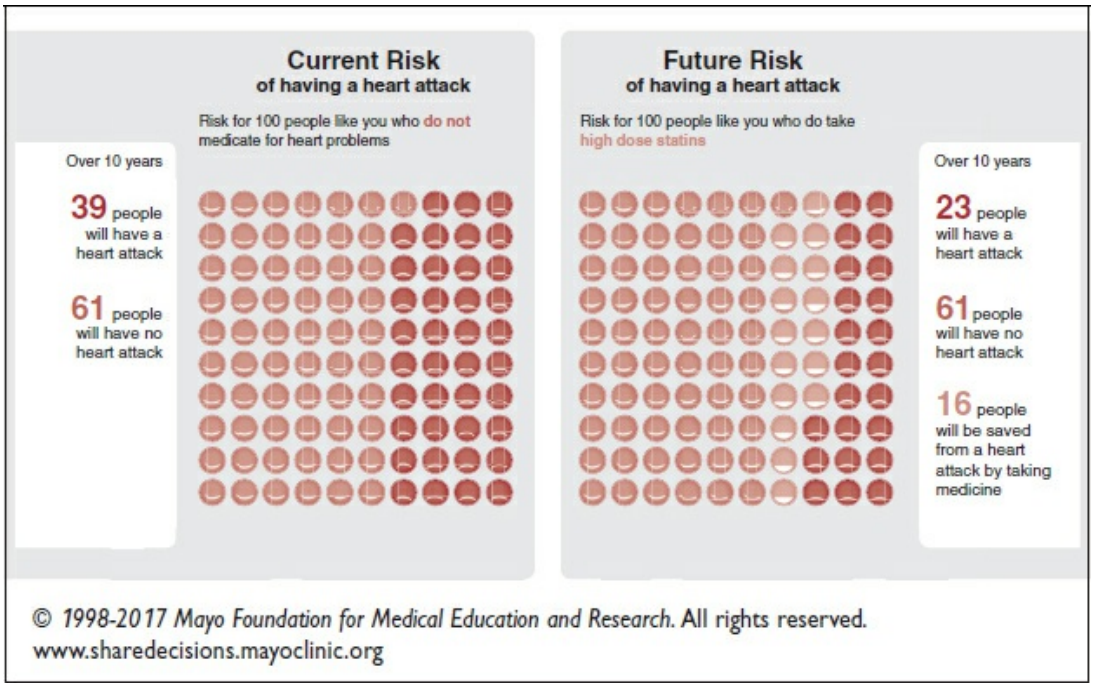
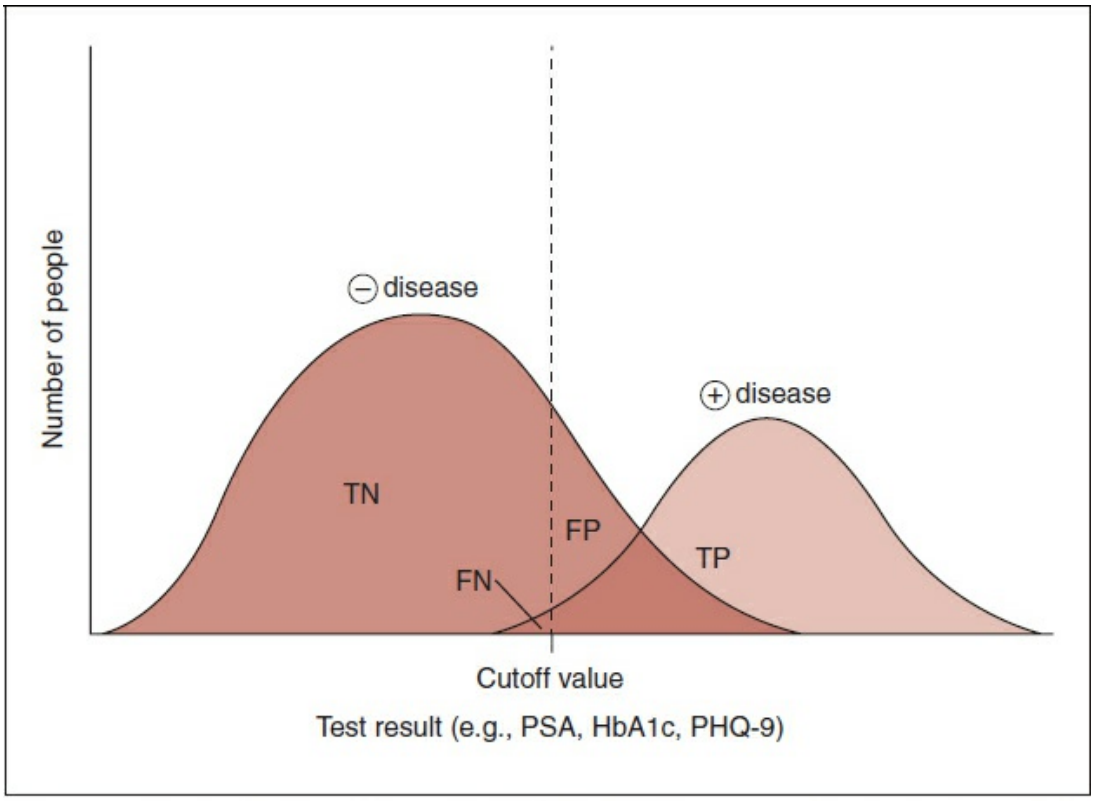


Figure 1-1. Example of Visual Representation of Risk Reduction; Mayo Clinic Statin Decision Aid; for use during clinical encounter)

DISEASE SCREENING

Background

- **Definition:** Screening intended to identify disease in asx individuals when **early detection** is feasible & early tx **improves outcomes**
- Screening test rarely used to to *diagnose* dz; instead used to identify persons at ↑ risk → further testing



Higher cutoff value leads to false ⊕,↑Sp/PPV, ↓Se/NPV; lower cutoff value leads to ↑Se/NPV, ↑Sp/PPV

Figure 1-2. Characteristics of Screening Test

- **Benefits of screening:** Can be difficult to compare direct outcomes btw 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

Characteristics of Ideal Screening Test	
Disease	High disease prevalence (↑ PPV of ⊕ test) Tx of early disease is effective: can improve outcomes/avoid complications

	Disease has known asx/early stage which can be identified
Test	Can detect disease while still asymptomatic Is not overly time-consuming, cumbersome, or financially prohibitive Is sensitive (unlikely to give false ⊖); ideally, is also very specific (unlikely to give false ⊕), but this is more important for confirmatory tests

- **Screening recommendations:** Several government agencies (incl 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
- **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 or FIT-DNA (q1–3y), CT colonoscopy (q5y, requires bowel prep) or colonoscopy (q10y) benefits & burdens greatest w/ colonoscopy (most lives saved, most complications)
Breast Cancer	**40–49 y ♀:** Consider mammography q2y after discussion w/ pt **50–74 y ♀:** Mammography q2y Excludes those at ↑ risk (known genetic mutation, hx chest XRT) 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 **30–64 y ♀:** Pap q3y **or** (Pap + HPV q5y), n.b. draft 2018 recommendation See *"Cervical Cancer Screening"*
Prostate cancer	See *"Prostate Cancer";* most groups recommend pt discussion
Lung cancer)	55–79 y w/ 30 pack-y tobacco hx **and** smoked w/in past 15 y: Annual low-dose CT, stop 15 y after quit; quitting >> effective in ↓ lung CA than screening CT
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 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 May ↓ testing interval if borderline; ↑ interval if repeatedly nl
Osteoporosis	**All ♀ >65; ♀ <65 at ↑ risk:** DXA of hip & lumbar spine **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 1945–1965:** Once **Pts at ongoing risk (IVDU):** More frequent testing
HIV	**All adults:** Once **↑ Risk (MSM, IVDU):** More frequently (see *"HIV"*)
Chlamydia	**Sexually active & (<26 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

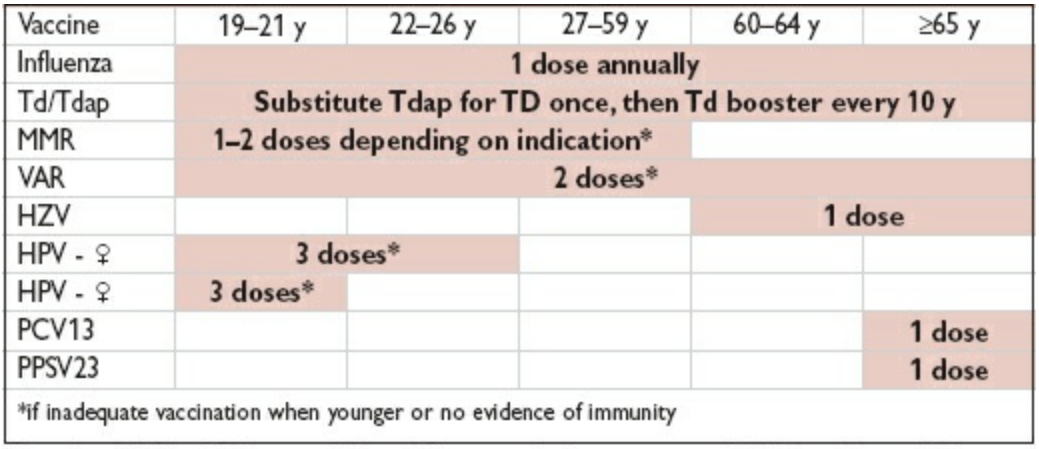
- USPSTF recommendations available as application for mobile devices at http://epss.ahrq.gov/PDA/index.jsp; enter basic pt info (age, gender) to see list of screening & other recommendations
- National Guidelines Clearinghouse at http://www.guidelines.gov lists recommendations from major government/nongovernment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

IMMUNIZATIONS

Background (*Healthy People 2020,* cdc.gov, *MMWR Surveill Summ* 2016;65:1)

- Current US guidelines recommend adults be immunized against up to 14 pathogens w/ the goal of ↓ infectious disease incidence & complications
- **Immunization goals:**
  - **Protect individuals** from infection, ↓ complications of infection
  - **Reduce transmission** to at-risk population (infants, elderly, poor health)
  - **Reduce population disease burden:** Smallpox eradicated, polio, & diphtheria almost
  - **Confer herd immunity:** High immunization rates can ↓ the number of susceptible members in a population; this ↓ overall probability of transmission of infection
- Rates improving, but many at risk still inadequately covered
  - *Elderly:* 61% have adequate pneumococcal coverage, 20.7% VZV, 67% influenza
  - *High-risk adults* <65: 20.3% have adequate pneumococcal coverage

- CDC estimates that ↑ immunization would → elimination of diphtheria, measles, mumps, rubella in US; 75% reduction in hepatitis A & B incidence since vaccines developed



Vaccine	19–21 y	22–26 y	27–59 y	60–64 y	≥65 y
Influenza	1 dose annually				
Td/Tdap	Substitute Tdap for TD once, then Td booster every 10 y				
MMR	1–2 doses depending on indication*				
VAR	2 doses*				
HZV				1 dose	
HPV - ♀	3 doses*				
HPV - ♀	3 doses*				
PCV13					1 dose
PPSV23					1 dose

*if inadequate vaccination when younger or no evidence of immunity

(From Kim DK, Riley LE, Harriman KH, et al. Recommended immunization schedule for adults aged 19 years or older, United States, 2017. *Ann Intern Med* 2017;166(3):209–219. Copyright © 2017 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.

Figure 1-3. CDC Vaccine Schedule for Healthy Adults, by Age

Additional Vaccines for Adults >19 y, by Indication (*Ann Intern Med* 2017;166:209)

Additional Vaccines for Adults >19 y, by Medical Condition/Indication	
Diabetes	PPSV23, HepB
ESRD	PCV13, PPSV23*, HepB
Heart or Lung Disease	PPSV23
Liver Disease	PPSV23, HAV, HepB
Asplenia or Complement deficiency	PCV13, PPSV23*, 1 dose each of MenACWY or MPSV4, Hib (>14d pre-splenectomy if possible), MenB
HIV see "*HIV*"	*CD4 < 200:* **contraindicated:** MMR, VZV, HZV *All CD4:* PCV13, PPSV 23*, MenACWY or MPSV4, extend window of HPV - ♂ series up to age 27
Immunocompromised (other, HIV-)	PCV13, PPSV23* Post-HSCT: add 3 doses Hib **contraindicated:** MMR, VZV, HZV

EtOH dependency	PPSV23
Healthcare workers	HepB
MSM	HepA, HepB; HPV series extended up to age 27

*2 doses of PPSV23, 5 y apart, prior to age 65

Specific Vaccines

Pneumococcal Immunization (*MMWR* 2015;64:944; *MMWR* 2014;63:822)

- 2 vaccines recommended which protect against different strains: PPSV23 & PCV13
- **Goal:** Prevention of invasive pneumococcal disease (IPD, e.g., bacteremia, meningitis) & PNA
- **Target population:** Both vaccines recommended for adults ≥65 or immunocompromised <65 y; PPSV23 also recommended for adults 19–64 y w/ chronic illness
- **Dosing:** See table for details
- **Efficacy:** PPSV23: 50–80% reduction in IPD in observational studies; up to 74% effective in meta-analysis of 15 RCTs (*MMWR* 2010;59:1102); in large RCT of adults >65 y, PCV13 assoc w/ 45%↓ in PNA, 70%↓ in IPD (*NEJM* 2015;372:1114)

Pneumococcal Vaccine Schedule	
Dosing Pearls • PPSV23 doses should all be ≥5 y apart if more than 1 dose is needed in lifetime • PCV13 single lifetime dose • If both indicated, PCV13 should be given 1 y *before* next dose of PPSV23 • For PPSV23, everyone should get exactly 1 dose after age 65; timing depends on prior PCV13 & PPSV23	
Clinical Scenario	**Schedule**
<60 y **needs PPSV23**	PPSV23 now PCV13 at age 65 2nd PPSV23 once ≥1 y since PCV13 *&* ≥5 y since 1st PPSV23
<60 y **needs PCV13 & PPSV23**	PCV13 now PPSV23 1 y later 2nd PPSV23 5 y later

	3rd PPSV23 once age 65 & ≥5 y since 2nd PPSV23
60–65 y needs PPSV23	PPSV23 now PCV13 at age 65 2nd PPSV23 once ≥1 y since PCV13 & ≥5 y since 1st PPSV23
60–65 y needs PPSV23 & PCV13	PCV13 now PPSV23 1 y later 2nd PPSV23 once age 65 & ≥5 y since 2nd PPSV23
≥65 y no prior pneumococcal vaccine	PCV13 now PPSV23 1 y later
≥65 y prior PPSV23 at age <65	PCV13 now PPSV23 once ≥1 y since PCV13 & ≥5 y since last PPSV23
≥65 y prior PCV13 & PPSV23 at age <65	PPSV23 once ≥1 y since PCV13 & ≥5 y since last PPSV23

Influenza *(MMWR* 2010;59:1102; *NEJM* 2016;375:126; *JACI* 2016;137:868)

- **Goal:** Prevention of individual infection & spread of influenza virus
- **Strain variability:** Flu strains vary by season → each year, vaccines developed to protect against 3 strains of influenza (trivalent: two A & one B; quadrivalent: two A & two B)
- **Target population:** All adults; esp. pts w/ asthma, DM, chronic lung disease, obesity, people >65
- **Dosing:** 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
- **Dosage forms:** 2016–17 ACIP guidelines do not recommend one vaccine over another among trivalent, quadrivalent, high or regular dose; these recommendations change annually; visit cdc.gov/flu/professionals/vaccination for latest information

Influenza Vaccines	
Forms	**Notes**
Trivalent inactivated (IM)	Ok for pregnant, HIV⊕; avoid admin during febrile illness *Contraindications:* h/o GBS after prior immunizations, anaphylactic

	reaction to egg or vaccine components
Egg-free trivalent inactivated (IM)	Healthy adults <50 y; vaccine not produced in eggs
High-dose trivalent activated (IM)	Approved for ≥65 y; RCT showed 24% ↓ risk of influenza compared to std dose, although some ↑ in mild s/e (*NEJM* 2014;371:635)
Quadrivalent inactivated (IM)	Adults 18–64 y
Quadrivalent inactivated (intradermal)	All adults
Live-attenuated vaccine (intranasal)	Not recommended by ACIP for 2017–2018 2/2 ↓↓ efficacy; when available, for use in healthy adults <50 y; *contraindications:* chronically ill, immunosuppressed, h/o GBS, egg allergy; s/e can include rhinorrhea, HA

- **Egg allergy:** Anaphylaxis to flu vaccine extremely rare (1.3/million vaccines given) & not necessarily ↑ in persons with egg allergy; ACIP 2017 recommendations are for:

  Nonsevere (e.g., hives) egg allergy: any vaccine ok
  Severe (e.g., anaphylaxis) egg vaccine: any vaccine ok, but monitor for 30 min w/ provider able to manage severe reactions, if they develop

- **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)

Responses to Common Patient Objections to Influenza Vaccination (*JAMA* 2013;309:881)
"I never get sick": Even asx pts may then infect 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, mild reaction to vaccine, 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, cdc.gov/std/hpv)

- Background: HPV most common STI in US (14 million new infections/y); most resolve spontaneously, but some persist & → cancer (19,000 ♀ & 11,600 ♂ annually)
- **HPV strains:** low-risk strains (HPV 6,11) assoc w/ low-grade cervical cell changes, genital warts; high-risk strains (HPV 16,18) assoc w/ cervical or anogenital CA (70% cases)
- **Goal:** Reduce current rates of genital HPV infection & transmission
- **Target population:** Ideally vaccinate prior to initial sexual activity; however, sexually active individuals should still be vaccinated; also ok if HPV ⊕
- **Dosing schedule: if >15 y, standard is 3 doses at 0, 1–2 mos, & 6 mos**

  Pts who did not receive during childhood → 3 doses
  Pts who received 1 dose before age 15 → 1 more dose
  Pts who received 2 doses either <5 mos apart or after age 15 → 1 more dose
  Pts who received 2 doses, >5 mos apart, before age 15 → no further doses necessary

- **Dosage forms:** All are inactivated; all protect against 16,18

  HPV9 (Gardasil 9): 9-valent, Gardasil 4 + HPV 31, 33, 45, 52, 58 (contraindication: immediate hypersensitivity rxn to yeast);
  HPV4 (Gardasil): Quadrivalent against HPV 6,11,16,18
  HPV2 (Cervarix): Bivalent against HPV 16,18 (contraindication: severe latex allergy)

- **Efficacy:** Successfully reduces HPV infection; >90% efficacy against CIN2⊕ containing HPV 16/18; also ↓ risk of CIN grade 2/3, & adenoCA *in situ* (*Lancet* 2007;369:2161; 2007;369:1861)

Herpes Zoster (*MMWR* 2008;57:1; *NEJM* 2005;352:2271)

- **Goal:** To prevent zoster or prevent/reduce the severity & duration of postherpetic neuralgia (see *"Herpes Zoster"*)
- **Target population:** Pts aged ≥60 y, including those w/ prior episode of zoster (give 6 mos after last episode)
- **Contraindications:** H/o anaphylaxis to gelatin, neomycin, or

previous VZV vaccine; immunocompromised (see table above), including 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
- **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%

Vaccine Adverse Reactions

- **Overview:** Most pts can receive most vaccinations w/ only local s/e or minor cold sx
- **True contraindications:** Hx anaphylaxis to a vaccine → avoid only that vaccine; anaphylaxis to egg → avoid MMR, yellow-fever; 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; not giving immunization → ↑ risk of individual infection → ↑ risk of transmission
- **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 after 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

THE PATIENT VISIT

Pre-Visit Preparation (*JAMA* 1997;277:350; 2011;305:1802)

- **Preparation:** Review medical records, health maintenance to create tentative agenda; pre-order any labs (e.g., A1c, BMP); determine your 1–2 top priorities for the visit (e.g., "discuss ⊕ FOBT" or "review home glucose readings"); engage care team in this work to ↓ admin burden and ensure provider practicing at top of license
- **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; 1999;304:2532; *NEJM* 2013;368:2445); consider brief pause before knocking to restore focus/reset

In the Visit

- **Establishing a provider–patient partnership** (*Arch Intern Med* 2007;167:1172)
  - *Greeting:* Warmly greet pt by preferred name (default should be w/ title, e.g., Mr. Smith)
  - *Introduce yourself:* Pts who are new to you prefer hearing your full name and your role
  - *Introduce your guests:* If any, introduce & ask for permission; "[First Last] is a 1st-y medical student working with me today; is it all right if he joins us?"
  - *Introduce yourself to pt guests:* Elicit identity in nonjudgmental fashion (e.g., "Hi, I'm Dr. [Lastname]; it's nice to meet you. How

do you know [pt name]"?); ask if pt is comfortable w/ their presence before getting started

Rapport-building: Apologize for any delay; begin & end visit w/ small talk, e.g., "How was your Thanksgiving?"

- **Technology:** Acknowledge computer in room, explain its purpose during your visit, "I am going to write down some notes about what we talk about;" "I am going to order those medications so they can be ready when you pick them up;" share screen, "Here are your A1c values for the past year"
- **Agenda-setting:** Approach visit w/ own tentative, flexible agenda, but elicit pt agenda up front; asking for pt agenda → improvement in understanding of pt concerns, which can → ↑ pt satisfaction and ↑ pt adherence (*JGIM* 2005;29:267; *Ann Intern Med* 2005;143:766)
- Asking about patient "concerns" or topics better than asking if they have "questions" (*Patient Educ Couns* 2016;99:718)
- Determine agenda for day's visit vs. future visits; should be shared decision-making: "It sounds like your main concern today is this rash; I'd also like to talk a bit about your blood pressure, and let's plan to talk about your headaches next time;" (*NEJM* 2012;366:1653)

History Pearls

- **Medications:** Include OTC & supplements, pt adherence & s/e

  Ask patients to bring in their medications to show you (or clinic PharmD, MA, RN)
- **Allergies:** Ask about details of reaction "What happened (when you took penicillin)?" distinguish btw true hypersensitivity & medication s/e
- **Social history:** An opportunity to understand pt identity and "life forces" which influence their health and their interaction with medical system; **obtained over many visits**

Comprehensive Social History (*NEJM* 2014;371:1277)
Individual characteristics: Self-defined race/ethnicity, language, education, job history, military (including where s/he served), disability, trauma hx, gender identity/sexual practices, leisure activities, significant travel
Life circumstances: Family structure & living situation (who else is at home), housing environment (home, apt, shelter, street), food security, legal/immigration issues,

employment, disability
Emotional health: Social stressors and supports, religious/spiritual beliefs
Perception of health care: Current priorities & how health fits into them; prior significant medical experiences, alternative medicine practices, advance care priorities
Health-related behaviors: Healthy and unhealthy practices and influences (incl tobacco, alcohol, recreational drugs), facilitators and barriers to med adherence, environmental safety (presence/storage of firearms, smoke detectors, seat belts, neighborhood safety)
Access to/utilization of health care: Health insurance status, medication access, health literacy, barriers to appointments (copays, transportation, work allowance, childcare)

- **Family history:** Age, health status, cause of death; specifically assess for screenable and/or heritable disorders: breast, colon, prostate cancer, cardiac disease, diabetes; FHx is dynamic, 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 preferences ("Do you have sex w/ men, women, or both?"), practices ("When you have sex, who puts what where?"), number of recent/current partners, incl those outside of current relationship, protection, hx STIs, contraception, sexual dysfunction, hx abuse or IPV
- **Advanced directives:** See "*Advance Care Planning*"

Concluding Visit (stepsforward.org/modules/pre-visit-planning)

- **Summarize visit:** Verbally and in writing; e.g. med changes, recommendations
- **Schedule f/u:** Establish appt time & agenda of f/u ("Let's make an appt in 3 mos to talk about your diabetes…")
- **Order pre-visit labs/studies:** For pt to complete *before next visit* ("…Come a few days early to get your A1c done so we can talk about it then"); this ↓ need for results calls/letters btw visits *and* helps develop plan during the next visit
- **Results:** Establish plan for communicating results as well as back-up plan for pt: Obtain permission to leave voicemail, confirm phone number
- **Follow-up:** Encourage pt to contact w/ any questions or concerns; "If you haven't heard from me about your CT by next week, please call"; "If your rash doesn't get better by the end of the week, let me know"

- **Documentation:** Include mechanism to organize issues/agenda for future visits; share message or note with consultants when appropriate, cc PCP if an urgent/1× visit
- **After difficult visits:** Reflecting on experience may help; consider colleagues, Balint groups, Schwartz Center Rounds, Healer's Art (stepsforward.org/modules/empathetic-listening)

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:** Pt who engenders a negative reaction from providers (frustration, distress, exasperation), with whom it is difficult to establish a therapeutic relationship, who threatens provider safety, or who fails to assume the "patient role"; pt families may also be perceived as difficult; can → clinical errors, boundary violations, & legal concerns
- **Pt characteristics:** Pts ↑ likely to have an anxiety d/o, substance use d/o, personality d/o, poor functional status, ↑ affective intensity, ↓ satisfaction with care, & ↑ use of health services (*Arch Intern Med* 1999;159:1069; *J Gen Intern Med* 1996;11:1).
- **Physician factors:** Poor attitude re: psychosocial aspects of pt care, working >55 h/wk; depression/anxiety; ↑ number of patients with psychosocial problems or substance use d/o (*BMC Health Serv Res* 2006;6:128); lack of understanding/empathy regarding the patient, loneliness, different socioeconomic backgrounds, (*NEJM* 2012;367:1284); labeling a patient as "difficult" can allow providers to dismiss or blame pt
- **Epidemiology:** Up to ~15–30% of primary care encounters; no evidence for association with pt demographics or nature of physical illness (*JGIM* 1996;11:1)

Management (*AFP* 2005;72:2063; *J Am Board Fam Med* 2006;19:533; *JAMA* 2011;306:94)

- **Safety:** Trust your instincts; if feeling uncomfortable or pt begins to escalate behavior, okay to open the door, say "Your shouting is

making me uncomfortable," or simply excuse yourself from the room

- **Behavior with staff:** Patients may be rude to staff & then kind to you; offer a simple reminder that you & staff are aligned and such behavior is not acceptable
- May need to develop a behavioral plan for pts w/recurrent behavioral issues
- **Physician training & factors** (*Arch Intern Med* 1999;159:1069)
  (1) Increase awareness/compassion for pt psychosocial context
  (2) Dx & treat comorbid Ψ illness
  (3) Focus on physician well-being, work-life balance (Balint groups, Schwartz rounds, communication with colleagues)
  (4) Restore collaboration by prioritizing patient concerns, using a nonjudgmental attitude
  (5) Set limits & boundaries—be firm but compassionate
  (6) Mindfulness: Awareness & acknowledgement of own emotional responses
  (7) Engage others in care of patient (paperwork, forms, letters) to ↓ administrative burden
  (8) Have security on site at time of appointment (where available) if safety concerns exist
  (9) Document safety concerns & decision-making
- **Empathic interactions:** Naming/validating pt emotion ("I can see you are upset"). Active listening ("tell me why X is so upsetting";) Engage patient ("What may we do to help you feel better?")

Pt Characteristic	**Management Recommendation** (***AFP* 2005;72:2063; *NEJM* 1978;298:883)**
Neediness	Professional behavior, boundaries (e.g., 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
Entitlement	Mindfulness, address specific pt emotion; inform pt they deserve to get good medical care & team is working in their best interest; apologize for legitimate grievances (e.g., wait times)
Pessimism "Eeyore"	Engage by sharing disappointment at poor results; offer realistic expectations; focus on symptom control rather than cure

Self-destructive	Realistic expectations; celebrate small successes; examine cause of nonadherence; respect autonomy; motivational interviewing (see "*Counseling Patients"*)

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, & engage pt in planning 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 is 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)

Motivational Interviewing (*AFP* 2009;79:277)

- Pt-centered technique proven helpful in tx of substance, EtOH use d/o; can help develop therapeutic relationship & set individual goals (*Cochrane Data System Rev* 2011;5:CD008063; Motivational interviewing: Helping People Change, Miller & Rollnick, 2013)
- Idea that arguments for & against change already exist within the pt; frame conversation so that pt voicing reason for change to provider, not vice versa; goal is a guided, collaborative conversation that

engages & empowers pt, strengthen's pt's motivation/commitment to change

- Encourage pt to envision him/herself in the future, when they are successful & look back at what made them successful; use past success as a template for future success—what worked before, how could they use that now?

Sample Process of Motivational Interviewing (Adapted from Miller WR, Rollnick S, Butler CC. *Motivational Interviewing in Health Care*. 2008)
(1) What would motivate you to make this change? (2) What are the 3 best reasons to do it? (3) How important is it to you to make this change, & why? (4) How would you go about it in order to succeed? (5) *Reflect answers back to pt* (6) So what do you think you'll do?
R: RESIST telling patients what to do **U: UNDERSTAND** patient motivators to change & not to change **L: LISTEN** to your patient **E: EMPOWER** your patient to make good decisions

- **Transtheoretical:** Behavioral changes occur in stages; provider assessment of pt readiness for change
  - **Precontemplation:** Not interested in change; advise pt of risks & ask for their thoughts
  - **Contemplation:** Considering change; "What are the pros/cons of quitting?"
  - **Preparation:** "Do you think you could start making those changes next week?"
  - **Action:** Support & reflect on what they are doing well/personal strengths they are using
- **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

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 (Stuart 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: Identifying a specific part of a problem makes it manageable & provides something PCP may assist w/, "What *troubles* you 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"; try to address main issue, e.g., "Would you like to talk to our social worker about housing resources?"

GRIEF (*JAMA* 2013;310:416)

- **Definition:** Grief is bereavement after a loss, often the death of a loved one, typically lasting 6–12 mos; *Complicated grief:* Yearning for/preoccupation w/ the loss, preoccupation w/ surrounding circumstances, 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/loss, death of spouse, social support/resources available, EtOH/illicit use

- **Epidemiology:** ~7% of pts experience complicated grief
- **Diagnosis:** Clinical; Ddx includes depression, anxiety, PTSD, all of which may coexist
- **Treatment:** Bereavement support groups, mgmt of comorbid d/o, targeted psychotherapy
- **Patient information:** *JAMA* 2005;293:2686

Breaking Bad News

- Providers often have responsibility for sharing potentially upsetting news; wide ranges in nature of pt–provider relationship & in emotional impact of news
- Providers can often have significant positive impact on encounter by preparing & supporting the pt appropriately
- Consider SPIKES protocol; for further discussion of pt wishes in setting of poor prognosis, see *"Advance Care Planning"*

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

Setting: Private area, tissues ready, pager/phone set to silent; let pt decide who is present; **sit down w/ pt,** establish rapport

Perception: **Assess pt understanding** of medical situation/nature of conversation

Invitation: Ask pt what information they wish to know

Knowledge: Share 2–3 key facts, as simply as possible, & w/ pauses 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 why your skin is yellow"

Empathy: Recognize & respond to pt emotion, goals, & hopes; "We were all hoping for a different result;" sometimes helpful to name pt emotion, e.g., "You seem upset"

Respond to pt 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")

Invite pt response: "I imagine this is really difficult to hear"

Strategy/Summary: Discuss next 1–2 steps – referrals, studies, f/u plan for PCP "I've set you up to talk w/ the surgeons about this, & I'll see you back in 2 wks"

OBESITY

Background (*NEJM* 2017;376:254)

- Obesity is a multifactorial, chronic disease affected by social, behavioral, cultural, metabolic, & genetic factors
- **Body mass index:** (weight [kg]/height [m^2]); 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)
- **Classification:** Obese: BMI ≥30; overweight: BMI >25
- **Comorbidities:** Health risks assoc w/ obesity include prediabetes & DM2, HTN, HLD, CVD, gallstones, NAFLD, GERD, OA, cancer, OSA, stroke, mood/anxiety/eating d/o, disability, ↑ mortality (obesity itself accounts for ~5–15% US deaths/y) (*NEJM* 2009;361:2252)
- **Epidemiology:** >1/3 US adults obese, >2/3 overweight or obese; dramatic (>2×) ↑ prevalence in past 30 y, now leveling off (*JAMA* 2016;315:2284)
- **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, hypothyroidism); *Meds:* Especially those w/ wt-related s/e (atypical antipsychotics, antidepressants, antiepileptics, diabetes medications, glucocorticoids); *Social hx:* Support system, resources (time, money), motivations for wt loss, barriers to wt loss; stressful life events
- **Weight history:** Past wt loss attempts (incl meds, surgery), diet (esp fast food, sugary beverages, snacks, portion size, timing of eating), physical activity, ⊕ FHx obesity
- **Physical exam:** Height, weight, waist circumference, BP; look for signs of insulin resistance (acanthosis nigricans), hypothyroidism, & Cushing syndrome

  Visceral abdominal adiposity strongly associated w/ obesity complications: 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 (frequently comorbid Vit D deficiency)

Treatment (*Obesity* 2014;22(S2):S1)

- **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 5–10% wt loss recommended
- **Indications for weight loss:** Recommended if BMI > 25 kg/m^2 **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; may encourage small steps toward change if not ready for lifestyle overhaul; see "*Counseling Patients*"; set goals/metrics for success to keep motivated
- **Energy balance equation:** Net body balance (wt) = Energy input (food) – Energy output (metabolism, physical activity)
- **Diet:** Low-calorie diet essential; recommend ~1200–1500 kcal/d ♀, 1500–1800 kcal/d ♂; reduction of 500 kcal/d results in wt loss of 1 lb/wk; nutritionist can offer more precise calc.
- Low carbohydrate, low fat, Mediterranean diet, DASH diet, & other diets all effective → patient preference & adherence key factor (*NEJM* 2009;360:859)
- Recommend ↓ soda & sugary beverage consumption as appropriate (25% of US consumes >200 kcal/d of soda) (*NCHS Data Brief* 2011;71:1); reframe as "liquid candy"
- Recommend ↓ EtOH intake as appropriate (20% of men consume >300 kcal/d of EtOH ≈ 2 beers) (cdc.gov, NHANES 2013)
- **Exercise:** Exercise alone may not → significant wt loss (*Obesity* 2011;19:100), but important for prevention of wt gain & ↓ CV/DM risk independent of wt loss (*Arch Int Med* 2008;168:2162); AHA recommends ≥150 min/wk moderate to vigorous activity (e.g., 30 min/d 5 d/wk)

- **Weight Self-Monitoring:** Encourage weighing at home ≥1×/wk, both for wt loss & wt maintenance
- **Behavioral therapy:** offer referral to high-intensity comprehensive lifestyle intervention (14 visits in first 6 mos), where pt will have regular feedback & support from trained healthcare professional, complete behavior change curriculum, & monitor food/exercise/wt
- **Group programs:** YMCA diabetes prevention program (*AJPH* 2015;105:2328) & commercial wt loss programs like Weight Watchers (*JGIM* 2013;28:12) effective for some patients

Pharmacotherapy (*J Clin Endocrinol Metab* 2015;100(2):342)

- **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; newer nongenerics costly & usually not covered by insurance
- **Orlistat** (*Xenical, Alli*): FDA-approved for chronic wt mgmt
  - *Mechanism:* Lipase inhibitor → ↓ fat digestion/absorption
  - *S/e:* Bloating, flatulence, oily stools, ↓ fat-soluble vitamin absorption
  - *Contraindications:* Pregnancy, chronic malabsorption, gallbladder disease
  - *Notes:* Less costly ½ strength OTC formulation available (*Alli*); Rx w/ multivitamin
- **Phentermine/Topiramate ER** (*Qsymia*): FDA-approved for chronic wt mgmt
  - *Mechanism:* (P) Inhibits NE/5HT reuptake & (T) enhances GABA activity, glutamate antagonist → ↓ appetite, ↓ food intake
  - *S/e:* (P) Tachycardia, HTN → monitor BP/HR; (T) teratogenic, cognitive dysfunction, metabolic acidosis, constipation, dysgeusia
  - *Contraindications:* Pregnancy, hyperthyroidism, MAOI use, glaucoma
  - *Notes:* Qsymia more effective than phentermine alone (CONQUER, *Lancet* 2011;377:1341); phentermine alone is generic, FDA-approved for wt mgmt for ≤ 3 mos

- **Lorcaserin** (*Belviq*): FDA-approved for chronic wt mgmt
  Mechanism: 5HT 2C receptor agonist → early satiety, ↓ food intake
  S/e: HA, nausea, fatigue, constipation, hypoglycemia (if DM)
  Contraindications: Pregnancy, serotonergic drug Rx (SSRI, SNRI)
  Notes: No effect on 5HT 2B receptor (which in fenfluramine → valvular disease)
- **Bupropion SR/Naltrexone SR** (*Contrave*): FDA-approved for chronic wt mgmt
  Mechanism: (B) Inhibits NE/dopamine reuptake & (N) opioid antagonist → ↓ food intake
  S/e: Tachycardia, HTN → monitor BP/HR; HA, nausea, vomiting, dizziness, insomnia
  Contraindications: Pregnancy, seizures, uncontrolled HTN, chronic opioid use, MAOI use
  Notes: Helpful for pts w/ frequent thoughts of food & food cravings
- **Liraglutide** (*Saxenda*): FDA-approved for chronic wt mgmt
  Mechanism: GLP-1 agonist → early satiety, ↓ food intake
  S/e: nausea, vomiting, diarrhea, pancreatitis
  Contraindications: Pregnancy, hx pancreatitis, hx medullary thyroid cancer or MEN2
  Notes: Liraglutide FDA-approved for DM (Victoza) w/ lower max dose (1.8 mg/d) vs. max dose 3.0 mg/d for Saxenda

Bariatric Surgery (*Cochrane Database Syst Rev* 2014;8:CD003641; *NEJM* 2007;357:741; *Ann Int Med* 2005;142:547)

- **Indications:** Pts w/ BMI ≥40 **or** BMI ≥35 w/ related comorbidities (HTN, OA, OSA) who have failed conventional Rx **or** BMI ≥30 w/ DM
- **Contraindications:** Tobacco/nicotine use, Ψ d/o not well treated for 1 y, eating d/o
- **Efficacy:** Surgery more effective at ↓ wt & ↓ comorbidities (DM, HLD, HTN, OSA) than medical Rx for pts w/ BMI >30
- When referring, document prior wt loss attempts, medical necessity, pt comprehension & accountability; refer to experienced ctr → ↓ surgical risk (*Can Fam Physician* 2010;56:873)
- **Laparoscopic sleeve gastrectomy:** Most common procedure (*Obes*

Surg 2013;23:427; asmbs.org); typical wt loss 25–30%; mortality 0.2–0.5%; shorter operative time & decreased malabsorption complications compared to RnY

- **Laparoscopic Roux-en-Y gastric bypass:** 2nd most common procedure; Gold standard bariatric surgery → greatest improvement in GERD, type 2 DM, & HTN; typical wt loss 30–50%; mortality 0.5–0.9%; complications include wound infection/dehiscence, stromal stenosis, hernias, gallstones, vitamin deficiencies, dumping syndrome
- **Other procedures:** Laparoscopic adjustable gastric banding less commonly performed in the US due to ↓ effectiveness & complications (band slippage/erosion, pouch dilatation); Investigational & uncommon procedures include intragastric balloon, biliopancreatic diversion, duodenojejunal bypass sleeve, & transoral surgical approaches
- **Weight Regain After Bariatric Surgery:** Common (≥20% prevalence; *Nutrition* 2008;24:832); DDx includes dietary nonadherence, fistula, gastric pouch enlargement, anastomosis dilation. Refer to bariatric center for evaluation & consideration of EGD
- **Monitoring After Bariatric Surgery:** patients should continue to be monitored for pre-existing comorbid conditions (HTN, HLD, NAFLD, DM), as well as nutritional deficiencies, depression, & complications of malabsorption (e.g., osteoporosis)

CHRONIC PAIN

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

- **Definition:** Pain persisting **beyond timeframe of expected healing** or due to ongoing/recurrent insult; generally, >3–6 mos in duration
- **Classification:** *Neuropathic pain:* Damage or malfunction of nerves; may be peripheral (e.g., diabetic neuropathy, postherpetic neuralgia; see *"Peripheral Neuropathy"*) or central (e.g., spinal cord injury, multiple sclerosis, stroke); *Nociceptive pain:* Initiated by inflammation or tissue damage; may be superficial (burns,

abrasions), deep somatic (arthritis, sprain), or visceral (IBD, bowel obstruction)

- **Pathophysiology:** Can be due to mechanisms at many levels of peripheral & central nervous systems including abnormal neuroplasticity (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 20% of ♀ & 17% of ♂ in US; may be 40% in older adults (*MMWR Weekly* 2013;62:342): LBP, arthritis, & HA all common; many people have pain at multiple sites; chronic pain more prevalent among pts w/ ↑ social stressors, ↓ SES, older age, poorer physical health
- **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)
- **Risk factors/comorbidities** (*Gen Hosp Psych* 2009;31:206)
  - **Depression:** Up to 1/2 of pts w/ MDD have chronic pain; >25% of pts w/ chronic pain have MDD; often underdiagnosed (*Arch Intern Med* 2003;163:2433); ↑ disability, ↓ coping, ↓ response to tx
  - **Anxiety:** Pts w/ chronic pain more likely to have anxiety & panic d/o (*Depress Anxiety* 2008;25:593)
  - **PTSD:** Higher rates of chronic pain (up to 80% of Vietnam combat veterans) (*J Psychosom Res* 1997;43:379)
  - **SUD:** In primary care, rates of SUD in pts w/ chronic pain range from 3–34%; may be higher in pts on chronic opioids (*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 in future need for pain meds, hopelessness re: ability to relieve pain (*Pain Med* 2010;11:1599)

Evaluation

- **General approach:** A thorough initial hx can be therapeutic; even if unable to determine etiology, listening helps reassure pt & provider that a search for potential causes 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 (*NEJM* 2015;22:2209)
  - **Impact:** What has been the effect on pt QoL, activity level, occupation, social life?
  - **Assoc sx:** Depression, anxiety, stress
  - **Beliefs:** Pt's understanding of dx studies & responses to specific tx, including Rx & OTC medications (noting dosage, duration), CAM, & nonpharmacologic approaches
- **Past medical history:** Assess for comorbidities that may impact tx plan: mood d/o, SUD, mobility restrictions, advanced chronic disease (e.g., CHF, COPD)
- **Social history:** What is current & prior level of functioning? Assess recreational & fitness activities, occupational hx; ask about social supports (*see "The Patient Visit"*)
- **Exam:** Complete PE recommended, w/ particular focus on MSK & neuro exam; additionally, observe for pain behaviors (e.g., moaning, facial expressions)
- **Diagnostics:** As per clinical scenario

Nonpharmacologic Treatment (*BMJ* 2017;357:j1284)

- **General approach:** Identify & definitively treat underlying cause whenever possible; if pain persists, **focus on function;** multimodal is best (*Rheumatology (Oxford)* 2008;47:670)
  - *If cause known:* Tx of cause & exacerbating factors as able; review of available tx options & periodic reassessment of tx course appropriate (see *"Peripheral Neuropathy," "Fibromyalgia," "Inflammatory Bowel Disease," "Herpes Zoster," "Pelvic Pain," "Headache," "Jaw & Dental Pain,"* Musculoskeletal ch.*, "Depression," "Anxiety"*)
  - *If cause unknown after complete eval:* Provide reassurance (pts w/ chronic pain often have ↑ level of health anxiety) & periodically reassess, consider further eval as indicated (*J Psychosom Res* 2006;60:155)
- **Discuss:** 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 "curable"); establish function as tx goal, not resolution 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, focusing on function: Ask "How does the pain interfere w/ enjoyment of life/general activity?" (*JGIM* 2009;24:733)

- **Safety/side effects:** Most nonpharmacologic interventions are low/no risk

Nonpharmacologic Interventions for Chronic Pain		
Intervention	**Conditions Recommended**	**Evidence**
Exercise	Fibromyalgia, LBP, hip/knee OA	**Beneficial for most chronic pain** (*Cochrane Database Syst Rev* 2017;4:CD011279); specific benefit for fibromyalgia (*BMJ* 2002;325:185); chronic low back pain (*Ann Intern Med* 2008;148:247); consider low-impact (swimming, tai chi, gentle yoga) for pts w/ knee or hip OA (*Arthritis Care Res* 2012;64:465)
Psychotherapy	Fibromyalgia, neuropathic pain, LBP	*Cognitive Behavioral Therapy (CBT):* ↓ disability & improve mood; ↓ 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):* Awareness of experiences & movement toward personal goals; ↓ functional limitation & ↓ pain-related anxiety (*Pain* 2011;152:2098)
Mind-body medicine (biofeedback, meditation, yoga, tai chi)	LBP, neck pain, headaches, fibromyalgia	Improved function, decreased pain, & disability (*JAMA* 2016;315:1240; *J Pain* 2012;13:1;*NEJM* 2010;363:743)

Acupuncture	Fibromyalgia, neck, & LBP	Improved pain/reduced stiffness; true acupuncture better than sham acupuncture (*Cochrane Database Syst Rev* 2013;5:CD007070; *Arch Intern Med* 2012;172:1444; *JAMA* 2014;311:955)
Manual (massage, chiropractics)	MSK pain, HA, fibromyalgia	Benefit in LBP, shoulder pain, HA, fibromyalgia (*Lancet* 2011;377:2226; *Evid Based CAM* 2007;4(2):165)
Transcutaneous electric nerve stimulation (TENS)	Neuropathic pain, MSK pain	Limited RCT evidence (*Cochrane Database Syst Rev* 2008;16(3):CD003222)
Sleep	All	Poor sleep assoc w/ ↑ incidence of pain, ↓ pain threshold, ↑ emotional response to pain (*Eur J Pain* 2012;16:522; *Pain* 1996;68:363; *J Sleep Research* 2007;16: 185); no studies re: sleep interventions, but reasonable to review sleep hygiene
Thermal (heat/ice)	All	Limited RCT evidence

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:** Treat comorbid mood or anxiety d/o; antidepressants ↓ pain & MDD sx simultaneously (*Arch Int Med* 2003;163:2433); **can also help pts w/o depression** by Δ how brain interprets painful stimuli (*Pain* 1999;83(3):389)

Pharmacotherapy for Chronic Pain by Pain Type	
Pain Type	**Treatment**
Neuropathic pain (*Mayo Clin Proc* 2015;90:532)	*1st-line:* TCAs, gabapentin (see *"Neuropathy"*) *Adjunct:* Topicals (lidocaine, capsaicin)
Fibromyalgia & myofascial	*1st-line:* SNRIs, TCAs

pain (*JAMA* 2014;311:1547)	*2nd-line:* Non-BZD muscle relaxants, gabapentin (see *"Fibromyalgia"*)
OA (knee, hip, hand) *(Arthritis Care Res* 2012;64:465)	*1st-line:* APAP, topical NSAIDs (knee, hand) *2nd-line:* NSAIDs *3rd-line:* Tramadol, intra-articular corticosteroids *4th line (should be used rarely):* opioids; see "*Chronic Opioid Use*"
Low back pain (*Spine J* 2008;8:173; *AFP* 2009;79:1067)	*1st-line:* APAP, NSAIDs *2nd-line:* TCAs, SSRIs (see *"Low Back Pain"*)
Localized MSK pain	Topical agents (lidocaine, capsaicin, topical NSAIDs)
Complex regional pain syndrome (*Pain Med* 2013;14:180)	NSAIDs, TCAs, gabapentin, topical agents; tx similar to neuropathic pain (above)

Pharmacotherapy for Chronic Pain by Medication Type

Medication	**Conditions 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, LBP; Topical NSAIDs for hand, shoulder, knee, 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)	Use as NSAID or opiate-sparing adjunct; 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	For neuropathic & MSK pain (incl OA) when	Applied BID, max efficacy not reached until ~2 wks 2/2

	limited to focal area	substance P depletion
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, LBP	HoTN, sedation, dizziness
Opioids	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 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)
- **Therapist:** Can assist w/ pain-related distress-coping techniques, mgmt of mood or SUD
- **Palliative care:** Co-mgmt of sxs in pts w/ life-limiting illness

CHRONIC OPIOID USE

Background (*MMWR* 2011;60:1487; *JAMA* 2013;309:657; cdc.gov/drugoverdose/epidemic/)

- **Definition:** An ***opioid*** is any substance that binds to opioid receptors (found in CNS, PNS, & GI tract); ***opiates*** are naturally derived from poppy (e.g., morphine, opium)
- **Epidemiology:** 3–4% of US adults receive chronic opioid tx (*Pharmacoepidemiol Drug Saf* 2009;18:1166)
- **Efficacy:** No long-term (>1 y) studies of opioids for chronic pain;

dose-dependent risk of adverse effects; a select subset of individuals can safely use opioids for long-term pain relief (*Cochrane Database Syst Rev* 2010;1:CD006605; *Ann Intern Med* 2015;162:276)

- **Side effects:** Nausea, constipation, somnolence, ↑ fall risk in elderly, hyperalgesia (paradoxical ↓ pain tolerance), hypogonadism, medication misuse (5% of US adults have used opioid Rx for nonmedical reasons, in excessive dose, or via unauthorized routes), addiction (up to 25% of pts receiving chronic opioids in primary care have opioid use d/o) (*J Pain* 2007;8:573; *Ann Intern Med* 2007;146:116; *AFP* 2012;85:49; *Drug Alcohol Depend* 2008;94:38)
- **Risks:** Opioids responsible for 61% of drug O/D deaths, usually unintentional (*MMWR Weekly* 2016;65:1445); for chronic pain, opioid Rx assoc w/1.64× ↑ risk of death when compared with nonopioid regimens (*JAMA* 2016;316:2415); since 1999, 4× ↑ in no. of US opioid Rx's & 4× ↑ in no. of US Rx opioid O/D deaths; recent slowing in rate (excluding illicit fentanyl) due to restricted prescribing (drugabuse.gov/related-topics/trends-statistics/overdose-death-rates)

Evaluation

- **Should a trial of chronic opioids be initiated?**
  1. Have other agents w/ more favorable s/e profiles been tried?
  2. What is the risk of misuse? (See *"Risk Assessment",* below)
  3. What are potential benefits & tx goals? Do these outweigh the risks?
- **Risk Assessment:** Multiple screening tools exist; not intended to supplement clinical judgment (*J Pain* 2009;10:131); (see *"Opioid Use Disorder"*)

  Opioid risk tool: 5-question survey; predicts risk of aberrant behavior (early refills, unauthorized dose escalation, hx 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 opioid 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 (*MMWR* 2016;65:1)

- **Deciding not to prescribe opioids:** "Based on my medical opinion, I would not recommend using opioids for this pain;" or "Opioids are not a safe option for your pain, but there are some other txs I would recommend;" acknowledge pt frustration; discuss other tx, offer reassurance; consider referral to pain specialist
- **High-risk patients:** Avoid opioid use; very close monitoring if Rx opioids; consider referral to pain specialist
- **Initiation of opioid therapy** as part of a comprehensive tx plan (see *"Chronic Pain"*)
    1. Start as a trial (e.g., 7–30 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. Use short-acting initially, not long-acting opioids; avoid escalating above 50 morphine-equivalents (MED) per day (e.g. ~30 mg oxycodone)
    3. Write prescriptions with partial fill option, in case patients do not want to accept the full prescription (particularly for initiation trial)
    4. Create & review opioid tx agreement for all pts; frame as informed consent & chance to be explicit about expectations, avoid term "contract" (tx decisions bound by provider's best judgment of benefit & safety, rather than by written document)
    5. 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 progress toward goals, continue Rx; if lack of benefit or significant s/e → taper 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, other tx which have been tried
Time frame	E.g., initial 7–30 d trial

Goals of Rx	Agreed upon w/ pt
Potential risks	S/e, med interactions (other sedating Rx, EtOH), activity restrictions/hazards (driving, other activities that put self/others at risk), physical dependence, addiction
Comprehensive tx plan	E.g., other activities for pain mgmt (exercise, PT), tx for substance use or mood d/o
Provider expectations	Obtaining opioids from one (named) provider, one (named) pharmacy, no unauthorized ↑ in dose; limits on early refills or replacing lost/stolen medications, rules of requesting refills, offer partial fill option
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; many Rx require monitoring due to safety risks (e.g., isotretinoin "iPLEDGE"); 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, risk determines freq (↑ risk = ↓ freq)
    Prescription Drug Monitoring Program: one in every US state; review at least q 3 mo
    Behavioral: Aberrant behavior assessment, pill counts, corroborative reports of others
- **Preventing overdose:** Consider naloxone Rx to prevent O/D in pts prescribed chronic opioids, particularly if prior O/D, higher doses (≥50 MED), concurrent sedatives (*Ann Intern Med* 2016;165:245)
- **Preventing constipation:** Persistent s/e; ensure bowel regimen (stool softeners, laxatives, GI-specific opioid antagonists) (*Am J Gastroenterol* 2013;108:1566)
- **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; express concerns that such behavior is problematic
4. Consider potential causes of aberrant behavior & treat the causes as able
5. therapeutic structure; more frequent visits, urine drug testing (incl *at time of behavior* when feasible) remind pt that aberrant behavior signals increased risk
6. If behavior continues, taper to alternative meds; if addiction suspected, recommend eval/tx (see *“Substance Use Disorders”*)

Aberrant Behaviors which Predict Addiction or Opioid Use Disorder	
Selling meds or falsifying Rx Obtaining medications from nonmedical sources Resistance to changing medications despite ↓ in function or significant s/e Lack of control over substance use *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	
Asking for more or specific medication Stockpiling medications during times when pain is less severe Use of the pain medications to treat other sx Reluctance to ↓ opioid dosing once stable *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 mgmt	Stable condition but inadequate pain control Progressive condition/pathology, tolerance to opioids
Inability to comply w/ tx	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 opioids:** Frame it as the medication, not the pt, that has failed; 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; continue tx of chronic pain using other Rx/modalities

ADVANCE CARE PLANNING

Background (*Ann Intern Med* 2010;153:256; 2012;156:ITC2-1; *NEJM* 2004;350:7)

- Identifying pt values, end-of-life wishes, & surrogate decision makers in advance of critical illness can ↑↑ chance of following pt wishes at end of life, ↓ pt & family stress, & ↑ pt & family satisfaction (*BMJ* 2010;340:c1345)
- Multiple ways of helping pts ensure their wishes carried out: eliciting pt values, offering recommendations, documenting wishes, identifying preferred decisional surrogates, referring to other healthcare providers for additional support
- **Who should have ACP discussion:** Medicare reimburses for advance care planning & considers (optional) part of annual wellness visits; discuss w/ elderly or poor prognosis, but **helpful to get a sense of values & identify surrogates in all pts**; ↑ depth/frequency of discussion with ↑ age &/or ↓ prognosis
- Pt culture influences end-of-life discussions (*AFP* 2005;71:515); some pts prefer to partially or fully defer prognosis discussion **and**/or tx decisions to family members; **confirm** beforehand: "Some people want to be very involved in their medical decisions, & others prefer I talk with their [family]. What's your preference?"
- **Prior to discussion of ACP:** assess decision-making capacity & pt understanding of medical conditions; assess pt's desired involvement in medical decisions vs. deferring to family surrogates; if preference for family involvement, invite them for ACP discussions; if relevant, communicate prognosis (see "Breaking Bad News" in *"Counseling Patients"*)

Definitions

- **Capacity:** Ability to communicate choices, understand/retain relevant info & use it rationally, appreciate situation & benefits/consequences of offered txs (*NEJM* 1988;319:1635; 2007;357:1834);

may be determined by *any* treating provider & does not require legal determinations; psych input often useful if Ψ d/o affects pt decision-making

- **Competence:** *legal* right of a pt to make decisions; determined by a *judge*
- **Surrogate decision-maker:** also known as health care proxy (HCP); person(s) designated to make pt's medical decisions if they are no longer capable; jurisdiction often includes all medical decisions, not just life-sustaining tx
  - *Pt-assigned:* does **not** require lawyer or judge; can ask pt "If you were sick who would make decisions for you?" (*AFP* 2012;85:461) & document their response; members of healthcare team cannot be surrogate decision-maker; encourage pt to complete HCP form & share wishes re: decision-makers w/ family
  - *Court-assigned:* If not identified by pt, **assignment order varies by state,** but order of priority usually spouse, then adult children, then parents, then siblings; if pt has court-appointed guardian, guardian usually takes precedent
- **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
- **Advance directive: written document** describing pt's wishes re: medical care, incl guidance for future care should s/he be unable to make own decisions; made by pt, often in consultation with family & PCP
  - **Living will:** *Legal* advanced directive—becomes valid only when pt unable to make wishes known for him/herself & is terminally ill or permanently unconscious; many states use "Five Wishes" forms: http://www.agingwithdignity.org/five-wishes.php
  - **MOLST/POLST:** Medical (or Provider) Orders for Life-sustaining Treatment; form outlines preferences for life-sustaining tx (specifics vary by state), includes pre-hospital resuscitation/transfer preferences; signed form = legally binding medical orders w/in state
- **Hospice:** Comprehensive care for pts w/ limited life expectancy (<6 mos); enrollment → **full coverage** (for Medicare beneficiaries) of

nursing, meds, hospital equipment, social work, palliative tx, bereavement support for survivors (*AFP* 2008;77:807); may be provided at home or in SNF; open hospice/"bridge to hospice" allows life-prolonging tx (e.g., chemotherapy) & some add'l hospice support services (*JCO* 2001;19:2057); eligibility varies by insurance provider & disease; recommendations for language during discussion of hospice also available (*Ann Intern Med* 2007;146:443)

- **Palliative care:** Focus on symptom mgmt, quality of life, goals of care regardless of prognosis in pts w/ serious illness

Advance Care Discussion (*AFP* 2005;72:1263; 2008;77:167; *NEJM* 2004;350:2582; *JAMA Intern Med* 2014;174:1994)

- **For healthier patients (e.g., Medicare AWV):**
  - **Introduce topic:** "Have you thought about what kinds of care you would want if you were to become seriously ill?
  - **Explain rationale for discussion:** "It's helpful to think about this now while you are relatively healthy, so we can keep your goals & wishes in mind over time"
  - **Elicit pt values and goals:** "If you were to become very ill, what is most important to you in your care? Are there situations you want to avoid? What does QOL mean to you?"
  - **Review** pt information annually & PRN
- **For sicker patients:**
  - **Assess pt understanding of condition/prognosis:** "So that we are on the same page, what is your understanding of your medical condition(s)?"
  - **Introduce topic:** "Have you thought about what care you would want if you became seriously ill/if things got worse?"
  - **Acknowledge emotions:** Expect that discussion may elicit strong emotions; acknowledge feelings & use as opportunity for discussion "I can see this really worries you—is it okay if we talk more about this? What is it that worries you the most?
  - **Elicit pt values and goals:** "As we talk about your health/illness, what is most important to you in your care? Are there situations you would like to avoid?"
- **Review risks & benefits of tx options:** Discuss options & align w/ pt's values & goals "Based on what you've shared, it sounds like

QoL is the most important issue; knowing what types situations you'd like to avoid, let's talk about what tx options make sense."

- **Share prognostics of resuscitation:** Use the GO-FAR "Good Outcome Following Attempted Resuscitation" calculator at www.gofarcalc.com to help pt understand prognosis after CPR (*JAMA Intern Med* 2013;173:1872); 17% of adults w/ in-hospital resuscitation survive to discharge; rates lower w/ elderly, ESRD, liver disease, cancer patients (*Resuscitation* 2010;81:302)
- **Give a recommendation:** If pt & family seem ready: "I've heard about what is important to you, we've talked about what tx options would make sense for you, & I agree with you that we will do/not do the following (CPR, intubation, dialysis, feeding tubes, pressors, noninvasive respiratory support); based on what you've told me, I would recommend (_____)"
- **Complete living will/advanced directives & document:** Key elements to document include: (1) Who was present for the discussion, (2) Who was the decision-maker, (3) Estimated prognosis, (4) Pt's stated values & goals, (5) Clinician's recommendations, & (6) Patient's decision; sample forms by state at uslwr.com/formslist.shtm
- **Encourage pt to share decisions/goals w/ family:** especially identified surrogate
- **Patient information:** *AFP* 2004;70:725; 2008;77:817; 2012;85:467; *JAMA* 2012;308:200; caringinfo.org (state-specific HCP & living will forms)

FALL PREVENTION

Background (*NEJM* 2003;348:42; *JAMA* 2010;303:258; *MMWR* 2016;65:993; *BMJ* 2016;353:1419)

- **Epidemiology:** Falls are leading cause of fatal & nonfatal injuries among adults ≥65 y; in 2014, 28.7% of older adults reported falling; 2.8 million older adults req'd treatment for fall-related injuries, w/ 800K hospitalizations & 27K deaths 2/2 falls
- Increased injuries in elderly 2/2 ↑ frequency of falls + more risk of harm from falls (↓ protective reflexes, ↓BMD, ↑ risk of SDH,

prolonged recovery)

- **Risk factors:** ↑ age, recent falls, fear of falling, weakness, gait, or balance problems, LE/foot pain, visual or sensory deficits (incl neuropathy), orthostasis, incontinence, dementia, ↓ functional status, polypharmacy or ↑-risk meds, EtOH use d/o

Evaluation (*NEJM* 2003;348:42; *AFP* 2010;82:81; *J Am Geri Soc* 2011;59:148; *BMJ* 2016;353:1419)

- **Screening:** Ask about (1) recent fall, (2) ≥2 falls in prior 12 mos, (3) difficulty w/ walking or balance; if any ⊕ → multifactorial fall assessment below
- **Fall History:** Determine nature of & precipitants for fall, assess risk factors
  - *Circumstances:* place, time, activity being performed
  - *Complications:* injury, head trauma, time down (need for medic alert bracelet)
  - *Assoc sx:* prodrome (orthostasis or cardiac), syncope (see *"Syncope"*)
  - *Mechanical triggers:* poor footwear, use/absence of eyeglasses, assistive device
  - *Environmental triggers:* rugs, lighting, cluttered floors, stairs, curbs
- **Medical History:** Vision problems, joint pain/arthritis, EtOH use, neuropathy, PD, incontinence (running to bathroom), nocturia, hx stroke, diabetes, weakness, orthostatic hypotension
- **Medications:** New meds or recent dose changes, timing of meds in relation to falls; *High-risk meds:* **sleep aids** (1.4–1.6× ↑ risk for hypnotics, trazodone 1.2× ↑ risk), antidepressants (1.7–2×↑ risk, incl TCAs, SSRIs), antipsychotics (1.6× ↑ risk) BZDs (1.6×), also concern w/ diuretics, antihypertensives, antiarrhythmics, βB, hypoglycemic agents (*NEJM* 1998;339:875; *Arch Intern Med* 2010;170:477)
- **Exam:** *VS:* Assess for orthostasis; *Gen:* Notice footwear, presence/absence of assistive device; *HEENT:* Visual acuity & visual fields; *CV:* Arrhythmias, valvular disease: See "Valvular Heart Disease"); *Neuro:* Mental status, strength, LE sensation (neuropathy); gait, Romberg (balance), coordination
- **Timed up and go test (TUG):** Requires stopwatch & line on floor 10 ft away from armchair where pt is sitting; pt may use assistive device

for support

Instructions: When I say "Go," I want you to:

1. Stand up from the chair
2. Walk to the line on the floor at your normal pace
3. Turn
4. Walk back to the chair at your normal pace
5. Sit down again

>12 sec to complete = ⊕ test = 13.5× ↑ in fall risk (*BMJ* 2016;353:1419); test can also reveal deficits to target

- **Workup:** Consider HCT, B_{12}, Chem-7, TFTs, 25OH-VitD, med levels; additional tests (event monitor, TTE, brain, & spine imaging) should be guided by Hx/PE

Management (*J Am Geri Soc* 2011;59:148; *Ann Intern Med* 2012;157:197; *BMJ* 2016;353:1419)

- **General principles:** Exercise program & Vit D supplementation recommended for *all* pts >65 w/ increased risk of fall; for pts at ↑ risk, using multidisciplinary approach (*AFP* 2011;84:1287)
- **Exercise program:** Balance, gait, & strength training; at least 12 wks duration w/ 30–90 min sessions occurring 1 to 3 times/wk (*AFP* 2011;84:1287); early mobilization after a fall (*JAMA* 2012;308:2573); Tai chi may be esp beneficial for balance (*Gait Posture* 2007;25:205–214)
- **Vitamin D:** Prevents fractures (*NEJM* 2012;387:40); may prevent falls by ↓muscle atrophy; goal 25OHVit D level >30; AGS recommends a supplemental vitamin D dose of 1000 units daily (*J Am Geri Soc* 2014;62:147)
- **Pts at ↑ risk:** Tx varies by cause of fall; may include PT eval (for balance, strength, gait), home safety assessment by VNA/OT, assistive devices (walker, cane); med review (incl ↓ & d/c of high-risk meds if possible); pain management; eval & tx of osteoporosis; grab bars in bathroom; ophthalmology referral; podiatry referral; nonskid, well-fitted footwear; bedside commode or urinal; medic alert bracelet (esp if pt lives alone)
- **Warfarin:** H/o falls is not an absolute contraindication for anticoagulation: risk of SDH is so low that a patient w/ avg risk of embolic CVA on AC must fall 300×/yr for risks of AC to outweigh benefits; shared decision-making & risk eval advised (*Arch Intern Med*

1999;159:677; *Am Heart J* 2011;161:241)

- **Head trauma while on systemic 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; *J Emerg Med* 2015;48:137); some advocate for 24-h obs followed by a 2nd CT scan to detect delayed bleeds (*Ann Emerg Med* 2012;59:451)

Patient Information

JAMA 2010;303:288; www.cdc.gov/steadi/patient.html (English and Spanish patient education material)

PERIOPERATIVE EVALUATION

Background (*Ann Intern Med* 2016;165:ITC81; *J Hosp Med* 2012;7:697; *BMJ* 2011;343:d4331)

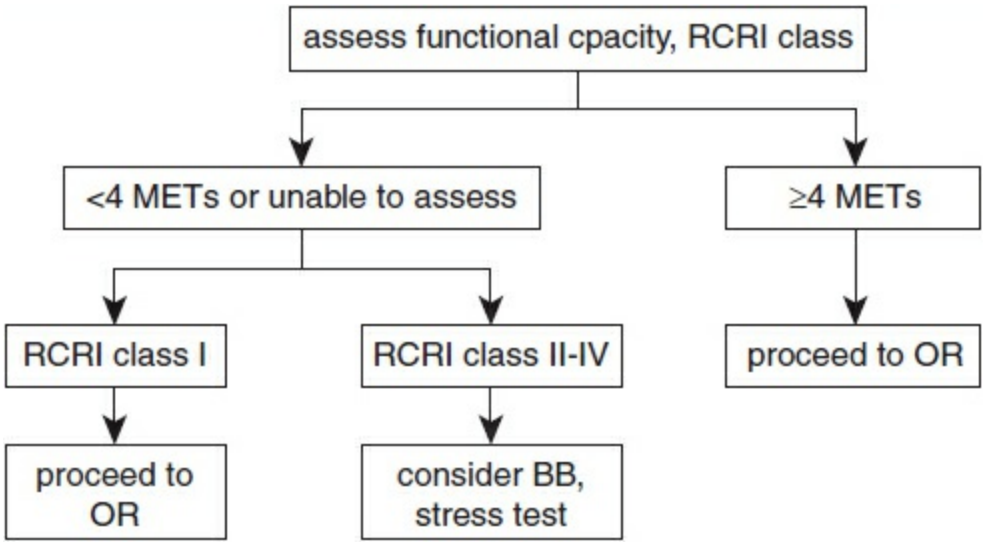
- **Epidemiology:** 27 million pts undergo surgery in US each yr; complication rates vary by site, surgery, surgeon, & pt population; some estimates 12–21% of surgeries → post-op complications which prolong hospital stay or ↓ pt functional status (*Arch Surg* 2002;137:611)
- Ambulatory preoperative risk assessment may ↓ length of stay, complications, & mortality
- **Goals of preoperative eval: Assess risk & offer recommendations to å risk**
- **Pathogenesis of perioperative MI:** (1) Volume shifts; (2) ↑ O_2 demand (stress), incl 2/2 blood loss; (3) Post-op ↑ PLT reactivity
- Perioperative MI affects ~3.3% of surgeries in pts >45 y at risk; CV complications leading cause of death <30 d after noncardiac surgery

Stepwise Surgical Evaluation
(1) **Surgical emergency? → proceed to OR**
(2) **Cardiac contraindications present? → delay surgery** Unstable/severe angina, recent MI (<6 wks), decompensated, worsening, new-onset, or class IV HF, high-grade AV block, symptomatic arrhythmias, new VT, severe AS or symptomatic MS
(3) **Low-risk surgery? → proceed to OR**

(4) **Vascular surgery? → consider β & stress test if it will Δ mgmt**

(5) **nonemergent, moderate–high risk surgery without cardiac contraindications → See below**

Moderate–High Risk Surgery Evaluation



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

- **History:** PMHx w/ thorough eval of current/prior cardiac & pulmonary disease, incl h/o toxic meds/tx (e.g., chest XRT, doxorubicin, bleomycin); bleeding disorder
  - *Exercise*/functional capacity (see below)
  - *Meds* incl antihypertensives, diabetes meds, potentially renotoxic meds (NSAIDs, diuretics), antiplatelet or anticoagulants, herbals, OTCs, pain meds, psychiatric meds
  - *Substances* (alcohol, tobacco, drug use)

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: BP, HR, SaO2, evidence of PAD (carotid bruits, peripheral pulses), pulmonary disease, liver disease, bleeding/bruising, mental status, any wounds**
- **Studies:** ✓ β-hCG in premenopausal ♀; other pre-op lab testing, incl coags, generally not indicated in healthy pts <50 y undergoing low-risk elective surgery (*Lancet* 2003;362:1749); "specific tests by indication below"

  Creatinine in pts undergoing mod–high risk surgery

  Hgb/HCT in elderly or pts undergoing surgery w/ significant anticipated blood loss

  PTT, PT, PLT in surgery w/ ↑ bleeding risk (i.e., prostate, neurosurgery, ophthalmic, intrabdominal/thoracic, mastectomy, laparoscopy, arthroscopy)

  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 disease, or if >50 y undergoing thoracic/abdominal surgery (*Ann Intern Med* 2006;144:581)

  PFTs in pt w/ dyspnea of unclear origin, hx COPD or asthma; consider

  TTE if pt has dyspnea of unclear origin, pathologic murmur, hx valvular disease, pulm HTN or CHF w/ change in clinical status & no echo in past 12 mos

  BNP or NT-proBNP: Consider ✓ in patients with CHF w/ change in clinical status. BNP ≥92 ng/l or NT pro-BNP ≥300 ng/l predictive of ↑ risk of death or MI (*NEJM* 2015;373:2258; *JACC* 2014;63:170)

Cardiac Risk Assessment

- CV Risk assessment includes pt Hx/PE & predictors of cardiac risk: RCRI class or NSQIP, functional capacity, surgery-specific risk, & (if appropriate) results of stress testing/TTE (*Circulation* 2009;120:e169; *JACC* 2007;50:e159; *NEJM* 2015;373:2258)

CV Risk by Type of Surgery (cardiac death, nonfatal MI, nonfatal cardiac arrest)

High risk (≥5%): Aortic/major vascular surgery, peripheral arterial surgery
Intermed (1–5%): CEA, head & neck, intraperitoneal/thoracic, orthopedic, prostate
Low risk (≤1%): Outpt surgery, endoscopy, cataract & breast surgery, dental procedures

RCRI Risk Factors
(1) Diabetes treated w/ insulin (2) Hx HF (3) Cr > 2.0 (4) Hx CVD (5) High-risk surgery (intrathoracic/peritoneal, suprainguinal vascular) (6) Hx MI or ⊕ ETT, current nitrate Rx, CP due to CAD, ECG w/ pathologic Q-wave**

# RCRI Risk Factors	Class	CV Risk* (95% CI)
0	I	0.4% (0.05–1.5%)
1	II	0.9% (0.3–2.1%)
2	III	6.6% (3.9–10.3%)
≥3	IV	11% (5.8–18.4%)

*_Major cardiac complications_ included acute MI, pulmonary edema, VF, cardiac arrest, complete heart block

**Hx coronary revasc does not count unless other criteria for CAD present (_Circulation_ 1999;100:1043)

- **RCRI limitations:** Does not predict all-cause mortality, excludes emergency surgery; less sensitive methods (CK-MB) were used in MI dx; ↓ accuracy for AAA, vascular surgery, elderly
- **NSQIP/Gupta risk calculator:** surgicalriskcalculator.com/miorcardiacarrest; outperforms RCRI based upon improved C statistic (_Circulation_ 2011;124:381)

Consideration of Additional Testing (_AFP_ 2012;85:239; _JACC_ 2007;50:e159; _JACC_ 2009;54:2102)

- **Stress testing:** Generally, stress testing has a high NPV/low PPV for peri-op CV events; see _"CP & Noninvasive Testing"_ for details; **not appropriate if no cardiac sx, functional capacity ≥4 METS & 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; if indicated, ETT preferred over pharmacologic
- **Angiography:** Decision based on results of stress test/echo, or if pt

has an indication independent of need for surgery (e.g., ACS, uncontrolled angina)
- **Revascularization:** Considered in pts w/ left main/3v disease, or 2v disease w/ proximal LAD stenosis, LV dysfunction/ischemia on stress testing; benefit weighed against risk of delaying surgery, d/c'ing (or continuing) anti-PLT agent peri-op

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Risk Management

Cardiovascular Disease

- **Recent PCI:** Delay surgery if at all possible to >14 d s/p balloon angioplasty, >30 d s/p BMS, & >6 m (>1 y is safer) s/p DES (*JACC* 2016;68:182)
- **CHF:** Typically, continue ACEI & diuretics; consider short-acting ACEI (i.e., captopril)
- **HTN:** Avoid elective surgery if poorly controlled HTN; continue BB or clonidine; consider holding ACEI/ARB, CCB on AM of surgery if BP well controlled
- **Pacemakers:** Consult EP (programming during surgery, post-op interrogation)
- Statins, ASA, BB: See "Medication management" below

Type 2 Diabetes Mellitus

- **Glucose goals:** Generally, less intensive control preferred; ↑ hypoglycemia w/ intensive (<120–150 mg/dl) perioperative targets (*Cochrane Database Syst Rev* 2012;(9):CD002752)
- **Surgery timing:** Pre 9 AM surgery ideal to prevent prolonged NPO.
- **PO med mgmt:** Hold most meds the morning of surgery (see above)
- **Insulin med mgmt:** Consider reducing PM insulin night before surgery if h/o AM hypoglycemia; hold short/rapid acting insulin AM of surgery; take ~½ of total usual AM dose (short+long) in intermed/long acting form only
- **Insulin pump:** Continue usual basal rate; endocrine c/s

Liver Disease (*Ann Surg* 2005;244:242)

- Pts w/ cirrhosis have ↑bleeding, infection risk; abd surgery, decompensation ↑↑ risk; suggest hepatology involvement, avoid nephrotoxic meds
- Risk assessment: MELD score ~ post-op mortality, with ↑↑ as MELD ↑ (e.g., MELD 5 = 5%, MELD 25 = 25%, MELD 35 = 50%) or Child Class (A~10%, B ~30%, C 75%, portal HTN ≥30%); ↓ albumin → ↑ morbidity/mortality (*Arch Surg* 1999;134:36–42)

Tobacco (*Arch Surg* 2012;147:373)

- Smoking assoc w/ ~2× ↑ risk of post-op dehiscence, wound complication, hernia, & surgical site infection; tobacco cessation prior to surgery ↓ post-op complications by 41%, incl wound healing & pulmonary complications (*Am J Med* 2011;124:144)

Chronic Corticosteroid Use

- Generally, pts on chronic steroids should continue on day of surgery; consider stress dosing if >20 mg prednisone/equiv for >3 wks & major surgery
- **Steroid stress dosing** (*Ann Intern Med* 2009;151:ITC-1)
  - *Major surgery (CT surg, oncologic, intra-abd):* 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 → 25 mg IV q8h × 3 doses → outpt dosing
  - *Low-risk surgery (e.g., cataract):* Outpt dosing day of surgery, double 1st post-op dose

H/o Stroke (*NEJM* 2007;256:706)

- Incidence of peri-op stroke varies w/ type of surgery (0.08–0.7% general surgery to 8.7% aortic repair); prior stroke major RF; surgery should be delayed until >2 wks after stroke

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)

Delirium Prevention (*NEJM* 1999;340:669)

- Common post-op in elderly (15–60%) & often unrecognized, esp if hypoactive; assoc w/ ↑ morbidity/mortality/LOS/institutional placement; **prevention** w/ behavioral protocols (mobilization, timely d/c of Foley, orientation, family at bedside) can ↓ incidence (60% risk reduction, NNT = 20); limit opioids, sleep aids, benzos post-op

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Medication Management

CV Medications (*Chest* 2008;133:299; 2012;141:e326S; *NEJM* 1997;336:1506; *Circulation* 2014;130:2215)

- **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
- **Antihypertensives:** Generally continued until time of surgery; clonidine & βB assoc w/ withdrawal syndrome (*JAMA* 2002;287:2043)
- **Beta-blockers:** Controversial due to variety of Rx intensity & outcomes studied in trials (*Circulation* 2014;130:2246; *JAMA* 2010;303:551); ↓ peri-op MI but ↑ stroke & total mortality (esp if high dose BB leading to ↓ BP); POISE, *Lancet* 2008;371:1839); in retrospective cohort 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); continue βB in pts already on; consider initiating 1–4 wks prior to surgery in pts who should be on a βB or who have CAD, stable angina, or those w/ >1 RCRI risk factor undergoing intermed or high-risk surgery (*NEJM* 2005;353:349); discuss risks/benefits w/ pt & document; titrate to HR 60–70 bpm; continue for 1 mo after & taper carefully if discontinuing; β1 selective agents preferred due to less HoTN; outcomes worse if βB stopped abruptly pre-op or if initiated on day of surgery

Antithrombotic Management

- ASA & P_2Y_{12} inhibitors (clopidogrel, prasugrel, etc.) irreversibly inhibit platelet function; each day they are held → 10–14% restoration of platelet function; platelets not fully restored to nl

function until 7–10 d after d/c

- **Aspirin:** Pts w/ recent coronary stenting (<90 d s/p BMS, <1 y s/p DES) should delay surgery or remain on ASA; for others, even w/prior PCI, ASA of unclear perioperative benefit in noncardiac surgery (*NEJM* 2014;370:1494) though withdrawal may ↑ risk; generally safe to continue in ↓ bleeding risk (see below); hold for surgery w/ ↑ bleeding risk (see below); d/c ASA 5–7 d prior to surgery; resume >24 h after surgery if sufficient hemostasis (*Chest* 2008;133:299; *Chest* 2012;141:e326S)
- **P_2Y_{12} inhibitors (e.g., clopidogrel):** Pts w/ recent coronary stenting (<90 d s/p BMS, <6 mos s/p DES) should delay surgery or remain on DAPT; consider d/c of DAPT 3–6 mos s/p DES if risk of surgical delay > thrombotic risk (*Circulation* 2016;134:e123; 2014;130:2215); pts at low risk of CV events can d/c clopidogrel 7–10 d prior to surgery; resume 24 h after surgery if sufficient hemostasis; MI risk after discontinuation of thienopyridine mostly unrelated to sites of prior stent (*Circulation* 2017;135:1720)
- **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)

Anticoagulant Management (*Chest* 2012;141:e326S; *JACC* 2017)

- Decisions to continue vs. interrupt anticoagulation, & if interrupted, whether or not to bridge, based on balance of (1) pt's thromboembolic risk (2) pt & procedural risk of bleeding
- For AF at low or moderate thrombotic risk (see above) bridging generally **not** needed; ↑ bleeding risk w/o benefit (BRIDGE, *NEJM* 2015;373:823); individualized risk assessment & recommendations from ACC: tools.acc.org/bridgeanticoag/ (*JACC* 2015;66:1392)
- **Higher thrombosis risk:**
  - *AF & 1 of following:* CHADSVASc > 6, valvular heart disease, stroke/TIA <3 mos
  - *Mechanical valves:* Any mitral, any caged-ball valves, any stroke/TIA <3 mos; aortic & any add'l thrombotic risk factors (AF, CHF, hx stroke/TIA)
  - *CAD:* Stent in last y, recent MI, nonstented PCI after MI (*Gastrointest Endosc* 2009;70:1060)

Stroke: Recent (<6 mos) stroke or TIA
VTE: Recent (<3mos) or recurrent VTE, malignancy-associated VTE
Other: Severe/multiple thrombophilia; protein C/S/antithrombin deficiency, APLAS, h/o intracardiac clot, stroke/TIA/VTE w/prior interruption of anticoagulants

- **Lower thrombosis risk:** Distant (>12 mos) VTE; AF w/o valvular disease or risk factors above; bioprosthetic valves
- **Higher bleeding risk:** Abnl renal or liver function, bleeding diathesis, elderly, abnl number/fxn of PLT, bleeding w/ prior procedures or w/ prior bridging
- **Procedures w/ ↑ bleeding risk:** NSG, urologic/renal procedures, cardiac/vascular
- **Procedures w/ å bleeding risk:** Arthrocentesis, cataract surgery, outpt dental surgery, minor dermatologic procedures
- **Novel anticoagulants (NOACs):** Assess procedural bleed risk; suggested timetable (based on ACC 2017 nonvalvular AF guidelines) below

Timeframe for Witholding NOACs Prior to Procedure, by GFR

	DTI: low bleeding risk	DTI: other/unk bleeding risk	FXa inhibitor: low bleeding risk	FXa inhibitor: other/unk bleeding risk
CrCl ≥80	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–79	≥36 h	≥72 h	≥24 h	≥48 h
CrCl 30–49	≥48 h	≥4 d	≥24 h	≥48 h
CrCl 15–29	≥72 h	≥5 d	≥36 h	✓ anti-Xa &/or hold ≥72 h

- **Warfarin:** Usually held 5 d prior to surgery; may consider 3–4 d if INR <2, >5 d if INR >3; for VTE disease, recommended to resume 12–24h later if adequate hemostasis

  Minor dental procedure: **Continue or stop 2–3 d prior to procedure**
  Minor dermatologic procedure, cataract surgery: **continue**
- **Heparin bridging recommendations:**

Unfractionated heparin: d/c 4–6 h prior to surgery
LMWH: Stop 24 h prior to surgery; resume 24 h after surgery (if bridging to warfarin or continuing on LMWH)

Other Medications

- **IBD medications:** Hold 5-ASA & 6-MP on day of surgery; resume 3 d post-op if nl renal function (*Mayo Clin Proc* 2011;86:748)
- **Stimulants:** Hold on AM of surgery
- **NSAIDs:** Can ↑ bleeding risk; hold 4–5 d prior to surgery

Commenting on Peri-operative Risk
[Pt's name] is seen for pre-operative eval. [Pt] reports no sx of CP at rest or w/ exertion, dyspnea at rest or w/ exertion, PND, LE edema, claudication, or palpitations. [Pt] has no h/o (ischemic heart disease, CHF, CVD, diabetes, recent anticoagulant or antithrombotic use, personal or FHx of coagulopathy). [Pt] reports no h/o (stress test, cardiac cath, or coronary revascularization). [Pt] reports being able to achieve __ METs of activity during (_____describe activities).
This pt's cardiac risk factors include (high risk surgery, ischemic heart disease, h/o CHF, h/o CVD, IDDM, SCr >2). According to the RCRI, this number of risk factors stratifies the pt to Class __, which carries a __ percent risk of major CV complications (*Circulation* 1999;100:1043). In this case, however, the RCRI potentially (over/under) estimates the pt's true cardiac risk given the h/o __. It also does not take into account comorbid conditions such as ___.
The risks of ___ were discussed w/ the pt, in light of the benefits of possible surgery. This assessment was conveyed to the surgery & anesthesia teams.

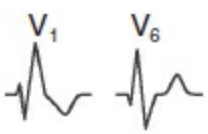
APPROACH TO THE ECG

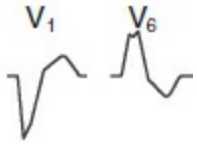
Systematic Interpretation

- **Rate:** Estimate by 300/number of small boxes between complexes (e.g., R waves); HR >100 = tachycardia, <60 = bradycardia
- **Rhythm:** Regular or irregular QRS? *Sinus:* Regular upright P-wave in II/III/aVF/V_5/V_6, P before every QRS, QRS after every P
- **Axis:** *Heart rotates toward hypertrophy and away from ischemia;* Look at lead I and aVF

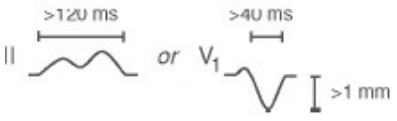
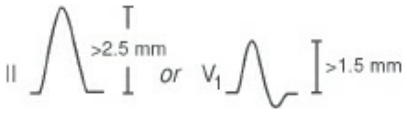
I	aVF		Differential
+	+	Normal axis	
+	−	Left-axis deviation	"physiologic," LVH, LBBB, inferior MI LAFB, WPW
−	+	Right-axis deviation	RVH, RBBB, LPFB, WPW, lateral MI

- **Intervals:** (1 horizontal big box = 200 ms = 5 small boxes, 1 small box = 40 ms)
  - *PR:* Normal 120–200 ms (<1 big box); If >200 ms, 1st-degree AV block
  - *QRS:* Normal <100 ms; 100–120 ms → interventricular conduction delay (IVCD)
- **Territory:** Septal (V_1), Ant (V_2–V_3), Lateral (V_4, I, aVL), Apical (V_5, V_6), Inferior (II, III, aVF)

Bundle Branch Blocks (if QRS ≥ 120 ms) (Circulation 2009;119:e235)		
RBBB		1. rSR' in R precordial leads (V_1, V_2) 2. Wide S-wave in I and V_6

LBBB		1. Broad, slurred, monophasic R in I, aVL, V_5 V_6 (± RS in V_5–V_6 if cardiomegaly) 2. Absence of Q in I, V_5 and V_6 (may have narrow q in aVL) 3. ST and T-wave opposite major QRS deflection, LAD

- **QT:** Measure from start of QRS to end of T-wave; correct for HR: QTc/ = QT/$\sqrt{RR}$ Prolonged QT/QTc (>440 ms ♂, >460 ms ♀); DDx: Electrolytes, meds, congenital
- **Chamber size:**

ECG P-wave criteria	Left Atrial Abnormality (LAA)	Right Atrial Abnormality (RAA)
		

- **LVH:** Sokolow–Lyon: S in V_1 + R in V_5 or V_6 ≥35 mm, or R in aVL ≥11 mm
- **RVH:** R > S in V_1 or R in V_1 ≥7 mm, S in V_5 or V_6 ≥7 mm
- **Ischemia** (*Circulation* 2007;116:2634),
  - **Q-waves** (prior MI)**:** Q-wave ≥20 ms in V_2–V_3 OR ≥30 ms and ≥1 mm in 2 contiguous leads
  - **ST elevations (STE):** ≥1 mm ST elevation in any 2 contiguous leads except V_2–V_3, where it has to be ≥1.5 mm in ♀ or ≥2 mm ♂; *DDx:* LBBB, early repolarization, electrolytes, PE, Brugada
  - **ST depressions (STD):** Horizontal or down-sloping ≥0.5 mm in 2 contiguous leads; *DDx:* Ischemia, LVH with strain, hypokalemia, digoxin
  - **T-wave Inversion (TWI):** *DDx:* Ischemia, cardiomyopathy, abnl repolarization, electrolytes, cerebral event
  - **If LBBB:** STEMI by Sgarbossa's criteria: STE ≥1 mm in lead with +QRS, or STD >1 mm in lead with—QRS, or STE ≥5 mm in lead with—QRS; paced rhythm precludes assessment
  - **New LBBB** in setting chest pain/ischemic equivalent is STEMI until proven otherwise

Sudden Cardiac Death

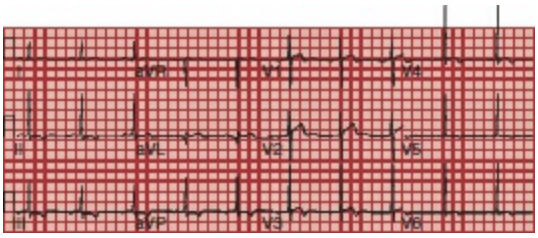
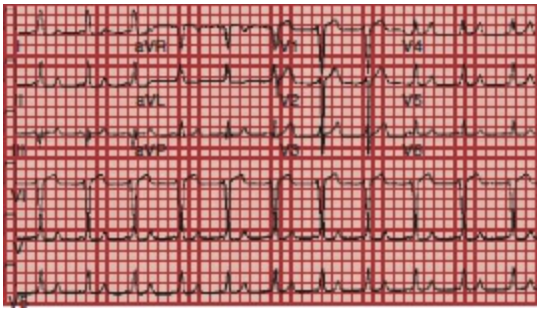
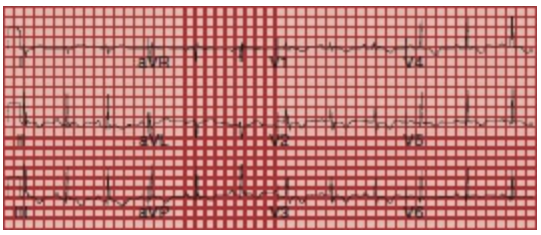
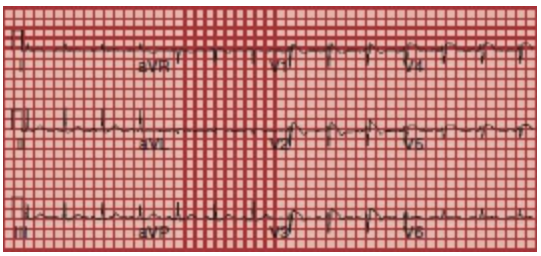
Background (*Circulation* 1998;98:2334; *NEJM* 2001;345:1473)

- **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); primary arrhythmia is typically VF, VT, or VT → VF; bradyarrhythmias are thought to cause only 7% of SCD

Evaluation

- **Evaluation: Sx:** Palpitations, chest pain, **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
- **Exam:** Signs of HF, valvular disease, hypertrophic changes, particularly HOCM
- **Initial workup: ECG** (prior MI, conduction delays [incl LBBB, ↑QT], LVH, ventricular ectopy); **TTE:** If ↑ suspicion for heart failure or HOCM, **stress test** (if medium prob CAD—see *Noninvasive Testing,* or if indicated for sports clearance (see *Sports Eval*); further w/u per cardiology may include cardiac MRI for arrhythmogenic right ventricular CM (ARVC)

Inherited Disorders in Sudden Cardiac Death (Cardiology 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) **ECG:** LVH, STE, apical TWI, Q-wave in I, aVL, V_4–V_6; abnl ECG found in 95% of	

pts (*JAMA* 2002;287:1308)	
WPW: Accessory tract bypasses AV node. In SVT (AFib esp), risk of rapid, 1:1 conduction down the bypass tract → VF **ECG:** Shortened PR interval & slurred upstroke of the QRS (delta waves)	
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	
Arrhythmogenic right ventricular dysplasia: Fibrous replacement of the RV>>>LV → arrhythmia; 2nd–4th decade of life; 50% with + FHx (*NEJM* 2017; 376:61). **ECG:** TWI in V_1–V_3, ε waves, RBBB, & prolonged QRS **Cardiac MRI:** E/o fatty infiltration, scarring, dilation/dysfunction of RV	
Brugada syndrome: Mutations → ↓ Na current; may have ⊕ FHx **ECG:** Pseudo RBBB in w/ ST ↑ in V_1–V_3 (type 1) or a "saddle-back" morphology, most prominent in V_2 (types 2 & 3); may be transient/only in context of inciting factors: Meds (antiarrhythmics, antidepressants, βB), fever, EtOH, cocaine, electrolyte disturbances	

Acquired Disorders in Sudden Cardiac Death
Heart failure: Many pts w/ EF ≤35% qualify for ICDs; cards consultation advised (see "*Heart Failure*").
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 h/o MI: See "*Coronary Artery Disease*" for secondary prevention
Electrolyte abnormalities: Monitor Mg, K in pts with renal failure or on diuretics, especially if baseline ECG is abnormal (see "*Potassium Disorders*")

CORONARY ARTERY DISEASE

Background (*Circulation* 2012;126:e354; *NEJM* 2012;366:54)

- **Coronary artery disease (CAD)/Ischemic heart disease (IHD):** Signs, Symptoms, or complications of atherosclerotic deposition in the coronary vasculature; stable if sx controlled
- **Epidemiology:** 1 in 2 ♂ & 1 in 3 ♀ will develop CAD (*Circulation* 2015;131:e29); CAD is the leading cause of death in US, responsible for 1 in 6 deaths (*Circulation* 2010;121:948)
- **Pathophysiology:** Endothelial + intimal dysfunction, cholesterol deposition, 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)
- **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; CKD: ↓ GFR & ↑ proteinuria assoc w/ ↑ risk of CV events (*Lancet* 2010;375:2073); ↓ **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:** Complex inheritance 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 ♀

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)

CAD Presentations (*Circulation* 2012;126:e354)

- **Asymptomatic:** Incidentally discovered on noninvasive testing
- **Stable angina:** Substernal chest discomfort when myocardial O_2 demand > supply with characteristic quality that is provoked by exertion or emotional stress and relieved by rest or nitroglycerin; unstable angina occurs at rest or in escalating pattern
- **Acute coronary syndrome:** Sx or asx (silent) 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 angiography (*NEJM* 2007;356:830); due to microvascular CAD or hypersensitivity to cardiac pain (*Circulation* 2004;109:568); treated w/ βB, CCB, nitrates, reassurance

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; ASCVD risk calculator available (risk estimate includes CAD and stroke risk) at tools.acc.org/ASCVD-Risk-Estimator-Plus/
- **Diagnosis:** Based on clinical history of angina in the presence of risk factors:

  Noninvasive testing: See "*Noninvasive Testing*"

  Coronary angiography: If high-risk noninvasive results (≥1 large or ≥2 mod size territories of ischemia on stress, or LV dilation), unexplained LV dysfunction, unable to undergo test, medically refractory angina, indeterminate noninvasive study
- **Workup:** Waist circumference, BMI, lipids, & DM2 screening (see

"Screening"); Holter useful in dx of silent ischemia, variant angina; may consider use of CRP & LpA for further risk stratification (*Arch Intern Med* 1997;157:1170; *Circulation* 2003;107:363; 499)

Coronary Artery Disease Prevention

	Primary prevention	Secondary prevention
Goal	Prevent disease	Prevent harm from disease
Exercise, healthy diet	**X**	**X**
Quit smoking, moderate 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**
Aspirin	Based on risk of CVD, age	**X** (unless contraindicated)
ACE inhibitors/ARBs		DM2, HTN, MI, EF <40%, CKD
β-blockers		H/o MI or CHF

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

Primary Prevention

- **Diet:** ↑ Fruits, vegetables, fiber; ↓ red meat, trans fatty acid, sat fats, high-fructose corn syrup; stepwise 1–2 improvements q3–6mo may ↑ compliance (*AFP* 2009;79:571)
  - **Mediterranean diet:** ~30% ↓CV events in high CV risk (*NEJM* 2013;368:1279); ↑ vegetables, locally sourced, min processed foods, ↓ red meat, <4 eggs/wk, moderate dairy, 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 (*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)

- **Diabetes, lipid, and blood pressure management;** smoking cessation
- **Aspirin:** In pts without known CAD, ASA ↓ risk of nonfatal MI (NNT = 162) but no mortality benefit & ↑ 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); bleeding risk likely to outweigh benefit 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); **Dose:** 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)

USPSTF Recommendations for Aspirin in Primary Prevention of CAD (*AFP* 2016;94:660A)				
Population	<50 y	50–59 y & ≥10% 10-y CVD risk	60–69 y & ≥10% 10-y CVD risk	≥70 y
Recommendation	None given	Initiate aspirin	Shared decision making	None given

Secondary Prevention (*Circulation* 2012;126:e354; *NEJM* 2005;352:2524; 2007;357:1762)

- **Risk factor modification:**
  Diabetes: A1c goal <7% (avoid rosiglitazone)
  Blood pressure: Goal per 2017 AHA/ACC guidelines <130/80
  Lipid lowering (↓ LDL better): Mod–high potency statin; ezetimibe if statin intolerance
  Weight loss: BMI 18.5–24.9, waist circumference <40″ ♂, 35″ ♀
  Exercise: 30–60 min of moderate-intensity aerobic activity 5–7x/wk
  Smoking cessation: 36% reduction in mortality for pts with hx ACS (*JAMA* 2003;290:86)
  EtOH: limit ♀ to 1 drink/d; ♂ 1–2 drinks/d; **Influenza vaccine**
- **Aspirin:** 75–150 mg QD or 325 mg QOD; ↓ CV morbidity & mortality by 20–25% (*NEJM* 2005;352:2524); variable absorption of enteric-coated ASA may ↓ effectiveness (*Circulation* 2013;127:377); clopidogrel in ASA intolerance

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 between 75 and 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)

- **ACE inhibitors:** Pts w/ angina and CHF, DM2, CKD, HTN; meta-analysis of ACEI or ARB in pts w/ stable angina and a normal EF shows ↓ risk of overall mortality, nonfatal MI, CVA, and revascularization compared to standard medical Rx (*AFP* 2012;86:21)
- **Cardiac rehab:** Multidisciplinary program of exercise training, psychosocial support, nutritional/risk factor counseling; ↓ risk of MI, 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; Index of programs in US: www.aacvpr.org/Resources/Program-Directory
- **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 wk 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 & α-blockers as can cause serious vasodilation/hypotension; should be used cautiously in pts w/ active ischemia, HF, low baseline BP, or on multiple BP meds (*JACC* 1999;33:273)

Coronary Artery Disease Treatment

Medical Management of CAD and Angina (*Ann Int Med* 2014;160:ITC1–16; *NEJM* 2016;374:1167)			
Therapy	**Considerations**	**Pathophysiology**	**Toxicities**
βB	1st line; titrate to HR	Bind to β receptors, ↓	HoTN,

	55–60; compared to CCB, similar rate of MI/cardiac death, ↓ s/e (*JAMA* 1999;281: 1927). No clear survival benefit in angina	O_2 demand by ↓ HR & ↓ contractility, resulting in ↑ exercise tolerance, ↓ sx	bronchoconstriction (safe in stable COPD), fatigue, nightmares, insomnia, worsening depression/ Raynaud's (less so w/ β1-selective agents); taper rather than abrupt d/c due to w/d effects; antacids ↓ bioavailability of atenolol
CCB	May be used alone if βB contraindicated (i.e., bradycardia) or in combination w/ βB if sx not controlled by βB alone	Vasodilate & reduce contractility (*NEJM* 1982;307:1618)	Edema; verapamil & diltiazem may worsen CHF & should be used cautiously in pts w/ sinus or AV node dysfunction; verapamil s/e include constipation
Nitrates	Long acting: used as 2nd line; combine with βB or in place Sublingual: Acute angina or ppx before activities	↑ Arterial & venous dilatation, ↓ preload, ↓ myocardial O_2 demand (*NEJM* 1998;338:520)	Flushing, HoTN, HA, syncope, nausea; tolerance; contraindicated in pts on sildenafil or w/ HOCM. Tachyphylaxis; 12–14 h nitrate-free interval (usually at night).
Ranolazine	↓ Angina in pts w/ continued sx on βB, CCB, or nitrates	Works by ↓ Ca overload in ischemic myocytes	QTc prolonging; contraindicated in cirrhosis

Coronary Angiography & Revascularization (*Circulation* 2014;130:1749; *JAMA* 2013;310:2086; *NEJM* 2016;374:1954)

Indications: (1) Sx limit activities despite optimal medical Rx; (2) Pts do not tolerate medical Rx; (3) High likelihood of severe CAD based on noninvasive assessment (i.e.,

>50% left main disease, large area of myocardium at risk for ischemia)

Percutaneous coronary intervention (PCI): Includes stenting & balloon angioplasty (w/o stenting); preferred for 1 or 2 vessel disease w/o left main involvement, or in pts who are not surgical candidates; consider for *highly select* & stable pts w/ left main disease

Bare metal stent (BMS): ↑ Restenosis compared to DES; requires a *minimum* of 1 mo of dual antiplatelet Rx compared to 3–6 mo for DES, ∴ BMS preferable in pts at ↑ risk for bleeding, noncompliance, or antiplatelet interruptions for procedures (*NEJM* 2007;356:984)

Drug eluting stent (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/ >3 mo of dual antiplatelet Rx due to ↑ risk of stent thrombosis 2/2 to delayed endothelialization compared to BMS (*NEJM* 2013;368:254)

CABG: (1) >50% stenosis in LM (↑ survival); (2) Diffuse 3 vessel disease (>70% stenosis) w/ large area of myocardium at risk or EF <40%; (3) Proximal LAD + another major coronary artery, or pts who are not PCI candidates; greatest benefit if LIMA–LAD

Medical Management Following Revascularization for MI (*Circulation* 2013;127:529)

In addition to secondary prevention medications in table above:

- **Antiplatelets:** ASA + thienopyridine or ticagrelor for 12 mo (regardless of stent)
- **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
- **βB:** Continue for at least 3 y & consider indefinitely (*Circulation* 2011;124:2458)
- **NTG:** Pts should be instructed on PRN use & when to seek medical attention

Antiplatelet Therapy (*JACC* 2016; 68:1082)
After CABG: ASA (75–100 mg QD) indefinitely + clopidogrel, may improve graft patency (*JACC* 2011;57:1639)—or ASA 325 mg QD for 9–12 mo 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)
PCI (DES/BMS) for stable angina: ASA (75–100 mg QD) indefinitely + clopidogrel (75 mg QD) OR prasugrel (10 mg BID) OR ticagrelor (90 mg BID) for a minimum of 1 mo (BMS) or 3 mo (newer DES). ≥12 mo preferred if ischemic > bleed risk (DAPT Score: tools.acc.org/DAPTriskapp; *JAMA* 2016;315:1735) as risk of MI, predominantly, unrelated to stent, persists until at least 30 mo post PCI (*Circulation* 2017;135).
***Indefinite clopidogrel:** Shared decision for indefinite clopidogrel in PCI patients (DES or

BMS), especially if at risk for catastrophic consequences from stent thrombosis (i.e., left main or proximal LAD stent) (*NEJM* 2014;371:2155); cardiology consultation advised

Warfarin + dual antiplatelet Rx (i.e., ASA + clopidogrel) – "Triple therapy": If warfarin is needed for AF, mechanical valves, hx DVT, etc., use ASA 81 mg QD (*JACC* 2008;51:172); If w/ stent, consider stopping ASA after 1 mo (*Lancet* 2013;381:1107)

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

Before elective noncardiac surgery: Elective noncardiac surgery should be delayed for 30 d after BMS, 3 mo after DES. Cardiac consultation advised if DAPT must be held. If DAPT held, restart ASA ASAP and then 2nd antiplatelet agent

CHEST PAIN AND NONINVASIVE TESTING

Background (*AFP* 2011;83:603; *Circulation* 2003;107:149; *JAMA* 2002;288:2745; *NEJM* 1979;300:1350)

- **Epidemiology:** 6 million pts present w/ chest discomfort each year in US; Dx for pts presenting to PCPs: Musculoskeletal (36%), GI (19%), CV (16%), nonspecific (16%), psychiatric (8%), pulmonary (5%); Dx of CV disease ↑↑ in pts presenting to ER (54%)
- **Pretest probability of coronary artery disease:** Stress testing indicated for pts w/ intermediate pretest probability (discussed below)
  - **Definite/"classic" angina:** (1) Substernal chest discomfort; (2) provoked by exertion/emotional stress; (3) relieved by rest/nitroglycerin
  - **"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

Pretest Probability of CAD					
Age (y)	**Sex**	**Typical/Definite**	**Atypical**	**Nonanginal**	**Asymptomatic**
30–39	M	Intermediate	Intermediate	Low	Very low

	F	Intermediate	Very low	Very low	Very low
40–49	M	High	Intermediate	Intermediate	Low
	F	Intermediate	Low	Very low	Very low
50–59	M	High	Intermediate	Intermediate	Low
	F	Intermediate	Intermediate	Low	Very low
60–69	M	High	Intermediate	Intermediate	Low
	F	High	Intermediate	Intermediate	Low

Definition of probabilities: High >90%, intermediate 10–90%, low <10%, very low <5%
↑ **pretest probability:** DM2, HLD, smoking, Q-waves, or ST abnormalities

Differential Diagnosis of Chest Discomfort		
	Diagnosis	**Clues** (*AFP* 2013;87:177)
Cardiovascular	Angina	Typically discomfort/pressure/burning/squeezing brought on by exertion, ↓ 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
	Diagnosis	**Clues** (*AFP* 2013;87:177)
Cardiovascular	Coronary vasospasm	Rest angina that abruptly resolves
	Aortic dissection	"Ripping or tearing" pain radiating to back, >20 mmHg difference in BP between arms, widened mediastinum on CXR. Loss of pulses; may be associated with new neurologic deficit or syncope.
	Pulmonary embolus	Dyspnea, tachypnea, tachycardia, hypoxemia, ± sudden pleuritic pain; H/o immobility, clotting, malignancy; ECG S1Q3TWI3.
	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
Pulmonary	Pneumonia	Fever, chills, cough, sputum, pleuritic pain, consolidation on chest exam; ⊕ CXR
	Pneumothorax	Acute onset pleuritic pain, dyspnea; ↓ breath sounds
	Pleurodynia	Chest pain 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, h/o vomiting/instrumentation.
	Other	Cholecystitis, pancreatitis, biliary & peptic ulcer disease
Other	Muscular pain	Pain w/ palpation, h/o injury, strain, repetitive use
	Rheumatic (fibromyalgia, rheumatoid/osteoarthritis)	Pain in other joints/tender points, h/o RA, OA, fibromyalgia
	Shingles	Dermatomal distribution, rash
	Psychiatric/anxiety	H/o φ problems, anxiety, ROS often pan-positive
	Rib fractures, bone mets	H/o 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), 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, history of clotting, long plane/car rides, malignancy

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

Atypical Presentations/Disparities: ↑ triage errors in women, minorities, elderly, diabetics, pts w/ dyspnea

- **Physical exam:** VS: Including SaO_2 sat, BP in both arms (>10 mmHg difference → consider aortic dissection); ask patient to point where pain is; CV (JVP, heart murmurs, rubs, S_3, S_4, pulses), pulmonary (rales), abdominal (epigastric TTP), chest wall exam (TTP/reproducible), breast exam if sx; LE: edema, Homans sign
- **Diagnostics:** CXR (PNA, widened mediastinum), ECG, labs (CBC, electrolytes, D-dimer, troponin/CK per clinical suspicion); CT scan, stress testing (if intermediate pretest probability of CAD), TTE as needed
- **Management:** Immediate ER referral of pts w/ life-threatening causes of chest pain (i.e., aortic dissection, pneumothorax, intermediate or high pretest probability for ACS or PE)
- **Patient information:** *JAMA* 2009;301:1498; 2014;312:858; 2015;314:1990

Noninvasive Cardiac Testing

Indications

- **CAD diagnosis:** Stress testing beneficial in pts w/ *intermediate* pretest probability of CAD to avoid false negatives in pts w/ ↑ pretest probability and to avoid false ⊕ in pts w/ ↓ pretest probability (*NEJM* 1979;301:230); see "Pretest Probability" table above; exercise ETT does not localize/quantify myocardial viability; pharmacologic/exercise imaging studies needed instead
- **Prognosis:** In pts w/ stable angina after diagnosis or change in

symptoms
- **Postrevascularization:** Assess exercise tolerance & localize residual ischemia (need imaging)

Screening

- **Asymptomatic pts:** In asx pts w/ low pretest 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 preferred (*Ann Int Med* 2016;164:479; *NEJM* 2003;349:465)
- **Diabetes:** 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)
- **Prior to initiation of a rigorous exercise program:** Consider exercise ETT in diabetics and in pts w/ intermediate or high risk of CAD

Pretest Counseling

- **To establish diagnosis of CAD as cause of symptoms:** Hold βB, CCB, dipyridamole, and nitrates for 48 h and caffeine for 12 h prior to ETT/stress TTE (note: if concerns, d/w cardiology prior to testing); ACEI, statin ok to continue
- **To determine if known CAD is cause of current sx, for prognosis, or postrevascularization:** Continue regular medications without interruption; βB/CCBs may limit ability to reach max HR

Choice of Test

- **Screening ECG:** USPSTF & AHA recommend **against** ECG CAD screening in low-risk pts; insufficient evidence re: int/↑ 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 radionucleotide myocardial perfusion imaging [rPMI]) preferred in pts w/ prior PCI or CABG

Radionucleotide choice: Thallium detects viable myocardium; MIBI provides better images in ♀ or obese patients due to higher-energy photons, measures LVEF

- **"Stress testing"**: Induces situation which (1) ↑ O_2 demand or ↑ coronary flow and (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, pulmonary 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 rPMI preferred for pts w/ prior PCI/CABG

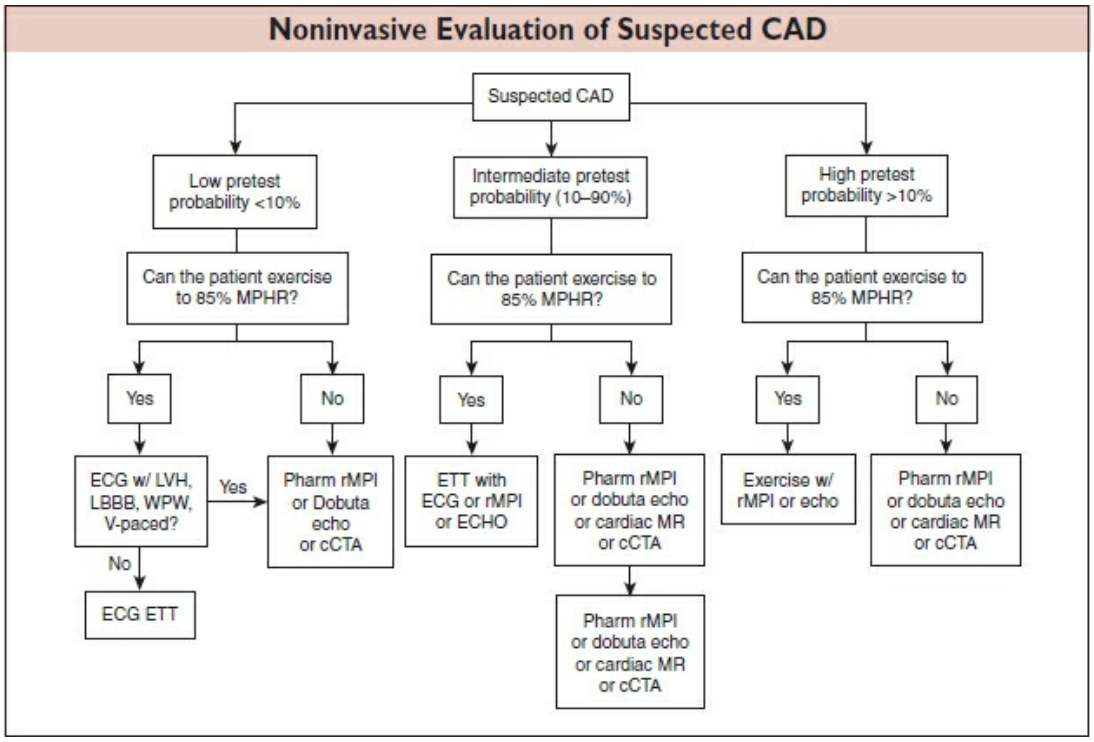
- **Ordering stress test:** Choose stress modality **(S)** and ischemia assessment modality **(I)**

  (S) Stress modality: Exercise (treadmill/recumbent bicycle) OR dobutamine OR vasodilator (adenosine, regadenoson, dipyridamole); generally, exercise preferred for diagnosis, but may be limited due to arthritis, claudication, poor functional status, pulmonary disease, or inability to achieve 85% max predicted HR

  (I) Ischemia assessment: ECG +/– radionuclide myocardial imaging OR echo OR MRI; if pharmacologic **(S)** chosen, **(I)** must be an imaging modality (ECG not sufficient); TTE or rMPI preferred in pts w/ prior PCI or CABG, abnormal baseline ECG, or those who can't exercise/need pharmacologic testing

  Radionuclide choice: Thallium detects viable myocardium; sestamibi ("mibi") provides better images in ♀ or obese pts due to higher-energy photons, measures LVEF; assoc w/ 10–12 mSv (10x annual exposure in someone living at sea level; more than a diagnostic coronary cath); for comparison, US radiation workers allowed occupation exposure of ~50 mSv annually)

- **Coronary artery calcium scoring:** Screening in low-risk populations not recommended due to ↓ Sp and ↑ false ⊕ rate (*AFP* 2012;86:405; *JACC* 2007;49:378; *JAMA* 2014;312:837; *NEJM* 2012;366:294); consider ETT in pts w/ coronary calcium score >75th percentile



Features of Different Stress Testing Modalities (*AFP* 2007;75:2129)	
Test	**Comments**
ETT ~$160 (68% sensitive, 77% specific) (*Ann Intern Med* 1999;130:719; *JAMA* 2015;314:1968)	**Pros:** Standard test for most pts; cost-effective, widely available, gives functional capacity, prognosis, and provides information on pt symptoms; **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 V_1–V_3 nondiagnostic in pts w/ RBBB; *does not localize/quantify ischemia or myocardial viability;* **Contraindications:** Recent MI (<2 d), unstable angina, symptomatic valvular heart dz, 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 TTE ~$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; ↓ sensitivity/specificity in LVH; ↑ false ⊕ in pts w/ HTN response to exercise, ↓ specificity w/ prior MI

Dobutamine TTE (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 sensitivity/specificity of pharmacologic tests, may be used for prognosis after MI; **Cons:** Does not measure functional capacity, ↓ sensitivity 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 rPMI (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 TTE; **Cons:** Cost, radiation exposure, variability between labs, high false ⊕ in pts w/ LBBB, or V-paced
Vasodilator (dipyridamole or adenosine) rPMI (89% sensitive, 75% specific) (*Circulation* 2003;108:1404)	**Pros:** No exercise involved, ↑ accuracy in pts w/ LBBB; Useful for dx and 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. **Contraindications:** COPD/asthma, SSS, heart block; dobutamine rPMI may be used in pts w/ COPD or w/ adenosine/dipyridamole allergy
Coronary CT angiogram (Sensitivity ≥50% stenosis 85–98%, specificity 88–96% (*Am J Med* 2008;121:715)	**Pros:** AHA recommends against CTA screening in asx pts; may be useful in sx pts of int risk or w/ equivocal stress test results (*Circulation* 2008;118:586); useful to evaluate for anomalous coronary arteries **Cons:** Incidental findings (i.e., pulmonary nodules) ↑ pt anxiety and further diagnostic testing; radiation exposure. HR must be between 60 and 70 bpm or iv βB used. Pts w/ renal dysfunction, cardiac stents, severe calcification, and afib may be ineligible; cardiac MRI may be used in pts w/ contrast allergy or coronary artery calcification. (*Am Heart J* 2006;151:404)

Testing Modality by Patient Characteristic (*Circulation* 2007;116:e418)	
Patient Characteristic	**Test Choice & Comments**
Intermediate pretest probability (10–90%) w/o factors below	Exercise ECG treadmill test
WPW or >1 mm ST↓ at rest	Exercise perfusion or TTE
H/o PCI or CABG	Exercise perfusion or TTE
V-paced	Adenosine/dipyridamole rPMI

LBBB	Adenosine/dipyridamole rPMI, dobutamine TTE
Digoxin/LVH w/ <1 mm ST ↓	Exercise rPMI, TTE, or dobutamine TTE
Unable to exercise	Adenosine/dipyridamole perfusion, dobutamine TTE

- **Management of results:** Cardiology consultation advised for intermediate- and high-risk stress test results; low-risk results may be medically managed
- **Patient information:** *Ann Intern Med* 2012;157:1-38; *JAMA* 2008;300:1836

DYSLIPIDEMIA

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

- **Epidemiology:** 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 cholesterol (LDL-C):** "Bad cholesterol"; transports cholesterol to tissue; taken up by macrophages & 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, smoking cessation, diet; **low HDL alone is not an indication to initiate drug treatment**
  - **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, EtOH, liver disease, medications (progestins, estrogens, anabolic steroids, corticosteroids, protease inhibitors, atypical antipsychotics, retinoic acid derivatives, thiazides, βB, CsA) (*Am J Cardiol* 2012;110:823)

- **Screening:** ♂ >35 y, ♀ >45 y; if risk factors for CAD then ♂/♀ >20 y; ✓ q5y if TC <200, more frequently if RFs or approaching tx threshold

Evaluation (*Circulation* 2014;129:S1; *JAMA* 2001;285:2486)

- **History:** Lifestyle (activity), diet, ⊕ FHx premature CAD; risk factors (HTN, DM, smoking); **presence or absence of clinical atherosclerotic cardiovascular disease (ASCVD):** Includes ACS w/ or w/o resvascularization, CVA, TIA, & PAD; 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 only 2–10% w/ fasting status; **∴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: If tx to target number, ✓ q6–8wk until goals reached, then q6–12mo; for most patients (tx based on CV risk assessment, not target lipid value), repeat *only if clinically indicated* q3–12 mo
- **Risk assessment:** For those w/o known ASCVD, use Pooled Cohorts Equations Risk Calculator to **predict 10-y risk of ASCVD events** (defined as coronary death, nonfatal MI, fatal & nonfatal stroke) http://tools.acc.org/ASCVD-Risk-Estimator-Plus/ **variables are age, gender, race, TC, HDL, DM, SBP, HTN Rx, smoking status**

AHA Treatment Guidelines by Indication (*Circulation* 2014;129:S)	
Indication	**Recommendation/Notes**

History of ASCVD	Pts **≤75 y:** High-intensity statin Pts **>75 y:** Moderate-intensity statin
10-y ASCVD risk ≥7.5%, age 40–75 y	Moderate- or high-intensity statin
Diabetes, age 40–75 y	Moderate intensity statin If 10-y ASCVD risk ≥7.5% → high-intensity statin
LDL-C ≥190 mg/dL	High-intensity statin

Treatment (*AFP* 2011;84:551; *Circulation* 2014;129:S1; *NEJM* 1999;341:498)

- **General approach:** Tx aim is to ↓CV risk; **lifestyle & statins are primary tx;**
  - ACC/AHA 2013 guidelines (*Circulation* 2014;129:S1) moved away from treating to target LDL; current paradigm is that initiation & intensity of therapy is dictated indication & calculated ASCVD risk
  - **Patients with LDL >190 mg/dL:** Consider familial combined hyperlipidemia (1–2% population) or familial hypercholesterolemia & lipid specialist referral
- **Lifestyle:** Aerobic exercise 30 min 3–4×/wk; some benefit after ~6–12 mo; 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
- **Statins:** HMG-CoA reductase inhibitors; ↓ cardiac & overall mortality in pts w/ or w/o CAD
  - **Timing:** QHS (liver cholesterol synthesis mostly at night when dietary intake lowest)
  - **Contraindications:** Pregnancy (category X), breastfeeding
  - **S/e:** HA, nausea, (0.5–2%), sleep disturbance; ↑ LFTs
  - **Muscle toxicity:** Common (5%), may be bothersome but not dangerous; can be managed w/ reassurance, counseling, exercise, trial of alt statin; placebo effect may contribute (~25% of pts reported myalgias w/ placebo alone in recent statin trial) (*JAMA* 2016;315:1580); true rhabdomyolysis/myositis rare (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

Interactions: Digoxin, warfarin grapefruit: Up to 8 oz or ½ a fruit QD OK

Monitoring: Baseline LFTs & CK; LFTs 12 wk after start; no need to re ✓ 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; no benefit in cancer prevention, conflicting evidence about prevention of dementia and increased risk of cognitive dysfunction

Statin Intensity and Dosing Recommendations			
Statin intensity	**High**	**Moderate**	**Low**
Atorvastatin	40–80 mg	10–20 mg	
Fluvastatin		80 mg	20–40 mg
Lovastatin		40 mg	20 mg
Pitavastatin		2–4 mg	1 mg
Pravastatin		40–80 mg	10–20 mg
Rosuvastatin	20–40 mg	5–10 mg	
Simvastatin		20–40 mg	10 mg

Features of Individual Statins			
Statin	**Dose (mg)**	**LDL ↓**	**Comments**
Atorvastatin	10–80	38–54%	Generic; preferred in CKD
Rosuvastatin	5–40	52–63%	May be taken at any time; ↑ HDL; ↓ drug–drug interactions; may have ↓ muscle toxicity
Simvastatin	10–80	28–41%	Generic; take in evening; highest drug–drug interactions (incl amlodipine), avoid 80 mg unless already tolerating >1 y 2/2 ↑myopathy risk
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

Lovastatin	20–80	29–48%	Generic; take in evening
Fluvastatin	20–80	17–33%	Preferred in CKD; ↓ muscle toxicity; OK w/ warfarin
Pitavastatin	1–4	31–41%	May be taken at any time; OK w/ warfarin

- **Nonstatin lipid-lowering agents:** 2013 guidelines do not advocate for addition of any nonstatin drug therapy given lack of evidence they ↓ ASCVD events; more recent evidence suggests addition of ezetimibe to simvastatin may improve CV outcomes (*NEJM* 2015; 372: 2387–2397); PCSK9 inhibitors (alirocumab, evolocumab) >> LDL reduction than statins, also shown to improve CV outcomes (*NEJM* 2015;372:1489; 1500)
  - **PCSK9 inhibitors:** SC dosing, ↓LDL 61%; *evolocumab;* 140 mg q2wk, 520 mg q mo, *alirocumab;* 75–150 mg q2 wk; approved for pts w/FHx and/or ASCVD requiring further LDL lowering; s/e: injection site-reactions, myalgias, ?neurocognitive effects
  - **Fish oil (Ω3-acid ethyl esters):** 4 g QD or 2 g BID; may ↑LDL, ↓TG 20–50%; no Δ in HDL
  - **Ezetimibe:** 10 mg QD; ↓LDL 17%; can ↑LFTs when used w/statins
  - **Fibrates:** ↓LDL ~10%, ↑HDL 5–20%, ↓TG 40–50%; s/e include ↑gallstones, ↑ risk of rhabdo with statins; *gemfibrozil*; (600 mg BID): can ↑INR on warfarin, *fenofibrate*; (145 mg/d nanocrystal, 160–200 mg/d micronized) can → rash, GI upset, myalgia, ↑LFTs, ↑CsA, avoid if CrCl <30
  - **Bile sequestrants:** ↓LDL 15–30%; *Cholestyramine* (2–24 g/d), *Colestipol* (5–30 g/d): effect additive to statins, take w/ meals; s/e: GI upset, ↓ drug absorption; avoid in biliary/bowel obstruction; effect additive to statins
- **Hypertriglyceridemia** (*AFP* 2007;75:1365; *J Fam Pract* 2006;55:S1; *NEJM* 2007;357:1009)
  - Screen pts w/ ↑ TG for metabolic synd; 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 chol (TC – HDL) is a 2° target w/ a goal 30 mg/dL higher than LDL

goal; statins↓ TG 5–33%
≥**500:** Ω3-acid ethyl esters (fish oil), fibrate, nicotinic acid to avoid pancreatitis

- **Patient information:** JAMA 2013;309:1419; AFP 2010;81:1103

HYPERTENSION

Background (*JACC* 2017 AHA/ACC guidelines; *JAMA* 2014;311:507; *J Clin HTN* 2014;16:14)

- **Classification:** Different cutoffs exist for ambulatory (home) readings, but office measurement cutoffs are below

Classification of Blood Pressure				
	Normal	**Elevated** (previously pre-HTN)	**Stage I HTN** (previously pre-HTN)	**Stage II HTN** (previously stage I and II HTN)
Value (mm Hg)	**<120/<80**	**120–129/<80**	**SBP 130–139 or DBP 80–89**	**SBP ≥140 or DBP ≥90**
• To diagnose HTN, BP readings must be elevated on ≥2 visits spaced >1 wk apart unless signs of end-organ damage, hypertensive emergency, or BP ≥ 180/110 mmHg • If SBP and DBP in 2 different categories, use the higher BP category				

- **Epidemiology:** According to 2017 guideline definitions, HTN affects 45% of US adults (although pharmacologic treatment is not recommended for many stage 1 patients; per prior guidelines with higher HTN cutoff of ≥140/≥90, affected 31% of US adults, all of whom had pharmacologic tx recommended)
- **BP control:** According to 2017 guidelines, 53% of Americans are above target BP (by JNC 8 guidelines, 39% of Americans are above target BP)
- **Risk factors:** Age, FHx, obesity, African ancestry, renal disease, high sodium diet, DM2, sedentary lifestyle, EtOH
- **Risks of HTN:** Each 20 mmHg ↑ in SBP or 10 mmHg ↑ in DBP over 115/75 mmHg doubles risk of ASCVD-associated death (*Lancet* 2002;360:1903)

- **Benefits of lowering BP:** 10 mmHg lower SBP → 20% ↓ major cardiac events, 28% ↓ HF, 13% ↓ mortality (*Lancet* 2016;387:957)

Evaluation (*Ann Intern Med* 2011;154:781; 2015;162:192; 163:778; *NEJM* 2003;348:610; 2006;355:385)

- **Screening** (USPSTF): Annually if >40 y or obese or pre-HTN; q3–5 y if 18–39 w/o risk factors
- **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? Over the past 2 weeks, how many days did you not take your blood pressure medicine?"
- **Exam:** Cardiac exam (LVH, murmurs, volume status, pulses), fundoscopic, neuro, thyroid, BMI, auscultation for bruits (carotid, renal); average several BP measurements;
  - **BP measurement:** Seated, arm supported/level to heart, measured in both arms (*JAMA* 1995;273:1211); difference in BP measured by auscultation through bell vs. diaphragm of stethoscope is not clinically significant (*Blood Press Monit* 2016;21:178; *J Hypertens* 2005;23:499); proper cuff size key: small cuff overestimates SBP by up to 10 mmHg; manual cuffs should be inflated to 200–200 mmHg; high values on automatic cuffs should be confirmed manually; 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 pts w/ ↑ BP (eval for coarctation)
  - **Home BP monitors:** Should be calibrated in office; pts should keep daily log
  - **Ambulatory (24 h) BP Monitoring (ABPM):** For episodic, resistant or white coat HTN; device measures BP q15–60 min while awake/sleeping
  - **PseudoHTN:** Incorrect ↑ in BP due to stiffened arteries; should be suspected if brachial artery still palpable or may be rolled when cuff inflated 30 mmHg above systolic BP (Osler maneuver) or in pt w/ resistant HTN and no end-organ damage

- **Initial workup:** CBC, electrolytes, LFTs, lipids, TSH, U/A, ECG, HbA1c

Treatment (*Ann Int Med* 2014;161:ITC1–15; *JAMA* 2013;310:1274; 2014;311:2216; *NEJM* 2015;373:2180)

Treatment Thresholds and Agents (JNC VIII; *JAMA* 2014;311:507; AHA/ACC 2017)						
	Hx CVD or ASCVD risk >10%	**ASCVD risk <10%**	**Age >65***	**CKD**	**DM**	**Hx Stroke**
Start Rx if BP ≥	130/80	**<140/90**	SBP 130	130/80	130/80	140/90 (130/80 if lacunar)
Goal BP <	130/80	130/80	SBP 130	130/80	130/80	130/80

*community-dwelling, ambulatory, noninstitutionalized seniors

- **Lifestyle modification** for 3 mo can ↓ SBP by 10 mmHg (*NEJM* 2010;362:2102)

Benefit of Lifestyle Modifications (AHA/ACC 2017)		
Modification	**Average BP reduction**	**Notes**
Weight loss	−5 mmHg	Aim for ideal body weight, est −1 mmHg/ 1 kg lost
DASH Diet	−11 mmHg	Fruits, vegetables, whole grains, and low-fat dairy products w/ ↓ saturated/trans fats (see nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf)
High K	−4–5 mmHg	3.5–5 g/d, preferably via potassium-rich foods
Low Na	−5–6 mmHg	Reducing intake by at least 1 g/d, goal intake <1.5 g/d
Aerobic exercise	−5–8 mmHg	120–150 min/wk at 65–75% max HR Strength training (dynamic or isometric resistance) also beneficial
Alcohol	−4 mmHg	Reduce intake to ≤2 drinks/d (♂) or ≤1 drink/d (♀)

- **General principles:** 1st-line drugs (ACEI, thiazides, CCB) have equal efficacy (*BMJ* 2009;338:b1665; *JAMA* 1993;270:713), except for pts w/ proteinuria (ACEI/ARB to ↓CKD progression, strong recommendation), pts of African ancestry (thiazide or CCB in

absence of CKD; some data ACEI/ARB less effective, moderate–weak recommendation); overall degree of CV benefit related to how well BP is controlled; fewer side effects if lower doses of multiple meds (but concern for decreased adherence); mortality benefit to CCB + ACEI > CCB + thiazide (ACCOMPLISH *NEJM* 2008;359:2417)

Pharmacologic Agents		
Agent	**Preferred pts**	**Considerations**
ACEI/ARB	CKD; CHF; DM2	Cough w/ ACEI (~15% pts); ↑ K in CKD; angioedema; avoid in ♀ who are/may become pregnant
CCB	AF African ancestry	Peripheral edema (esp amlodipine); Verapamil/diltiazem: nodal agents & ⊖ inotropes, contraindicated in ↓ EF or heart block; dihydropyridine (ie, amlodipine) preferred for isolated systolic HTN in elderly
Thiazides	Osteoporosis; Kidney stones (↓ renal Ca) African ancestry	Hypokalemia, most common in 1st wks of tx, prevented by dietary salt restriction; hyperglycemia, esp in DM; hyponatremia; may exacerbate gout & erectile dysfunction; ineffective in pts w/ CrCl <30; can combine with triamterene (Na^+ channel antagonist); preferred in elderly with isolated systolic HTN

2nd-Line Agents		
Drug class	**Indications**	**Notes**
αB	BPH, PTSD	Doxazosin, prazosin: ↑ risk of CHF (doxazosin), postural HoTN, nasal congestion; preferred in pheochromocytoma
Aldosterone antagonists	EF<40%	Spironolactone, eplerenone: ↑ K, esp w/ ACEI, DM, CKD; **recommended in hyperaldosteronism or refractory HTN**; gynecomastia & breast pain (less w/ eplerenone)

βB (*JAMA* 2013;310:1851)	AF, CAD; Propranolol if migraines, anxiety, ↑ thyroid	Atenolol, carvedilol, metoprolol, propranolol, nadolol, bisoprolol: Angina/rebound HTN on w/ abrupt discontinuation; may mask ↓ glucose in DM; may exacerbate asthma, COPD, impotence; caution in pts w/ conduction disease (heart block), pheo (unopposed α-stimulation); can cause nightmares, fatigue, ↓ exercise tolerance
Clonidine	Anxiety	Available in transdermal weekly dosing to help w/ adherence; anxiolytic; taper to avoid rebound HTN on discontinuation
Hydralazine		TID or preferably QID dosing so difficult med adherence; may cause rebound ↑HR, drug-induced lupus (rare)
Loop diuretics	CHF	Furosemide, bumetanide, torsemide: Useful in refractory HTN w/ CKD (CrCl <30 mmol/min)

- **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, so 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)
  - **Resistant hypertension:** HTN despite 3 drugs (including a diuretic) or 4 drugs dosed at 50% of the maximal dose (*JAMA* 2014;311:2216); important to r/o medication nonadherence or improper BP cuff size (*Hypertension* 2016;67:1085); general treatment approach is to r/o secondary causes of HTN (below) or pseudoHTN (above), discontinue any medications that may ↑ BP, check ambulatory BP; initial 3-drug treatment involves an ACEI/ARB + CCB + diuretic (chlorthalidone or furosemide if EGFR <30); if HTN persists then spironolactone may be added as a 4th agent; consider referral to HTN specialist in cases of failure of 4-drug regimens

Secondary Causes (*JAMA* 2014;311:2216)	

Cause (% prevalence in resistant HTN)	**Notes** (Consider if < 30 y, sudden, severe or resistant HTN)
Sleep apnea (60–70%)	"Do you snore, wake up tired, fall asleep during the day?" (see "*Obstructive Sleep Apnea*")
Hyperaldosteronism (7–20%)	↓ K suggestive, but >50% pts normokalemic; ratio of plasma aldosterone:renin >20 off aldosterone antag/ACEI/ARB; confirm w/ saline infusion test; CT for ? adrenal adenomas or bilat adrenal hyperplasia (see *"Adrenal Nodules"*); Rx w/ aldosterone antagonist
Renal artery stenosis (2–24%)	Carotid/abdominal bruits; ↑ Cr w/ ACEI/ARB; resistant HTN in young (fibromuscular dysplasia); renal artery U/S, CTA, or MRA
Medications and illicit substances (2–24%)	Antidepressants, NSAIDs, celecoxib, estrogen-OCPs, steroids, decongestants, diet pills, CsA, tacro, herbal meds, ginseng, cocaine, amphetamines
CKD (1–2%)	Proteinuria, elevated Cr, volume overload
Endocrine (1%)	Cushing syndrome, hypercalcemia, hyperthyroidism
White coat HTN	Seen in 10–20% of patients; consider in refractory HTN; ✓ home BP log vs. ambulatory BP monitoring (*NEJM* 2006;354:2368)
Pheochromocytoma	Palpitations, diaphoresis, pounding HA, episodic HTN; 24-h urine fractionated metanephrines, catecholamines
Aortic coarctation	Discrepancy in BP btw arms/legs, ↓ femoral pulses; abnl CXR

HTN Urgency/Emergency

- **Urgency:** SBP ≥180 or DBP ≥110: May be safely treated in office/home if no significant CV comorbidities, good adherence, and follow-up (*JAMA Intern Med*. 2016;176:981); ↓ BP to <160/<100 mmHg or by max 25%, then baseline BP in the next hours–days (to avoid cerebral/myocardial/renal ischemia from acute ↓); then standard BP goals
- **Emergency:** HTN urgency + symptoms (chest pain, headache, CVA, papilledema, retinal hemorrhage, AKI): Refer to ED

PALPITATIONS AND ARRHYTHMIAS

Background (*AFP* 2005;71:743)

- **Definition:** Sensation that the heart is beating abnormally; common complaint in ambulatory setting, ~16% of outpatient 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% psychiatric, 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 patient to "tap out" rhythm; assoc sx: chest pain/pressure, neck pulsations, syncope/presyncope (most likely CHB or ventricular arrhythmia, rare in SVT), onset, duration, provocative factors (anxiety, exercise, EtOH, caffeine), palliative factors; Has this ever happened before? Review medications, supplements, illicits, EtOH; screen for depression (see "*Depression*"), anxiety/panic attacks (see "*Anxiety & Panic Disorders*")

Noncardiac 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 disorder	Situational triggers (i.e. crowds), paresthesias, fear of losing control/dying, derealization, sweating (see "*Anxiety & Panic Disorders*")
Hypoglycemia	Diaphoresis, relieved by eating
Medications/habits	Assoc w/ taking medication or habit (i.e. caffeine)
Thyrotoxicosis	Insomnia, weakness, frequent bowel movements, brittle hair,

	weight loss; (see "*Thyroid Disorders*")
Postural tachycardia syndrome	Chronic fatigue/dizziness/lightheadedness, unexplained spells, inappropriate sinus tachycardia (*Mayo Clin Proc* 2012;87:1214)
Pheochromocytoma	HA, HTN, orthostasis, weight loss, hyperglycemia
Cardiac Palpitations (*NEJM* 2006;354:1039; 2012;367:1438)	
Diagnosis	**Clinical Features**
AFib/Aflutter	Older at presentation, "irregular/fluttering" sensation; may present with presyncope, but syncope rare
Atrial tachycardia	Similar to ST but without 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 RVOT may terminate with vagal maneuvers
Premature atrial contraction	"Skipped" beat or "flip-flop" sensation, usually at rest (↑ incidence at ↓ HR)
PVCs	Similar to PACs; more common in pts with 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 "*Vaivular Heart Disease*")
Ventricular tachycardia, nonsustained ventricular tachycardia	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, and pulmonary exam for CHF; mid-systolic click associated w/ mitral valve prolapse
- **Workup:** Electrolytes + Mg, ECG; otherwise directed by sx; consider CBC (evaluate anemia), TSH (thyrotoxicosis), serum/urine catecholamines/metanephrines (pheochromocytoma), fingerstick
  - **ECG:** Baseline rarely documents culprit arrhythmia, but should be obtained on all pts with palpitations since can help w/ diagnosis of ischemic heart disease (see table below)

Continuous (Holter) monitoring: 24–48 h or 7–14 d for Zio patch; best for pts with frequent sx or sx w/ activity; requires pts to keep log of symptoms/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 with infrequent episodes

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

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

EP testing (referral): Consider in pts w/ palpitations → syncope or serious sx, in pts who have known structural heart dz, or who are at risk for structural heart dz (*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 dz, CAD, CMP, HOCM, recurrent sx → ambulatory ECG monitoring; if ambulatory ECG (–) but arrhythmia still suspected → EP referral

  Low-risk: No evidence of structural heart disease/arrhythmia; H&P + ECG is sufficient

Resting ECG Findings and Potential Etiology (Adapted from *NEJM* 1998;338:1369)

ECG Finding	Etiology
Short PR, delta wave	Wolff–Parkinson White, AVRT
Long QT (often + bradycardia)	Polymorphic VT
Q waves (prior MI)	PVCs, NSVT, VT
Q waves in I, aVL, V_4–V_6 + LVH	Hypertrophic cardiomyopathy
P mitrale, LVH, PACs	Large L atrium → atrial fibrillation
PVCs with LBBB morphology & + axis	Right ventricular outflow tract tachycardia
PVCs with RBBB morphology & (–) axis	Left ventricular outflow tract tachycardia
Mobitz II	Complete heart block
Inverted T wave in V_2, +/-epsilon wave	Arrhythmogenic right ventricular dysplasia

Identification of Tachycardia			
QRS	**Regular**	**Regularly Irregular**	**Irregularly Irregular**
Narrow	Sinus rhythm Atrial tach Atrial flutter AVNRT/AVRT	Mobitz I Mobitz II Bi-/tri-geminy	Sick sinus Atrial fibrillation Multifocal atrial tach/wandering atrial pacemaker
		Regular rhythm w/ variable AV conduction	
Wide	Above rhythms w/ aberrant conduction (baseline IVCD or BBB)		
	Ventricular tach WPW Ventricular pacing		PVC Torsades/polymorphic VT VF

Management (*AFP* 2011;84:63)

- **ER referral:** (1) Syncope/near syncope with high-grade AV block; (2) Syncope in pts w/ known or high risk for cardiac disease (i.e., positive FHx for SCD); (3) Concern for VT; (4) Afib 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 otherwise stable pt; (3) Persistent SVT or PVCs not managed with β-blockers; (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 and 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 antiarrhythmic Rx or EP evaluation (*NEJM* 2006;354:1039)
- **PACs:** Reassurance; discontinue triggers (i.e., caffeine, nicotine, EtOH, avoid stress); consider β-blockers for persistent symptoms

Atrial Fibrillation and Flutter

Background (*Ann Int Med* 2008;149:ITC5–2; 2017;ITC-34; *Circulation* 2014;130:2071; 2015;131:1648; *JAMA* 2001;285:2370; *Mayo Clin Proc* 2013;88:394)

- **Paroxysmal:** <1 wk, terminates spontaneously or with Rx; **persistent:** >1 wk, can be terminated w/ cardioversion; **long-standing persistent:** (>1 y); **permanent:** (no sinus rhythm)
- **Valvular:** 2° to valve dz (MR, MS, MVP, valve replacement/repair) vs. **nonvalvular**
- **Secondary causes:** Pericarditis, myocarditis, thyrotoxicosis, COPD, obesity, OSA, pheocromocytoma, cardiac surgery, MI, PE, CHF, PNA, EtOH ("holiday heart"), caffeine (69% of pts have no precipitant identified)
- **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 and loss of atrial muscle mass → nonhomogeneous wave propagation → creates multiple wavelets and focal automaticity (often originating in the pulm veins) → anatomical and electrical remodeling
- **Risk factors:** ↑ atrial pressure (valvular disease, CHF, MI, cor pulmonale, PFO, COPD, CMP, HTN w/ LVH), ↑ atrial size (obesity, AFlutter), SVT, atrial ischemia (CAD), atrial fibrosis/infiltrate (age, amyloid, atrial neoplasm), neuro (SAH, CVA), genetics (family hx, European ancestry), EtOH abuse

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

- **Symptoms:** Asymptomatic (esp elderly, recurrent AF), SOB, DOE, fatigue, ↑ urination, lightheadedness (syncope rare), angina, palpitations, CVA, CHF; symptoms more prominent w/ paroxysmal, less evident w/ persistent and permanent
- **Exam:** Irregularly irregular pulse, tachycardia, irregular heart sounds, ± HoTN
- **Workup:** H&P (focused on classification criteria above, and signs of reversible causes), ECG (LVH, prior MI, bundle branch block, WPW which changes management options), CXR (cardiomegaly, pulm pathology), TTE (for new-onset AF); TSH and free T4 (hyperthyroidism), electrolytes, renal and LFTs 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 and 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, AFlutter, 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, associated medical problem (i.e., 2° cause of AF), DCCV, initiation of antiarrhythmic therapy or heparin
- **Indications for cardiology referral:** Failure of rate control, complex cardiac disease, candidates for PPM, defibrillator, ablation, or surgery (*AFP* 2011;83:61)

Rate Control (*Circulation* 2010;123:104; *JAMA* 2015;314:278; *NEJM* 2002;347:1825; 2002;347:1834; 2008;358:2667)

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

Pharmacologic Therapy (*Ann Int Med* 2008;149:ITC5–2; *Circulation* 2006;114:e257)

	Agent	Maintenance (PO)	Comments
βB	Atenolol Carvedilol Metoprolol Propranolol	25–100 mg QD 3.125–25mg BID 25–100 mg BID/TID 80–320 mg/d (total)	Preferred in CAD, CHF. Caution w/ COPD, asthma. Contraindicated in WPW. Use cautiously in *decompensated* CHF. Propranolol w/ minimal BP effect. Atenolol does not cross BBB.
CCB	Diltiazem Verapamil	120–360 mg QD divided doses 120–360 mg QD divided doses	Preferred in COPD/asthma; caution in CHF w/ decreased EF due to negative ionotropy; ↓ HR & BP through myocardial suppression. ↑

			digoxin levels. Contraindicated in WPW.
	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.

- βB are the 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 because of additive effect to βB or CCB on HR

Rhythm Control (*Circulation* 2010;123:104)

- **Therapeutic goal:** Pursue rhythm control if AF symptomatic, rate control has failed, or if there is reasonable chance for prolonged SR (structurally normal heart); rhythm control associated with ↑ adverse drug effects and ↑ 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 NSR (Cardiology Consultation Advised)		
Drug (Class)	**Dose (PO)**	**Adverse Effects and Comments**
Amiodarone (III) (*Arch Intern Med* 2000; 160:1741; *JAMA* 2008;300:1784; *NEJM* 2005;352:1861; 2007;356:935)	200–400 mg QD (Load: 600–800 mg in divided doses QD up to 10 g total)	Most effective at maintaining NSR and least proarrhythmic but most long-term side effects: Pulmonary/thyroid/hepatotoxicity, neuropathy, skin photosensitivity, ↓ HR, optic neuritis, torsades, ↑ QTc; episodic Rx after cardioversion ↑ mortality and AF recurrence; ✓ TFTs, LFTs q6mo, baseline PFTs, CXR & ECG q12mo; ↓ warfarin/digoxin metabolism, follow INR/digoxin level closely; preferred for CHF, CAD, HTN w/ LVH; outpt initiation in select patients; anticoagulate prior to Rx due to

		CVA risk w/ conversion to NSR
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) (*J Cardiovasc Electrophys* 2010;21:597; *NEJM* 2007;357:987; 2008;358:2678; 2009;360:668; 2011;365:2268)	400 mg BID	↓ HR & SBP, ↑ QTc, rare hepatotoxicity. ↑ mortality in symptomatic or severe HF (EF <35%); ↑ CVA, MI, systemic embolism, or CV mortality in pts w/ permanent AF and h/o CAD, CVA/TIA, symptomatic CHF, PAD, EF <40%, or ≥75 y w/ HTN & DM; better tolerated than amiodarone but ↓ effective; ✓ LFTs first 6 mo. May be initiated outpt. ↑ digoxin levels; no warfarin interaction
Flecainide (IC)	200–300 mg	VT, CHF, AFlutter. Avoid in pts with CAD or structural heart disease; pretreat w/ βB or CCB to prevent AFlutter
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; patients may have fewer and shorter episodes; rhythm control associated w/ arrhythmia → warn pts about significance of syncope/palpitations
- **Nonpharmacologic Tx:** Alternative in *symptomatic* patients who have failed antiarrhythmic tx
  - **Radiofrequency ablation:** AV node ablation + PPM if pharmacologic Rx inadequate (*NEJM* 2001;344:1043; 2002;346:2062); ~80% success; requires uninterrupted anticoagulation (*NEJM* 2012;367:1587; *JAMA* 2014;311:692)
  - **Surgical "maze" procedure:** 70–95% success if undergoing cardiac surgery

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

- **When:** First episode or symptomatic 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/ Aflutter
- **Anticoagulation:** Risk of embolization identical for spontaneous, pharmacologic, or electrical cardioversion; if AF >48 h **or** ? duration **or** <48 h w/ mitral stenosis **or** h/o thromboembolism → 3–5% risk of CVA; therefore, anticoagulate all patients for DCCV; **Anticoagulate:** >3 wk prior to cardioversion and ≥4 wk postcardioversion (due to atrial stunning), regardless of CHA_2DS_2-VASc score

  TEE: Consider if patient hospitalized, at risk for bleeding from prolonged anticoagulation, or unlikely to tolerate prolonged AF; if TEE negative for thrombus, cardioversion may be performed with 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) especially if prior DC cardioversion failed

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ANTICOAGULATION (*Circulation* 2014;130:2071; *JAMA* 2015;313:1950)

- **Risk stratification:** CHA_2DS_2-VASc most validated and clinically useful score for long-term anticoagulation in paroxysmal, chronic AF, and s/p cardioversion (*JACC* 2008;51:810)

  Other risk factors (less validated): Age 65–74, female sex, CAD

  Risk–benefit: Benefits of anticoagulation weighed vs. pt hx (i.e., GIB, falls, ICH, ↓ PLT, nonadherence, substance/EtOH abuse, psychiatric history, heavy NSAID use, liver disease, pregnancy); prognostic scores for bleeding risk available (*Am J Med* 2013;126:105); generally, anticoagulation ↑ risk of intracranial hemorrhage by ~2x 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; risk–benefit analysis: **www.sparctool.com**

CHA_2DS_2-VASc Scoring for Stroke Risk (*Circulation* 2014;130:2071)
CHA_2DS_2-VASc: **C**HF (1 point), **H**TN (1), **A**ge 65–74 (1); **D**M (1), hx **S**troke/TIA (2), **V**ascular disease (prior MI, PAD, aortic plaque) (1), **A**ge ≥75 (2), **S**ex, if female, (1)
CHA_2DS_2-VASc score **0** → Consider ASA (81–325 mg); **1** → ASA, warfarin, or direct oral anticoagulant (DOAC) based on pt preference & shared decision-making; **≥2** → Warfarin or DOAC; *Pts w/ low initial score 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

- **Valvular AFib:** *All valvular AF* (i.e., rheum MS, valve prosthesis or repair, severe valvular disease) should be anticoagulated as stroke risk very high; DOACs not yet studied
- **Nonvalvular AF:** Unless a reversible cause for AF is corrected, AF → long-term anticoagulation (even if in SR) regardless of AF classification (paroxysmal vs. persistent) or treatment (rate vs. rhythm) because CVA risk no different (*Circulation* 2015;131:1648); average CVA risk w/o anticoagulation ≈5%/y vs. 1.4% with warfarin; AF → 15% of CVA 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 ↓ CVA 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, & h/o TIA/CVA or intracardiac thrombus
  - **Use w/ antiplatelet agents:** For pts on warfarin (i.e., AF w/ stent) ASA 81 mg QD and/or clopidogrel 75 mg QD may be used; aim for INR 2.0–2.5 due to ↑ bleeding
  - **Comparison w/ newer agents:** Rivaroxaban/dabigatran: Fixed dose, rapid onset, ↓ drug & no food interactions, no monitoring, & no antidote (*Am J Med* 2013;126:105)
- **ASA w/ clopidogrel:** Inferior to warfarin for stroke prevention (*Lancet* 2006;367:1903). Superior to ASA alone but with higher bleeding risk (*NEJM* 2009;360:2066); acceptable if pt/physician preference against

warfarin or if pt unsuitable for warfarin

- **Periprocedural:** Patients at low risk for thromboembolism (i.e., no mechanical valves, h/o thromboembolism, low EF, or mitral stenosis) do not need a heparin bridge during periprocedural discontinuation of anticoagulation if interruption is <7 d; consider bridging if high CHA_2DS_2-VASc (*NEJM* 2015;373:823)

Direct Oral Anticoagulants (DOAC) for Nonvalvular AF		
Agent	**Dosing**	**Efficacy & Safety vs. Warfarin**
Dabigatran (Direct thrombin inhibitor)	150 mg BID (75 mg BID if CrCl 15–30)	↓ ischemic stroke & ICH; no ↑ in major bleeding (*NEJM* 2009;361:1139) Risks: GI side effects
Rivaroxaban (FXa inhib)	20 mg QD (15 mg QD if CrCl 15–50) w/ pm meal	≈ischemic stroke (*NEJM* 2011;365:883)
Apixaban (FXa inhib)	5 mg BID (2.5 mg BID if ≥2 of: ≥80 y, ≤60 kg, Cr ≥1.5 mg/dL)	≈ischemic stroke, ↓ mortality. (*NEJM* 2011;365:981)
Edoxaban (Fxa inhib)	60 mg QD if CrCl 51–95 (30 mg if CrCl 15–50)	60/30 mg: ≈ischemic stroke & ↓ major bleed incl ICH, 14% ↓ CV death (*NEJM* 2013; 369: 2093)
Caution with med interactions (ketoconazole, clarithromycin, rifampin, phenytoin); onset w/in hours; 1 missed dose may ↓ protection; dabigatran reversed w/ idarucizumab (*NEJM* 2015;373:511)		

- **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; 2015;313:1070

Atrial Flutter

Evaluation

- **Definition:** Reentrant atrial rhythm (typical cycle at rate of 300/min)

- **History:** Similar to AFib
- **Risk factors:** CHF, COPD, obesity, thyroid disease, mitral valve prolapsed, 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 symptomatic or if rate poorly controlled/tolerated
- **Rhythm control:** Many of the same drugs used to maintain NSR in AF used in flutter
- **Rate control:** CCB (verapamil or diltiazem)—use w/ caution in pts w/ sick sinus syndrome, AV block, and CHF; βB and digoxin also useful
- **Anticoagulation:** Managed in same way as pts w/ AF, including pericardioversion

SYNCOPE AND ORTHOSTASIS

Background (*Eur Heart J* 2009;30:2631; *Heart Rhythm* 2017:S1547; *NEJM* 2000;343:1856; 2002;347:878)

- **Definition:** Abrupt, brief, total LOC & postural tone w/ spontaneous recovery **Presyncope:** Prodrome to LOC; **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 ER 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%), neurologic (7–10%), situational (3–5%), medications (3%), psychiatric (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
- **DDx: Cardiovascular:** Valvular heart disease (i.e., AS), PE, CAD, pHTN, subclavian steal, aortic dissection, cardiomyopathy, arrhythmia, tamponade, PPM failure; **Neurologic:** TIA/CVA, seizure, atypical migraine, SAH, cataplexy, drop attacks; **Other:** Falls, hemorrhage (GIB, ruptured aortic aneurysm, spleen, ectopic pregnancy), orthostasis/vasovagal, hypoglycemia, psychiatric, anaphylaxis, meds, EtOH, illicit, hyperventilation/hypocapnia, postexercise hypotension

Evaluation (*AFP* 2011;84:640; *Ann Intern Med* 2011;155:543; *Circulation* 2006;113:316; *NEJM* 2013;369:966)

- **H&P:** Does episode meet definition of syncope? Happened before and how often? What was pt doing prior? Does pt remember hitting ground? Associated sx: Chest pain, dyspnea, palpitations, prodrome, postictal state; provocative factors (exertion, changing position, eating, coughing, sneezing, swallowing, anxiety, pain, defecation/micturition); collateral historians; medication Δs; family hx of cardiac disease, SCD

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

Reflex: Nausea, warmth, diaphoresis, pallor, lightheaded, fear, pain, emotional distress, instrumentation (i.e., blood draw), or prolonged (>20 min) 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 (DM, amyloid, Parkinson's, Shy-Drager, EtOH, prolonged bedrest), adrenal insuff, postural tachycardia syndrome (POTS); may present as fatigue/cognitive impairment in elderly
Drugs: Medication changes or new medications? Vasoactive (α- and β-blockers, CCB, nitrates, antiHTN), diuretics, digoxin, EtOH, antidepressants, sedatives, erectile dysfunction medications, insulin. Antiemetics, antiarrhythmics, or antipsychotics (↑ QT)

- **Exam/Workup:** Orthostatic BP, cardiac, pulmonary, neuro exams; survey body for trauma; ✓ tongue for injury; ✓ carotid bruits; ✓ volume status (JVP, mucous membranes, skin tenting); murmur concerning for aortic stenosis; consider rectal exam & guaiac if GIB suspected; ✓ UE vs. LE BP and 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; BP should be measured at 2 and 5 min after position change

Carotid massage: Consider in pts >40 y (avoid in pts w/ h/o carotid stenosis/bruits, severe arrhythmia, acute MI or TIA/CVA); *Unilateral* pressure to angle of jaw for 5–10 s; ⊕ test: ↓ SBP ≥50 mmHg (vasodepressor), asystole ≥3 s (cardioinhibitory), or both (mixed); perform in monitored setting w/ IV access (*JAMA* 2004;292:1221)

Potential Studies to Obtain in Syncope and Diagnostic Yield		
Study	**Yield**	**Patient Population** (*Med Clin North Am* 2001;85:423)
H&P	45%	General pts w/syncope
ECG w/ rhythm strip	5%	General pts w/syncope
TTE	5–10%	Known or suspected heart disease
ETT	1%	Suspected CAD or exertional syncope. Perform after TTE
Holter	19%	Heart dz, suspicion for arrhythmia, abnormal ECG
Event recorder	34%	Frequent syncope, suspicion for arrhythmia, neg cardiac w/u
Implanted recorder	59%	Negative cardiac w/u & tilt table, infrequent syncope
EP studies	60%	Heart disease & suspicion for arrhythmia
EEG	1–2%	Witnessed seizure, h/o seizure, postictal state
Head CT	4%	Focal neuro deficits, seizure, head trauma, suspected TIA
Tilt testing	49%	Unexplained syncope, workup otherwise negative
Labs (based on history)		INR if on warfarin, UA/UCx if elderly, hCG, CBC, Chem-12, B12, am cortisol, syphilis, HIV, A1c, BNP, 24-h urine Na • **Labs:** INR if on warfarin, UA/UCx if elderly, hCG, CBC, Chem 12, consider B12, AM cortisol, syphilis, A1c, HIV, BNP, 24-h

		urine Na depending on clinical scenario

ECG findings: Bradycardia, tachycardia (usually associated w/ palpitations), afib/flutter, VT, AV or bundle branch blocks, abnormal PR, QT, or QRS intervals, pauses, Brugada syndrome (RBBB + STE in V_1–V_3), Q-waves, 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; exclude arrhythmias first in pts w/ heart dz

TTE: Only if valvular or structural disease suspected by H&P or ECG

Cardiac monitor: If high arrhythmia suspicion; type determined by frequency of episodes: Holter (24–72 h), event or loop monitor (2–6 wk), external patch (2–14 d), implantable loop recorder (ILR) (2–3 y)

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

- **Red flags to consider hospitalization or intensive workup:** Known or suspected heart dz (i.e., CAD, CHF, AS); abnormal ECG (see above); severe lab abnormalities; FHx of SCD; syncope w/ exertion or when supine; syncope w/ palpitations, headache, chest pain, neurologic deficits, or dyspnea; older age & multiple comorbidities; abnormal physical 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
- **Orthostatic HoTN:** Hydration (2–2.5 L/d) & drink water rapidly (0.5 L in 5–15 min → up to 20 mmHg ↑ SBP that lasts 1–2 h), stand slowly & in stages, avoid hot weather, sleep w/ HOB 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, and not stand or do vigorous activities after eating (*NEJM* 1983;309:81). D/c precipitating meds & use short-acting antiHTN Rx (i.e., nitropaste) qhs when supine (*Lancet Neurol* 2008;7:451)

  Fludrocortisone: ↑ fluid retention and blood volume; titrate dose in 0.1 mg increments each week; 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).

- **Preventing recurrent vasovagal syncope:** Physical counterpressure (cross legs and tense, abdominal, & gluteal muscles, grip one hand with 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, and 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 Restrictions in Syncope		
Diagnosis	**Private Drivers**	**Commercial Drivers**
Unexplained syncope (single episode)	No restriction unless absence of prodrome, occurrence during driving, or heart disease	Determined after diagnosis and treatment 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 symptoms controlled	Permanent restriction unless effective treatment established

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

- **Prognosis:** Cardiogenic syncope associated w/ 2-fold ↑ CV and all-cause mortality, up to 10% in 6 m and 50% in 5 y; no increased risk

of CV or all-cause mortality w/ vasovagal syncope (*NEJM* 2002;347:878).

- **Patient information:** JAMA 2004;292:1260

HEART FAILURE

Background (*Circulation* 2013;128:1810; *JACC* 2009;53:e1; *J Card Failure* 2010;16:475; *NEJM* 2003;348:2007)

- **Definitions:** Heart failure (HF) is a clinical syndrome of dyspnea, fatigue, & fluid retention; due to inability of the heart to pump sufficient blood to meet the body's metabolic needs
  - **Asymptomatic LV dysfunction:** EF ≤40% noted on imaging done for other reasons (i.e., post-MI, revascularization); no prior hx clinical HF sx; progresses to sx HF ~10%/y
  - **HF w/ reduced ejection fraction (HFrEF, systolic HF):** Sx of HF & low EF (≤40%); *Causes:* CAD, valvular disease, HTN, PE, HIV, peripartum cardiomyopathy (CMP), cardiotoxic agents (doxorubicin), EtOH/substance abuse, infiltrative disease, connective tissue dz, thyroid disease, myocarditis, chronic tachycardia; varying degrees of LV enlargement may accompany HFrEF
  - **HF w/ preserved EF (HFpEF, diastolic HF):** Normal EF (≥50%) w/ sx of HF; half of all HF pts; most are elderly, ♀, & have HTN; ↓ diastolic relaxation, ↓ ventricular filling most commonly due to HTN, ischemia, or restrictive/infiltrative CMP; asx diastolic dysfunction assoc w/ progression to diastolic HF (*Ann Int Med* 2013;158:ITC5–1; *JAMA* 2003;289:194; 2011;306:856; *NEJM* 2017;376:897); other causes include valvular/pericardial/congenital disease (*Lancet* 2003;362:777; *NEJM* 2008;359:2456); survival similar to slightly better than HF w/ ↓ EF (*NEJM* 2006;355:260)
  - **HFpEF, borderline:** EF 41–49%, with clinical characteristic & treatment patterns ~ HFpEF
  - **High-output HF:** Syndrome of HF sx, ↑ CO & ↓ SVR, normal or ↑EF, due to AV fistula, pregnancy, hyperthyroidism, anemia, liver/renal dz, Paget, Beriberi, VSD
- **Epidemiology:** 5.1 million adults in US, ~2.2% prevalence which ↑

w/ age; accounts for >1 million hospitalizations annually (*Circulation* 2010;121:e46; *JAMA* 2003;289:194)

- **Risk factors:** HTN, DM, metabolic syndrome, atherosclerotic coronary disease, 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	Exam
First presentation with HF Referral to cardiologist for complete initial evaluation	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 Risk factors (above), depression, FHx; hx substance use, esp EtOH, cocaine, chemotherapy, alt medicines	✓ BMI, orthostatics Lung crackles (not always present), S_3 and/or S_4, displaced apical impulse, LV/RV heave, JVP Peripheral edema, ascites Pulsus alternans, peripheral vasoconstriction Signs of CAD/PAD (peripheral pulses, carotid bruits)
Subsequent visits (routine)	Dyspnea, fatigue, PND, orthopnea, edema, palpitations, CP, ? exercise tolerance, functional level Patient-reported outcome measures (PROMs),[a] ? depression Review log of daily wt, diet & med & exercise regimen adherence Can pt afford meds + healthy food?	Establish & document dry wt JVP, lung/cardiac exam as above
Subsequent visits (new/worse symptoms)	Change in symptoms Review log of daily wt, diet, & med adherence **Exacerbation triggers:** Infection, medication/diet adherence, arrhythmia (esp AF), anemia, EtOH, renal dysfunction, ischemia	Orthostatics Signs volume overload: Lung crackles, S_3 +/– S_4, JVP, edema, ascites Signs low cardiac output: tachycardia, pulsus alternans peripheral vasoconstriction

[a]**PROMs:** Detailed symptom questionnaires to better evaluate and track symptoms; lower scores assoc w/ HF hospitalizations, death; Kansas City Cardiomyopathy Questionnaire (KCCQ), Rose Dyspnea Scale (RDS), Minnesota Living w/ Heart Failure (MLHFQ), PHS2 (Patient Health Questionnaire)

	Labs	Studies
First presentation with HF	CBC, electrolytes, BUN/Cr, Ca, Mg, A1c, BNP/NT-proBNP,[a] LFTs (↑ in hepatic congestion), lipids, TSH, UA; if anemic ✓ iron studies, B12, folic acid	ECG, TTE, CXR (r/o pulmonary causes of dyspnea) Consider based on pt hx, usually by cardiologist: 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
Subsequent visits (routine)	Electrolytes, BUN, Cr when titrating meds Establish BNP/NT-proBNP at dry weight	ECG TTE per guidelines for follow-up of moderate/severe valve dz, or to reassess EF after MI, if candidate for ICD/CRT
Subsequent visits (new/worse symptoms)	Electrolytes, BUN, Cr BNP/NT-proBNP	ECG TTE usually NOT helpful, unless concern for worsening valvular dz/missed MI

[a]**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 (*J Am Coll Cardiol* 2003;42:1793; *NEJM* 2002;347:161); NI 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)

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

- NYHA class used to guide therapy and determine treatment options

NYHA/AHA Heart Failure Classification			
New York Heart Association		**ACC/AHA Task Force**	
I	Sx w/ greater than normal activity	**A**	CHF risk factors. No sx or structural abnorm.
II	Sx w/ normal activity	**B**	⊕ structural dz. No sx
III	Sx w/ minimal activity	**C**	⊕ structural dz. Current or prior HF

			symptoms
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.
Prognostic calculator: Seattleheartfailuremodel.org (*Circulation* 2006;113:1424).

General Treatment Principles

- **Referral:** Cardiology for new dx, workup, periodic evaluation; HF specialist/transplant center for pts w/ severe disease; consider advanced HF referral if:
  (1) severe symptoms of HF with dyspnea at rest or minimal exertion (class IIIb–IV),
  (2) episodes of fluid retention or evidence of peripheral hypoperfusion at rest,
  (3) inability to exercise, 6-min walk distance ≤300 m, peak VO_2 <12–14 mL/kg/min (as determined by cardiopulmonary exercise testing)
  (4) ≥1 HF hospitalization in past 6 mo
- **HFpEF/Diastolic dysfunction:** Focus on tx of underlying conditions; salt restriction & cautious use of diuretics; control HTN & rate in AF; ACEI/ARB assoc w/ ↓ mortality in observational but not RCT (*JACC* 2013;62:e147; *JAMA* 2012;308:2108), use βB if hx ischemia (*NEJM* 2004;351:1097); referral for cardiac rehabilitation
- **Asymptomatic ↓EF:** Initiate Rx (ACEI + βB as tolerated) when EF ≤40%
- **Treat reversible causes:** Thyroid disease, tachycardia, anemia, hemochromatosis, HTN, renovascular disease, CAD, valvular disease, EtOH/cocaine abuse, malnutrition, SLE, sarcoid; CPAP in OSA & HF: ↑ EF & exercise tolerance but = survival (*NEJM* 2005;353:2025)
- **Lifestyle:** Smoking/EtOH cessation, salt restriction (<2 g/d), fluid restriction (1.5–2 L/d), wt loss; nutrition referral; cardiac rehab & supervised exercise (*JAMA* 2009;301:1439; 2009;301:1451)
- **Immunizations:** Influenza & pneumococcal vaccination
- **Care coordination/self-management:** Daily wts (pt to call if ↑ >2–3 lb for 2 straight days), edema check, symptom log; prompt f/u appt (7–14 d for in-person visit, or telephone follow-up within 3 d after d/c for CHF flares (*JAMA* 2010;303:1716); involvement of cardiology, RNs,

social workers, nutrition; frequent pt education & clinician contact; consider multidisciplinary HF-disease management program for those at high-risk of readmission

HF postdischarge visit goals: (1) initiate/titrate guideline-directed med tx, (2) identify causes of HF and barriers to care, (3) assessment of volume status and BP, adjust HF therapy accordingly, (4) check renal function and electrolytes, (5) HF education, self-care, emergency plan and adherence, (6) assess need for palliative care

- **Medications to avoid/use cautiously in HF pts:** NSAIDs, corticosteroids, CCB (except amlodipine, felodipine (*Br Heart J* 1995;73:428; *NEJM* 1996;335:1107)), 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); monitor patients taking metformin (can ↑ HF sx; *JAMA* 2003;290:81)
- **Correction of anemia:** Controversial; IV iron in NYHA II or III pts w/ iron deficiency ± anemia did ↓ 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
- **Anticoagulation:** HF pts w/o AF have ↑ risk of stroke, DVT, PE (*Circulation* 2007;115:2637); for pts w/ EF ≤35% in sinus rhythm 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 HF unless hx thromboembolism or AF
- **Atrial fibrillation:** No survival benefit for rate vs. rhythm control in HF pts (*NEJM* 2008;358:2667), but rhythm control may ↓ severe sx (*Circulation* 2004); amiodarone (*Circulation* 1998;98:2574) & dofetilide (*NEJM* 1999;341:857) preferred; dronedarone assoc w/ ↑ mortality in severe systolic HF (*NEJM* 2008;358:2678); if rate control used, β-blockers are preferred unless otherwise contraindicated (can use verapamil and diltiazem in HFpEF); if treatment refractory, consider AV node

ablation and CRT

- **Patient information:** JAMA 2011;306:2175; AFP 2008;77:967; 2003;68:339

Treatment of HFrEF (*Circ* 2013;128:e240; 2016;135:839; *JACC* 2009;53:e1; *J Card Failure* 2010;16:475)

Treatment of HFrEF by ACC/AHA Stage	
Stage	**Intervention** (*NEJM* 2003;348:2007)
A	Treat HTN, DM, HLD, CAD, afib, obesity, metabolic syndrome, thyroid dz. 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). Cardiac rehab referral.
C	Above interventions + diuretics/salt/fluid restriction in appropriate pts. ACEI in all pts, BB in stable pts. Avoid drugs that may worsen HF. Consider specialist referral, aldosterone antagonists, digoxin, hydralazine/nitrates, and CRT/AICD in select pts. Cardiac rehab referral
D	VAD, transplantation or hospice.

- **Drugs that ↑ survival:** ACEI, βB, ARB, hydralazine/nitrates (in African-Americans), aldosterone antagonists if EF<40%, ARNI
- **Drugs that ↓ symptoms:** Digoxin, diuretics, βB, ACEI, ARBs, ARNI

Medications Used in Heart Failure with Reduced Ejection Fraction (*NEJM* 2010;362:228)	
Rx Class, Starting Dose	**Notes**
Loop diuretics Furosemide 20 mg QD Bumetanide 0.5 mg QD Torsemide 5 mg QD Can give TID-QID; ideally q8 am, 1–2 pm	Titrate to wt ↓ 1 kg/d until euvolemic; monitor for ↓ Mg; If lack of urine output after dose, ↑ 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[a] Enalapril 2.5 mg BID Lisinopril 5 mg QD	↑ Survival in asx or sx pts w/ EF ≤35% (*NEJM* 1992;327:685; 1991;325:293), NYHA class II-IV (*NEJM* 1987;316:1429) **Target dose:** Enalapril 10 mg BID or lisinopril 20–35mg QD
βB[a] Bisoprolol 1.25 mg QD Carvedilol 3.125 mg BID	↑ Overall & event-free survival in NYHA II–IV & EF ≤35–40% (*JAMA* 2000;283:1295; 2002;287:890; 2002;287:883; *Lancet* 1999;353:9; 2001;353; *NEJM* 1996;334:1349); improvement additive to ACEI

Metoprolol XL 12.5 mg QD	(*Ann Intern Med* 2001;134:550); pts should be stable 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). **Target dose:** Bisoprolol 10 mg QD or metoprolol XL 200 mg QD or carvedilol 25 mg BID
Angiotensin receptor blocker (ARB) Candesartan 4 mg QD Losartan 50 mg QD Valsartan 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 → combo contraindicated (*Arch Intern Med* 2007;167:1930); use *very cautiously* in pts w/ hyperkalemia, HoTN, or renal insufficiency due to ACEI **Target dose:** Losartan 150 mg QD, candesartan 32 mg QD
Angiotensin receptor neprilysin inhibitor (ARNIs) Sacubitril/valsartan fixed dose 24–26 mg BID	ARB added to inhibitor of neprilysin (enzyme that degrades natriuretic peptides, bradykinin, and other vasoactive peptides). ARNI decreased composite of CV death or HF hospitalization by 20%, similar across subgroups; ARNIs assoc w/ risk of HoTN, renal insufficiency and angioedema (*NEJM* 2014; 371:993) ARNI can *replace* ACEi/ARB in patients with persistently symptomatic HF to further reduce morbidity or mortality **Target dose:** Sacubitril/valsartan 97 mg/103 mg BID
Aldosterone antagonists Spironolactone 25 mg QD Eplerenone 25 mg QD (in pts w/ nl GFR)	↑ Survival in NYHA II–IV & EF ≤35% (*NEJM* 1999;341:709; 2011;364:11); 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) and ↑ survival in pts w/ NYHA II HF and EF ≤ 35% (*NEJM* 2011;364:11) or in pts w/ EF ≤40% after MI (*NEJM* 2003; 348:1309) **Target dose:** Spironolactone 50 mg
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 use in all patients who cannot tolerate 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); titrate to goal serum digoxin 0.5–0.9 ng/mL; ↑ levels ↑ toxicity & mortality (*JAMA* 2003;289:871); ✓ levels 6 h after dose

Ivabradine 5 mg BID	Blocks I_f channel in SA node to reduce HR in patients with HR ≥70 bpm at rest; can reduce HF hospitalization for patients with stable, chronic class II-I-II HF and LVEF ≤35% on GDMT; should *not* be administered to patients with MI in prior 2 mo

[a]Double dose every 2 wk in stable HF pts; target maximally tolerated 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 mo (ischemic: >40 d post-MI) (*NEJM* 2005;352:222;225); candidates should have >1 y expected survival w/ good functional status; recent evidence for no improvement in mortality in nonischemic CM (*NEJM* 2016; 375: 1221)
- **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% & multivessel CAD or proximal LAD stenosis >70%, CABG pts had ↓ morbidity and CV mortality (*NEJM* 2011;364:1607); CABG may also ↑ survival in patients with significant CAD and mild–mod LV dysfunction (LVEF 35–50%)

VALVULAR HEART DISEASE

Evaluation (*JAMA* 2015;313:1050)

Auscultation of Murmurs (*JAMA* 1999;281:2231)		
	Systolic	**Diastolic**
Early	Mitral or tricuspid regurgitation Ventricular septal defect	Aortic or pulmonic regurgitation
Middle	Aortic sclerosis, aortic stenosis, bicuspid aortic valve Atrial septal defect "Innocent" benign flow murmur HOCM Anemia or pregnancy	Mitral stenosis Tricuspid stenosis
Late	Mitral or tricuspid valve prolapse Pulmonic stenosis	
Holo	Mitral or tricuspid regurgitation Ventricular septal defect	
General approach: Murmurs are described by intensity (below), quality (harsh, blowing, scratchy), configuration (crescendo, decrescendo, crescendo–decrescendo), timing (systolic vs. diastolic), location, and radiation.		
Murmur intensity: I: Softer than S_1/S_2. **II:** Equivalent to S_1/S_2. **III:** Louder than S_1/S_2, no palpable thrill. **IV:** Palpable thrill present. **V:** Loud with thrill; may be heard with slight stethoscope touch. **VI:** Heard without stethoscope.		

Aortic Stenosis (*AFP* 2016;93:371; *Ann Int Med* 2017;166:ITC-1; *JACC* 2014;63:e57; *JAMA* 2013;310:1490; *Lancet* 2009;373:956; *NEJM* 1997;337:32; 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)
  - **Supravalvular:** 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 heard at the base of the heart & radiates to 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 & V_5–V_6; **TTE:** Peak/mean gradients, jet velocity; natural progression w/ reduction of 0.1 cm^2/y & ↑ in mean gradient of 7 mmHg/y (*Circulation* 2008;118:e523)

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

Classification of Aortic Stenosis (*JACC* 2014; 63(22))

Stage	Aortic Valve Area (cm^2)	Aortic Jet Velocity (m/s)	Mean Gradient (mmHg)	Check TTE
Mild	>1.5	2–2.9	<20	q3–5y
Moderate	1–1.5	3–3.9	20–39	q1–2y
Severe	<1.0	≥4	≥40	q6–12mo
Very severe		≥5	≥60	Cardiology referral

Sclerosis: Focal thickening or calcification of valve cusps w/ a peak transaortic velocity ≤2 m/s; determination of valve area, jet velocity; precursor to mild AS

- **Treatment:** Avoid isometrics (even if asx if severe AS);

dehydration/hypovolemia

Medical: βB, ACEI for HTN & CAD; statins do not ↓ progression or diastolic dysfunction (*Cardiovasc Ultrasound* 2011;9:5; *Circulation* 2010;121:306); *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: Offered for high-risk surgical pts; ↓ mortality but ↑ incidence of stroke & vascular events, recent data suggest safety/efficacy in intermediate-risk pts (STS risk score = 4–8%) with similar rates of death or disabling stroke (*Ann Int Med* 2010;153:314; *NEJM* 2010;363:1597; 2016; 374:1609)

Aortic Regurgitation (*Circulation* 2005;112:125; *JAMA* 1999;281:2231; *NEJM* 1997;337:32; 2004;351:1539; 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 root dilation* → leaflet malcoaptation; idiopathic, cystic medial degeneration (Marfan's, Ehlers Danlos), annuloaortic ectasia, osteogenesis imperfecta, 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 & V_5–V_6; LA dilatation, QRS prolongation

(assoc w/ poor prognosis); **TTE:** If severe, monitor LV function q6–12mo

- **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

Mitral Stenosis (ACC/AHA guidelines *Circ* 2017; *Lancet* 2009;374:1271; *NEJM* 1997;337:32)

- **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), radiation

Classification of Mitral Stenosis (*JACC* 2014; 63:2438)

Stage	Definition	Valve Anatomy	Hemodynamic Consequences	Check TTE
A	At risk of MS	Valve doming during diastole	None	N/A
B	Progressive MS	Valve doming during diastole, MVA >1.5 cm^2	Mild–moderate LA enlargement	q3–5y
C	Asymptomatic severe MS	MVA <1.5 cm^2, or <1.0 cm^2 in very severe MS	Severe LA enlargement; PASP >30 mmHg	q1–2y
D	Symptomatic severe MS	MVA <1.5 cm^2, or <1.0 cm^2 in very severe MS	Severe LA enlargement; PASP >30 mmHg	q6–12 mo

- **History:** Pulm congestion (dyspnea, hemoptysis); periph edema, 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 (best if in L lateral decubitus); loud, delayed S_1, opening snap (early diastolic, in expiration). **Maneuvers:** ⊕ murmur at ↑HR (exercise such as sit ups, squats)
- **Workup: ECG:** Left atrial abnorm, AF, RVH (late stage); **CXR:** LA dilatation = straight upper L heart border; pulm congestion, ↑ main

PA size; **TTE:** Transvalvular peak & mean gradients, valve area, restriction, & thickness of leaflets, RVSP

- **Treatment:** Na restriction, diuresis for pulm congestion; rate control to ↑ diastolic filling time

  Anticoagulation: Indicated if AF, or prior embolic event, or LAA thrombus

  Percutaneous balloon valvotomy: In symptomatic pts with severe MS; contraindicated if heavily calcified valve, LAA thrombus & ≥ mod MR; consider in asymptomatic very severe MS (MVA <1.0 cm^2) with favorable anatomy

  Surgical: Valves generally replaced (not easily repairable); 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:** Caused by damage or distortion of MV apparatus; it is **critical** to distinguish between primary and secondary MR. **Primary:** Components of valve (leaflets, chordae, papillary muscle) cause valve incompetence, caused by myxomatous degeneration, IE, CTD, RHD, cleft mitral valve, radiation; acute MR due to pap muscle rupture during MI **Secondary/functional:** Valve is normal, but an abnormal/dilated LV causes annular dilation and prevents valve coaptation; acute funct MR due to inferior wall hypo/akinesis
- **Presentation: AF** (↑ LA pressure); **Pulm congestion/HF** (LA pressure → ↑ pulm pressures→ fatigue, dyspnea); **Right sided HF** (↑ LA pressure→ pHTN → ↑ RV pressure)
- **Exam:** Holosystolic, decrescendo murmur at apex, radiating to axilla; w/ posterior mitral leaflet prolapse/flail, regurgitant jet is eccentric & directed anteriorly, striking the LA wall adjacent to the aortic root, so sound transmitted to the base; soft S_1, low-pitched S_3 (tensing of papillary muscles & chordae tendineae). In acute MR: S_4, shorter, softer murmur that is often hard to hear.

  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); **TTE:** Estimate of severity based on

color Doppler, regurgitant volume/fraction, jet width

- **Treatment:** Avoid isometric exercises, keep afterload/BP low normal
  - **Medical:** Na restriction, BP control, diuresis; if AF, digoxin, βB. If secondary MR, medical therapy for symptomatic pts with systolic dysfunction
  - **Surgical:**
  - **Primary severe MR:** Sx pts w/ LVEF >30%, asx pts w/ LVEF 30–60% and/or LVESD ≥40 mm. Prefer MV repair >> replacement. Consider repair in asx pts, with low surgical risk (STS risk score <1%) or those with atrial fibrillation and/or pulmonary hypertension (PASP >50 mmHg); if AF, may have valve reconstruction + annuloplasty ± LA Maze procedure or RFA. Patients with sx despite max med therapy and with prohibitive surgical risk can consider transcatheter mitral valve repair
  - **Secondary:** MV repair or replacement may be considered for severely sx patients who have sx despite GDMT +/– CRT for HF or those undergoing other cardiac surgery

Mitral Valve Prolapse (*Circulation* 2002;106:1355; *NEJM* 1997;337:32; 1999;341:1; 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. Pts w/ mitral valve prolapse have an approximately 1%/y risk of CHF, endocarditis, CVA, significant MR, or CHF
- **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 S_1 (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 as above (*NEJM* 2009;361:2261)

Tricuspid Regurgitation (*JACC* 2014; 63:2438)

- **Etiology:** 20% are *primary:* Rheumatic, congenital (Ebstein), myxomatous degeneration, endocarditis, trauma from procedures (pacemaker, RV biopsy); 80% are *secondary* to RV dilatation
- **Presentation:** Often asx until advanced severe TR; right-sided volume overload (periph edema, bloating, ascites)
- **Exam:** Holosystolic decrescendo murmur at RLSB; mod–sev TR audible over liver
- **Workup: ECG:** RA hypertrophy, signs of RV dx (RVH, old IMI). **TTE;** if chronic severe TR, check LFTs, abdo US for cardiac cirrhosis
- **Treatment:** Diuretics, pulmonary vasodilators if pHTN; surgery if other valve sx and mod-sev sx TR, or mild–mod TR if annulus dilated/prior Rt HF; may consider for asx severe primary TR if progressive moderate/severe RV dilatation/dysfunction in the absence of pHTN

Tricuspid Stenosis (*JACC* 2014; 63:2438)

Very rare; generally rheumatic, and occurs along with tricuspid regurgitation; often presents as abdominal discomfort due to hepatic congestion; may be treated w/ percutaneous valvuloplasty if ≤mild TR; otherwise, TVR if sx and severe TS

Pulmonary Regurgitation (*JACC* 2014; 63:2438)

- **Etiology:** Most often congenital, either primary or after valvotomy/right ventriculotomy for childhood repair of pulmonic stenosis (see "*Adult Congenital Heart Disease"*); endocarditis, carcinoid. Mild-moderate PR without another pathology is not concerning as long as RV normal size/function
- **Presentation:** Often asx until severe; right-sided volume overload (periph edema, bloating, ascites), dyspnea, palpitations (Aflutter). If RV dilatation, may present w/ SCD/VT
- **Exam:** Early diastolic blowing murmur at LUSB; louder w/ inspiration (more venous return)
- **Workup: ECG:** RA hypertrophy, signs of RV dilation **TTE:** RV size, function
- **Treatment:** Diuretics; BB and ACEi may be beneficial for RV

remodeling; surgery for severe PR and symptoms or RV enlargement

Pulmonic Stenosis (*JACC* 2014; 63:2438)

- **Etiology:** Most often congenital (valvular stenosis, subpulmonic or supravalvar stenosis); carcinoid, tumors possible
- **Presentation:** Dyspnea, right-sided HF
- **Exam:** Systolic ejection murmur at LUSB; pulmonic stenosis opening click *becomes* **softer w/ inspiration** (only Rt-sided heart sound to do that)
- **Treatment:** Valvulotomy (with great long-term results for ≤ moderate isolated PS) vs. PVR depending on pathology

AORTIC DISEASE

Background (*AFP* 2006;73:1198; 2015;91:538; *Circulation* 2006;113:e463; 2008;117:242; 2010;121(13); *JAMA* 2007;297:395; *Lancet* 2005;365:1577; *NEJM* 2014;371:2101)

- **Location:** Thoracic (TAA), abdominal (AAA), thoracoabdominal or multiple

Aortic Diameter in Health and Disease

		Upper Limit Normal (cm)		Abnormal (cm)	
		Women	Men	Women	Men
Thoracic	Aortic root	3.7	3.9	>5.6	>5.9
	Ascending	2.9	2.9	>4.3	>4.3
	Descending	2.6	2.0	>4	>4.5
Abdominal	Suprarenal	2.7	3.0	>3.0	>3.0
	Infrarenal	2.2	2.4	>3.0	>3.0

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 AAA (5–10% cases): Pts typically p/w back/abdominal pain; CT/MRI notable for periaortic inflammation & fibrosis; ESR/CRP ↑ (*JAMA* 2007;297:395)

- **Prevalence: AAA:** 1.3–8.9% in ♂ & 1–2.2% in ♀, ↑ w/ age; ~10k deaths/y
- **Risk factors: AAA:** Age, ♂, smoking, HTN, HLD, bicuspid AV, CAD or PAD, FHx; **TAA:** Incl most AAA risk factors, consider familial syndrome, genetic syndromes, e.g., Marfan, Loeys–Dietz, and inflammatory disorders, e.g., GCA, Takayasu's
- **Dissection:** If acute → ER; Risk factors: HTN, bicuspid AoV, coarctation, h/o rapid progression, connective tissue dz (e.g., Marfan), cocaine, trauma, recent cath (*JAMA* 2002;287:2262); type A (**TAA:** ascending aorta and/or aortic arch) → surgical emergency; type B (descending **TAA** w/o involvement of the ascending aorta, or **AAA**) → medically managed with BP control, unless perfusion to kidneys/other organs compromised

Evaluation (*Circulation* 2005;111:816; *EHJ* 2014;34:2873; *JAMA* 2009;302:2015; 2015;313:1156)

- **History:** Both **TAA** and **AAA** are often asx and incidental; may have vague, chronic CP/abdominal radiating to back/flank
- **Exam:** Often unremarkable; **TAA:** Rarely evident on exam, should eval for associated pathology, e.g., AoV dz. **AAA:** 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," radiating to back, mediastinal or aortic widening on CXR, or >20 mmHg BP difference between arms; *If suspected* → ED (*Arch Int Med* 2000;160:2977)
- **Screening:** If aneurysm identified, perform assessment of the entire aorta and AoV

  AAA: USPSTF grade B recommendation for men ages 65–75 who have ever smoked to receive one-time screening ultrasound; grade C recommendation for one-time screening in male

nonsmokers ages 65–75; no routine screening recommended for women unless clinical history warrants evaluation (*EHJ* 2014; 34:2873–2926); CT or MRA useful for inflammatory AAA & for perioperative eval to define anatomy; consider targeted screening of 1st-degree relatives of patients with AAA

TAA: Recommended for 1° relatives of pts w/ TAA to r/o familial syndrome; preferred diagnostic strategy is CT/MR angiography or TTE/TEE (similar high sens/spec) (*Arch Intern Med* 2006;166:1350); MRI preferred if aortic root involvement; consider evaluation of 1° relatives of pts w/ bicuspid AoV for asymptomatic TAA and/or bicuspid AoV

- **Surveillance of known aortic aneurysms:**

TAA: Rupture risk ↑ w/ larger diameter, ↑ rate of expansion; repeat imaging at 6 mo & then annually if stable; also screen for coexisting AAA

AAA: 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), however optimal screening intervals are debated

AAA Surveillance (*EHJ* 2014; 34:2873–2926; *Eur J Vasc Surg* 2011; S1–S58; *Circulation* 2013; 127)

AAA Diameter	Interval (ACC/AHA)	AAA Diameter	Interval (ESC)
4–5.4 cm	q6–12mo	4–5–5.4 cm	q12mo
Annual rupture risk by diameter (cm): <5.5: ≤1%, 5.5–5.9: 9.4%, 6–6.9: 10.2%, ≥7: 32.5%		4–4.4 cm <4 cm	q2y q3y

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

- **Medical:** Smoking cessation, manage 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 likely to outweigh risk given ↑ prevalence of CAD in this population
- **Surgical:**

AAA: Repair if diameter >**5.5 cm,** expansion >5 mm in 6 mo, complications (e.g., hematoma, ulcer, infection), genetic

syndrome, pregnancy or if pt is symptomatic; consider repair in ♀ if >5 cm (*Lancet* 1998;352:1649; *NEJM* 2002;346:1437)

TAA: Repair if >**5.5 cm;** consider repair >**5 cm** if sx, rapid expansion, FHx dissection, at experienced center in low-risk pt, familial syndrome (Marfan, Ehlers–Danlos) (*JACC* 2016;133:680); consider repair if >**4.5 cm** if Loeys–Dietz, or FHx dissection at <5 cm

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 (*J Vasc Surg* 2011;53:1167; *Nat Rev Cardiol* 2013;10:122; *NEJM* 2010;362:1863; 2015;373:328), but requires surveillance imaging, has higher leak rates/reoperation.

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

CAROTID DISEASE

Background (*JAMA* 2008;300:81; *NEJM* 2000;342:1693; 2013;369:1143; *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 mo; carries ↑ risk of future vascular events so managed more aggressively

Evaluation (*Circulation* 2011;124:e54; *JAMA* 2015;313:192; *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; consider screening in high-risk pts with ≥2 of HTN, HLD, smoking, FHx of atherosclerosis <60 y or CVA (IIB, LOE C) or in pts w/ symptomatic PAD, CAD, or aortic aneurysm (IIb, LOE C)
- **History and exam:** Most asx cases detected due to a 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-systolic 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)
- **Surveillance:** Periodic surveillance with yearly duplex is reasonable for patients with >50% stenosis identified by prior testing; longer intervals or cessation of surveillance may be appropriate after stability is proven

Management (*Circulation* 2011;124:e54; *JAMA* 2013;310:1612; *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 (*Circulation* 2011;124:e54; *J Vasc Surg* 2009;50:431)

Indication	Regimen
Asymptomatic[a]	ASA 81 mg QD **or** clopidogrel 75 mg QD
2° prevention	ASA/dipyridamole 25/200 mg BID **or** ASA 75–325 mg QD **or** clopidogrel 75 mg QD
S/p carotid artery stenting	ASA 81–325 mg QD **&** periprocedural clopidogrel (loading dose + 75 mg QD ×4–6 wk)
	ASA/Dipyridamole 25/200 mg BID **or** ASA 81–325 mg

S/p CEA (*Chest* 2008;133:630S)	QD **or** clopidogrel 75 mg QD

[a]Benefit in stroke prevention is not clearly established, though can prevent MI and other ischemic CV events.

- **Revascularization:** Choice of interventional tx w/ carotid endarterectomy (CEA) or carotid artery stenting (CAS) is controversial & evolving, thus a vascular medicine or surgery consult is reasonable for any ICA stenosis >50%; following revascularization (CEA or CAS), reasonable to perform noninvasive imaging at 1 mo, 6 mo, and yearly to assess patency and exclude new or contralateral lesions
- **Asymptomatic:** Consider CEA in pts w/ ≥70% stenosis on U/S; if ultrasound shows moderate stenosis (50–69%) despite high clinical suspicion, consider CTA/MRA for further evaluation; CEA pts should have reasonable life expectancy & be a good surgical candidate; CEA should be done by experienced surgeons in center w/ <3% morbidity/mortality; NNT to prevent 1 stroke in 3 y = ~33 pts (*Cochrane Database Syst Rev* 2005;CD001923); CAS controversial as effectiveness not studied against medical therapy alone (Crest, *NEJM* 2010;363:11); CAS noninferior to CEA in ASx pts (*NEJM* 2016;374:1011)
- **Symptomatic:** In good surgical candidates who have reasonable life expectancy, interventional options include (*Cochrane Database Syst Rev* 2011; *NEJM* 1991;325:445):

  CEA: Indicated for patients at average or low surgical risk who suffer nondisabling CVA or TIA within 6 mo if ipsilateral ICA is >70% stenotic and rate of perioperative stroke is <6%; **CEA timing:** Greatest benefit if done ≤2 wk for mild stroke/TIA to avoid early CVA risk (*Lancet* 2004;363:915)

  Stenting (CAS): Indicated as alternative to CEA for symptomatic pts at low–intermediate risk for complications and anticipated rate of perioperative stroke or mortality is <6% in patients with anatomy suitable to endovascular intervention; other clinical scenarios favoring CAS include high-risk surgical patients, restenosis after prior CEA or CAS, FMD-related disease 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)

<50% stenosis: CEA nonbeneficial or harmful
Total occlusion: Intervention is contraindicated (Class III)
Risk modeling: stroke.ox.ac.uk

- **Patient education:** ncbi.nlm.nih.gov/pubmedhealth/PMH0004669

PERIPHERAL ARTERY DISEASE

Background (*AFP* 2013;88:306; *Am J Med* 2010;123:790; *Circulation* 2013;127:1425; *JAMA* 2006;295:536; 547)

- **Definition:** Atherosclerosis, most commonly found in the aorta, iliac, & LE arteries; **Critical limb ischemia** is severe PAD w/ e/o chronic (>2 wk) of rest pain, nonhealing wounds, ulcers, or gangrene (*JAMA Surgery* 2016;151:1070)
- **Epidemiology:** ~20% of adults > 55 y & is assoc w/ ↑ risk for CV events & all-cause mortality
- **Risk factors:** Age > 40 y, race (non-Hispanics & pts of African ancestry disproportionately affected, even after controlling for risk factors), smoking (5-fold ↑ in PAD compared to lifetime nonsmokers), DM (risk doubles w/ impaired glucose tolerance, up to 4-fold ↑ w/ DM), HTN (independent risk factor, ↑ severity assoc w/ ↑ risk), HLD, FHx, other atherosclerosis, e.g., coronary, carotid, mesenteric

Evaluation (*Ann Int Med* 2007;ITC3–1; *JACC* 2017;69:e71; *NEJM* 2001;344:1608; 2016;374:861)

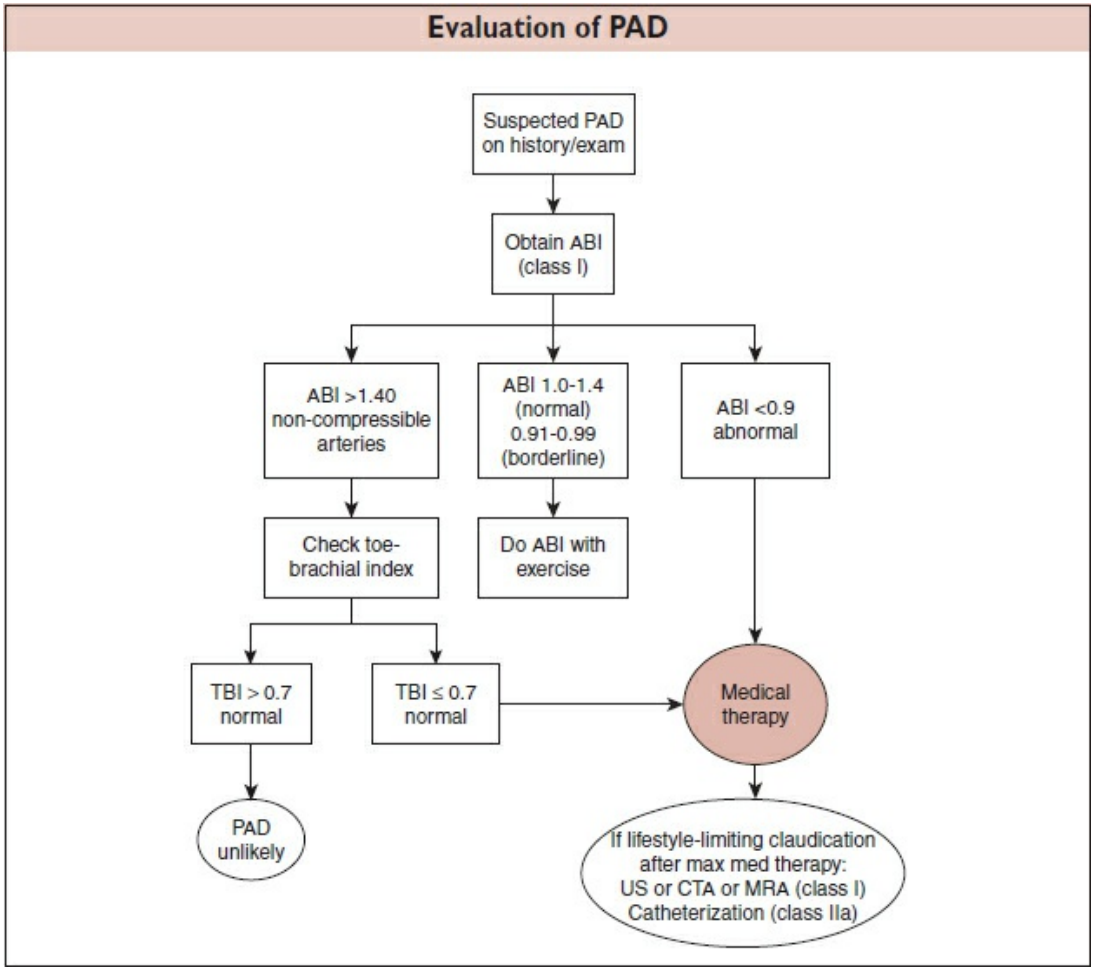
- **History:** *Claudication:* Exertional leg pain relieved w/ rest; 50% of PAD pts asx; atypical sx (exercise intolerance, joint pain, or limb numbness) more common in ♀; pain at rest suggests critical limb ischemia = 50% risk of amputation or death at 1 y
- **Exam:** ↓ or absent distal pulses, bruits, but can also be nl; look for ulcers, gangrene, elevation pallor and dependent rubor, and pulses/bruits in other vascular beds
- **Ankle–brachial index (ABI):** Systolic ankle to systolic arm pressure; simple, inexpensive, noninvasive doppler SBP of leg (higher of dorsalis pedis or posterior tibial arteries) divided by higher

SBP of right/left brachial arteries (*NEJM* 2009;361:e40); pts w/o sx should not be screened for PAD (*JAMA* 2016;316:1486)

ABI ≤0.9: Abnormal, **0.91–0.99:** Borderline, **1.0–1.4:** Normal, **≥1.4:** Noncompressible calcified arteries won't compress w/ cuff; ∴ falsely ↑ SBP reading

Exercise treadmill ABIs: Consider in pts w/ borderline/normal ABIs with exertional non–joint-related leg discomfort

- **Other studies:** Duplex U/S, CTA, & MRA used more for endovascular or surgical revascularization planning; consider screening for AAA in patients with symptomatic PAD
- **Contrast angiography:** Gold standard, only performed if plan for endovascular tx



Treatment (*Circulation* 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** assoc w/ ↓ progression, rates of amputation, incidence of rest ischemia; aggressive DM, HTN, HLD management; structured exercise can ↑ walking distance by 100–150%, comparable to surgery
- **Pharmacologic therapy**
  - **Anti-PLT:** ASA 75–325 mg; clopidogrel may be superior (CAPRIE *Lancet* 1996;348:1329) to ↓ risk MI, CVA & vascular death in pts w/ sx PAD (class I) or ASx PAD (class IIa); utility of antiplatelet use in borderline ABI (0.91–0.99) is uncertain; role of dual antiplatelet therapy (aspirin and clopidogrel) in PAD is uncertain in pts who have not undergone revascularization
  - **Vorapaxar:** Adding vorapaxar to existing antiplatelet therapy ↓ acute limb ischemia and peripheral revascularization, but did not ↓ risk of CV death, MI or CVA (*Circulation* 2013;127:1522), practice guidelines offer as IIb recommendation
  - **Cilostazol (PDE inhibitor):** Improves sx and walking duration in claudication
- **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; when surgery is chosen, autologous vein bypass to the popliteal artery is preferred over prosthetic grafts
- **Follow-up after revascularization:** Periodic clinical evaluation including re-assessment of cardiovascular risk factors and limb symptoms; pts undergoing revascularization should receive periodic ABIs and duplex ultrasound
- **Patient information:** JAMA 2009;301:236

LOWER EXTREMITY EDEMA AND

ULCERS

Lower Extremity Edema

Background (*AFP* 2005;71:2111; 2013;88:102)

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

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, TR, RV heave, S_3/S_4), abdominal (HSM, pulsatile liver, 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 min 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; monitor for ↓ K, AKI, dehydration
- **Patient information:** AFP 2005;71:2118

Lymphedema (*AFP* 2013;88:online; *Am J Med* 2001;110:288; *BMJ* 2000;320:1527)

- **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 and dependent positioning for long periods; avoid phlebotomy, vaccination, IVs in affected limb; hot climates, baths, & saunas may exacerbate; encourage 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*

Chronic Venous Disease

Background (*JAMA* 2012;308:2612; *J Vasc Surg* 2011;53:2S; *NEJM* 2006;355:488; 2009;360:2319)

- **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 (*BMJ* 2007;335:83; *NEJM* 2006;355:488; 2009;360:2319); incidence ↑ w/ age, pregnancy, ⊕ FHx, obesity, hx LE trauma, DVT; following DVT, cumulative rates 7% at 1 y, 14% at 5 y, & 20% at 10 y

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; categorized by CEAP classification involving clinical signs, etiology, anatomy and pathophysiology, scored 0–6; scores >2 warrant referral to vascular specialist (*AFP* 2008;78:1289; *J Vasc Surg* 2009;49:498)
- **Stasis dermatitis:** Eczematous reaction: Pruritic, erythematous, papular rash w/ overlying scale; simultaneous contact dermatitis (from topical agents) or infection
- **Evaluation:** Clinical dx; severity of s/sx correlate w/ degree of venous incompetence; refer sx pts for duplex U/S to assess acute vs. remote DVT, reflux severity/site, as this guides tx options; venous reflux (>0.5 s of reverse flow) c/w diagnosis of venous insufficiency
- **General treatment:** Walking, seated ankle flexion, leg elevation, stockings & massage to promote O_2 transport, prevent edema &

progression to venous insufficiency

Compression stockings: Effective but poor compliance; avoid in pts w/ PAD and ABI <0.5; ↑ pressures work better; *Class I:* DVT ppx (10–18 mmHg), *Class II:* ↓ edema (20–30 mmHg); Contraindicated: severe PAD, acute cellulitis

Skin care: Nonsoap cleansers, emollients, short course of topical corticosteroids

Medications: Pentoxifylline + compression effective at ulcer healing; venoactive agents (e.g., escin & stanozolol ↓ sx)

- **Intervention:** Consider vein ablation after 6 mo 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 and 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 recordings once PAD diagnosed; duplex imaging, ESR/CRP, CTA/MRA, MRI for osteomyelitis as indicated; consider plain films

for foreign body; biopsy ulcers present >3 mo to rule out malignancy

Clinical Features of Ulcers by Etiology			
Ulcer Type	**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 *AFP* 2010;81:989; *Ann Intern Med* 2003;138:326; *J Vasc Surg* 2000;31:S1)

Treatment (*AFP* 2010;81:989; *Ann Int Med* 2016;ITC18–1; *Cochrane Database Syst Rev* 2007;CD001733; *JAMA* 2005;293:217; *NEJM* 2004;351:48; *Wound Rep Regen* 2006;14:649):

- **Local therapy:** 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; wound care/podiatry/vascular referral for osteomyelitis prevention
  - **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 severe PAD) + pentoxifylline; worn indefinitely to prevent recurrence; abx only if infection present; elevation 30 min QID & o/n; skin grafting in chronic ulcers; ASA may help venous ulcer healing: abx not useful unless e/o systemic infection (↑ pain, ↑ redness, fever)

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 q6mo for neuropathy, q1–3mo if hx ulcer; for ulcer; (see "Diabetic Foot Infection" subsection of *"Skin & Soft Tissue Infection"*); Amitriptyline, gabapentin, or pregabalin for neuropathic pain

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

SPORTS AND EXERCISE CLEARANCE

Background (*AFP* 2010;81:55; 2015; 92:371; *JAMA* 2003;289:2913; 2005;294:3011)

- **Exercise recommendations:** 30 min of aerobic activity at least 5 d per week & preferably all days, or 25 min of vigorous physical activity 3×/wk AND moderate–high intensity muscle strengthening activity at least 2 d per week (~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 30–40% ↓risk of CV disease vs. 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)
- **Types of exercise:** Range in intensity, risk of collision (Adapted from *Circ* 2015;132:e326)

→ **Increasing Static Component** →	**High (>30%)**	Bobsledding/ Luge Field events (throwing) Gymnastics Martial arts Rock climbing Sailing Water Skiing Weight Lifting Windsurfing	Body building Downhill skiing Skateboarding Snow boarding Wrestling	Boxing Canoeing Kayaking Cycling Decathlon Rowing Speed skating Triathlon
	Moderate (10–20%)	Archery Auto racing Diving Equestrian Motorcycling	American football Field events (jumping) Rodeoing Rugby Running (sprint) Surfing Synchronized swimming “Ultra” racing	Basketball Ice hockey Cross-country skiing Lacrosse Running (middle distance) Swimming Team handball Tennis
	Low (<10%)	Bowling Cricket Curling Golf Riflery Yoga	Baseball/softball Fencing Table Tennis Volleyball	Badminton Cross-country skiing (classic technique) Field Hockey Orienteering Race walking Racquetball/squash Running (long distance) Soccer
		Low (<50%)	**Moderate (50–75%)**	**High (>75%)**
	→ **Increasing Dynamic Component** →			

*High intensity dynamic exercise ↑ volume load on LV by ↑ HR and stroke volume (↑ EDV, ↓ ESV). High intensity static exercise ↑ pressure load on LV by ↑ ventricular arterial pressure and contractile state.

- **Common pathologies encountered with physical activity:**

  Young adults: HOCM (0.2% prevalence), coronary artery anomalies, 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: See *"Asthma"* (*AFP* 2011;84:427); asthma should be well controlled at rest and with exertion prior to clearance; rescue inhaler should be available

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 (*Circulation* 2015;132:e256; *NEJM* 2003;349:1064)

- **Guidelines:** ACC/AHA recommend 14-step hx/exam (below); ideally performed 6 wk prior to start of activity to allow for further testing
  - **ECG:** Adding ECG is cost-effective based on European data ($42,900/y of life saved), not known in US where prevalence of LQTS and ARVD is lower (*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); ACC/AHA suggests screening may be considered in small cohorts with close physician involvement, though mass screening is not recommended
- **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 murmurs)

AHA 14-Step Preparticipation Screening of High-School & College Athletes	
Personal History (*Circulation* 2007;11512: 1643; *Circulation* 2015; 132:e262)	**(1)** Exertional CP/discomfort; **(2)** Syncope or near syncope; **(3)** Excessive exertional or otherwise unexplained dyspnea/fatigue; **(4)** Hx heart murmur; **(5)** HTN **(6)** Prior restriction from sports **(7)** Prior testing of the heart
Family History	**(8)** Premature death related to heart disease or SCD; ask about drownings, car accidents, specific syndromes to ↑ recall; **(9)** Disability from heart disease in close relative <50 y; **(10)**

	Knowledge of FHx of hypertrophic/dilated CMP, ion channelopathy, long QT, Marfan, or arrhythmias
Physical Exam	**(11)** Murmur (listen supine & sitting, looking for signs of LVOT obstruction); **(12)** Femoral pulses to r/o aortic coarctation **(13)** Stigmata of Marfan; **(14)** Brachial artery BP (seated)

Contraindications for Sports Participation (*AFP* 2015;92:371)

• Myocarditis or pericarditis • Acute hepatomegaly or splenomegaly • Untreated eating disorders • Recent concussion (avoid contact sports) • Severe, uncontrolled HTN • Sickle cell dz (no high exertion, contact, or collision sports) • Hemophilia or von Willebrand dz (contact sports)	• Hypertrophic cardiomyopathy • Long QT syndrome • Poorly controlled convulsions (no dangerous activities) • Recurrent burning UE pain/weakness until C-spine cleared • Suspected CAD until fully evaluated • Drug abuse

- **Cardiology referral:** If abnl exam, FHx suspicious for SCD, or concerning factors found in 14-step exam; pt should not be cleared to participate prior to cardiology visit; recommendations for sports clearance & allowed sports for pts 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 14-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 (*JACC* 2015;66:2385; *JAMA* 2003;289:2913)

- **Previously inactive pts:** Begin w/ short duration, moderate-intensity exercise & ↑ duration as tolerated; ETT prior to vigorous exercise program in pts w/ DM2 or cardiac risk factors (♂ >40 y, ♀ >55 w/ >2 CAD risk factors [see "*Coronary Artery Disease*"])
- **Chronically ill:** As for previously inactive pts, *unless:* severe HTN, arrhythmias, uncontrolled metabolic dz, high-degree AV block, unstable angina, severe AS, recent ECG changes/cardiac event,

acute myocarditis/pericarditis, 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 light exercise after 1 wk, sports after 4–6 wk, specific cardiac rehab program recommended; post-CABG pts may exercise after 4–6 wk if sternal wound is stable
- **Mitral valve prolapse (MVP):** No specific recommendations exist for pts with MVP and history of syncope, arrhythmia, personal or family history of SCD; if these issues exist, they should be thoroughly investigated independent of valvular disease (*JACC* 2006;48:e247); if MVP leads to severe mitral regurgitation, pt should be limited from at least some sports if evidence of LV enlargement or LVEF <60%
- **Anticoagulation:** Patients receiving therapeutic long-term anticoagulation should not engage in sports where impact is expected, e.g., ice hockey, American football
- **Sickle cell trait:** Not justification to disqualify from competitive sports, however preventative strategies for acute events and prospective awareness of emergency medical strategies is recommended should one occur
- **Known predisposition to SCD, arrhythmia, Brugada syndrome, myocarditis, HOCM, long-QT, Marfan, congenital heart disease:** Detailed recommendations by ACC/AHA Scientific Statement (*JACC* 2015;66:2385); 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), 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

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

ADULT CONGENITAL HEART DISEASE

Background (*Circulation* 2008;118:2395; 2015;131:1884; *NEJM* 2000;342:256)

- **Epidemiology:** Birth incidence ~0.8%; significant ↑ in pediatric survival due to surgical and medical therapies have led to ↑ adult congenital heart disease (CHD) population; since 2000, prevalence adults >children with CHD (*Circulation* 2007;115:163; *Semin Thorac Cardiovasc Surg* 2010;13:26), resulting in ↑ medical complexity, resource use (*AJC* 2016;118:906)
- **Etiology: Genetic** (sporadic vs. syndromes w/ assoc cardiac abnl [Down, Turner's, Di George]); **in utero exposures:** ~8–10%; maternal EtOH, infections (rubella), meds (dilantin, isotretinoin, thalidomide), metabolic synd (poorly controlled DM, PKU)
- **Noncyanotic CHD:** BAV and VSD are most common CHD overall > ASD > coarctation (*Circulation* 2008;118:1768); in adults, ASD > VSD; many with CHD diagnosed as adults for the first time; if suspect ACHD, obtain history of exercise capacity, cardiac ROS, cyanosis (blue lips, fingers with exertion); h/o gestational exposures, growth and childhood sx, FHx
- **Cyanotic CHD:** Most severe forms of CHD, including R → L shunts leading to hypoxia; most patients require palliative shunts in childhood to allow some flow to the lungs and development of pulmonary tree (shunt from subclavian artery, aorta, or SVC, IVC; see below); tetralogy of Fallot (TOF) most common cyanotic CHD in adults

- **Simple CHD:** Bethesda classification (*JACC* 2001;37:1161): isolated congenital AV or MV disease (except parachute or cleft MV), isolated PFO/small ASD/small VSD; mild pulmonic stenosis; ligated or occluded ductus arteriosus; repaired secundum or sinus venosus ASD without other defects/shunts
- **Frequent complications in adulthood:** Arrhythmias, heart block, sudden cardiac death, HF, pHTN, renal insufficiency, liver disease, and cirrhosis; many reversible if treated early

Evaluation

- **Detailed history crucial:** Diagnoses, prior surgeries; 1 or 2 functional ventricles; presence of Eisenmenger syndrome (pulmonary pressures > systemic pressures); baseline BP and O_2 (many cyanotic pts have "normal" O_2 ~ 80s at rest, 60s w/ exertion)
- **Exam:** CV exam, JVP, surgical scars (sternotomy vs. thoracotomy), O_2 saturation, BP both arms; absent/weak pulse in one arm normal if prior Blalock–Taussig shunt
- **Workup:** ECG (atrial vs. ventricular arrhythmias), CXR, labs (NTproBNP ↑ at baseline in complex ACHD and "normal" ranges undefined; however ↑ above baseline assoc w/ HF and has prognostic value; obtain copies of prior records/outpatient physician

Diagnosis of Adult Congenital Heart Disease		
Diagnosis	**Suggestive Features in History, Exam**	**Suggestive ECG, Imaging**
Atrial septal defect (ASD)	Unexplained TIA/CVA/ arterial emboli, atrial arrhythmias. ASD flow is silent (low gradient). May have wide fixed S_2, loud P2, RV heave, PA tap. Look for ASD if unexplained RV overload	LAD in 15% primum ASD; RAD if large secundum or venosus ASD. Ectopic atrial rhythm in 15% sinus venosus ASD, 1st AVB if primum ASD
Ventricular septal defect (VSD)	Often murmur since childhood Holosystolic murmur; louder if smaller defect (higher gradient). Supracristal VSD may → aortic leaflet prolapse → AI murmur	RBBB; LAD/AVB if AV canal defect. LA + LV dilated if large shunt. RAD + RVH if pulmonary HTN
Bicuspid aortic valve	Soft aortic ejection click; AS or	Assoc w/ ascending aortic

	AI murmur. Check arm/leg BP for ?coarct	aneurysms, coarctation
PDA	Continuous murmur	LV dilatation, dysfunction
Sub/supra-AS	Dyspnea, CP w/ exertion. FHx, AS murmur	
Ebstein anomaly	Hx palpitations. PFO, secundum ASD common. TR murmur on exam	WPW in 25%, RA enlarged 1st AVB, RBBB
Transposition of great arteries	Progressive HF from failing RV. AV valve regurgitation. Prominent S_2 (aortic valve closer to sternum)	Heart block (2% per year) Q-wave in Rt precordial leads (V_1, V_3R, inferior leads)

Management

- **Cardiology follow-up:** All ACHD pts should have cardiologist; moderate–severe ACHD need regular follow-up with ACHD cardiologist (q6mo–1y depending on diagnosis); tertiary care follow-up assoc w/ more guideline-based care and improved outcomes (*Circulation* 2014;129:1804); all pts with moderate–severe ACHD should see ACHD cardiologist regularly
- **Prevention:** Screen for atherosclerotic risk factors, including diabetes, metabolic synd, CAD are increasingly common, especially as pts often sedentary; encourage lifestyle changes, check cholesterol and treat per general guidelines; age-appropriate cancer screening (esp since life expectancy continues to ↑)
- **Endocarditis prophylaxis:** Per general guidelines (see "*Infectious Diseases*")
- **Resources for patients:** International Society for Adults with Congenital Heart Disease (isachd.org), Adults with Congenital Heart Disease Assoc (ACHA.org)

APPROACH TO SKIN LESIONS

Background

- The ability to concisely characterize lesions is important for communicating w/ colleagues & formulating Ddx
- A complete exam includes skin, mucosal surfaces, nails, hair, & LN (when appropriate)
- **History:** Duration, timing, sx, where/how did lesion(s) start, PMHx, meds (esp new)

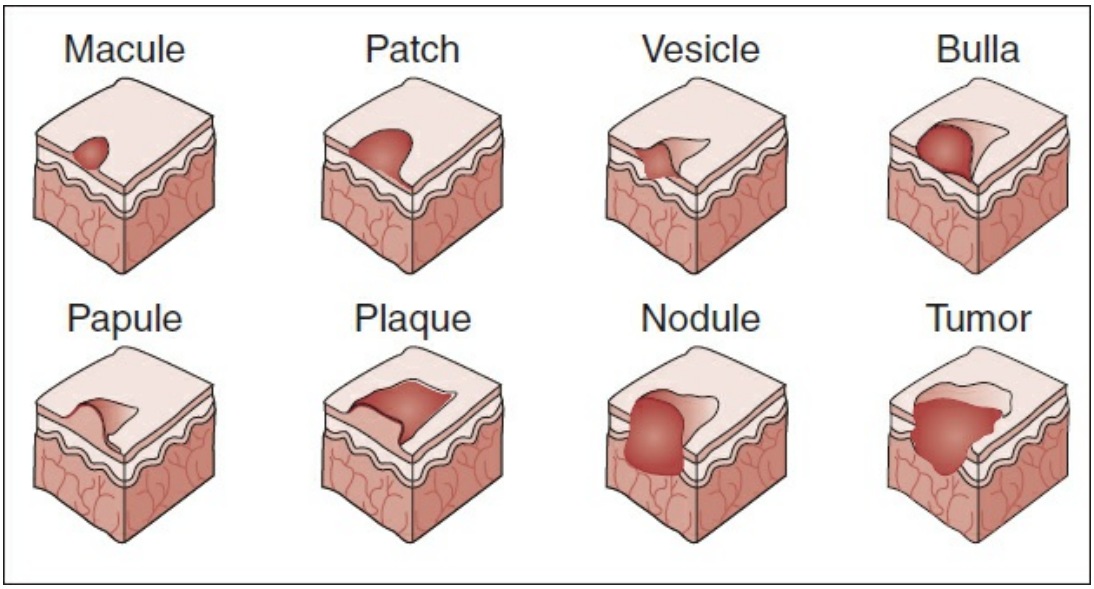
Approach to Describing Skin Lesions

- Every description must include
  (1) Color (if applicable)
  (2) **Primary lesion**
  (3) Secondary characteristics (if applicable)
  (4) Distribution
  (5) Grouping (if applicable)
- Example: “Ms. ___ is a 46-year-old woman w/ well-demarcated **erythematous plaques** w/ silvery **scale** on her **extensor surfaces,** scalp, & gluteal cleft” (psoriasis)

Color

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

Primary Lesions



- **Macule:** Flat, nonpalpable lesion <1 cm diameter (⊕ color or min textural change)
- **Patch:** Flat, nonpalpable lesion >1 cm
- **Papule:** Palpable, solid lesion <1 cm
- **Plaque:** Elevated or depressed, often flat, palpable lesion >1 cm
- **Nodule:** Palpable rounded lesion that usually denotes deep dermal or SC process >1 cm
- **Tumor:** Palpable solid lesion either above or beneath skin's surface, usually >2 cm
- **Vesicle:** Elevated lesion containing 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

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"

Distribution—Where are the Lesions?

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

Grouping—What is their Relationship to Each Other?

- Linear (contact dermatitis), herpetiform (herpes simplex, zoster), annular: Ring-like w/ central clearing (tinea corporis, granuloma annulare), 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, eschar (anthrax)

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
- **“Eczematous”:** Definition of a clinical reaction pattern but also implies characteristic pathologic features (spongiosis); 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, in skin cancers, often firm
- **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—benign, atypical
- **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 – primarily due to chronic UV exposure, less often autoimmune disease
- **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:** Sun spots; 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

COMMON BENIGN GROWTHS

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, atopic dermatitis,

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 q3wk; 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 min, gently exfoliate w/ pumice/file, then apply QHS; S/e: Irritation (d/c if severe), maceration

  Second line: Other destructive modalities (curettage, electrodessication), duct tape
- **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—biopsy may be needed,** periungual location (assoc w/ SCC) (*JAAD* 2011;64:1147), consideration of advanced tx (immunomodulators: imiquimod, intralesional Candida Ag; immunotx: squaric acid, DNCB; podophyllin toxin, topical 5-FU (*Br J Dermatol* 2011;165:432)

Angioma (*JAAD* 1997;37:887)

- Most common acquired cutaneous vascular neoplasm, benign, present in most by age 60; ↑ in number & size w/ age; unknown etiology (hormonal influences); ↑ blood vessels seen on bx
- *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
- *S/sx:* SC, soft, mobile nodule **often w/ punctum,** yellow/blue appearance; cyst rupture can → inflamed (sterile or bacterial)
- *Dx:* Clinical; Ddx includes pilar cyst (scalp), dermoid cyst (eyebrow), lipoma, dermal tumor
- *Tx:* Inflamed: intralesional steroids → refer to dermatology for future excision for definitive tx; Infected: I&D, oral antibiotics; avoid manipulation and extraction of contents unless I&D needed for superinfection

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; many lipomas deep, w/ fascial component; if large or over a joint, consider referral to plastic surgery

Fibromas

- **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—often upper outer arms, ⊕ 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 pale 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

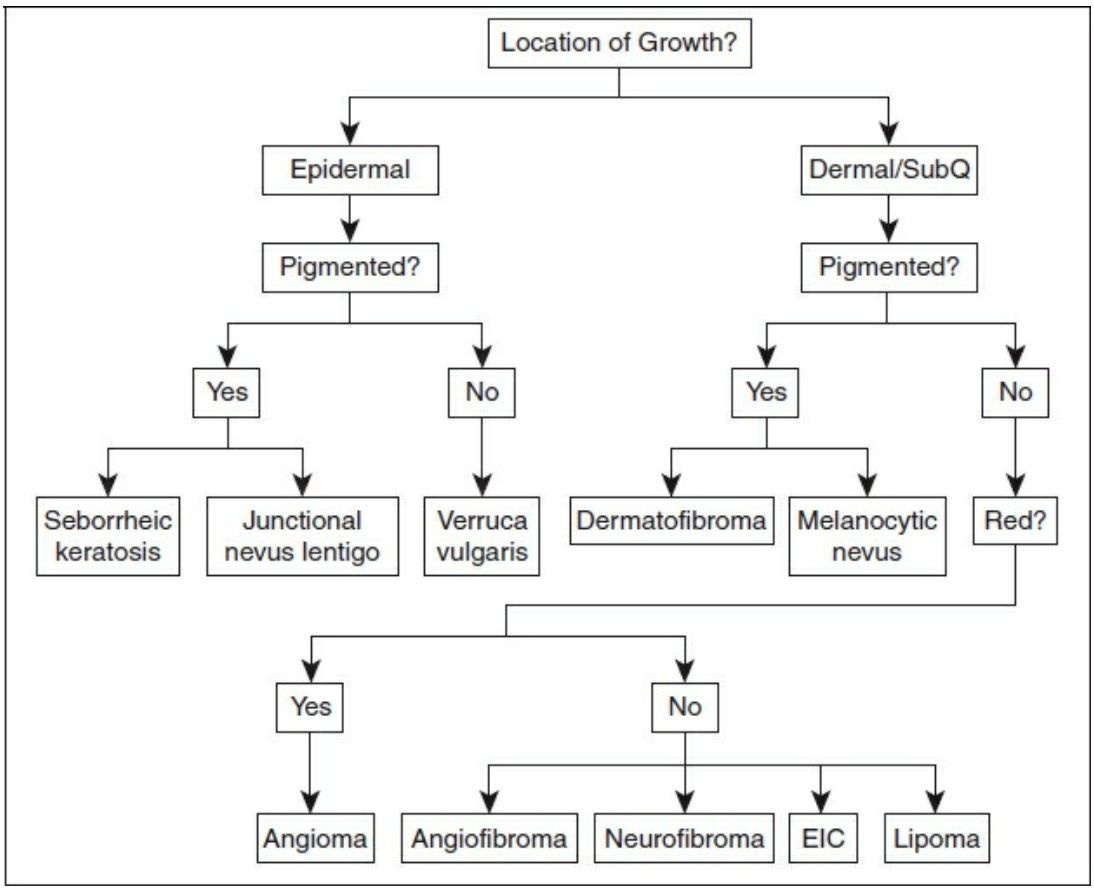


Figure 3-1. Diagnostic algorithm for common benign growths

ACNE

Background (*JAAD* 2009;60:S1; ***JAMA* 2016;316:1329)**

- **Definition:** Chronic disease of pilosebaceous follicle, characterized by comedo formation & assoc inflammatory lesions
- **Epidemiology:** Affects 50 million people, 85% of adolescents; can persist into adulthood, particularly in ♀ (affects 12% of adult ♀); 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 epilepsy, asthma, DM, can → 2–3x ↑ 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); role of diet controversial

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

Cosmetic	Occlusive creams/makeup/pomades, "anti-frizz" serums
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 hyperpigmentation ± "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	Comedonal & inflammatory lesions present; mild disease of the trunk
Moderate–severe	Numerous papules & pustules (>40), occasional tender nodules & cysts; ⊕ truncal involvement, ± scarring
Severe	Many large, painful nodules & cysts, **significant scarring** +/– systemic sx

Treatment (*NEJM* 2005;352:1463; *JAAD* 2016; 74:945; *JAMA Dermatol* 2016;152:655)

- Aimed at correcting follicular keratinization, ↓ sebum production, ↓ bacterial colonization, & ↓ inflammation
- Treatment algorithm largely divided into topical ± systemic tx based on severity; algorithm-based initiation of tx by PCPs ↓ need for dermatology referral by 72%

Common Acne Treatments		
Class	**Example Medication Rx**	**Side Effects/Notes**
Topical Tx: 1st-line for pts w/ Mild Disease		
Retinoids	**Tretinoin 0.025–0.1%** (C,G, microsphere gel vehicle) QHS	**Irritation,** photosensitivity
Topical antimicrobials[a]	**Benzoyl peroxide** 2.5–10% (C,G,L,W) QD–BID	Irritation, bleaches clothing/linens
	Clindamycin 1% (preferred)	bacterial resistance
Other agents	Azelaic acid 15–20% (C,G) QD–BID	Irritation
	Salicylic acid OTC QD–BID	Irritation, dryness

Systemic Therapy		
Oral antibiotics (1st line)[a]	**Doxycycline 50–100 mg QD–BID**	GI upset, photosensitivity; more effective than tetracycline
Oral antibiotics (2nd line)[a]	TMP–SMX DS BID	Hypersensitivity, photosensitivity, TEN
	Macrolides (azithromycin, erythromycin)	Erythromycin—antibiotic resistance, GI s/e
Hormonal agents (♀ only)	Spironolactone 50–200 mg	Menstrual irregularities, breast tenderness, teratogenicity, hyperkalemia, gynecomastia
	Estrogen-containing OCP	See *"Contraception"*
Oral retinoids	Isotretinoin 0.5–1 mg/kg/d	Usually Rx'ed by dermatologist; teratogen, xerosis, ↑ LFTs, visual changes

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

[a]Should be used in combination w/benzoyl peroxide or retinoid to limit incidence of abx resistance.

- **Combination therapy with topical retinoid + antimicrobial agents preferred approach** for almost all pts w/ acne, especially for ≥ moderate acne; many add'l combination agents available beyond those in above table
- Topical or oral **antibiotics should be combined w/ benzoyl peroxide or retinoid** to limit incidence of abx resistance; monotherapy w/ systemic antibiotics not recommended
- Limit oral abx to shortest duration possible (<3 mo); ideal use as to bridge until topical tx becomes effective
- Oral isotretinoin most effective acne medication; federally mandated Rx regulation program (ipledgeprogam.com) due to ↑risk of teratogenicity
- **Adjunctive treatments:** no dietary modifications definitively improve acne, but some evidence low glycemic load diets may be beneficial

When to Refer to Dermatology

- **Scarring, severe disease**
- **Treatment-refractory: If fail 3-mo course of oral antibiotics + topicals**
- For consideration of additional adjunctive tx: **oral retinoids,** extractions/peels, & laser/light-based therapies (e.g., photodynamic Rx); intralesional steroids for cystic, tender lesions (caution: can →

permanent atrophy even at low dose)

- **Systemic/severe variants:** Especially, acne fulminans (usually adolescent ♂ w/ fever, arthralgias, large inflamm nodules, ↑ WBC, ↑ ESR, proteinuria, osteolytic lesions); acne conglobata (usually 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), PAPA-HS (+ hidradenitis suppurativa)

ROSACEA

Background (*J Invest Dermatol Symp Proc* 2011;15:1; *JAMA Dermatol* 2015;151:1213)

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

Diagnosis (*NEJM* 2005;352:793)

- **Clinical diagnosis:** 4 major subtypes; features may overlap; bx used only to r/o other dx; use Hx to **distinguish from other causes of flushing** (e.g., menopause, anxiety, carcinoid, mastocytosis, pheo) & **assess ocular sx**

Rosacea Subtypes (*NEJM* 2005;352:793)

Subtype	Morphology/Characteristic
Erythematotelangiectatic (most common)	Persistent **centrofacial erythema, flushing, telangiectasias,** ↑ cutaneous Se; classically spares periocular skin
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; may also involve chin, forehead, ears, eyelids
Ocular	May be seen w/ other subtypes; nonspecific ocular itching, gritty sensation, dryness, conjunctival injection, recurrent chalazion or hordeolum, blepharitis; rarely can → keratitis, uveitis, scleritis, or episcleritis

- **Triggers:** Sun exposure, temperature extremes, EtOH, hot liquids, spicy foods, exercise, topical irritants
- **Differential dx** 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 is essential tx for all types; use physical barriers** (titanium dioxide or zinc oxide) given chemical sunscreen may ↑ rosacea; moisturizers, avoid harsh cleansers w/ acetone & vasodilating drugs (e.g., CCBs or niacin), 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; evidence for light-based or laser therapies—intensed pulsed light (IPL), pulsed-dye laser (PDL) → refer to dermatology; *topical tx to consider;* brimonidine gel 0.33%QD (caution with s/e: rebound erythema, burning), oxymetazoline hydrochloride cream 1% QD
- **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 or cleanser; azelaic acid 15% gel or foam BID (↑ effective but ↑ irritating, less with foam); benzoyl peroxide 2.5–10% gel, crm, or lotion QD–TID;

ivermectin 1% cream QD

Systemic tx: If mod/severe, **doxycycline 50–100 mg QD or BID** × 6–12 wk; minocycline 50–100 mg BID × 6–12 wk; or MNZ 200 mg QD or BID × 4–6 wk; consider adjunct 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)

NONMELANOMA SKIN CANCER

Background (*JAMA* 2016;316:436)

- Nonmelanoma skin cancer accounts for 98% of US skin cancers; 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; *JAMA* 2016;316:436)

- Highest incidence in older, fair-skinned pts w/ long-term sun exposure; ♂ > ♀, pts with hx sunburn
- 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 (10x ↑ risk of BCC, 65x ↑ risk of SCC: Heart/lung >> kidney >> liver, esp those on AZA, CsA (*JAAD* 2011;64:981), chronic voriconazole, vemurafenib, photosensitizing meds such as HCTZ assoc w/ ↑ risk of SCC; hx ionizing radiation (esp as child) (*Dermatol Surg* 2016;42(9): 1107)
- **SCC-specific associations:** CLL, burns (Marjolin ulcers), chronic

wounds, HPV (subtypes 16, 18, 33), **smoking** (*Arch Dermatol* 2012;148:939)

- **Prevention: Photoprotection is foundation of prevention:** Daily sunscreen use for 4.5 y ↓ risk SCC by 35% (*Cancer Epi Bio Prev* 2006;25:46); see Prevention section of *"Melanoma"*

Red Flags

- Any lesion w/ rapid growth, ulceration, spontaneous bleeding, tenderness (concern for perineural invasion)
- 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

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); commonly distributed on **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 metastatic 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:** Refer to dermatology; low-risk lesions on the trunk, extremities → excision w/ appropriate margins; lesions on head/neck, large lesions on trunk or extremities, or high-risk lesions → Mohs micrographic surgery by a fellowship-trained Mohs surgeon (advantages include tissue preservation, margin-controlled, local anesthesia) (Mohs Surgery Appropriate Use Criteria (*JAAD* 2012;67:531)); 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

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 q3–6mo), CLL

MELANOMA

Background (SEER, seer.cancer.gov/statfacts/html/melan.html; *JAMA* 2016;316:436)

- **Epidemiology:** Lifetime risk 2.2% in US; incidence ↑ w/ age, but relatively common type of cancer in the young; median age at dx: 64 y
- 75% of melanomas develop de novo, not from pre-existing nevi; high-risk sites: trunk/back of ♂, lower legs of ♀; **50% of all melanomas initially discovered by pt** (*JAAD* 1992;26:914)
- **Strongest risk factors:** Personal hx melanoma (~8% risk of 2nd melanoma at 2 y), family (1st-degree relative) hx of melanoma, multiple dysplastic nevi (if 5 atypical moles, 10x ↑ risk of melanoma), congenital nevus >20 cm, familial dysplastic nevi syndrome (*NEJM* 2004;351:998; *JAAD* 2005;52:197)
- **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)
- **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

Definitions (*NEJM* 2004;351:998)

- **Dysplastic nevi** (graded mild/moderate/severe atypia): Considered benign, but for lesions w/ severe (+/- moderate) atypia, 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; includes lentigo maligna
  - **Superficial spreading melanoma:** (70% of melanomas); 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, desmoplastic (↑ risk of local recurrence), uveal, amelanotic (erythematous eroded papule/nodule, often confused w/ BCC or pyogenic granuloma)

Evaluation (*JAMA* 2004;292:2771)

- **History:** PMHx or FHx of dysplastic nevi/melanoma? Blistering sunburns? Tanning bed use? **Changing moles**? Sx 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), especially growing in diameter

Evolving (or symptomatic—pain, pruritus, bleeding)

- **Diagnosis: Suspicious lesions → timely referral to dermatology for eval and biopsy**
- Biopsy: if unable to obtain prompt referral to derm, may biopsy in office

  Margins: **Avoid partial bx;** capture entire *breadth* of lesion w/ 1–2 mm clinical margins; capture entire *depth* (critical for staging)

  Technique: Elliptical, punch excision w/ sutures or shave removal as needed for depth

  Interpretation: **Path should be read by dermatopathologist**

Prevention & Treatment (*NEJM* 2004;351:998; *Crit Rev Oncol Hematol* 2010;74:27; *JAAD* 2011;65:1032)

- **Sun protection:** Avoid or seek shade during peak hours of sunlight (10 am–3 pm); ~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
- **Sunscreen pearls:**

1. SPF ≥30; daily use of SPF 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—1 tsp to head & neck; "underdosing" of sunscreen common
4. Reapply at least every 2 h
5. Use cream or lotion; sprays likely less effective (*Br J Dermatol* 2007;156:716)

- **Monthly self-skin checks:** Educate pts about ABCDEs, ugly duckling nevi
- **When to refer to dermatology**

  Clinically suspicious lesions or bx with atypical nevus

  Personal hx of melanoma or otherwise high risk; risk of recurrence highest in first 2 y after initial dx (*Int J Cancer* 1997;73:198; *Cancer* 2003;97:639)

  All new melanoma diagnoses (may also need surgical oncology or medical oncology)

- **Pt information:** aad.org/media-resources/stats-and-

facts/prevention-and-care/sunscreens

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 foreign body, 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** "Dogmentin" (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 postexposure Ppx** (human diploid cell vaccine ASAP [day 0] + HRIg [day 0, 3, 7, 14, & 28 if no prior vaccine; days 0 & 3 if prior complete cell culture vaccine]) **for all wild animal bites** (incl raccoons, etc); for domestic animals, observe animal × 10 d → if nl

behavior, no rabies PEP, if animal ill → sacrificed & tissue tested

Human Bites (*CID* 2005;41:1373)

- **Background:** Risk of infection ↑ compared to other 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; cdc.gov/parasites/lice.index.html)

- **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
  - *Environment tx:* wash sheets/clothes on hot + hot dryer x 10 min (delicate items which cannot be washed in hot water → hot dryer x 30 min); helmets, headphones, hats → freezer o/n *or* sealed plastic bag x 2 wk; inspect household members and tx if ⊕
  - *Head tx:* topical **permethrin 1% (OTC), 2 applications 1 wk**

apart (alt: Malathion, benzyl EtOH, 0.5% ivermectin lotion); TMP–SMX w/ permethrin or PO ivermectin for tx failure

- **Body lice** (pediculosis corporis): Vector for typhus, trench, & recurrent fever; ↑ prevalence in crowded living quarters (shelters, prisons, SNFs), poor hygiene; *S/sx:* Waist, axillae, nuchal pruritic/excoriated papules; **visualize louse or nit on clothes** (often in seams)

  Ddx: Scabies, allergic dermatitis; skin scraping useful if dx unclear
  Tx: Primary treatment is improved hygiene (cannot survive >24 h away from human host); heat-wash linens/clothes and regular change of clothes; may tx with pediculocide if unable to arrange this/add'l tx desired (o/n application of permethrin to body; see Scabies treatment)

- **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 (OTC),** return in 1 wk, re-treat PRN; tx partner/notify partners from last 30 d, heat-wash lines/clothes; **eval for other STIs**

Spider Bite (*Lancet* 2011;378:2039; *NEJM* 2005;352:700)

- Most spiders are not toxic to humans; 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 that insect 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, consider topical corticosteroids; if superinfected → abx (see *"SSTI"*)
- **Eradication:** Very difficult; requires systematic effort; usually professional assistance; prevention advised (inspect hotel rooms, items purchased 2nd-hand, library books)

Scabies

Background (*NEJM* 2010;362:717; *Lancet* 2006;367:1767; *Ann Intern Med* 2014;161:5)

- Infestation by mite *Sarcoptes scabiei* affects ~300 million worldwide; more common in debilitated pts or hx neuro d/o (crusted scabes), impoverished communities, homeless, group/crowded housing facilities; ↑ in winter mo 2/2 crowding
- **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 wk 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, atomic dermatitis, 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:** Low Se for mite, shows only 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** to tx newly hatched mites
- **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 in 1 wk;** 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 lb (*MMWR* 2005;54:533–535)
- **Decontamination:** Mites cannot survive w/o human host for >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 wk 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

TINEA

Background (*BMJ* 2012;344:e4380)

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

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")	Range from asx to intensely pruritic, usually **bilateral;** gradually progressive, duration of months to years *Interdigitary skin:* (Most common/initial site) **white maceration/fissuring or dry scale** *Soles/lateral feet:* Well-demarcated erythema w/ powdery or hyperkeratotic, occasionally peeling "moccasin scale" Often w/ simultaneous tinea cruris or onychomycosis (check groin & buttocks if feet involved) **Ddx: Psoriasis,** AD, pityriasis rosea, 2° syphilis

Tinea unguium (onychomycosis)	Common w/ ↑ age, DM, tinea pedis, occlusive footwear Yellow, thickened nail plate, **subungual hyperkeratotic debris,** nail plate lifting off nail bed (**onycholysis**) Types: Distal plate (most common), also white superficial (spots which coalesce at nail plate), proximal subungual (HIV) Ddx: Candida, other yeast (esp in tropical climates & in pts w/ DM or immunosupp); psoriasis
Tinea corporis "ringworm"	Common in younger adults; ⊕ pruritus, on legs, arms, or torso Erythematous pinpoint papules initially → slowly enlarging **annular** patches w/ **central clearing** & enhanced border; **trailing scale** Ddx: Allergic contact dermatitis, atopic dermatitis psoriasis
Tinea cruris ("jock itch")	More common w/ ♂ gender, obesity Well-demarcated dull red/tan plaques w/ overlying scale on thighs, inguinal region (scrotal involvement rare) 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)
- **Tinea incognito***:* any tinea presentation where scale is obliterated by use of emollients (usually steroids); key to dx is annular morphology, leading edge
- **Dermatophyte-related eruptions**
  - *Dermatophytids:* "Id reaction"; widespread hypersensitivity most common w/inflammatory tinea capitis; pinpoint monomorphic pruritic papules on palms/soles
  - *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 (modest

Se/high Sp)

(1) Use 15 blade or 2nd slide to scrape scale onto slide
(2) Apply coverslip & 1–2 drops of 10–20% KOH w/ DMSO or Swartz Lamkins
(3) 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 treated
- **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); nystatin **not** effective against tinea
- **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	**Terbinafine** 1% crm topical daily × 4–6 wk (OTC) **Topical azole** (e.g., econazole 1% crm) daily × 4–6 wk **Ciclopirox** gel/crm 0.77% BID × 1–4 wk (*BMJ* 1999;319:79; *Cochrane Database System Rev* 2007;3: CD00143)

Tinea unguium	**Terbinafine** 250 mg PO daily × 6 wk for fingernails, 12 wk for toenails—**most effective** (about 80%) (*Br J Dermatol* 2004;150:537) **Itraconazole** 200 mg daily × 3 mo; or 400 mg/d for 1 wk, monthly for 3–4 mo (latter regimen is not FDA approved) Nail avulsion (podiatry, dermatology)
Tinea corporis Tinea cruris	**Topical azole** (e.g., econazole 1% crm) daily × 4–6 wk **Terbinafine** 1% crm topical daily × 4–6 wk (OTC) **Ciclopirox** gel/crm 0.77% BID × 1–4 wk (*BMJ* 1999;319:79; *Cochrane Database System Rev* 2014;8:CD009992)

(*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 mo, 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 **"Spaghetti & meatballs"**—hyphal & round yeast forms on KOH	Selenium sulfide lotion QD × 1 wk (leave on for 10 min); **ketoconazole** crm or shampoo used as body wash QD × 2 wk (*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** Risk factors: Warmth, moisture, oral abx	Topical azole, nystatin cream (for dry areas) or powder (for wet/intertriginous areas; cream there can → maceration) consider fluconazole 150 mg PO × 1

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 allergic rhinitis
- **Pathophysiology:** Thought to be combination of environmental exposures & genetic predisposition; epidermal barrier dysfunction 2/2 *filaggrin* mutation → ↑ transepidermal water loss → dry skin
- **Risk factors: smoking** (*JAAD* 2016; 75:1119); IgE dysregulation in subset of pts; "**Hygiene hypothesis**": ↑ Atopy assoc w/ ↓ microbial exposure early in life, esp in developed countries; assoc w/ food allergies but causal relationship not established
- **Complications:**

  Mental health: ↓ health-related QOL on par w/psoriasis (*JAAD* 2017;77:274)

  Ocular: keratoconus, anterior subcapsular cataracts

  Infectious: **secondary infection** 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"*)

Evaluation (*JAAD* 2014;70:338)

- **General approach:** AD is a clinical diagnosis made w/ exam findings

  History: Location, duration, severity of itch (incl sleep disturbance), past tx, personal or ⊕ FHx of atopy (AR, asthma); **triggers:** foods, emotional stress, environmental factors (season/temperature; often ↑ in winter); skin irritants such as wool, solvents, & sweat

  Exam: *Acute:* Poorly defined, excoriated erythematous patches, vesicles, serous exudates, & crusts; *chronic:* Lichenified (↑ skin markings) & hyperpigmented plaques, prurigo nodules; *2°characteristics:* Excoriations, punctate erosions, ± impetigo
- **Labs:** Low threshold to culture crust or punctate erosions

American Academy of Dermatology Diagnostic Criteria (*JAAD*

2014;70:338)	
Essential Criteria (necessary for dx)	1. Pruritus 2. Typical morphology & age-specific patterns - Current or previous flexural lesions (in adults) - Sparing of the groin and axillary regions 3. Chronic or relapsing history
Important Features (seen in most cases)	1. Early age of onset 2. Personal or family hx of atopy and/or IgE reactivity 3. Xerosis
Assoc Features (support dx but ↓ Se)	**Atypical vascular responses:** Facial pallor or erythema, delayed blanch response, white dermatographism Ocular/ periorbital changes **Keratosis pilaris, hyperlinear palms, Ichthyosis,** pityriasis alba Perifollicular accentuation, **lichenification, prurigo lesions**

- **Differential diagnosis (must exclude):** *Infections/infestations:* Scabies, HIV, tinea
  Inflammatory: Seborrheic derm, irritant/ACD, psoriasis, hypersensitivity drug reaction
  Malignancy: Cutaneous T-cell lymphoma, Langerhans cell histiocytosis
  Immunologic: GVHD, connective tissue disease
- **Dishydrotic eczema** (aka dishydrosis or pompholyx): related to but distinct from AD; affects **palms of hands** > soles of feet; erythematous patches studded with small, skin-colored, pinpoint fluid-filled blisters ("**tapioca ball**"-like); assoc w/ water exposure, may have burning sensation; can co-occur w/ AD or can be assoc w/ exposure to allergen or irritant; tx is removing/avoiding irritants, drying thoroughly, wearing work gloves, and ↑ potency steroids; refer to dermatology if behavioral measures and short trial of ↑ potency steroids insufficient → consideration of systemic tx (*Am J Clin Dermatol* 2010;11:30)

Treatment (*NEJM* 2005;352:2314; *Pediatr Dermatol* 1997;14:321; *JAAD* 2014;70:338)

- **Moisturizers: Mainstay of tx and preventing flares; proper hydration of skin å need for topical steroid by ~50%;** many types available; consider ceramide-containing creams, petrolatum-based ointments (hydrolatum, Aquaphor, petroleum jelly; lotions generally inadequate if significant xerosis)**;** restore epidermal barrier function;

Proper technique: "Soak & seal" use of moisturizers soon after bathing → ↓ skin dryness, ↓ itching, protects from irritants, improves appearance; daily **lukewarm** (not hot) bath 15–20 min, cleanser only where/when necessary (pH-neutral, nonsoap preferred), followed by application of ceramide-containing moisturizer or petrolatum-based emollient

- **Topical corticosteroids: 1st-line** topical tx for mod/severe AD, rec BID dosing (see *"Topical Corticosteroids"*); use lowest effective potency at lowest frequency possible to prevent s/e; ointments preferred (most hydrating); intermittent maintenance use (BIW) can ↓ potential for relapse (*Br J Dermatol* 2002;147:528); s/e: **Irreversible atrophy, striae, hypopigmentation if used improperly**
- **Antipruritics:** Antihistamines PRN day (nonsedating) ± night, esp if significant sleep disruption, allergic dermatographism, or AR (see *"Allergic Rhinitis"*) (*JAAD* 2004;50:391;404)
- ↓ **Staph colonization:** For severe cases, twice-weekly **dilute bleach baths** (0.5 cup of 6% bleach to full bathtub, immerse × 5–10 min, then rinse, pat dry, emollients) plus **intranasal mupirocin** oint 5 consecutive d/mo; oral abx *not* recommended for routine use
- Elimination diets not recommended for AD tx; severe food allergies co-exist in subset of patients, esp children, but no clear causal relationship; consider review with allergist

When to Refer

- Severe or refractory disease (e.g., not controlled after 2–3 mo of topical steroid use), consideration of PO corticosteroids; erythroderma, skin **pain, ? of concomitant contact dermatitis**
- Consideration of topical calcineurin inhibitors (pimecrolimus, tacrolimus), other nonsteroidal treatments (crisaborole) phototherapy, immunomodulators (CsA, MMF, MTX)
- If suspect widespread viral or bacterial superinfection—e.g., eczema herpeticum—dermatologic emergency: Prompt tx w/ abx or antivirals; may need ED/hospitalization

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)
- **Risk factors:** Parkinson disease and other neuro d/o assoc w/ severe/refractory disease, trisomy 21, **HIV/AIDS** (in up to 85% of patients w/ CD4 <400); disease often ↑ w/ stress; certain medications (interferon, lithium, psoralen)

Clinical Manifestations

- **Scalp:** Most commonly affected; ranges from fine scaling (**"dandruff"**) to more inflammatory disease w/ erythema, pruritus
- **Face/neck: Erythematous, greasy,** ± pruritic patch w/ yellowish scale involving forehead, **glabella, eyebrows, lateral nose/nasolabial fold,** retroauricular fossa, external auditory canal (ddx discoid lupus, psoriasis), & other hair-bearing skin of head & neck (e.g., beard)
- **Other:** 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 r/o tinea; consider HIV testing if severe/refractory
- **Differential diagnosis:** Psoriasis, tinea, AD, contact dermatitis, impetigo, rosacea (⊕ telangiectasia), candidiasis, erythrasma, DM, & SLE (malar rash spares nasolabial folds)

Treatment (*Arch Dermatol* 2005;141:47; *Cochrane Database Syst Rev* 2015;5:CD008138)

- 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; may also use ciclopirox 1% shampoo w/similar dosing schedule; 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) & similar efficacy to the antifungals
- **Face/nonscalp areas: 1st-line ketoconazole 2% crm** or foam BID for at least 4 wk (*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
- **When to refer:** if not responding to ketoconazole or OTCs → dermatology

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Allergic Contact Dermatitis (ACD)

Background (*Dermatol Clin* 2012;30:87)

- T-cell–mediated, delayed (type IV) hypersensitivity reaction; time interval to sensitization may be weeks to years; subsequent rechallenge may cause ACD w/in hours to days
- **Epidemiology:** Prevalence ↑ w/ age (highest at age 60–69), ♀ > ♂
- 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)

Class	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, MCI/MI
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 (e.g., band from ring or watch); 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); ask about "wet wipes" esp in persistent anogenital dermatitis
- **Ddx:** ICD, AD, tinea, psoriasis, dyshidrotic eczema, scabies (esp if on hands), stasis dermatitis, & cellulitis
- **Dx:** Refer to Dermatology/Allergy for patch testing, which is the gold standard; Thin-layer Rapid Use Epicutaneous (TRUE) test commonly used & FDA-approved; customized patch testing also available including a wider spectrum of allergens

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

- Avoidance of allergen; 1st-line tx is mid-to-high potency topical steroids (see *"Topical Corticosteroids"*)
- Severe disease: Prednisone taper over ~2 wk (short "dose pack" may → 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

Background (*NEJM* 2012;366:2492; *JAAD* 2008;59:995)

- Case reports 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 d (exanthem); 4–21 d (TEN/SJS) ~21 d (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 reaction w/ eosinophilia and systemic symptoms (DRESS) (*JAAD* 2013;146:1373)	Most common presentation is morbilliform rash (incl face, trunk, UE) 2–6 wk after starting new Rx; facial edema, LAN Systemic sx may include fever (often precedes rash for days–wk), pruritis; organ dysfunction (hepatic > renal, pulm, CV); derm emergency → ED (mortality up to 10%)	**Anticonvulsants** (**carbamazepine,** lamotrigine, phenytoin) **Sulfonamides** (dapsone, sulfasalazine) Allopurinol NSAIDs (celecoxib,

		ibuprofen) Antivirals (Nevirapine) Antidepressants (buproprion, fluoxetine)
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), 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)

URTICARIA

Background (*Allergy* 2009;64:1427; 2011;66:317; *J Allergy Clin Immunol* 2014;133:1270)

- **Urticaria:** Type 1 (IgE-mediated) hypersensitivity reaction, characterized by the appearance of **wheals:** Pruritic, pink/erythematous edematous plaques, can be **arcuate or polycyclic** w/ central clearing, no scale; each **individual** lesion **must resolve in 24 h** → migratory appearance (a circled lesion "disappears")
- **Pathophysiology:** IgE → mast cell degranulation → histamine release → plasma leakage into skin → wheals
- **Classification:** *Acute:* <6 wks' duration of recurrent or continuous lesions; lifetime prevalence 20% (*AFP* 2011;83:1078)

  Chronic: ≥6 wk' duration; lifetime prevalence 1%, peak age 20–40 y, ♀ > ♂; often idiopathic; majority of cases will resolve w/in 1 y
- **Associated syndromes**

  Angioedema: soft-tissue edema of lips, upper airway, eyelids, genitalia; occurs in 40% of pts w/acute urticaria (*NEJM* 2002;346:175); can also occur w/o urticaria (e.g., ACEI s/e)

  Anaphylaxis: Urticaria or angioedema + extraderm manifestations (resp, CV, GI sx) = emergency requiring epinephrine; must be ruled out
- **Epidemiology & risk factors**

  Acute: **50% idiopathic; most commonly 2/2 infection (viral URI, GAS), medications (PCN, ASA, NSAIDs), food** (strawberries, peanuts, shellfish, tomatoes, eggs, milk, in pts w/ latex allergy: Chestnuts, banana, passion fruit, kiwi, avocados)

Evaluation (*Allergy* 2009;64:1417; 2009;64:1427; 2011;66:317; *NEJM* 2002;346:175)

- **History:**

  (1) Obtain hx of lesions (duration of lesions, frequency of attacks, pruritis)

  (2) Assess for s/sx of angioedema or anaphylaxis: wheezing, facial swelling, vomiting

  (3) Evaluate for potential triggers: PMHx, systemic health changes, allergies and ask about:

  Acute*: Infection:* URIs, strep; *Medications:* **PCN**, ASA, NSAIDs

  Food: strawberries, peanuts, shellfish, tomatoes, eggs, milk (in pts w/ latex allergy, chestnuts, banana, passion fruit, kiwi, &

avocado all identified triggers)

Chronic: Idiopathic most common (*J Allergy Clin Immunol* 2012;129:1307);

Autoimmune: SLE, Sjögren's, RA, anti-IgE receptor IgG antibodies, thyroid disease

Food additives: Yeast, azo dyes, benzoic acid, sulfites, nickel

Infections: HBV, HCV, *H. pylori,* parasitosis

Hematologic malignancy (rare) (*Arch Dermatol* 2012;148:103)

Physical: Exercise, cold weather, dermatographism ("skin writing")

- **Exam:** if lesions present, confirm **blanching** (r/o vasculitis)
- **Labs:** *Acute:* none needed unless dictated by hx/PE to r/o a chronic illness; skin testing can help confirm specific allergic cause if suggested by hx

  Chronic: AAAAI "Choosing Wisely" recommends against routine testing for chronic urticaria, given frequently idiopathic; targeted testing as dictated by hx/PE may include CBC w/diff, ESR, thyroid eval, *H. pylori*, HBV/HCV testing
- **Differential diagnosis:** Urticarial vasculitis (**painful**), bullous pemphigoid (esp in elderly; lesions **not** migratory), Sweet 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 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

Type	Interventions
Acute	1st line: Avoid trigger; add nonsedating H_1 antihistamines 2nd line: Consider oral corticosteroids (for 3–5 d, if no response to antihistamines; rebound may occur)
Chronic	"Stepped" approach; start w/ step appropriate for level of severity Step 1: avoid triggers; nonsedating antihistamine Step 2: add one of the following: dose increase of nonsedating antihistamine 4×

standard dose (*Allergy* 2011;66:317; 2002;346:175); second nonsedating antihistamine; H_2 antagonist, leukotriene receptor antagonist, sedating antihistamine QHS

————make derm/allergy referral, if have not already done so————

Step 3: add/increase potent antihistamine (doxepin, hydroxyzine) as tolerated

Step 4: omalizumab SC (*NEJM* 2013;368:2527), CyA, other immunologics/biologics

(*Cochrane Database Syst Rev* 2012;14:CD008596; *J Allergy Clin Immunol* 2014;133:1270)

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

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; effect 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; 80% of patients have mild–moderate disease; *risk factors:* Tob, EtOH, obesity, ⊕ FHx (1st-degree relative in 1/3 of psoriasis pts); also assoc w/ IBD, depression, NAFLD, CAD, SCC, lymphoma; disease severity may be ↑ in pts w/HIV
- **Classification:** Multiple subtypes; plaque most common (80–90%), then guttate

Psoriasis Subtype Classification (*Ann Intern Med* 2011;155:ITC2-1)

Subtype	Distribution & Morphology	Notes

Plaque	Symmetric, extensor surfaces (elbows, knees), scalp, penis, umbilicus, intergluteal cleft	Most common *Ddx:* AD, tinea, cutaneous lupus, mycosis fungoides
Guttate	Droplet-sized lesions on extremities & trunk, spares palms/soles	Abrupt onset, often younger pts after GAS infection (eval for s/sx) *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	*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 classification:** 5 patterns of joint involvement, individual pt's pattern can change over time (*NEJM* 2017; 376:957; *J Rheumatol* 2003;30:1022); 30–50% of pts also have **enthesitis**, most commonly Achilles or plantar fascia (*Arthritis Rheumatol* 2016;68:312)
  - **Asymmetric oligoarthritis** (usually hands/wrists, esp DIPs) most common
  - **Other variants:** Symmetric polyarthritis (RA-like), distal arthritis (DIPs only), sacroiliitis & spondylitis, or "arthritis mutilans" (severe, rapid joint destruction, & deformity)

Evaluation (*JAAD* 2008;58:851;1031; *JAAD* 2009;60:643; *Lancet* 2015;386:983)

- **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, antimalarials, ACEIs); provocation of lesions by skin **trauma (scratching, piercing, tattoos, sunburn:** Koebner phenomenon) or injury (sunburn, chemical irritants)
  - *Complications:* up to 30% of pts w/ mod–severe disease develop **psoriatic arthritis (**see below); up to 60% have **depression**

- **Exam:** Full cutaneous exam & joint exam (focusing on hands)
  - **Skin:** Subtype-specific morphology & distribution noted above; lesions are typically discrete erythematous plaques w/ adherent silvery scale; *Distribution:* **Scalp** commonly involved (Ddx: seb derm, tinea); 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
- **Studies:** Psoriasis dx is clinical; psoriatic arthritis dx supported by imaging and should obtain radiograph of hands if acro-osteolysis suspected, "pencil in cup deformity" classic); no particular labs helpful; consider labs to r/o RA if on arthritis on Ddx

Treatment (*JAAD* 2009;60:643; 2010;62:114; 2009;61:451; *JAAD* 2009;60(4):643–59)

- Initial management based on affected % of BSA (for BSA definition, see *"Burns"*)
- **Mild, limited disease (<3% BSA): Topical agents (below);** note choice of vehicle (ointment, crm, gel, etc) very important to successful delivery of medication, should be tailored to individual pt; occlusion of any topical agent (e.g., saran wrap) ↑↑ potency; **caution re: overuse,** can → permanent atrophy/hypopigmentation; see *"Topical Corticosteroids"* for details of dosing & s/e

Topical Tx of Psoriasis

Class	Example/Initial Dosing	Notes/Safety Monitoring
Corticosteroids	See *"Topical Corticosteroids"* Class I/II for torso or extremities; Class VI/VII for face, axilla,	Limit high dose to 4 wk of continuous use; gradually ↓ use/potency to class IV for torso/extremities, then to PRN as tolerated; monitor for s/e; limit use as monotherapy when possible

	groin BID	
Vitamin D analogs	Calcipotriene 0.005% oint, soln, crm BID Calcitriol 3 µg/g oint BID	Transient irritation; inactivated by UVA; <100 g/wk to avoid ↑ serum Ca; photosensitivity
Retinoids	Tazarotene 0.05% crm, gel QHS	Irritation (gel > crm), photosensitivity Pregnancy category X Best used in combination w/ topical steroids
Coal tar	Variety of preparations; apply QD; e.g., 5% liquor carbonis detergens	May stain skin & clothing; unpleasant odor; inexpensive
Misc	Topical tacrolimus/pimecrolimus; emollients; salicylic acid; anthralin	

(*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): → Derm for consideration of phototherapy, systemic retinoids or immunomodulators; rheumatology for evaluation of joint disease; **avoid systemic corticosteroids; risk of rebound, pustular, or erythrodermic flare that can → need for hospitalization**
- **When to refer: Dx uncertain—cutaneous T-cell lymphoma and other more severe diseases can mimic psoriasis;** refractory, or moderate–severe disease; inability to wean high-potency corticosteroids; consideration of systemic tx, phototherapy → Dermatology; erythrodermic or pustular subtypes → Dermatology (or ED if severe)
- **Pt information:** National Psoriasis Foundation, www.psoriasis.org/about-psoriasis

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 wk, <1%) → **telogen** (resting

phase, ~2–3 mo, 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**
- Categorized as **nonscarring alopecia:** Follicular openings visible on exam vs. **scarring alopecia:** Follicular ostia no longer visible (tissue architecture destroyed)

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:** Refer to dermatology to ensure proper technique and accessioning by a dermatopathologist—4-mm punch bx is standard (*J Cutan Pathol* 2008;35:82)

Etiologies (*NEJM* 2007;357:1620)

- **Male androgenetic alopecia: Most common;** occurs after puberty
  - *Causes:* Genetic, hormonal (DHT); 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
  - *Distribution:* Frontotemporal & vertex of head
  - *Tx:* Must be used indefinitely or progression will resume; minoxidil 5% soln BID or 5% foam QD (s/e: facial hypertrichosis, irritant dermatitis, possible ↑ shedding in 1st 2–8 wk); finasteride 1 mg PO QD in men (s/e: sexual dysfunction) (*JAAD* 2012;67:379); emerging data on dutasteride; hair transplant; consideration of red light lasers, combs, devices
- **Female pattern hair loss (FPHL):** typically 40s–60s, insidious

onset

Causes: Genetic, hormonal (postmenopausal, PCOS) etiologies
S/sx: Widened part & "thinner ponytail"; affected areas similar to ♂: progressive **follicular miniaturization** & shortening of anagen phase
*Distribution***:** Crown/**widened part;** frontal hairline preserved; "Christmas tree/Ludwig pattern"
Tx: **Consider derm referral** to r/o other etiologies and mimickers that can → scarring; minoxidil 2% soln or 5% foam (s/e listed above); spironolactone; hair transplant; consideration of red light lasers, combs, devices

- **Telogen effluvium:** Premature shift to telogen → diffuse shedding; starts 2–4 mo after trigger (*J Invest Dermatol* 2003;121:985)

  Causes: Stress, wt loss, infection, fever, hypothyroidism, **Fe deficiency, meds** (minoxidil [1st 2–8 wk]; heparin, coumadin, ramipril, βB, lithium, IFN-α, TCAs, oral retinoids, terbinafine, VPA, OCPs, postpartum [2–5 mo 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)
- **Traction alopecia:** Nonscarring hair loss 2/2 persistent tension applied to hair strands; seen w/ specific hair styles (e.g., tight braids); may affect 1% of US persons of African ancestry (*Arch Dermatol* 2006;142:377) often frontotemporal distribution; *Tx:* Reduce tension on hairs via change in hair style or ↓ pulling (softer hair ties, etc); derm referral for severe/refractory disease
- **Anagen effluvium** (*NEJM* 2007;357:1620; *JAAD* 2011;64:604); hair matrix arrest → tapered fractures of the hair shaft; starts 7–14 d 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; rarely lesions are inflammatory (w/ erythema)

Tx: **Refer to dermatology;** intralesional corticosteroids (s/e: permanent dermal atrophy); topical immunotherapy; JAK inhibitor tofacitinib promising new tx (*JAAD* 2017;76:22)

Pt information: www.naaf.org

- **Scarring (cicatricial) alopecia:** *Causes:* **Multiple etiologies; may be primary process** (inflammatory follicular destruction; e.g., discoid lupus erythematosus, lichen planopilaris, dissecting cellulitis, folliculitis decalvans) **or secondary process** (indiscriminate follicular damage from another disease process; e.g., burns, sarcoid, malignancy); also characterized by type of cellular infiltrate (*JAAD* 2005;53:1); *S/sx:* **No follicular ostia; tufted hairs** ("doll's hairs"); refer to derm if suspected
- **Other: Trichotillomania:** Often childhood onset, impulse-control d/o assoc w/ psychiatric disease (OCD); *S/sx:* Bizarre pattern of w/ incomplete clearing areas *Tx:* behavioral/psychiatric (*AFP* 2003;68:93); **Tinea capitis:** *See "Tinea";* **Hair shaft disorders:** Acquired & congenital etiologies

When to Refer

- **Scarring alopecia or unclear etiology or if biopsy needed,** consider for alopecia areata/androgenetic alopecia especially female pattern alopecia

WOUND CARE

Background

- **Definitions:** *Erosion:* Epidermal injury; heals w/o scar;

Ulcer: dermal injury; scarring w/reduced tensile strength
Primary intention: Wound edges are surgically approximated
Secondary intention: Wound left to heal w/o approximation

- **Stages of wound healing** (*JAAD* 2008;58:185; *Adv Wound Care* 2016;5:32)
  Inflammatory phase: Platelets → PMNs → macrophages and fibroblasts; **chronic wounds often stalled here;** can mimic infection (red, warm)
  Proliferative phase: 1st week, angiogenesis, collagen production
  Remodeling phase: 2nd week; contraction via myofibroblasts; at 3 wk, at 20% of final tensile strength
- Multiple factors adversely affect wound healing, including advanced **age**, malnutrition, medications (glucocorticoids, chemotherapy), inadequate arterial perfusion (PAD, Raynaud's), **smoking,** immunosuppression, **diabetes**, hepatic or renal disease, poor self-care, venous insufficiency, allergic contact dermatitis (*JAAD* 2008;58:185)

Evaluation

- **History:** Attempt to determine etiology of specific lesion (trauma), precipitating/exacerbating factors (diabetes, PAD, venous insufficiency, neuropathy; see above), prior wounds and their tx responses; **pathergy** (worsening w/ trauma), prior tx for this wound
- **Physical exam:** Vitals (systemic infection); for extremity wounds, do full extremity exam (color, **edema**, symmetry w/other limb, **warmth, distal pulses,** capillary refill, sensation, tenderness, LAN)
  Wound assessment: Consider the "ABCDE"s of each wound; being able to concisely describe complex wounds invaluable for future visits to determine progress; consider including photograph in medical record (*BMJ* 2006;332:285)
  Area: wound size, depth (full vs. partial thickness) & location on body
  Base: viable: granulation/beefy red vs. nonviable: fibrinous (gray-yellow), necrotic (black), % viable/nonviable tissue
  Circumference: Describe periwound skin—erythematous, warm, dusky, black, callus
  Drainage: Serous, sanguinous, purulent, malodorous, minimal/moderate/copious
  Edge: Smooth, punched out, undermining, tunneling, rolled

borders (chronic wound)

- **Labs:** Routine labs not recommended; for wounds w/ delayed healing, investigation for etiologies which can delay wound healing above; all wounds colonized so routine culture unhelpful; (see "*Skin and Soft-Tissue Infections*")

Management (*BMJ* 2006;332:777; *Adv Wound Care* 2016;5:32; *JAAD* 2008;58:185)

- Initial wound management: *Irrigation:* Clean w/ normal saline, high pressure if significant contamination; *Tetanus vaccine:* PRN (see *"Immunizations"*)

General Approach to Chronic/Complex Wounds	
Keep wound **moist**, but not wet **Debride** nonviable tissue (except for arterial ulcers) Gently **Fill** wound (primary dressing) as needed **Cover** wound (secondary dressing)	Manage modifiable factors which may delay healing

- **Moisture:** If wound dry, petrolatum generally preferred over topical abx— ↓ infection rate & ↓ contact allergy; topical abx preferred in trauma, burns (*Ann Emerg Med* 2013;61:86)
- **Debridement:** Necrotic tissue on wound base impairs healing and should be removed **if adequate arterial flow (confirm pulses, do NOT debride wounds in setting if concern for arterial insufficiency at site);** many different mechanisms available; sharp mechanical debridement (scalpel; if sensate, premedicate with topical lidocaine or prilocaine 2.5% covered by plastic wrap x 30 min prior to debridement), enzymatic (collagenase), osmotic (Medihoney), autolytic (hydrogels such as Aquaform)
- "**Fill" wound:** Do not pack, gently fill; fill/partially fill if there is a potential space/depth left by the wound; can use sterile gauze or petrolatum-impregnated gauze (change gauze daily), calcium alginate (good for ↑ exudate), Medihoney, Aquacel; silver dressings (Aquacel Ag) can ↓ bacterial load in colonized/infected wounds; avoid iodine as can affect thyroid function and → tissue damage in acute wounds (*J Hosp Infection* 2010;76:191); if wound stable, alginate dressings can stay in for up to 1 wk

- **Cover wound:** This layer should be determined by need for managing exudate; consider skin protectant (e.g., Cavilon) to protect periwound skin and help bandages adhere

Commonly Used Wound Dressings (***BMJ*** **2006;332:777;** ***JAAD*** **2013;68:e117)**

Class/Example	Type of Wound	Function (***Moisture, Debride, Fill, Cover)***	Notes
Film (Tegaderm)	Superficial, dry-min exudate	C	Caution w/ fragile skin (e.g., elderly) Flexible; good for joints
Telfa	Dry-min exudate	M, C	
Hydrocolloids (DuoDERM)	Dry-min exudate	Sheet: M, D, C Gel: M, D, F	↑ACD risk, "gel and smell"—produces malodorous d/c which can mimic infection Can be worn for several days
Hydrogels (Aquaform)	Low-med exudate, slough/escar	Sheet: M, D (autolytic), F, C Gel: M, D, F	Flat wounds, cavities, and sinuses May be left in place several days Can soften eschar for mechanical debridement; caution re: maceration of peri-wound skin
Alginates	High exudate	M, D (autolytic), F	May be left in place for several days Caution re: maceration of periwound skin
Hydrofibers Aquacel)	High exudate	M, D (autolytic), F	Highly absorbent, nonadherent
Foams (Mepilex)	Variable exudate (depends on foam)	M, F, ±C	Offer cushioning for wound May be left in place for up to 7 d on stable wounds

- **Venous stasis ulcers** (see *"Lower Extremity Edema"*); any pt w/ possible PAD should have ABI/TBI eval prior to initiating pressure wrap to avoid inducing ischemia in vulnerable limb

When to Refer

- Failure of wound healing, complex wound mgmt, consideration for topical growth factors, vacuum-assisted closure devices

Burns

- **Background:** 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 *NEJM* 2009;360:893; ameriburn.org)
- **General approach:**
  (1) **Evaluate mechanism of burn**
  (2) **Determine burn size, location, and depth**
  (3) **Determine if emergency treatment warranted (high-risk wounds)**
  (4) **If appropriate for outpatient management, provide pain control and wound care**
  (5) **Reassess frequently to ensure wound healing**
- **Burn mechanism:** Can be thermal, electrical (often deeper than suggested by cutaneous findings, can → compartment syndrome), chemical (acids, alkali, solvents), radiation (fluoroscopy or XRT)
  Sunburn: 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, some antimalarials
- **Burn size:** Calculated by body surface area (BSA): Reference is one palm = 1% BSA; less accurate in obese pts
- **Burn location: high-risk locations include face, neck (assess airway regardless of burn size),** hands, feet, genitals, or over major joints (risk contractures)
- **Burn depth:** determines severity & prognosis (*NEJM* 1996;335:1581)
  Superficial (epidermis only): erythema, dry, painful; e.g., sunburn; heals w/o scarring
  Partial thickness (epidermis & superficial-full dermis): bullae, erythema, intense pain, ↓sensation → heals w/significant scarring
  Full thickness (epidermis, dermis, and below): Whitish, charred or translucent, no pinprick sensation in burned area

- **High-risk wounds (need referral to burn center): concomitant trauma (e.g., fracture), electrical or chemical burn, partial thickness >10% BSA, full-thickness burns, high-risk location (see above) or concern for inhalation injury;** *If in doubt, call a burn center for phone triage;* list at www.ameriburn.org
- **Outpatient management:**
  - **Superficial burn:** Analgesia as needed (NSAIDs); soothing gel/ointment (aloe vera)
  - **Partial thickness:** Analagesia as needed; **tetanus** immunization if not current; ensure wound clean (sterile water irrigation); larger blisters/those over joints may need debridement, but should also be considering referral if considering debridement; cover wound with antibiotic ointment or silver sulfadiazine, then cover by occlusive dressing; larger wounds may require more dressing, such as Aquacel Ag (silver- impregnated absorptive dressing) (*J Burn Care Res* 2009;30:380)
  - **Larger partial-thickness or full-thickness wounds:** Referral for early surgical management

TOPICAL CORTICOSTEROIDS

Background (*JAAD* 2009;60:643)

- Topical corticosteroids have anti-inflammatory, antimitotic, vasconstrictive and immunosuppressive properties that make them effective in treating a variety of dermatologic processes, but improper use can → permanent s/e
- **Mechanism of action:** pass through cell membrane to react with receptor proteins → into nucleus, alter transcription of genes that are involved in inflammatory pathways (e.g., ↓ phospholipase A2 release)
- Class/potency assoc w/ drug's ability to produce vasoconstriction & determined by:

  (1) Drug structure (individual molecule)

  (2) Drug concentration (for individual drug; e.g., hydrocortisone 2.5% more potent than hydrocortisone 1%, but *not* more potent

than desonide 0.05%)
(3) Vehicle of application (determines absorption)

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; table below includes only generics
  (5) Counsel pts on appropriate use: amount, duration, & s/e (see below)

Vehicle (www.aad.org)

- Vehicle 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 agents
- 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 w/ thick plaques/scale); 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 thick skin (e.g., acral skin, lichenified lesions) or lesions refractory to lower potency steroids; avoid use in intertriginous areas (e.g., axilla, groin)

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%** Hydrocortisone 1% (OTC)	C, L

Vehicle and Potency by Site

Site	Suggested Steroid Class
Scalp	Consider starting w/ Class VI → 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/Groin	Class V–VII

(Adapted from Schalock PC (ed.). *Primary Care Dermatology*. 2010)
C, cream; F, foam; G, gel; L, lotion; O, ointment; So, solution

Application (*AFP* 2009;79:135; www.aad.org; *JAAD* 2009;60:643)

- **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 entire avg adult → 30 g
  1 wk's worth of BID application: covering entire avg adult → 400 g
  1 mo'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 use occlusive dressing on acral surfaces to ↑↑ potency, but → ↑ risk of s/e

Counseling (*JAAD* 2009;60(4):643–59)

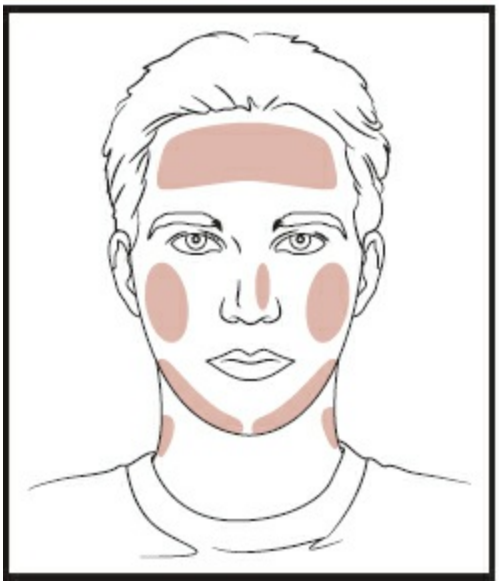
- **Duration:** ≤4 wk of consecutive use advised, stop tx when condition resolves (taper by ↓ freq and/or potency q2wk to avoid rebound); ≤3 wk of consecutive use for face, intertriginous areas, **or** class I (ultra-high potency): If recurrent issue, use for 1–2 wk intervals to avoid s/e, consider derm referral
- **Side effects:** ↑ **Potency & duration** → ↑ **risk;** should be discussed w/ all pts; write on all higher-potency Rx: "Not for face, armpit, or groin"; **many s/e are permanent** include **atrophy** (striae, telangiectasias, ↑ fragility); **infection** (can worsen/mask); **hypopigmentation; systemic s/e** (if ↑ potency/duration/BSA; weekly clobetasol or halobetasol dosing should be ≤50 g; **glaucoma/cataracts** in chronic periocular use; flare rosacea or perioral dermatitis

When to Refer

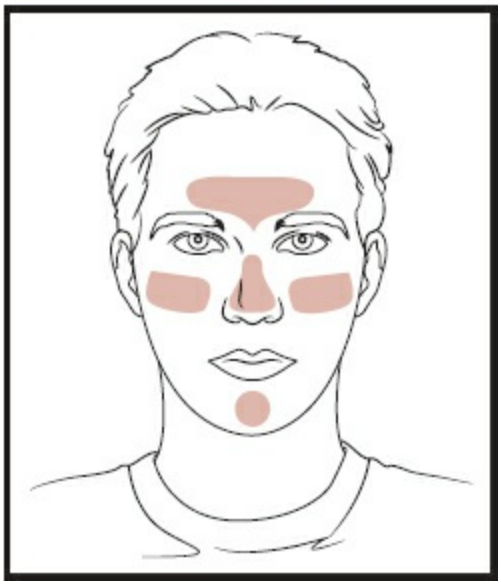
- Patients who are not responsive despite above recommendations → **refer to dermatology,** regardless of etiology; consider referral in pregnant/breastfeeding pts

CLASSICAL DISTRIBUTION OF COMMON SKIN DISORDERS

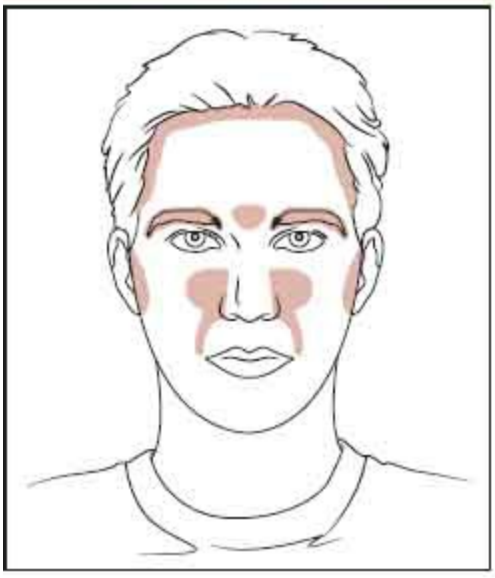
Acne



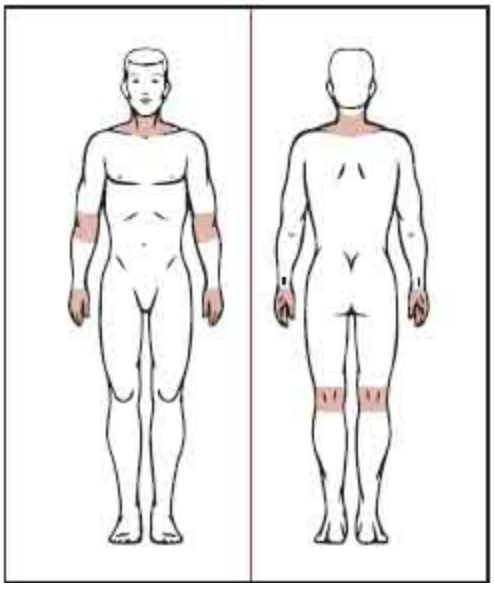
Rosacea



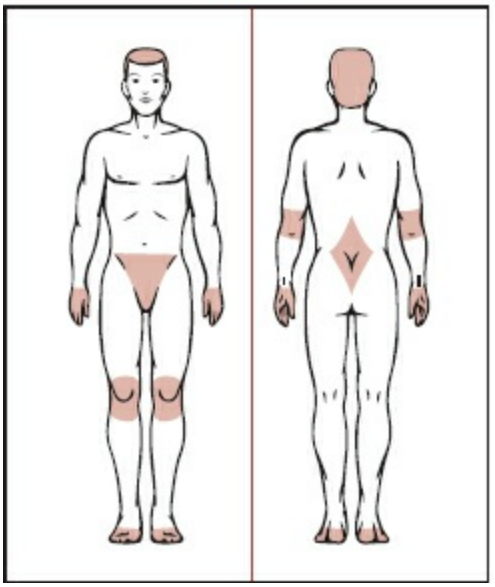
Seborrheic Dermatitis



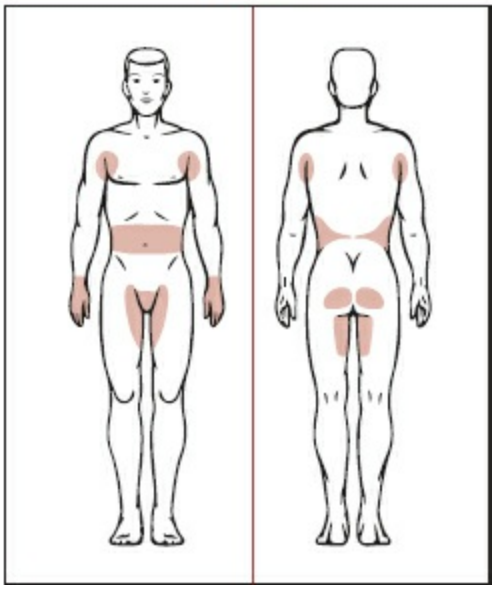
Atopic Dermatitis



Psoriasis



Scabies



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 9.3% of all US adults, 26% of people >65 y; 28% of people are undiagnosed; 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 (*JAMA* 2014;131:1778)
- **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, lower-limb amputations, & blindness**
- **Glycemic Control:** Despite treatable nature of DM, 23% of US diabetes pts have A1c >8% and 13% have A1c >9; many disparities in DM control and complications (cdc.gov/diabetes)
- **General approach:** Tx is multifaceted; requires focus on glycemic control to prevent complications, screening for/management of complications, *and* ↓ CV risk

Classification (*Diabetes Care* 2017;40:s1; *Lancet* 2009;373:1773)

Selected Glycemic Disorders (*Diabetes Care* 2013;36:S67)	
Disorder	**Notes**
DM2 (90–95%)	Assoc w/ *insulin resistance* in target organs & *relative insulin deficiency;* tx targets resistance and/or deficiency
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, or extreme hyperglycemia despite tx w/ oral agents

	shortly after dx; ⊕ pancreatic autoantibodies (GAD, ICA, IA2, or insulin); ~30% present with DKA
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%, or OGTT 2 h BG 140–199 mg/dL after 75 g glucose challenge; **5 y risk of progression to DM2 ~15–30%** (cdc.gov/diabetes; *Diabetes Care* 2004;27:S47)
Other syndromes	**Ketosis-prone** "Flatbush" **DM:** Characterized by severe, **reversible** β-cell dysfunction: Demographics ≈ DM2 (obese, racial/ethnic minorities) but p/w ⊕DKA; with aggressive control, some β-cell function restored & insulin/med needs ↓↓ (*Diabetes Care* 2006;29:2755) **MODY** (Mature Onset DM of the Young) = **monogenic diabetes;** rare, presents in young, generally normal BMI, ⊕ FHx *autosomal dominant inheritance* (*Diabetes Care* 2011;34:1878)
Secondary DM	Etiologies incl hemochromatosis, CF-related DM, pancreatic CA, surgical resection, Cushing's, chronic pancreatitis
Medication-induced	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, CVD, HLD, hx GDM; hx prediabetes, ↑ 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 min/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 (see *"Obesity"*)

Diagnosis (*Diabetes Care* 2017;40:s1; *Annals Int Med* 2015;163:861)

- **Hemoglobin A1c >6.5% (preferred),** random glucose >200 mg/dL + symptoms of hyperglycemia, FBG ≥126 mg/dL, or OGTT 2 h-BG >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:** (*see "Disease Screening") USPSTF:* 40–70 y with BMI ≥25; *ADA:* All adults >45 and if ≤45 y, screen if BMI ≥25 *and* add'l risk factors (76% of US adults meet ADA criteria (*JGIM* 2015;30:612)); screen q3y, shorter interval if prior values approach DM or prediabetes threshold

Evaluation (*Diabetes Care* 2017;40:s1)

- **General approach:** For initial eval of pts w/ known DM, hx key to assessing DM-related behaviors, disease severity and risk for/presence of complications; will guide tx approach
- **History:**

  Diabetes history: Age at onset (disease duration), medications used, prior glycemic control, known complications
  Behaviors: Physical activity, dietary habits (incl juice/sweetened beverages, meal patterns)
  Social context: Financial, housing
  Medications: Adherence, side effects
  Hyperglycemia s/sx: Polyuria, polydipsia, vision changes
- **Home glucose readings:** All pts on insulin; ask pt to bring glucometer to every visit; examine for highs/lows/patterns, if lows assess hypoglycemia awareness (see "Hypoglycemia"); management below
- **Complications risk/presence:** *CV:* Known CAD, angina, claudication, CV risk factors/comorbidities (HTN, stroke, smoking)

  Ophtho: Vision changes/decreased visual acuity
  Renal: CKD risk factors (HTN), review prior urine alb/Cr ratios, Cr
  Peripheral neuropathy: Often starts w/ feet burning at night, (see *"Peripheral Neuropathy"*)

Autonomic neuropathy: ED, orthostatic HoTN, gastroparesis – if ⊕, strongly assoc w/ CAD

- **Exam:** BMI, BP; *Derm:* Acanthosis nigricans, *CV:* distal pulses, carotid bruits, *Foot:* PAD, callus, deformity, tinea, *Neuro:* Monofilament, vibratory, cold/pinprick testing, ankle DTRs
- **Hemoglobin A1c:** (% of Hgb molecules which are glycosylated) 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, significant blood loss/anemia, CKD/ESRD; if in doubt correlate w/ glucometer readings

  Frequency: Repeat q3mo if above target A1c, q6mo if at goal
  Interpretation: **HbA1c 7% ≈ mean glucose 154 mg/dL; for every 1% HbA1c ↑ mean glucose ↑ ~30 mg/dL;** e.g., HbA1c 8% ≈ 180 mg/dL
- **Other labs:** Yearly urine microalb/Cr ratio and creatinine; baseline & q5y lipids
- **Cardiac testing:** Baseline ECG (no further cardiac testing warranted if asx & nl ECG, although may consider if starting vigorous exercise regimen; see *"CP & Noninvasive Testing"*)

Management: Behavioral (*NEJM* 2012;366:1319 & 2013;368:1613; *Ann Intern Med* 2011;154:554)

- **Behavioral tx:** Improves glycemic control (which ↓ microvascular complications) and ↓ CV risk; recommended for all patients
- **Diet:** Low-carbohydrate or Mediterranean recommended; "Plate method" = ½ nonstarchy vegetables, ¼ lean meat/protein, ¼ whole grains; heart-healthy diet low in saturated/trans fats; monitoring & awareness of CHO intake, esp in items of low nutritional value; reframe soda as (reframe as "liquid candy") see sugarstacks.com for visuals)
- **Weight loss:** 5–10% body wt loss good initial target in the obese; see *"Obesity"*
- **Exercise:** 36% of pts with DM are physically inactive (cdc.gov/diabetes); exercise improves glycemic control independent of wt loss, ↓ CV risk factors; goal is 30 min, 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)

Management: Complications

- **Cardiovascular risk:** Pts w/ DM have 2–4× ↑ risk of MI, stroke, & death compared to otherwise similar pts 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)
  - **HLD:** 43% of pts not at target LDL; goal LDL <100, HDL 40, TG <150; however, all pts >40 or w/ ASCVD risk factors (LDL >100, HTN, ⊕ tob, ⊕ FHx CVD, CKD incl proteinuria) should be on mod-high intensity statin, consider ezetimibe + mod-intensity if cannot tolerate high-dose statin
  - **Hypertension:** 28–48% of pts not at target BP; goal <140/90 mmHg recommended by ACCORD trial and JNC8 (*NEJM* 2010;362:1575; *JAMA* 2014;311:515); consider ↓ systolic target if high-risk CVD or younger pts/on individual basis (*Diabetes Care* 2017;40:S75); BP control more important than Rx choice
  - **Smoking:** 22% of pts w/ DM smoke; accounts for ~1/2 of their CV risk; see "*Tobacco*"

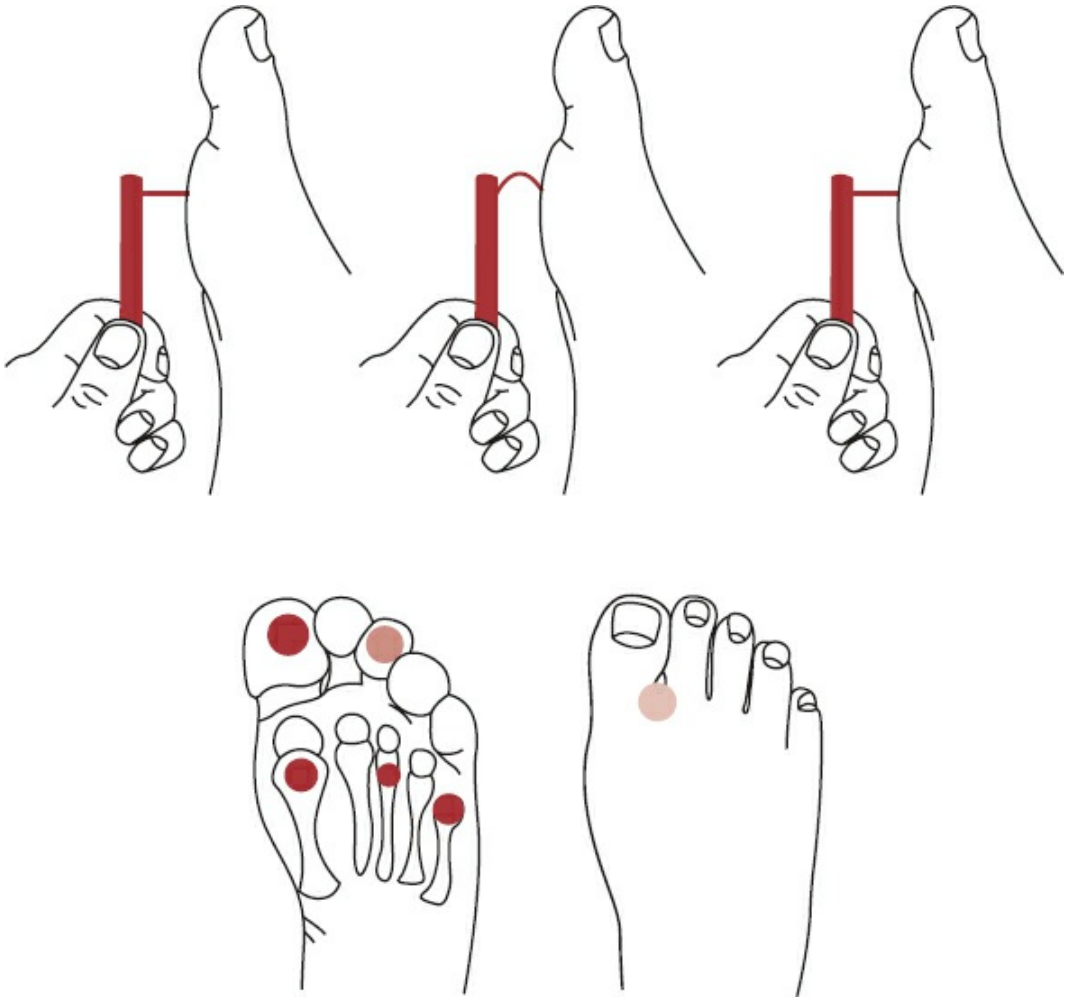
Pharmacologic Management of CV Risk Factors in Diabetes	
Rx	**Notes/Indications**
ASA 81 mg	All pts w/ known ASCVD; consider for 1° prevention if ≥50 y with 1 other ASCVD risk factor unless ↑ bleeding risk
Mod-high intensity statin	All pts w/DM ≥40 y, regardless of lipid levels Pts <40 w/ ASCVD risk factors; see *"Lipids"* 10–20 mg atorvastatin = moderate, 40–80 mg atorvastatin = high
HTN Rx	First-line agents the same (ACEI/ARB, CCB, thiazide) **unless** evidence of CKD (by ↓Cr *or* ⊕ microalbuminuria) → ACEI/ARB 1st-line; proven to ↓ progression of CKD

- **Immunizations:** PPSV23, annual influenza, hep B series (recommended for pts <60 y, consider in pts ≥60 y; see *"Immunizations"*)
- **Complications Screening: Start at time of DM2 dx, 5 y after dx for DM1**

Complications Screening/Management	
Screening should be performed annually unless otherwise noted Risk of all below complications ↓ w/ glycemic control	
Retinopathy	Retinal exam; may space to q2y if multiple nl exams Retinal photography (interpreted by ophthalmologist) appropriate alternative to in-person visit if no abnormalities on comprehensive ophtho exam
Nephropathy	Urine alb/cr ratio & GFR; ACEI/ARB for all pts with microalbuminuria Treatment of HTN (↑↑ risk of CKD progression)
Peripheral neuropathy	History: ("Any numbness or burning/tingling in your feet at night?") Exam: Monofilament, vibratory, and pinprick/cold sensory testing; for pinprick, apply disposable pin proximal to hallux proximal nail fold, using just enough pressure to deform skin Pregabalin or duloxetine 1st-line for sx; see *"Peripheral Neuropathy"*
Foot ulcers, amputations	Foot exam (above); Rx tinea pedis to ↓DFI risk Counsel all pts re: appropriate footwear (e.g., avoid open-toed shoes) Pts who smoke, have hx LE complications, ↓ sensation, deformity or PAD → podiatry referral; Rx Diabetic footwear if ↑ risk

Monofilament Testing

- **Autonomic neuropathy:** Screen for s/sx in all pts w/ microvascular neuropathic complications



Instruct pt: “I’m going to test the feeling in your feet.” Demonstrate monofilament on your finger. “Close your eyes, and let me know when you feel this touching your foot.”
Use 10 g monofilament; place perpendicular to skin on areas indicated in diagram (avoid callus) and apply pressure until monofilament buckles; hold in place for 1 sec & release.

(From Boulton AJM, Armstrong DG, Albert SF, et al. Comprehensive foot examination and risk assessment. *Diabetes Care* 2008;31(8):1679–1685. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.)

Management: Glycemic

- **Glycemic control:** Primary purpose is to ↓ microvascular complications; intensive control not shown to ↓ risk of CV disease or mortality in DM2 (ACCORD *NEJM* 2011;364:818)
- **Target HbA1c:** Generally <*7%;* however, should individualize; consider less intensive goals (e.g., HbA1c <8, FBG 100–150 mg/dL)

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**; may adjust lower end of target to 70–90 depending on individual pt's risk of hypoglycemia or glycemic goal)
- **Target postprandial blood glucose: <180 mg/dL**, check 1–2 h after beginning of meal (*Diabetes Care* 2013;36:S11);
- **Home glucose monitoring:** Indicated for pts on insulin or at risk of hypoglycemia; **have pts bring glucometer or glucose log to each visit**
  - *Noninsulin regimens:* Not shown to improve outcomes (*BMJ* 2008;336:1174; *JAMA* 2017;177:920); can be used PRN to monitor for hypoglycemia (if on hypoglycemic PO regimen) or illustrate effect of various behaviors/foods on blood glucose
  - *Single-dose insulin:* AM fasting & after biggest meal of the day and/or before bed
  - *Multiple-dose insulin:* Prior to meals/snacks, at bedtime, prior to exercise or critical tasks, and if suspect hypoglycemia; ± postprandial
- **Monitoring supplies:** Rx for (1) glucometer, (2) test strips, & (3) lancets

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Diabetes Medications

- **Metformin:** Biguanide (↑ insulin Se & ↓ gluconeogenesis*)*; **1st-line Rx for DM2** → 1–2% avg ↓ in HbA1c, wt loss common, hypoglycemia rare, ↓CVD events;
  - *Dosing:* start 500 mg QD–BID, uptitrate to 1 g BID, take w/ meals (↑ absorption)
  - *S/e:* GI upset common, minimize by starting at low dose, taking with food, & titrate ↑; lactic acidosis (type B, very rare (*Cochrane Data System Rev* 2010;20:CD002967), B12 deficiency; caution in CHF, ESLD; **max dose 1000 mg daily if CrCl <45** mL/min/1.73 m^2

Contraindications: CrCl <30 mL/min/1.73 m^2; hold in AKI

Other Pharmacologic Agents (each ↓ HbA1c by 0.5–1.5%) (*NEJM* 2012;366(14):1319)		
Class (e.g.)	**Mechanism**	**Notes**
Sulfonylureas (glipizide—shorter t½, cleared by liver; also: Glyburide, glimepiride)	↑ β cell sensitivity to glucose, ↑ insulin release	High failure rate over time due to ↓ β cell function; long t½, 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 receptor agonists (exenatide, liraglutide)	⊕ Insulin secretion & delays gastric emptying	Injectable, expensive Assoc w/ wt loss, hypoglycemia rare; can → N/V, pancreatitis; adjust dose in CKD; ↑ C-cell hyperplasia/medullary thyroid tumors in animals Liraglutide assoc w/ ↓CVD events in pts w/ CVD (*NEJM* 2016;375:311;322)
Thiazolidinediones, (TZDs) (pioglitazone)	↑ Insulin sensitivity	Assoc w/ wt gain, CHF exacerbation, ↑ fractures, hepatotoxicity; monitor LFTs
α-Glucosidase inhibitor (acarbose)	Inhibits GI tract CHO metabolism	GI intolerance common
Meglitinides (repaglinide, nateglinide)	↑ β cell insulin secretion	Like sulfonylureas but shorter duration of action; can → wt gain & hypoglycemia Expensive
DPP-4 inhibitor (sitagliptin)	Blocks inactivation of incretins, e.g., GLP-1	Dose adjustment in CKD 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
SGLT2 inhibitor (empagliflozin)	Blocks renal glucose reabsorption → ↑glucosuria	Expensive; assoc w/ wt loss, ↓BP, ↓CVD events in pts with CVD (*NEJM* 2015;373:2117),↑GU infections, polyuria, vol depletion, normoglycemic DKA

Insulin

- **Indications:** Pts with DM2 with HbA1c >10% or on 3 meds with HbA1c >goal on 2 occasions, 3 mos apart, performing self-testing with a glucometer
- **Advantages:** Less expensive than 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 (Adapted from *JAMA* 2003;289:2254)

Class	Name (Brand)	Onset	Peak	Duration
Long-Acting	**Glargine** (Lantus) **Detemir** (Levemir)	~2 h	Minimal	20–24 h
Rapid-Acting	**Aspart** (NovoL**og**) **Lispro** (Huma**log**)	5–15 min	30–90 min	5 h
Short-Acting	**Regular** (Humulin **R,** Novolin **R**)	30–60 min	2–3 h	5–8 h
Intermediate-Acting	**NPH** (Humulin **N,** Novolin **N**)	2–4 h	4–10 h	10–16 h

Insulin Troubleshooting

Problem	Strategy

am glucose ↑↑	↑ Glargine or evening NPH; consider ✓ 2 am BG to r/o overnight hypoglycemia (can → rebound hyperglycemia)
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; ↑ risk needle stick if injection given by another person; disposable pens come w/ single cartridge but still need to change needle, more $$; 1 pen cartridge = 300 units, 1 box = 5 pens = 1500 units; *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 *Sample Rx:* Glargine (Lantus) 3 vials for 1 mo/8 vials for 3 mos *Syringes:* 0.5 cc size for <60 units, 1 cc for doses >60 units, all w/ 31 g needle; Rx: 1 box	

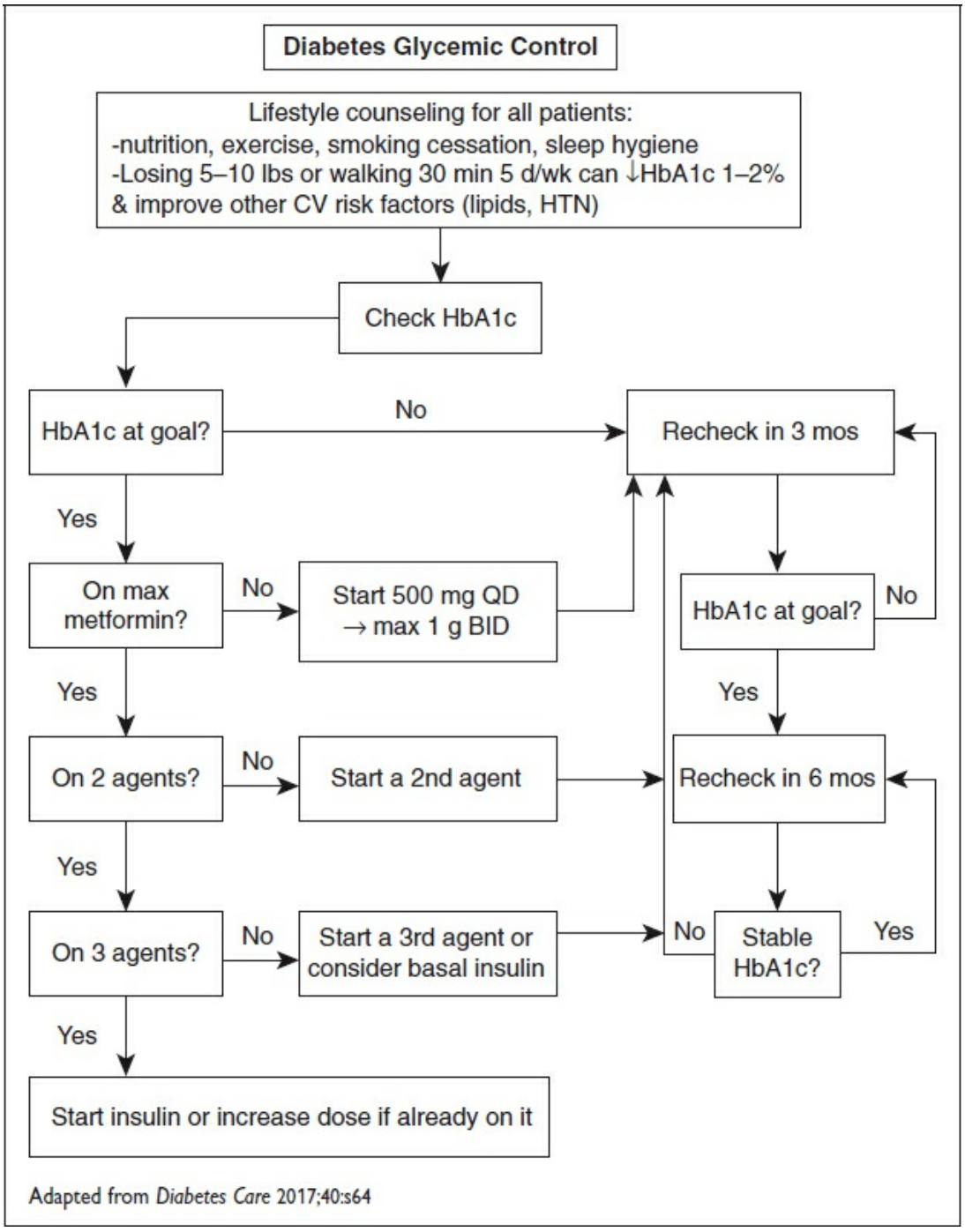

Figure 4-1. Hyperglycemia management in type 2 diabetes.

Insulin Initiation

- **Step 1:** Start **basal** insulin (0.1 mg/kg/d); usually safe to start glargine 10 units QHS, increase by 2 units Q3rd 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; Continue metformin +/− other agents based on cost, complexity

- **Step 2:** Add **prandial** insulin with largest meal **OR GLP-1** receptor agonist (*Diabetes Care* 2014;37:2763; *Lancet* 2014;384:2228); indicated when HbA1c > goal & postprandial hyperglycemia *despite fasting sugars at goal;* usually safe to start w/ 4 units insulin/meal, ↑ by 2 units every 3rd d until postprandial BG <180; d/c sulfonylurea before starting prandial insulin; combo formulations GLP-1 RA + basal insulin available ($$$)
- **Step 3:** Add **prandial** insulin before all meals if HbA1c goal not met w/ Step 2; stop GLP-1 RA if started; consider carb counting (→ nutritionist referral)

3 Common Basal + Prandial Insulin Regimens
NPH with breakfast and dinner (1/2 total daily insulin dose) + regular insulin* with meals (1/2 total dose)
Glargine QHS or QAM (1/2 total dose) + lispro* with meals (1/2 total dose)
"70/30" (Premixed 70% NPH/30% regular insulin) before breakfast (2/3 total dose) + 70/30 before dinner (1/3 total dose)

*Multiple combinations of basal + prandial Rx, including different prandial w/ this basal agent

When to Refer

- **Podiatry:** Pts who smoke, have hx of lower-extremity complications, loss of protective sensation/neuropathy, structural abnormalities or PAD
- **Nutrition:** Baseline and PRN, including if adding carb-counting
- **Renal:** All pts w/ stage IV CKD, pts w/ stage III CKD and uncertainty about etiology, difficulty w/ management, or rapid progression of CKD, persistent urine alb/cr >300 mg/g
- **Ophthalmology:** Annually (can → q2–3y if >1 nl exam)
- **Endocrinology:** If pt requiring >80 units of basal insulin w/o adequate control of fasting glucose; persistent, frequent episodes of hypoglycemia; suspect late-onset DM1
- **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; 2014;370:2002); rec if BMI ≥40 (≥37.5 in Asian-Americans) or if BMI 35–39.9; if uncontrolled DM (32.5–37.4 in Asian Americans); consider for patients with T2D and BMI 30.0–34.9 (27.5–32.4 in Asian Americans) if hyperglycemia uncontrolled despite optimal tx; long-term effects unknown; surgery has perioperative risk & possible complications; (see "*Obesity*")

Hypoglycemia

Background (*Diabetes Care* 2017;40:155)

- **Definition:** Serum glucose ≤70 mg/dL = glucose alert value; <54 mg/dL = clinically significant hypoglycemia; may be +/− sx, 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:** Serum glucose affected by food intake, **exercise**, drug interactions, **EtOH use,** insulin absorption, clearance. Occurs in pts on insulin or insulin-secreting agents (e.g., sulfonylureas); should *not* occur in pts only 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 DM pts, physiologic response to hypoglycemia impaired: Insulin levels do not ↓, glucagon does not ↑, & attenuated ↑ in epinephrine; DM pts w/ prior hypoglycemic episodes less likely to have hypoglycemic sx; some of this likely reversible
- **Risk factors:** ↑ Age, ↑ duration of DM, ↑ Cr, liver disease, ↓ 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; ***Autonomic****:* Palpitations, sweating, tremor, hunger; ***Neuroglycopenic****:* Primarily altered mental status, can → to sz, coma, even death (*Diabetes Care* 2005;28:1245)

Treatment

- **Counseling:** Counsel all pts re: precipitants & potential consequences (incl driving); should have plan in place if develop sx (i.e., glucose tabs available); screen for hypoglycemia unawareness by determining threshold at which sx sensed; if level is <60 mg/dL, relax glycemic targets & recommend checking BG before driving or other dangerous activity
- **Prevention:** Modify glycemic target/meds if 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** ≈ ½ cup fruit juice/sugar soda (not diet) ≈ 4 glucose tabs ≈ 1 Tbs sugar/honey; **recheck glucose in 15 min; if still <70, repeat glucose load;** counsel pts to **call provider** if recurrent episodes/unclear precipitant; prescribe **glucagon kit** to pts at ↑ risk of clinically significant hypoglycemia

OSTEOPOROSIS

Background (cdc.gov; *NEJM* 2016;374:254; *Osteoporosis Int* 2014;25:239)

- Osteoporosis is a condition of ↑ bone fragility which is major cause of fractures in adults; it can be prevented, diagnosed, & treated *prior to fracture;* **screening plays critical role in ↓ disease burden,** as disease is clinically silent until fracture
- **Physiology:** Multiple determinants of bone strength: Size/shape of bone, BMD, mineralization, bone turnover, & microarchitecture
- **Definitions: 1° osteoporosis:** Occurs w/ 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 = **pathognemonic for osteoporosis, regardless of BMD**; represents majority of fractures in ≥50 y; however, only 23% of women >67 w/ fragility fx received osteoporosis tx or DXA in 6 mos after fx

Major osteoporotic fracture: Affecting hip, spine, proximal humerus, or forearm

- **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 > white > African-Americans); 50% of white women & 20% of white men will have osteoporotic fracture in their lifetime; highest RR if osteoporosis, but most fractures occur in pts w/ osteopenia
- **Disease burden:** Hip fx major source of ↑ mortality in elderly; only 40% regain prior functioning after fx, and pts have 2.5× ↑ risk of future fx; vertebral fx can → pain & disability; → importance of early detection & tx to ↓ risk

Evaluation (*Ann Intern Med* 2011;154:356; 2011;155:ITC1–1; *JCEM* 2012;97:1802)

- **General approach:** All pts should be assessed for presence of risk factors (below); if present → FRAX ± BMD testing
- **History:** *Screening:* **All** adult pts should be assessed for risk factors for osteoporosis, incl history of any fractures after age 50 y, any fragility fractures (above) and risk factors

Patients with osteoporosis dx: Determine underlying etiology or assess for contributing factors (below), review prior treatment, assess for presence of complications

Selected Risk Factors for Osteoporosis & Fractures

Risk Factors	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), HAART, high-dose thyroxine
Medical history	RA, IBD, any **prior fracture** (as adult), celiac disease, s/p gastric bypass, HIV, ESLD, COPD, CHF, MM/MGUS

Diet/lifestyle	↓ 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), DM1, DM2, ↓ or ↑ cortisol, ↑ thyroid

(Adapted from Nat'l Osteoporosis Foundation, 2014 Clinician's guide)

- **Exam:** Height (watch for ↓), weight, BMI, signs of medical conditions (above), presence of complications (kyphosis, focal back pain suggestive of compression fx), & fall risk (evaluate gait & balance; see *"Falls"*)
- **Labs:** *For pts w/ new dx:* CBC, Ca, phos, Cr, 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"*)
- **Determining fracture risk:** Myriad risk factors play a role in bone density & risk of fracture; fracture risk assessment tool (**FRAX**) available at shef.ac.uk/FRAX/ estimates 10 y risk of major osteoporotic fx *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)
- **Bone Mineral Density:** Assessed via dual-energy x-ray absorptiometry (DXA); process similar to standard radiograph (quick, painless)

  Indications*: Screening:* **All women >65** (USPSTF), men >70 (ACP, Nat'l Osteoporosis Foundation, Endocrine Society), & younger adults at equivalently ↑ risk of fracture by FRAX (~9.3% over 10 y)

  Fracture hx: All pts w/ fracture after age ≥50 (w/ exception of traumatic fx of face, skull, fingers, toes) and all adult pts w/ suspected fragility fx

  Treatment: Anyone being considered for or being treated for osteoporosis
- **DXA Interpretation:**

  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)

Scoring: Density of skeletal area compared & reported as standard deviations

T-score: "Compared to the best"; bone density as compared to *average 30 yo adult:* Should *not* be used to dx osteoporosis in premenopausal ♀ or ♂ <50 y

Z-score: "Compared to a peer"; Bone density as compared to *average person of* pt*'s age & gender;* useful in eval of premenopausal ♀ or ♂ <50 y; low Z-score for any pt raises suspicion of 2° etiology

Which score to use: When multiple sites measured, category of bone fragility typically determined by lowest ("worst") T-score

Classification: (For postmenopausal ♀ and ♂ ≥50) *Normal:* **T**-score ≥–1; *Osteopenia:* **T**-score between –1 & –2.5; *Osteoporosis:* **T**-score ≤–2.5 (WHO 2004; who.int/chp/topics/Osteoporosis.pdf)

- **DXA for monitoring response to treatment:** No clear consensus; reasonable to repeat 2 y after initiation of tx; expectation is that BMD stable or improved → less frequent checks; if worsened BMD, warrants further eval/referral

Treatment (*NEJM* 2010;363:2027)

- **Nonpharmacologic therapy: Indicated for all pts w/ ↓ BMD or fragility fracture**

Calcium: Carbonate or citrate; citrate can be taken w/ or w/o food & w/ PPI; goal is 1000–1200 mg total daily calcium intake either through dietary sources or supplements

Vit D: Replete to serum >20 ng/mL; typical dose 1000 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 all pts 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); n.b. **premenopausal women or men under 50 merit endocrinology referral**
- **Bisphosphonates:** Oral = **1st-line tx for most patients;** documented ↓ incidence of hip & vertebral fractures w/ generic alendronate & risedronate; prior to initiation of bisphosphonates ensure vit D replete (above) to avoid ↓Ca; risk ↑ w/ IV bisphosphonates

PO Bisphosphonate Properties (*NEJM* 2010;363:2027)	
Sample Rx	Alendronate 70 mg/wk Risedronate 35 mg/wk or 150 mg/mo
Pt instructions	Should be taken in am 30 min prior to meds or food; take w/ 8 oz water & remain upright for 30 min 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 very low, likely ↑ w/ Rx duration >5 y) hypocalcemia (↑ risk if Vit D deficient; ensure replete prior to initiating tx) (*JBMR* 2014;29:1)
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 (*JBMR* 2016;31:1910)

- **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 (minus esophagitis) + 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

- **Other:** (Rx'ed by endocrinology) includes rPTH (teriparatide), RANKL Ab (denosumab); emerging therapeutic options include rPTH-rP (abaloparatide), (*JAMA* 2016;316:722) and sclerostin antibody (romosozumab), (*NEJM* 2016;375:1532)

When To Refer

- **Endocrinology referral:**

  Early: Men <50 or premenopausal women with osteoporosis
  Unusual/difficult to interpret: Hx fragility fracture + nl BMD
  Severe or refractory disease: Recurrent fractures or ↓ BMD despite tx above
  Medical: Endocrinopathy or other condition that complicates mgmt options
  Advanced therapies: Consideration of other therapies (above)

CALCIUM DISORDERS

Background (*NEJM* 2011;365:2389)

- **Definition:** Abnormal serum calcium 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:** Ca homeostasis tightly regulated; serum Ca 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

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Hypercalcemia

- **Etiology:** In outpt setting, most commonly 2/2 **primary**

hyperparathyroidism (primary HPT): Overactive parathyroid gland secreting excess PTH despite ↑ or ↑-nl Ca; most commonly 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° HPT	See above
Meds (usually mild)	Lithium (via ↑ PTH), thiazides, excess Vit D, Ca, or Vit A, t
Malignancy	Solid organ tumors (PTH-rP production &/or local osteolysis >> ectopic PTH); MM (cytokines); lymphoma ($1,25(OH)_2$D-production)
Granulomatous diseases	Sarcoid, TB (25OH Vit D → $1,25(OH)_2$ Vit D w/in granuloma)
Renal disease (2ç and 3ç HPT)	*Early:* 2° HPT; ↓ conversion 1,25 D by kidneys → ↑ PTH often p/w **low** Ca) *Late:* **3° HPT;** Over time, stimulated parathyroid gland → autonomous PTH production ("tertiary hyperparathyroidism")
Other	Thyrotoxicosis, immobilization (esp w/ Paget), milk-alkali syndrome; adrenal insufficiency; familial hypocalciuric hypercalcemia (FHH, inactivating mutation of CaSR)

Evaluation (*AFP* 2003;67:1959)

- **General approach:** Determine if pt symptomatic; if so, consider admission; otherwise continue outpt w/u; if suspect medication-induced, d/c med if possible, then recheck Ca
- **Signs and symptoms:** Dehydration (↑ urinary Ca excretion → polyuria), hx nephrolithiasis, CKD, constipation, bone pain, weakness, nausea, can also cause → fatigue, mood, or cognitive changes; severe disease can p/w somnolence, large peaked T waves on ECG
- **Labs: Obtain PTH and vit D on all pts, PTH values guide Ddx**

  Suppressed PTH: Malignancy or excess Vit D ingestion/production (unregulated Ca release from bone by lytic lesions or PTH-rP

production)

Normal/elevated 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, suggest FHH

Other labs: If PTH is suppressed, consider SPEP, PTH-rP, TSH, LFTs

Management (*NEJM* 2005;352:373; *JCEM* 2009;94:335; *JCEM* 2014;99:3561)

- 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, clinical or radiographic nephrolithiasis;

  If medical mgmt: Serial monitoring of Ca (at least q12mos), avoid overrepleting Vit D, thiazides; avoid dehydration; bisphosphonates if ↓ BMD; consider cinacalcet (no improvement in bone health when used in 1° HPT)
- **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 wk; can use denosumab for cases refractory to IV bisphosphonates
- **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, genetic 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 min; ⊕ 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 infusion
- 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 now approved (*JCEM* 2016;101:2273)
- If hypercalciuria (>300 mg Ca/d), consider thiazide to ↓ risk of nephrolithiasis

VITAMIN D DEFICIENCY

Background (*NEJM* 2007;357:266; 2011;364:248)

- **Definitions:** *Deficiency:* Serum 25OH Vit D <20 ng/mL; *Insufficiency*; 25OH Vit D 20–29 ng/mL
- **Physiology:** Vitamin 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), and/or *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)
- **Risk Factors:** Elderly (↓ skin production), inhabitants of Northern climates, African-American or Hispanic background, obese (Vit D sequestered in adipose tissue) homebound, institutionalized, or otherwise inadequate sun exposure, no milk intake, postmenopausal

♀, GI disease (↓ absorption: IBD, celiac, biliary disease, s/p Roux-en-Y gastric bypass), 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, also ✓ PTH & 1,25OH Vit D (they may have insufficiency despite adequate 25OH Vit D due to ↓ renal conversion)

Treatment (*NEJM* 2007;357:266; *JCEM* 2011;96:53)

- **Vitamin D deficiency:** Ergocalciferol 50,000 IU weekly for 8–12 wk; obese patients, malabsorption, or extreme deficiency may require longer course
- **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 D_2 vs. Vit D_3: D_2** (ergocalciferol) available by Rx in high-dose formulations for weekly/monthly repletion, not animal-based for pts w/ objections; **D_3** (cholecalciferol) appears to ↑ serum Vit D levels higher at equivalent dose, although unknown if differences in adherence (*JCEM* 2011;96:E447; 2011;96:981)
- **Calcitriol:** Use restricted to CKD pts w/ hypocalcemia or parathyroid disease
- **Referral:** Consider referral if low Vit D is refractory or if etiology unclear

THYROID DISEASE

Background (*Lancet* 2004;363:793; *AFP* 2012;86:244)

- **Thyroid hormones:** Myriad functions, including calorigenesis, potentiating SNS tone, turnover/clearance of nutrients (lipids, CHO, vitamins) & tissues (muscles, bone)
- Inappropriate thyroid hormone levels affect every organ system, with presentation ranging from subtle/asx to life-threatening (myxedema coma or thyroid storm)
- **Thyrotropin-releasing hormone (TRH):** Secreted by hypothalamus, responsible for ⊕ anterior pituitary to release TSH
- **Thyroid-secreting hormone (TSH):** Secreted by pituitary, responsible for ⊕ thyroid gland synthesis, storage, & release of thyroid hormones (T4 > T3); best representation of amt of hormone available to tissues, since it ↑ quickly and logarithmically with ↓ in thyroid hormone
- **Thyroxine (T4):** Has 4 iodine molecules; made only in the thyroid; $T_{1/2}$ = 7 d; has some biologic activity but primary is pro-hormone for T3
- **Triiodothyronine (T3):** Has 3 iodine molecules; 4× more potent than T4; can be made from T4 in thyroid or in target tissues by removing one outer iodine (deiodination); regulates gene transcription in target tissues; $T_{1/2}$ = 1 d
- **Plasma concentrations:** >99% of T3 & T4 bound to proteins in serum (mostly to TBG); ∴ Change in serum-binding proteins will result in change in serum total [T3] and [T4]; free concentrations of T3 & T4 = biologically active, unaffected by changes in protein levels

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HYPOTHYROIDISM

Background (*JCEM* 2009;94:1853; 2002;87:489)

- **Epidemiology:** Affects 3–8% of the US population; ↑ incidence in elderly, ♀ > ♂, white/Hispanic > African-Americans; *Risk Factors:* Postpartum, hx autoimmune disease, Turner/Down syndromes,

childhood obesity, ⊕ FHx thyroid disease, chest/neck XRT

Etiology of Hypothyroidism (*Endocr Practice* 2012;18:988)	
Etiology	**Disease**
Autoimmune	Chronic autoimmune thyroiditis (**Hashimoto's) = most common**
Iatrogenic	S/p tx for hyperthyroidism or thyroid CA (RAIU, surgery); neck XRT
Central	CNS tumor, inflammatory, infiltrative disease, Sheehan's, surgery, or XRT
Thyroiditis	Postpartum thyroiditis, subacute painless or granulomatous thyroiditis
Infiltration	Amyloid, hemochromatosis, sarcoidosis, sclerosing thyroiditis
Medications	Lithium, amiodarone, thioamides, tyrosine kinase inhibitors, immune modulators (IFNa, IL-2, anti-PD1)
Other	Iodine deficiency (Rare in US; most common cause worldwide) or excess, congenital (all US newborns screened), thyroid hormone resistance

Evaluation

- **General approach:** Dx made by TSH + fT4; sx often subtle or nonspecific, tx effective, & ↑ prevalence; but, no evidence that screening asx, nonpregnant people improves outcomes; clinical guidelines differ in recs (see *"Disease Screening"*); test patients if ↑ risk, s/sx of disease
- **History/Exam:** If pt c/o s/sx consistent w/ hypothyroidism, assess "Thyroid ROS": Recognizing that sx highly variable & nonspecific (esp. if TSH ↑ is mild)

Hypothyroidism Manifestations/"Review of Systems"	
Constitutional: Wt gain, fatigue, cold intolerance *HEENT:* Voice Δ, goiter, periorbital edema *Pulm:* Sleep apnea, hypoventilation *CV:* Diastolic HTN, bradycardia *GI:* Constipation *GU:* Decreased libido, menstrual irregularities	*Heme:* Anemia *MSK:* Carpal tunnel syndrome, myalgias *Neuro:* **Delayed DTR relaxation** (↑ Sp) *Endo:* Dyslipidemia *Ext:* Nonpitting edema *Derm:* Brittle hair/nails, cool, dry/rough skin**,** lateral brow loss

Renal: ↓ GFR & water clearance, ↓Na	

- **Labs: TSH** best initial test; if TSH ↑ obtain **free T4** (fT4)**;** (always check TSH & fT4 if suspected pituitary disease); **if TSH ↑ and fT4 ↓, no further testing indicated;** T3 not indicated (poor assay Se/Sp)
- **Additional testing/special populations:**
  Pts w/ history of pituitary disease or suspect 2° hypothyroidism: Always ✓ TSH *and* fT4
  Pts w/ subclinical hypothyroidism: If TSH borderline, repeat as 62% normalize on recheck (*Arch Int Med* 2007;167:1533) consider anti-TPO Abs; if ⊕ predicts progression to overt hypothyroidism
- **Lab abnormalities associated with hypothyroidism:** ↑ LDL, ↓ HDL, anemia, ↑ CK, mild ↓Na, & hypoglycemia; however, these should not be ordered for dx

Interpretation of TFTs in Hypothyroidism	
Etiology	**TFT Pattern**
Primary (usually autoimmune)	↑TSH, ↓fT4; TPO Ab often ⊕ but not needed
Subclinical (variant of primary)	↑TSH, nl fT4;
Central (pituitary/hypothalamic)	↓ or nl TSH, ↓fT4; <1% of cases (*JCEM* 2012;97:3068)

Treatment (*Endocr Pract* 2012;18:988; *Thyroid* 2014;24:12)

- **Primary:** Uncomplicated 1° can be managed by PCP with levothyroxine (below)
- **Subclinical hypothyroidism:** TSH >10 (and possibly >7) assoc w/ ↑ CAD events/mortality (*JAMA* 2010;304:1365) & CHF (*Lancet* 2012;379:1142); TSH 5–10 may be protective in elderly >70 (*Arch Int Med* 2009;169:2011); Tx if TSH >10, consider tx if TSH >7–10, comorbidities, or ⊕ Anti-TPO; have a much higher threshold to tx in elderly; follow same dosing guidelines below for tx

Prescribing Levothyroxine (synthetic T4)	
Choice of Rx	All T4 brand & generic formulations are effective; mild difference in kinetics & bioavailability (*AFP* 2012;86:244); T3 is rarely needed

Initial dosing	Weight-based dose = 1.6 µg/kg/d (~110 µg for 70 kg pt); for healthy younger adults, okay to start at ½ or full dose; for elderly or pts w/ CAD, start 25–50 µg & slowly uptitrate (T4 ↑ myocyte O_2 demand)
Administration	In am 60 min prior to food (missed pill can be taken later/next day), 3–4 h apart from Ca or iron; if QHS, dose 3 h after last meal
Monitoring	Recheck TSH in 6–8 wk (T4 $T_{1/2}$ 7 d = 4–6 wk for steady state) after initiation, dose changes, or formulation changes; once at goal, ✓ q6–12mos; assess sx (see "Symptoms/Pt Education")
Goal	TSH in nl range; TSH <2.5 for child-bearing age ♀; aim for high end of the normal range for elderly (overtreatment is common)
Titration	Change by 12.5–25 µg increments depending on proximity to goal
Tx interruptions	Avoid if possible; if <6 wk, usually ok to resume prior dose if low CVD risk or significant wt loss (*Endocr Pract* 2012;18:988)
Persistent or new ↑ TSH on Tx	Assess for adherence (most common), timing of dose & meals, meds that interfere with absorbance/metabolism (e.g., Calcium, iron, PPI, phos binders, bile acid sequestrants, raloxifene), formulation change, weight gain, malabsorption (e.g., Celiac)

- **Symptoms/Patient Education:** Counsel pts that sx may take months–years to improve proportional to severity/duration of hypothyroidism; unfortunately, many pts with Hashimoto's have ↓ QOL and persistent "hypothyroid" sx despite nl TSH; further T4 dose ↑ usually not helpful (*Thyroid* 2011;21:161)

When to refer

- **Endocrine:** Difficulty achieving euthyroid state, cardiac disease, planning pregnancy (or currently pregnant), thyroid structural abnormalities, central hypothyroidism, other endocrine d/o (adrenal, pituitary), labs difficult to interpret, unusual cause suspected, consideration of using T3 tx (e.g., postthyroidectomy 2/2 deiodinase polymorphism)
- **Emergency Department:** Extreme/prolonged hypothyroidism + stressor (trauma, infection, drugs) can → **myxedema coma** (hypothermia, diffuse edema, HoTN, **AMS**, hypoventilation)

Hyperthyroidism

Background (*JCEM* 2002;87:489; *AFP* 2005;72:623)

- **Epidemiology:** 1.2% of US population (0.5% overt & 0.7% subclinical); 5× as common in ♀
- **Etiology: Graves disease** (autoimmune d/o with TSH-receptor stimulating Abs) **most common** (60–80% of cases); subacute thyroiditis (lymphocytic/painless or granulomatous/painful), toxic adenoma, toxic multinodular goiter (TMNG) 5% (pts often older w/ longstanding goiter); meds (excess thyroxine, **amiodarone**); gestational hyperthyroidism; rare causes incl TSH-secreting pituitary tumor, hCG-secreting tumors, struma ovarii, widely metastatic follicular thyroid cancer

Evaluation (*Endocr Pract* 2011;17:e1; *Thyroid* 2016;26:1343)

- **General Approach:** Hyperthyroidism dx made by TFTs; presentation of variable severity, most result from high adrenergic tone; may be atypical or "apathetic" in elderly (*J Am Geriatr Soc* 1996;44:50): Order TSH & reflective fT4, tT3 to confirm, and RAIU to help clarify etiology
- **History/Exam:** If suspicion for hyperthyroidism, evaluate other s/sx (below); additional history*:* Onset/duration of s/sx, as well as complete medication & supplement list, recent iodine exposure (e.g., CT contrast);

Hyperthyroidism Manifestations/"Review of Systems"	
Constitutional: Diaphoresis, wt loss, insomnia, heat intolerance *HEENT:* Stare, lid lag, exophthalmos (Graves') *Thyroid:* enlarged, tender, or nodular *Derm:* Onycholysis, hyperpigmentation, pruritus, thinning hair *Neuro:* Tremor, anxiety, hyperreflexia	*Heme:* Anemia *Endo:* ↓ BMD, hyperglycemia *Pulm:* DOE, ↑RR *CV:* ↑HR, AF, systolic HTN *GI:* Hyperdefecation *GU:* Menstrual irregularities *Ext:* Pretibial myxedema (Graves')

- **Labs: TSH** best initial test: if TSH ↓, then obtain total T3 **(tT3) & fT4;**

if hx suspicious for Graves', send thyroid receptor antibodies (TRAbs): TSII and TBII have Se/Sp >97% for overt Graves' (*JCEM* 2013;98:2247);

- **Radioactive iodine uptake and scan (RAIU):** Order if labs above abnl to characterize hyperthyroid etiology; best test if no recent iodine exposure (will falsely lower uptake);
- **Additional testing/special populations:**
  Subclinical hyperthyroidism: If ↓ TSH with nl fT4 and tT3 levels and asx, recheck in 2–3 mos
  Thyroid nodule on exam: Thyroid U/S (see "*Thyroid Nodules*")
  Concern for exogenous T4 overdose: Thyroglobulin (will be ↓ instead of ↑)
- **Lab abnormalities associated with hyperthyroidism:** ↓ LDL, ↓ HDL, anemia (↑ RBC mass, but ↑↑ plasma volume), ↑ AΦ; however, these should not be used for diagnosis

TFT Interpretation in Hyperthyroidism	
Etiology	**TFT Pattern**
Primary (usually Graves')	↓TSH, ↑fT4, ↑tT3 (↑↑tT3 suggests Graves')
Subclinical (variant of primary)	↓TSH, nl fT4, nl tT3
Central (pituitary, extremely rare)	↑TSH, ↑fT4, ↑tT3

Radioactive Iodine Uptake Interpretation	
Low Uptake	**High Uptake**
Subacute thyroiditis Exogenous hormone Struma ovarii Iodine exposure (amiodarone, contrast)	Graves disease (diffuse uptake) Toxic multinodular adenoma (multiple foci) Toxic adenoma (one focus) Gestational/trophoblastic hyperthyroidism

Treatment (*Endocr Pract* 2011;17:e1; *Thyroid* 2016;26:1343)

- **General approach:** All hyperthyroid pts → endocrine referral for management; acute mgmt may be initiated by PCP (below)
- **Graves disease:** Multiple effective tx choices include antithyroid medication (thionamides), ^{131}I tx, or surgery; mod–severe Graves ophthalmopathy: Options include glucocorticoids and surgery
- **Acute mgmt:** βB (e.g., propranolol 10–40 mg BID) are effective

immediately and indicated for all pts w/ sx, especially if CAD, resting pulse >90 or elderly; Methimazole 10–40 mg daily with baseline CBC/LFTs (risk of agranulocytosis, cholestasis ↑ with dose)

- **Subclinical hyperthyroidism:** *If asx,* repeat TSH, fT4, tT3 at 2–3 mos to document persistence vs. resolution, as 51% normalize w/ recheck; *If sx or persistent,* obtain RAIU; tx decision guided by (1) risk category: High-risk = postmenopausal women, elderly, pts w/ CV disease and (2) degree of TSH suppression (If TSH <0.1 and >60 y, atrial fibrillation risk ↑ 3× (*NEJM* 1994;331:1249), also ↑ osteoporosis and fracture risk)

  TSH <0.1: High risk = tx; low risk = consider tx
  TSH 0.1–0.5: High risk = consider tx (and/or tx βB, bisphosphonate); low risk = observe

When to Refer

- **Endocrinology:** All hyperthyroid patients
- **Emergency Department:** Extreme/prolonged hyperthyroidism + stressor (trauma, infection, drugs) can → thyroid storm (hyperthermia, HoTN or HTN, tachycardia +/− arrhythmias, **AMS**)

THYROID NODULES

Background (*NEJM* 2004;351:1764)

- **Definition:** Discrete mass w/in thyroid gland, palpated or visualized on imaging
- **Epidemiology:** 4–7% of adults have palpable nodule; 50% of pts >60 y have nodule evident on autopsy; ~5% of nodules are malignant

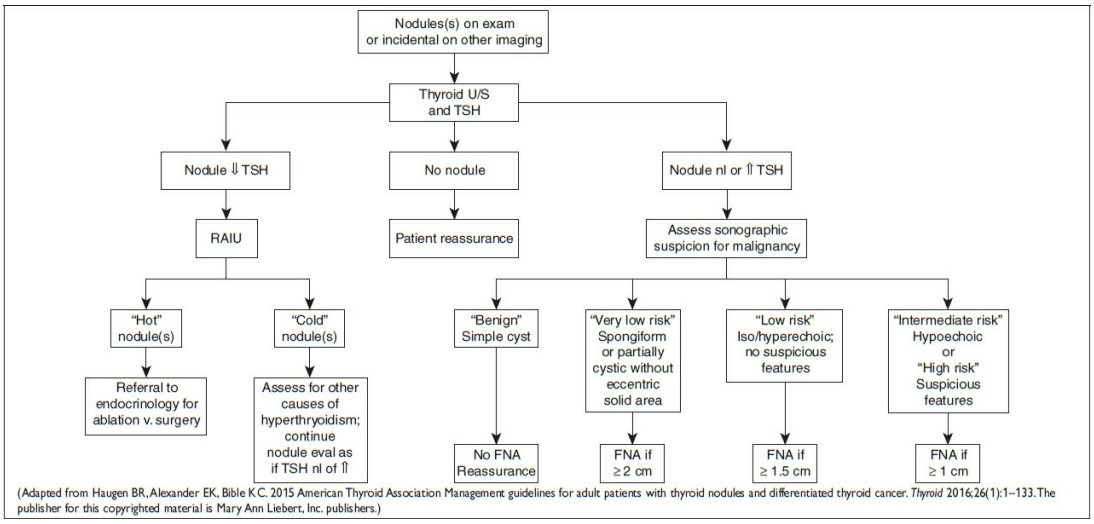
Evaluation (*Endocr Pract* 2010;16(Suppl1):1; *Thyroid* 2016;26:1)

- **History/Exam:** Full hx & physical w/ special attention to thyroid exam & paracervical LN; assess for s/sx of hyper- or hypothyroidism, factors which suggest ↑ likelihood of malignancy (below)

Features Associated with Increased Risk of Malignancy	

History	Exam, Imaging
Hx childhood head & neck XRT Hx accidental radiation exposure Hx total body XRT ⊕ FHx thyroid Ca or Ca syndrome (e.g., MEN2a, MEN2b, FAP, Cowden's) Rapid growth of mass/nodule Hoarseness	Vocal cord paralysis Fixed nodule, lateral cervical LAD **Suspicious U/S features:** Hypoechoic irregular margins, microcalcifications, taller-than-wide, interrupted rim calcifications, extrathyroidal extension

- **Diagnostics:** All patients w/ nodule should undergo dedicated **thyroid U/S and TSH;** those who meet criteria should undergo **Fine Needle Aspiration (FNA):** Can be done by endocrinology or radiology; offers cytology (but not histology)



(Adapted from Haugen BR, Alexander EK, Bible KC. 2015 American Thyroid Association Management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016;26(1):1–133. The publisher for this copyrighted material is Mary Ann Liebert, Inc. publishers.)

Figure 4-2. 2015 American Thyroid Association Guidelines for Management of Thyroid Nodules.

Management

- **General approach:** PCP surveillance of pts at avg malignancy risk with nl or not-indicated FNA appropriate; **endocrine referral for** anyone at ↑ malignancy risk or w/ abnl FNA results; consider endocrine referral for pts w/ multiple nodules, ambiguous RAIU results
- **Repeat FNA:** Indicated if high risk (above), or if nodule grows by 20% or more in 2 dimensions, develops new suspicious features, or

new sx; if two benign FNAs are obtained, surveillance usually no longer required

Management of Ultrasound Results: Nodule Surveillance	
Classification (see algorithm above)	**Management**
Does not meet size criteria for FNA	Repeat U/S in 6–12 mos
Cyst	No follow-up needed
Very low risk	Repeat U/S in 2–4 y
Low or intermediate risk	Repeat U/S in 1–2 y
High risk	Repeat U/S and FNA in 6–12 mos
"Bethesda System" FNA Results and Management	
Benign	**U/S surveillance**
Nondiagnostic (ND)	Repeat FNA; if ND again → close f/u or surgery
Indeterminate (AUS, FLUS, SFN)*	Repeat FNA w/in 3 mo; if indeterminate again → molecular testing or surgery; If FLUS/SFN, consider RAIU if TSH low-nl (hyperfunctioning = benign)
Suspicious for malignancy	Thyroidectomy
Papillary thyroid cancer	Thyroidectomy

*Atypia of undetermined significance, follicular lesion of undetermined significance, suspicious for follicular neoplasm

ADRENAL INSUFFICIENCY

Background (*NEJM* 1996;335:1206; *J Intern Med* 2014;275:104; *Lancet* 2014;383:2152)

- **Definition:** Inability of the adrenal glands to produce the amt of cortisol required for degree of stress; acute AI can present w/ adrenal crisis, but chronic AI is often subtle and making the dx requires clinician to consider it in Ddx for many common outpatient s/sx
- **1º (adrenal cause):** (♀ > ♂, incidence ↑ 30–50 y) Addison disease, most commonly **autoimmune** (anti-21-hydroxylase antibodies ⊕ in

86%), infectious (**TB,** CMV, histo), bilateral adrenal hemorrhage (*N. meningitidis* and other pathogens, DIC, APLAS, anticoagulation), cancer (metastases, lymphoma), meds (→ ↓ adrenal steroid synthesis: ketoconazole, fluconazole, etomidate), genetic (CAH, adrenal leukodystrophy)

- **2º (hypothalamus/pituitary cause):** (♀ > ♂, incidence ↑ 60–69 y) **Meds** (→ to HPA axis suppression: **Corticosteroids, opioids,** megestrol, medroxyprogesterone); hypopituitarism (mass lesions, infiltrative dz, infarction, hx head trauma, pituitary surgery/rads, postpartum pituitary necrosis)
- **Exogenous glucocorticoids most common cause of AI:** Cases have been reported by transdermal, inhaled, rectal, and intra-articular routes
- Patient may tolerate partially compensated AI until a stressor results in profound symptoms ± hypotension (adrenal crisis)

Evaluation (*JCEM* 2016;101:364; *Ann Clin Biochem* 2009;46:351)

- **General approach:** If suspicion for AI in stable pt, start w/ cosyntropin stimulation test when possible (↑Se/Sp), if not then 6–8 AM plasma and ACTH levels; for pts w/ suspected adrenal crisis → avoid diagnostic delay in tx/ER (obtain single ACTH/cortisol value prior to tx if possible)
- **History/exam:** Assess for s/sx suggestive of either 1º or 2º insufficiency: weakness, fatigue, anorexia, N/V, abd pain, wt loss, orthostatic hypotension, hypotension, hyponatremia, hypoglycemia, hypercalcemia, anemia, eosinophilia
  - *1º only:* hyperkalemia, salt craving (↓aldosteronism), hyperpigmentation at mucous membranes, creases, pressure areas (↑ACTH precursor → ↑melanin), other autoimmune disease
  - *2º only:* S/sx of hypopituitarism (hypogonadism, hypothyroidism, ↑PRL)
- **Labs: Cortisol** measured in corticotropin stimulation test (preferred) or AM cortisol testing; serum cortisol = bound + free cortisol; free = biologically active, ∴ serum measurement may be misleading when CBG is ↓ or ↑; **ACTH** should be measured with cosyntropin stim or AM cortisol test; ACTH >2× ULN c/w 1º AI, ↓ACTH c/w 2º AI

Corticotropin Stimulation Test (*JCEM* 2016;101:364)	
Test administration	(1) ✓ serum ACTH and cortisol (2) give cosyntropin (ACTH analogue) 250 µg IV/IM (3) ✓ cortisol 30 and 60 min later
Interpretation	*Normal response:* Peak serum cortisol level ≥18 µg/dL *Abnormal response:* In 1º AI due to adrenal gland destruction; in 2º AI due to adrenal gland atrophy *False ⊕:* Liver disease, critical illness (↓CBG) *False ⊖:* Pregnancy, OCPs (↑CBG); acute 2º AI (no time for adrenal atrophy)

- **6–8 AM cortisol:** (Serum cortisol usually at its highest in early AM): Definite AI if ≤3 µg/dL (100% Sp); rules out AI if ≥18 µg/dL (*JCEM* 2003;88:4193); if equivocal → corticotropin stim test
- If abnl cosyntropin stim test, ✓ aldosterone;
  - ↑*ACTH,* ↓ *aldosterone:* 1º AI → 21-hydroxylase antibody testing → if (−), adrenal CT
  - ↓*ACTH, nl aldosterone:* 2º AI → assess for culprit medications, pituitary MRI

Treatment (*JCEM* 2016;101:364; *JAMA* 2009;301:2362)

- **Endocrine referral:** For all pts w/ confirmed or suspected AI, however, PCPs may initiate/complete w/u (above), triage acute AI, and should be aware of steroid mgmt in situations such as drug–drug interactions, outpatient illness
- **Acute AI:** → ER for steroid replacement, volume repletion, and w/u for underlying trigger
- **Chronic AI:** Titrate dose to s/sx (e.g., blood pressure, body weight, energy level); counsel pts on 100% adherence, "sick dose" rules, med alert bracelet
  - *Glucocorticoids:* Hydrocortisone 15–25 mg daily in 2–3 divided doses (e.g., 10 mg q AM, 5 mg q 2 PM) or prednisone 3–5 mg q AM
  - *Mineralocorticoids* (for 1º only): Fludrocortisone 0.05–0.1 mg q AM
  - *Stress dosing:* Glucocorticoid requirements ↑ during stressor like illness, surgery; for outpt illness or minor procedure, double or triple dose (see "*Preoperative Medicine*")
- **Drug–drug interactions:** Major glucocorticoid drug interactions –

dose adjustments may be needed

CYP3A4 inhibitors: ↑ Levels (lower dose needed): Clarithromycin, ketoconazole, isoniazid, HIV/HCV antivirals (e.g., ritonavir, lopinavir), cyclosporine

CYP3A4 inducers: ↓ Levels (higher dose needed): Carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine, rifampin, St. John's wort

ADRENAL NODULES

Background (*Eur J Endocrinol* 2003;149:273; *AFP* 2010;81:1361; *NEJM* 2007;356:601)

- **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
- **Risk factors for malignancy:** Hx of extra-adrenal malignancy; lesion >4 cm in size, radiographic density >10 Hounsfield units, <50% washout at 10 min

Etiology of Adrenal Incidentaloma (*Eur J Endocrinol* 2009;161:513)	
Malignant (3%)	Primary adrenal carcinoma (ACC, 2%) Metastases (1%)*
Benign (97%)	Nonfunctional adrenocortical adenoma (90%) Subclinical Cushing syndrome (6%) Pheochromocytoma (3%) Aldosteronoma (1%) Myelolipoma, cyst

*For pts w/ current/prior CA hx, 52% of adrenal incidentalomas = metastases (*Surgery* 2001;6:1060)

Evaluation (*Endocr Pract* 2009;15:S1; *NEJM* 2007;356:601)

- **General approach:** Seek to answer 2 questions: Is nodule malignant, and/or is it functioning (producing hormones)?
- **History/Exam:** Evaluate for malignancy (mets) and for s/sx functioning lesion;

Hypercortisolism (Cushing syndrome): Wt gain, central obesity, facial rounding, Δ cognition, HTN, DM2, HL, osteopenia
Excess catecholamines (pheochromocytoma): HTN (paroxysmal or sustained), palpitations, headaches, diaphoresis
Hyperaldosteronism (Conn syndrome): HTN, hypokalemia, muscle cramps

- **Labs:** Always screen for Cushing's and pheochromocytoma; screen for Conn/ aldosteronoma only if pt also has HTN
- **Excess cortisol (Cushing's) screening:** 1 mg dexamethasone suppression test; ⊕ if AM cortisol ≥1.8 μg/dL; ↑Se, ↓Sp (many false ⊕, can be due to obesity, stress, ↑EtOH use, psychiatric disease, OCPs (↑ CBG), AEDs (↑ dexamethasone clearance)
- **Excess catecholamines (pheochromocytoma) screening:** 24-h **urine** metanephrines and catecholamines; plasma metanephrines (plasma assay > false ⊕, can be due to stress, illness, psychoactive agents (TCAs, amphetamines, etc.), decongestants, clonidine w/d
- **Excess aldosterone (Conn) screening:** AM plasma aldosterone concentration (PAC) and plasma renin activity (PRA); ⊕ if PAC ≥15 ng/dL and PAC/PRA ≥20

Treatment (*J Am Coll Radiol* 2010;7:754; *Endocr Pract* 2009;15:S1)

- **Endocrine referral:** If any of hormonal screening tests ⊕, refer for confirmatory testing
- **Surveillance:** If <4 cm, benign appearance, and nonfunctioning: (1) serial imaging at 3–6 mos, 12 mos, and 24 mos; (2) Hormonal evaluation annually for up to 5 y; interval growth of >1 cm or hormonal screen ⊕ → surgical evaluation
- **Surgery referral:** For excision (or biopsy) if size >4 cm (PPV 16% for malignancy; *JCEM* 2000;85:637), malignant imaging characteristics, or pt history of malignancy; consider referral at smaller size for younger pts whose surgical risks are lower
- Surgical excision should be considered for all hormonally active lesions, particularly pheo given risk of CV complications; medical management for hyperaldosteronism may be preferred to surgery in individuals with comorbidities

PITUITARY DISORDERS

Background (*Endocrinol Metab Clin N Am* 2008;37:151)

- **Pituitary incidentaloma:** Pituitary lesion discovered on imaging performed for other reasons (*macro:* ≥1 cm, *micro:* <1 cm)
- 10% of adult population have pituitary abnormalities on MRI compatible w/ pituitary adenoma (*Ann Intern Med* 1994;120:817)

Etiology of Pituitary Lesions		
Pituitary adenomas Nonfunctioning Functioning (PRL most common) **Cystic** Rathke cleft cyst Craniopharyngioma **Nonadenomatous neoplasms** Meningioma Germinoma	**Inflammatory** Lymphocytic hypophysitis Sarcoidosis Wegener granulomatosis **Infectious** Bacterial Syphilis Tuberculosis	**Metastases** Breast CNS lymphoma Lung Prostate **Vascular** Carotid aneurysm **Miscellaneous** Hyperplasia

(*JCEM* 2011;96:1633)

Evaluation (*JCEM* 2011;96:894)

- **General approach:** Goal is to identify hormone hypersecretion & hypopituitarism
- **History/Exam:** Assess symptoms of excess/deficiency of pituitary axes (below) and any CNS complaints (HA, Δ vision)

Clinical Manifestations of Pituitary Dysfunction	
Hormone	**Hypo- and Hypersecretion Manifestations**
Prolactin	*Low:* Generally asx *High:* Galactorrhea, menstrual irregularities; see *"Hyperprolactinemia"*
ACTH	*Low:* Fatigue, anorexia, orthostatic HoTN; *see "Adrenal insufficiency"* *High* (Cushing disease): Wt gain (esp central), facial rounding, supraclavicular fullness, fatigue, depression, ↑glucose, HTN, ecchymoses, hirsutism, myopathy

LH, FSH	*Low:* ♀: Menstrual irregularities, hot flashes; ♂: ↓ Libido; see "Male Hypogonadism" *High:* Generally asx
Growth hormone	*Low:* Generally asx; may have ↓ muscle mass, ↓ BMD *High:* ↑ Size of hands and feet, frontal bossing, macrognathia, macroglossia, spaces between teeth, carpal tunnel, deepening of voice, OSA, skin tags, hyperhidrosis
TSH	*Low:* Fatigue, wt gain, constipation, delayed DTRs; *see "Thyroid disorders"* *High:* Heat intolerance, palpitations, hyperdefecation, tremor, anxiety

- **Pituitary MRI** to further characterize lesion if identified by CT
- **Hormone evaluation:** Assess both hypo- and hyperfunction
  Hypofunction (esp if macro): ✓ AM cortisol or cosyntropin stimulation test (see Adrenal Insufficiency), TSH, fT4, FSH/LH, testosterone (if ♂), IGF-1
  Hyperfunction: ✓ **PRL**, IGF-1 (assess hypo- and hyperfunction), consider 24 h urine-free cortisol or late night salivary cortisol if any sx c/w ↑ ACTH (*JCEM* 2008;93:1526); if ↑ PRL mild but macroadenoma, repeat PRL assay w/ 1:100 sample dilution (can be falsely ↓ 2/2 "hook effect") (*JCEM* 2011;96:273)
- **Ophtho referral:** Visual field testing for lesions abutting optic nerves or chiasm on imaging
- **Biopsy** (infrequent) in cases of diagnostic uncertainty

Treatment (*JCEM* 2011;96:894; *Lancet* 2016;388:2403)

- **Endocrine referral:** If hyper- or hypofunction detected; see *Adrenal Insufficiency, Thyroid Disorders;* if both ↓ TSH and ↓ ACTH, cortisol replaced prior to thyroid hormone (concern for precipitating adrenal crisis)
- **Surgery referral:** Any evidence of mass effect (VF deficit, ophthalmoplegia, lesion abutting optic nerves/chiasm, or hyperfunctioning); consider referral if HA, considering pregnancy, any lesion growth, or hypopituitarism
- **Surveillance:** If no evidence of pituitary dysfunction and no mass effect
  (1) MRI in 6 mos if macro or 12 mos if micro, then repeated annually for at least 3 y

(2) Hormonal evaluation in 6 mos, and then annually if macroadenoma

HYPERPROLACTINEMIA

Background (*AFP* 2010;81:617; *JCEM* 2011;96:273)

- **Physiology:** Prolactin (PRL) is a hormone secreted by lactotrophs of anterior pituitary to induce lactation; tonically ↓ by hypothalamic dopamine (DA) and ↑ by estrogen and TRH
- **Signs/symptoms:** Oligomenorrhea, amenorrhea, infertility (even if regular menses given luteal phase abnormalities), galactorrhea, male hypogonadism, erectile dysfunction

Etiology of Hyperprolactinemia	
Class	**Examples**
Physiologic	Pregnancy, lactation (normalizes by 12 wk postpartum due to ↓ estradiol), smaller ↑ seen in nipple stimulation *in lactating* ♀, stress, exercise, sleep
Medical conditions	**CKD** (2/2 ↓PRL clearance), cirrhosis, PCOS, **1ç hypothyroidism** (2/2 pituitary hyperplasia)
Medications	(Interfere with DA inhibition, usually PRL <200 ng/mL) **antipsychotics** (esp **risperidone**), TCAs, metoclopramide, opiates
CNS pathology	(Interfere w/ DA inhibition) Craniopharyngioma, trauma, cranial XRT, sarcoid
Pituitary adenoma	Lactotroph adenoma = 40% of pituitary adenomas, PRL level correlates w/ tumor size; other pituitary adenomas may disrupt DA inhibition and → ↑PRL as well
Spurious	Macroprolactin complex (biologically inactive but detectable on PRL assay)
Idiopathic	May reflect a microadenoma too small to detect

Evaluation (*NEJM* 2010;362:1219; *JCEM* 2011;96:273)

- **General approach:** First exclude pharmacologic or extrapituitary causes, then proceed w/ pituitary MRI

- Hx/PE: Review **medications**, comorbidities and assess for other findings suggestive of pituitary adenoma, ask about ↑PRL symptoms (premenopausal ♀*:* Oligomenorrhea, galactorrhea, ♂*:* Hypogonadal sx)
- **Serum PRL: Repeat** if mild elevation to confirm persistence or w/ dilution if concern for "hook effect" (*see "Pituitary Lesions");* if med-induced suspected, d/c meds for 3 d then repeat (if cannot safely d/c meds → pituitary MRI)
- **Other labs:** β-hCG (if reproductive-aged ♀), TSH, FT4, Cr, LFTs, macroprolactin (if no sx), FSH/LH/T/SHBG (if ♂); consider macroprolactin assay if pt asx
- **Pituitary MRI:** For all pts with ↑PRL that is not medication-induced or if >100–200 ng/dL

Treatment (*JCEM* 2011;96:273; *Clin Endocrinol* 2006;65:265; *NEJM* 2010;362:1219)

- **Referral to endocrine:** If prolactinoma detected (see *"Pituitary Lesions"*); or if symptomatic or desiring pregnancy
- **Medication-induced:** Stop drug if clinically feasible; if not feasible, use estrogen or testosterone replacement for sx hypogonadism; avoid DA agonists (may ⊕ psychosis)
- **Prolactinoma tx:** *Macroadenoma:* DA agonist cabergoline 1st-line to normalize PRL and ↓ tumor size (1st-line); s/e: Nausea, HA, orthostatic HoTN, nasal congestion, fatigue), may ↑risky behaviors (rare); estrogen/testosterone therapy; transsphenoidal surgery for macroadenoma in select cases

  Microadenoma: Does not need Rx if asx and stable; if sx or enlarging, DA agonists (1st-line), estrogen/testosterone therapy PRN
- **Surveillance:** No guideline consensus; one approach for microadenomas if asx and not on tx, ✓ PRL and MRI annually × 3 y, then q2y (*NEJM* 2010;362:1219); 95% of microprolactinomas do not enlarge over 4–6 y of observation (*JCEM* 1989;68:412)

ABDOMINAL PAIN

Background (*NAMCS* 2010, http://www.cdc.gov/nchs)

- Abdominal pain is one of the top 20 reasons for ambulatory visits in US; complaint reflects wide array of potential etiologies & organ systems, varying in acuity & severity; careful hx & consideration of demographics key to guiding differential & identifying pts who merit emergent or specialty care

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); tempo/trajectory: worsening, stable, or improving?
  - *Assoc sx:* N/V, diarrhea, constipation, 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/chronicity)
  - *Aggravating/alleviating factors:* Eating, defecation (IBS), movement or lying still, pleuritic (thoracic), ↑ w/ tensing abd wall (hernia, myofascial abd wall pain)
  - *PMHx:* Cancer hx (tumor, hypercalcemia), prior abd surgery, immunosuppression, CAD/PAD (mesenteric ischemia), endocrinopathy (thyroid, adrenal disease); in women, LMP, new sexual partners (see *"Pelvic Pain*")
  - *Social hx:* EtOH (pancreatitis, hepatitis), tobacco (AAA, vascular insufficiency), travel hx (infection)
  - *Medications:* NSAIDs (PUD), 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)

Carnett sign: ↑ or stable pain when abdominal muscles tensed (usually ask pt to lift head off pillow & repalpate; suggests abdominal wall > intra-abdominal process)

Murphy sign: Inspiration interrupted w/RUQ pressure by examiner (acute cholecystitis)

Psoas sign: Pain if supine pt lifts thigh against resistance (peritonitis, appendicitis [if pain 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, lactate, lipase, U/A; chronic → CBC, BMP (including Ca), 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, hepatic thrombi) (*Emerg Med Clin N Am* 2011;29:175)

- **Endoscopy:** Highest yield in the presence of alarm signs (unexplained weight loss, B-symptoms, new iron-deficiency anemia, change in stool caliber, etc.) or overt GIB; diagnostic colonoscopy may be useful in chronic abd pain if concern for inflammatory or neoplastic process

Acute Abdominal Pain

- **General approach:** Organize differential by pain location (Fig. 5-1); Red flags → ED
- **Red flags:** Fever (esp in immunosuppressed), protracted vomiting or intolerance to POs, HoTN or e/o hypovolemia, jaundice, severe pain; e/o peritonitis (rigid abdomen, pain w/ minimal movement, incl flex hips, cough)
- **Nongastrointestinal causes:** Consider cardiac (MI, see *"Chest Pain"*), pulm (pleuritis), 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, *C. diff*); 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 + pain + low BP + AMS → Reynold pentad) → ED; sx cholelithiasis: recurrent, postprandial colicky RUQ pain, often nl bili & Aφ → RUQ U/S + surgical referral
- **Epigastric pain or dyspepsia:** Gastritis (burning, can be assoc w/ reflux sx; see *"GERD"* & "*Peptic Ulcer Disease*"); pancreatitis (worse w/ fatty 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)

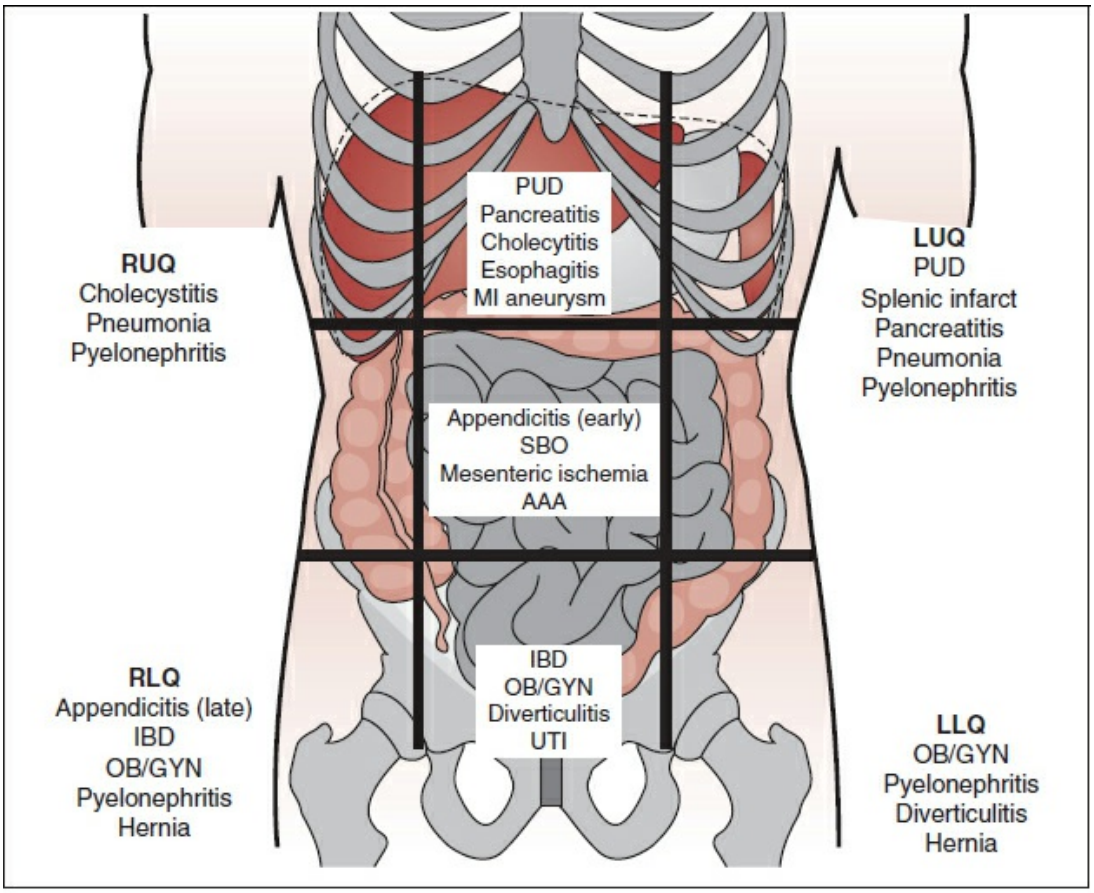


Figure 5-1. Differential of Acute Abdominal Pain by Location

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 in epigastrium/chest ± sx of reflux (see *"GERD"*)

PUD: Episodic burning epigastric pain 2-5h after meals or on empty stomach (see "*PUD*")

- **Inflammatory** (*AFP* 2011;84:1365; *AFP* 2007;76:1795; *NEJM* 1995;332:1482)
  IBD: Diarrhea, hemoccult ⊕ or grossly bloody stools, anemia, ⊕ fever, ⊕ extraintestinal sx, increased urgency, wt loss → lower endoscopy w/ bx (see *"IBD"*)
  Celiac disease: Variable sx including 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: ↓ stool frequency, straining, hard stools, sense of incomplete evacuation; see "Constipation"
  Gastroparesis: Often assoc w/ autonomic neuropathy in DM or postinfectious, ♀ > ♂; c/o postmeal N/V, bloating, pain, early satiety → gastric emptying study
- **Vascular:** *Chronic mesenteric ischemia:* PAD/CAD hx, postprandial pain & "food fear" with resultant wt loss → mesenteric Doppler U/S or angiography (*JACC* 2006;47:944)
- **Neoplastic:**
  CRC: **Typically asymptomatic unless advanced or rectal disease;** often p/w Fe-deficiency anemia → colonoscopy
  HCC: LFT abnormalities, rarely s/sx of biliary obstruction or evidence of ESLD → triphasic CT, RUQ U/S, MRI (most Se)
  Gastric: Dyspepsia, early satiety, overt or occult UGI bleeding → CT or endoscopy
  Pancreatobiliary: S/sx of cholestasis (jaundice, ↑ Aφ, bili) → CT, RUQ U/S → MRCP/ERCP
  Ovarian: Nonspecific bloating, fullness sensation, malignant ascites if late-stage → CT
- **Functional** (*NEJM* 2008;358:1692)
  Irritable bowel syndrome: Pain assoc w/ BM; pain onset assoc w/ change in stool freq/appearance; sx ↑ w/ stress; see *"IBS"*
  Functional abd pain syndrome: After appropriate evaluation, sx not fully explained by another d/o AND all of the following: episodic

or continuous abdominal pain that does not occur solely during physiologic events (e.g., eating, menses), occurs ≥4 times/mo for ≥2 mo, and insufficient criteria for IBS, functional dyspepsia, or cyclic vomiting syndrome/abd migraine

Functional dyspepsia: By Rome IV criteria, defined as one or more of the following bothersome sx for ≥3 mo (with onset ≥6 mo to establish dx): postprandial fullness, early satiation, epigastric pain, or epigastric burning AND no evidence of structural disease (including via EGD) to explain sx

Functional constipation: Presence of the following for ≥3 mo (onset ≥6 mo to dx):

(1) ≥2 of the following for at least 25% of BMs: straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction/blockage, manual maneuvers to facilitate, or fewer than 3 spontaneous BMs/wk

(2) loose stools rarely present w/o laxatives

(3) does not meet criteria for IBS (see "Irritable Bowel Syndrome")

- **Gynecology:** See *"Pelvic Pain"*

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

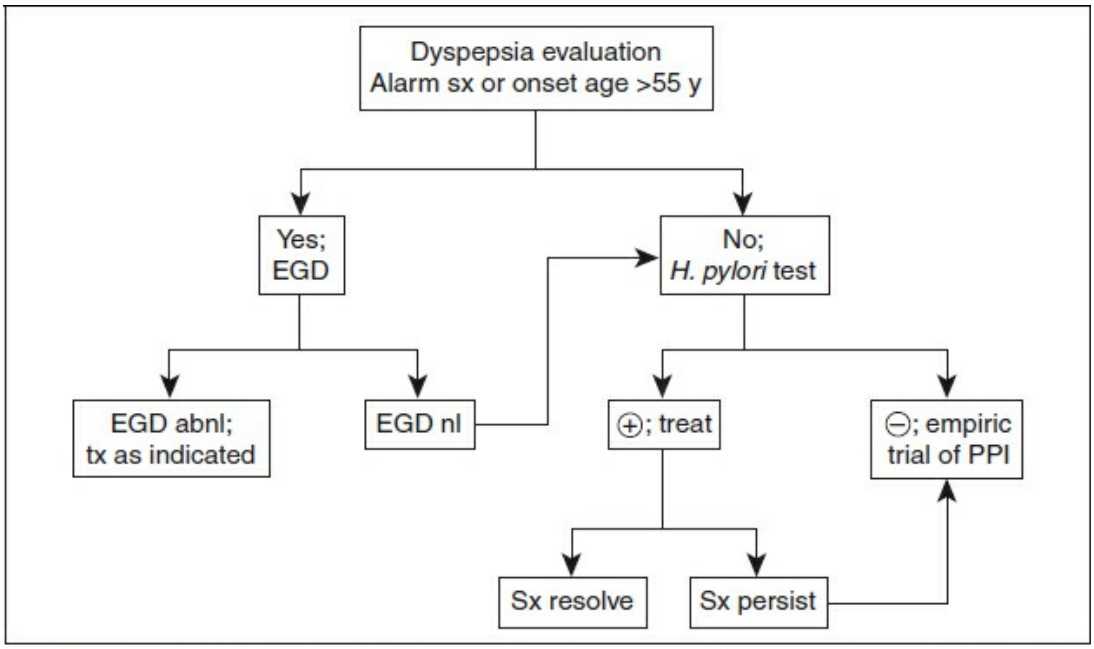


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Figure 5-2. Dyspepsia evaluation

GASTROESOPHAGEAL REFLUX DISEASE

Background (*NEJM* 2008;359:16)

- **Definition:** Reflux w/ troublesome sx or complications (*Am J Gastroenterol* 2006;101:1900); may have *esophageal* or *extraesophageal* sx (below)
- **Complications:** ♂ > ♀; *esophageal:* esophagitis, stricture, Barrett's, adenoCA; *extraesophageal:* laryngitis, cough, asthma (& possibly sinusitis, pulm fibrosis, pharyngitis, recurrent otitis media), w/o heartburn sx, rarely due to GERD alone
- **Epidemiology:** Affects 14–20% of US adults; most common GI-related complaint
- **Risk factors:** Central obesity, smoking, EtOH, 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:** Clinical dx; if CP, cardiac causes should be r/o (see *"Chest Pain"*)

Presentations of GERD	
Typical	*Heartburn:* Retrosternal burning, often postprandial or at evening, worse w/ fatty meals, lying down, or *after* exertion (89% Sp) *Regurgitation:* Sensation of refluxed gastric contents → hypopharynx or pharynx, often assoc w/ sour taste (95% Sp) **History of regurgitation and heartburn = 90% accurate for dx of GERD** Assoc sx: Sleep disturbances, dyspepsia
Atypical	Exercise-induced heartburn (must be distinguished from angina), CP (GERD >> esophageal spasm), cough, wheezing/SOB, hoarseness; n.b. these sxs unlikely to be due to GERD **w/o** concurrent heartburn/regurgitation

- **History:** Ask about RFs as above; PMHx, medications → esophagitis (NSAIDs, alendronate, tetracyclines); meds which can ↑ GERD sx (theophylline, anticholinergics, CCBs, α-antagonists, prostaglandins, nitrates, sedatives)
- **Features suggestive of alternative diagnosis/complications:** Weight loss, dysphagia, early satiety, fevers, odynophagia, persistent vomiting
- **Exam:** General, HEENT, cardiac, pulm, & abd exam
- **Differential diagnosis:** CAD, PUD, esophageal dysmotility, biliary colic, esophagitis
- **Diagnostics: Not required for dx of uncomplicated GERD**
  - **Empiric tx:** 8–wk trial of omeprazole 20–40 mg QD with increase to 40 mg BID after 2 wk if no/partial effect; as sensitive as 24-h pH monitoring in pts w/ erosive esophagitis
  - **Endoscopy:** Up to 50% have nl EGD; indicated if hx/PE suggests complications or alternative dx, sx not responsive to tx, vomiting, concern for extraesophageal sx
  - **Other diagnostic techniques:** pH test may be used if EGD unrevealing/sx refractory, but usually not necessary
  - ***H. pylori* testing:** *Not* routinely recommended for GERD sx (*Am J Gastroenterol* 2013;108:308)

Treatment (*Gastroenterol* 2008;135:1392; *Am J Gastroenterol* 2013;108:308)

- **General approach:** May be treated empirically; if complications suspected (see above) → EGD referral; extraesophageal sx may benefit from tx as part of full eval
- **Nonpharmacologic treatment**
  - *Dietary:* Avoiding foods that ↓ LES pressure or delay gastric emptying *may* help but not a long-term solution in chronic GERD (chocolate, peppermint, carbonated drinks, citrus/tomato, fatty foods, large meals)
  - *Behavioral:* **Weight loss,** head of bed elevation if nocturnal sxs, avoid supine position 3 h after meals, avoid EtOH & **tobacco**
- **Pharmacotherapy** (*Ann Intern Med* 2015;163:ITC1); Rx guided by sx frequency and severity; pt education on proper use of Rx key to effective tx (see table); consider "step-wise" tx
  - *Occasional mild sx:* PRN or standing H2-receptor antagonist (H2RA, 1st-line) or PRN antacid
  - *Moderate–severe sx:* Standing PPI (1st-line) or H2RA

GERD Pharmacotherapy

Class, Mechanism, & Sample Rx	**Notes & Side Effects**
H2-receptor antagonist Competitive inhibition of histamine receptors on parietal cells **Ranitidine 75–150 mg BID**	1st-line for mild or intermittent symptoms *Kinetics:* Onset in 1 h, lasts ~9 h; *S/e:* P450 inhibitor (esp cimetidine) → ↑ levels of phenytoin, warfarin, other Rx; can build tolerance; ↓ B12, drowsiness, myelosuppression (rare)
Proton-pump inhibitor Irreversible deactivation of parietal H^+/K^+ proton pump **Omeprazole** or **pantoprazole 20–40 mg QD–BID, 30 min before meals**	1st-line for mod–severe disease, most effective tx (NNT 3–4), 80–100% efficacy; no evidence for within class difference *Kinetics*: **Cannot be taken PRN** (ineffective; **onset is up to 5 d**) & may develop rebound acid hypersecretion with d/c (self-limited) *S/e:* Atrophic gastritis, ↓ Mg, ↓ B12, impaired Ca absorption (better with Ca citrate than Ca carbonate); growing body of literature/association studies ↑ SEs (see below); interaction with clopidogrel disproven (*NEJM* 2010;363:1909)
Antacids (e.g., $CaCO_4$/Tums) Neutralization of gastric acid	Used as PRN *Kinetics:* Shortest onset of action (30 m) *S/e:* Can affect absorption of other Rx; can → diarrhea or constipation (depends on compound)

$CaCO_4$ 1500–3000 mg PRN sx (max 7.5 g q24h)	

- **PPI Safety:** Multiple associative/observational studies link PPI tx to risk of *C. diff* infection, hepatic encephalopathy in ESLD, osteoporosis, CKD, dementia, and ischemic stroke; further investigation needed but present consensus is that PPI tx results in only a modest increase in absolute risk of each of these complications and PPIs generally safe over short-term; for those with long-term need, downtitration to lowest effective dose, discussion of tx alternatives, and appropriate patient counseling is necessary; assess pts for taper if sx well controlled for several months
- **Combination tx:** H2RA and PPI should *not* be taken together as ↓ PPI effectiveness; there may be benefit to adding QHS H2RA to PPI regimen (dosed several hours apart from PPI); $CaCO_4$ often used as adjunct for breakthrough symptoms
- **Other agents:**
  - Sodium alginate 10–20 mL QID: Physical barrier between esophagus and acid; used as an adjunct to PPIs, availability varies
  - SNRIs/TCAs: May modulate visceral hypertensitivity; used as adjunct in overlapping functional syndromes
- **Surgical therapy:** 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 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:* Incidence ↑ in obese/central adiposity, Caucasian, men, age >50 y, ⊕ reflux sx; decision to screen individualized but consider referral if ≥2 RFs
  - *Surveillance:* If diagnosed, routine surveillance via EGD; no dysplasia → EGD q3–5 y; low-grade dysplasia → q6–12 mo;

high-grade dysplasia → endoscopic mucosal resection > surveillance EGD (*Gastroenterol* 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: As dictated by sx; for refractory extraesophageal sx attributed to GERD which do not respond to PPI

PEPTIC ULCER DISEASE

Background (*Lancet* 2002;360:933; *J Clin Gastroenterol* 1997;24:2)

- **Definition:** PUD refers to focal mucosal damage in the stomach (gastric ulcer, GU) or proximal duodenum (duodenal ulcer, DU); can also occur in esophagus or more distal duodenum in pts w/ hypersecretory states; most frequent cause of UGIB
- **Epidemiology:** Lifetime prevalence up to 10%; ♂ > ♀; most commonly affects 25–64 y/o; incidence is ↓ w/ widespread use of PPI & *H. pylori* eradication (*J Glob Infect Dis* 2011;3:366)
- **Risk factors: *H. pylori* infection** (implicated in 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); others: 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 present w/ epigastric pain or concern for UGIB; ask about risk factors (above) & red flags (below)

Classical Presentation of PUD	
History	Episodic gnawing/burning epigastric pain; **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 *Alleviating sx:* **Relieved by antacids** or antisecretory agents *Assoc sx:* Bloating, fullness
Exam	Often exam findings relatively mild, may have epigastric TTP, ⊕ FOBT, 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, melena or frank GI blood loss, early satiety, anemia, dysphagia), *H. pylori* testing (see *"H. pylori"*)

Postulcer Care (*Gastroenterology* 2016;151:27; *NEJM* 2016;374:2367)

- **General approach:** Once dx confirmed and complications (e.g., UGIB, see *"GI Bleeding"*) assessed/managed, reduce bleeding/recurrence risk using strategies below
- **Treat underlying cause(s):** To promote healing & reduce risk of recurrence: **smoking cessation,** avoid EtOH, *H. pylori:* (see *"H. pylori"*), confirm eradication, avoid NSAIDs (see below)
- **Medication management:** For meds which may ↑ bleeding risk
  - **NSAIDs:** Permanently d/c NSAIDs if possible; if choose to restart, use selective COX-2 inhibitor (e.g., celecoxib) *and* concomitant PPI to ↓ rebleeding risk; risk of rebleeding 4–6% at 6 mo in pts restarted on either (1) standard NSAID + PPI or (2) COX-2 inhibitor alone
  - **Aspirin for ASCVD:** Generally okay to continue (*Ann Intern Med* 2010;152:1)
    - *Primary prevention:* In those w/ UGIB: consider risks/benefits
    - *Secondary prevention:* Restart w/in 7 d (mortality benefit and no ↑ rebleeding risk)
- **Gastric acid suppression: 8 wk for DU & 8–12 wk for GU;** PPI > H2RA but both >90% resolution at f/u; consider long-term suppressive tx in pts on dual anti-PLT agents or otherwise 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 EGD:** 6–12 wk after initial tx for gastric ulcer to r/o malignancy; indicated if ulcer large/complicated or symptoms (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

H. PYLORI

Background (*Lancet* 2009;374:1449; *AFP* 2007;75:351; *Epidemiol Rev* 2000;22:283)

- *Helicobacter pylori* is a gram ⊖ microaerophilic bacterium found in the stomach & proximal duodenum; thought to be oral–oral, fecal–oral, & contaminated water transmission
- **Epidemiology:** Estimated >30% of US adults infected w/ H. pylori; ↑ w/ age, immigrants from developing countries, African–American, & Hispanic populations; ⊕ FHx
- *H. pylori* infection is asx in majority of those infected & reflects colonization *but* accounts for majority (>80%) of PUD & implicated in dyspepsia; infection also assoc w/ ↑ risk of gastric CA (although eradication *not* assoc w/ ↓ risk, so tx not indicated for that purpose)

Evaluation (*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 complete eval in pts w/ alarm features; see *"Dyspepsia"*); may consider if long-term NSAID use or other ↑ risk of developing ulcer
- **Testing while on PPI:** PPI use ↓ Se of all tests *except* serology (which → more false [-]); hold PPI 1 wk prior to nonserologic testing if possible

***H. pylori* Testing Options**	
Serology	**Indicates current or past infection;** not appropriate for pts previously treated, as remains ⊕ for years; Se/Sp 85/79% (*Am*

	J Gastroenterol 1996;91:1138) Best test if ↑ pretest probability (PPV heavily influenced by local prevalence); Only test unaffected by concurrent PPI tx
Stool Antigen	⊕ *only* in current infection; **used to confirm eradication;** RNA testing; Se/Sp >90/90%; ↓ Sp w/ GIB Better than serology if ↓ pretest probability
Urea Breath Test	Can be used for initial dx or to confirm eradication; Se/Sp 95/95% (*Gastroenterol Clin N Am* 2000;29:895) Radiolabeled urea ingested by pts; exhaled breath measured for labeled CO_2 generated by bacterial urease; expensive, variable reimbursement
Endoscopic Tests	Biopsy-based: tissue culture, histology, or rapid urease test (aka "CLO test"): performed on tissue bx to detect for urease-splitting organism

Treatment (*Gastroenterology* 2016;151:51)

- **Choice of regimen:** Given ↑ antibiotic resistance, 4-drug regimen **"quadruple therapy" now 1st-line**; triple therapy reserved for local areas with known (1) clarithromycin resistance <15% and (2) triple-therapy success >85%; recall that more complex regimens generally → ↓ adherence

  PCN allergy: PBMT first-line
- **Duration:** Should be 14-d course for all patients

First-Line Treatment of *H. pylori*	
Regimen (% eradication)	**Medications** (example Rx)
PAMC (88%)	PPI (omeprazole 20 mg BID) Amoxicillin 1 g BID Metronidazole 500 mg **BID** Clarithromycin 500 mg BID
PBMT (77–80%)	PPI (omeprazole 20 mg BID) Bismuth subsalicylate (262 mg) 2 tabs QID Metronidazole 500 mg **TID** Tetracycline 500 mg QID
Regimen Notes	**PPI:** All dosing BID; higher doses okay; may also use, e.g., pantoprazole 40 mg BID **Metronidazole:** For PBMT, QID dosing may be simpler than TID **Bismuth:** Doubling standard dose BID may also be effective; multiple alternative formulations available:

	(1) Colloidal bismuth subcitrate (120 mg): 2 tabs BID or 1 tab QID (2) Bismuth biskalcitrate (140 mg): 3 tabs QID (3) Bismuth subcitrate potassium (140 mg): 3 tabs QID
Triple-Therapy Regimens (see indications, above)	
PAC (68.9%)	PPI (omeprazole 20 mg BID) Amoxicillin 1 g BID Clarithromycin 500 mg BID
PMC	PPI (omeprazole 20 mg BID) Metronidazole 500 mg BID Clarithromycin 500 mg BID
PAM	PPI (omeprazole 20 mg BID) Amoxicillin 1 g BID Metronidazole 500 mg BID
Rescue Regimens (for treatment failure)	
PAL (77–79%)[a]	PPI (omeprazole 20 mg BID) Amoxicillin 1 g BID Levofloxacin 500 mg QD Some evidence that adding bismuth may improve outcomes
PBMT (67–69%)[a]	If not used as initial regimen; see regimen details above

[a]No statistical significance between the 2 regimens in comparative studies

- **Follow-up:** If assoc w/ PUD or persistent dyspepsia after tx, eradication should be confirmed with stool testing 4 wk after tx completed (with pt off PPI × 1 wk before testing if possible); should also be confirmed in pts w/ gastric MALT lymphoma or early gastric CA
- **When to Refer:** >1 treatment failure → infectious disease and/or gastroenterology

DYSPHAGIA

Background (*AFP* 2000;61:3639; *BMJ* 2003;326:433)

- **Definition:** Difficulty passing solids, liquids, or both from oropharynx to stomach
- **Classification:** *Oropharyngeal:* Difficulty transferring food from OP to esophagus

Esophageal: Difficulty passing food from esophagus to stomach

- Dysphagia can be due to wide variety of disorders, can result in significant morbidity or mortality, and is an alarm symptom that always merits further investigation
- **Epidemiology:** Prevalence ↑ w/ age; affects 7–10% of pts >50 y; cancer more likely when pts ♂, >40 y, & present w/ wt loss; in otherwise healthy young men w/ or w/o history of atopy, esophageal dysphagia should warrant GI referral given increased prevalence of eosinophilic esophagitis (*Gastrointest Endosc* 2005;61:80)

Evaluation (*Gastroenterology* 1999;116:455*;* 1999;117:233)

- **General approach:** First, determine likely location of dysfunction based on predominant symptom (may be multifactorial), then further narrow Ddx based on additional hx

Presentation of Dysphagia Disorders	
Oropharyngeal	Difficulty initiating swallow; coughing, choking/aspiration *Structural* (abscess, Zenker diverticulum, tumor, post-XRT) *Neuromuscular* (dementia, MG, Parkinson, stroke)
Esophageal	Sensation of food ± liquids being "stuck" *Mechanical:* Solid > liquid; external or intrinsic compression (stricture, tumor, web, Schatzki ring, web, mediastinal mass) *Motility:* Solid & liquids affected equally (achalasia, scleroderma)

- **History:** Gradual or sudden onset, intermittent (Schatzki ring) vs. progressive (stricture, neoplasm); perceived location of food becoming "stuck" unreliable

  Assoc sx: Heartburn, pulm infections, fever, odynophagia (esophagitis), **weight loss,** CP, xerostomia, regurgitation (achalasia), 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/asthma (eosinophilic esophagitis), Raynaud's

  Meds/toxins: Smoking, EtOH, NSAIDs, alendronate, doxycycline, potassium (pill esophagitis)
- **Exam:** Neuro exam w/ careful CN eval; oral cavity: xerostomia,

thrush; neck exam: thyromegaly, LAD; abd exam

- **Diagnostics:** Varies by location of dysfunction

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 If this is nl or concern for structural cause, consider ENT eval; EGD indicated unless clear contraindications
Esophageal	**EGD:** Most common findings stricture > nl ≥ esophagitis/ulcer > tumor (*Dysphagia* 2012;27:101) If nl, consider MBS → if nl or concern for motility d/o, consider esophageal manometry

- **Referral:** *Oropharyngeal* → SLP eval & tx, ± neurology (e.g., ALS, MG) or ENT (structural); *all patients:* unless clearly OP dysphagia, refer to GI for consideration of endoscopy

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/classification:** 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 Parkinson disease, spinal cord injury), or medication-induced

Evaluation (*AFP* 2011;84:299)

- **General approach:** Consideration of dangerous or correctable causes w/ appropriate eval, & then emphasis on treating sx

- **History:** Onset, diet, fiber/fluid intake, bowel habits, rectal bleeding, alternation w/ diarrhea, abd pain; current & past treatment, including medications
  - *PMHx:* Thyroid, depression, DM, IBS, anorectal disease (fissures), neuro (Parkinson, MS, stroke, spinal cord injury), electrolyte abnormalities, history of vaginal deliveries
  - *Meds:* Many can → constipation, including antacids, iron, opioids, CCBs, TCAs, antihistamines, anticholinergics, antiparkinsonian, Ca supplements, antipsychotics
- **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 either 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 previous colonoscopy in pt >50 y/o → colonoscopy (may consider flex sig, CT colonography, barium enema as alternative depending on circumstances, see *"Disease Screening"*)
- **Assess type of 1° constipation** (recognizing that pt may have >1 process)

Types of Primary Constipation (*NEJM* 2003;349:1360)	
Type	**Presenting Features**
Normal Transit Constipation (NTC)	Most common, nl BM frequency but subjective sensation of constipation → sensory dysfunction (IBS-C)
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;349:1360; *Gastroenterology* 2013;144:218)

- Tx approach varies by subtype:
  - **Defecatory disorder:** Sx (e.g., straining, incomplete evacuation) do not always correlate with level of dysfunction; often requires biofeedback-aided pelvic floor retraining (efficacy well documented in RCTs: >60% respond w/ 5–6 sessions, 30–60 min each) (*Gastroenterology* 2005;129:86)
  - **Slow or normal transit:** Managed as below; STC may be ↓ responsive to osmotics, ↑ responsive to stimulants; emphasis of NTC treatment should be on alleviating subjective symptoms of constipation given normal function
- **Initial treatment:** Should be initiated as maintenance tx
  - **Lifestyle:** ↑ Physical activity may correlate w/ ↓ constipation; ↑ fluid intake does *not* improve chronic constipation unless pt also dehydrated; d/c offending meds as feasible
  - **Fiber: 1st-line treatment,** particularly for NTC: Data limited but safe, inexpensive, & may have other health benefits; can take weeks for desired effect; soluble fibers generally superior to insoluble fibers

    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; may be milder w/ synthetic/semisynthetic fibers (e.g., methylcellulose) than 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 days to take effect; stimulants typically used as "rescue" medication

Selected Pharmacotherapy in Constipation		
Class	**Medication**	**Notes**
Osmotic	**Polyethylene glycol 17 g QD–BID** Mg hydroxide, Mg citrate lactulose	PEG preferred due to ↑ efficacy & ↓ bloating vs. lactulose (*Cochrane*

		Data Syst Rev 2010;7:CD007570) *S/e:* Gas, bloating; caution w/ Mg-containing compounds in CKD (can ↑ serum Mg)
Stimulant	**Senna** (8.6-mg tabs) 2 tabs QD–4 tabs BID Bisacodyl 10 mg PR or 5–10 mg PO up to TIW	Preferred as PRN, effects of long-term use unknown *S/e:* Malabsorption, abd cramps, senna can → reversible staining of colonic wall "melanosis coli"
Secretory	Lubiprostone (typically Rx'd by GI)	Chloride channel activator *S/e:* N/V, teratogen
	Linaclotide (typically Rx'd by GI)	Well tolerated; activates CFTR to stimulate intestinal chloride & fluid secretion (*NEJM* 2011;365:527)
Other	Enemas (tap water, mineral oil, soap suds)	May be stool softener (mineral oil), mechanical lavage (tap water, soap suds), avoid phosphate enema in CKD *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 wk; *chronic:* occurring for >4 wk
- **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
- **Differential diagnosis:** Infectious (viral, bacterial, parasitic), medications, IBD, ischemia
- **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 (thirst, ↓ UOP, orthostasis), myalgias
  - *Exposures:* Recent hospitalization, travel (see *"Travel Medicine"*), camping, anal receptive intercourse (infection including STIs), 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 require additional testing unless persistent (>10–14 d)

Acute Diarrheal Laboratory Testing	
Test	**Indications**

C. diff	Recent abx, hospitalization, immunosuppression, chemotherapy
Fecal WBC	Mod–severe diarrhea, inflammatory sx (low Se)
FOBT	Mod–severe diarrhea, inflammatory sx
Stool Culture	Should not be ordered routinely, dictated by history (<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 to developing world, infant daycare exposure
Specific Organisms	Enterohemorrhagic *E. coli* (EHEC, O157:H7): Foodborne dysentery Vibrio if exposure to raw or undercooked seafood Consider microsporidia, isospora, 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* 2016;111:602)

- **Noninflammatory:** Often self-limited; supportive tx (oral rehydration, loperamide, bismuth subsalicylate; probiotics can ↓ stool freq & duration of sx × 24 h and assist with the gut dysbiosis that can result from antibiotic-associated diarrhea (*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; typically discouraged as most community-acquired diarrhea is viral, not shortened by antibiotics
  - *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 (see "C. difficile"):* 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, severe 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)

- **When to Refer:** If concerned for mod–severe *C. diff,* elderly, immunocompromised, chronically ill, & severe dehydration or unable to maintain PO intake → ED/inpatient

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Chronic Diarrhea

Evaluation (*Gastroenterology* 1999;116:731; 2004;127:287; *NEJM* 1995;332:725)

- **General approach:** May be due to a 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; 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:**
  - **Labs:** CBC, BMP, albumin, anti-TTG/total IgA (see *"Celiac"*), ESR, LFTs, TSH
  - **Stool studies:** FOBT, fecal calprotectin (⊕ suggests infectious/inflammatory), fecal pH (<5.3 suggests CHO malabsorption such as lactose intolerance)

- **Red flags:** Sx <3 mo 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}) Best to calculate rather than measure directly as measured may be artificially ↑ w/ delayed sample processing **Gap >125 (osmotic):** Osmotically active substance drawing water into intestinal lumen → consider lactose intolerance, ↑ sorbitol ingestion (in "sugar-free" items), laxative usage **Gap 50–125 (nl/mixed):** Consider IBS, celiac **Gap <50 (secretory):** Infection (Aeromonas, Giardia), anatomic abnl, endocrinopathy (hyperthyroid, Cushing), malignancy (pheo, VIPoma, carcinoid); bile acid malabsorption s/p ileal resection or CCY
Inflammatory	Fecal calprotectin, **colonoscopy**, stool culture, Giardia Ag testing
Malabsorptive	**Fecal fat,** stool O+P, consider stool chymotrypsin or stool elastase testing for pancreatic insufficiency, stool alpha-1-antitrypsin if concern for protein-losing enteropathy, **colonoscopy** with random bx if RFs for microscopic colitis (>age 60, compatible medication usage, etc)

- **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; random bx useful if concern for microscopic colitis as above

Management (*AFP* 2011;84:1119)

Selected Causes of Chronic Diarrhea	
Phenotype	**Differential Diagnosis**
Watery	*IBS:* Alternating constipation & diarrhea, ♀ > ♂; see *"IBS"* *Lactose intolerance:* Can be postinfectious or occur with aging, can be implicated on basis of timing symptoms to intake, improves w/ lactose-free diet and worsens with rechallenge *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 *UC:* Recurrent abd pain, fever, tenesmus, rectal bleeding, or ⊕ FOBT; see *"IBD"* *Microscopic colitis:* Elderly, ♀ nocturnal diarrhea, ?NSAID assoc *C. diff:* Subacute, recent abx use or hospitalization, fever *Other infections:* Aeromonas, Cryptosporidium, Cyclospora, Entamoeba, Giardia, microsporidia, Strongyloides
Malabsorptive	*Celiac disease:* Fatigue, bloating, anemia; see *"Celiac Disease"* *Giardia:* Gas, "frothy" stool, foul odor, camping/daycare/travel hx *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, bile acid sequestrants, or pancreatic enzyme as dictated by history; tx as per "Acute Diarrhea," above
- **When to refer:** Suspected inflammatory disease, dx unclear despite lab abnormalities, endoscopy indicated, or persistent/severe sx

IRRITABLE BOWEL SYNDROME

Background (*JAMA* 2015;313:949; *Gastroenterology* 2016;150:1262)

- **Definition:** 2016 Rome diagnostic criteria: recurrent abd pain or discomfort occurring, on average, ≥1 d/wk in the last 3 mo, assoc w/ ≥ 2 of the following:
  1. Related to 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 but IBS now considered a spectrum of disease; **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 & increased permeability, stress response & gut mucosal immune activation, altered gut microbiota → dysfunction of neurohormonal CNS–GI system & altered neurotransmitter release/visceral hypersensitivity
- **Epidemiology:** Affects ~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:** 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%); bowel habits, hard/loose stools, frequency, urgency, straining, sense of incomplete evacuation, mucous in stool; aggravating/alleviating factors (defecation, stress, diet)

  PMHx: Depression, anxiety, thyroid or autoimmune d/o, immunosuppression, travel hx

  Meds: Substances which can alter bowel habits (see *“Constipation” and “Diarrhea”*)

  FHx: Autoimmune, GI malignancy, celiac, IBS, IBD

  Social hx: Exercise, current stressors, hx abuse/IPV (see *“Intimate Partner Violence”*)
- **Exam:** Complete exam at time of initial dx, including exam of thyroid, skin, oropharynx, abd & rectal exam w/ 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:** Thyroid disease, celiac, IBD, infection, malignancy, diverticular disease, microscopic colitis, medication effect, lactose intolerance, chronic mesenteric ischemia, bile acid maldigestion
- **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 If IBS-D or IBS-M pt referred for screening colonoscopy, request 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:** Evolving role for dietary modification for IBS sx; small trials reveal significant benefit from gluten-free trial (*Am J Gastroenterol* 2011;106:508; *Gastroenterology* 2013;144:903); FODMAPs may be a trigger of meal-related symptoms in IBS patients, thought 2/2 underlying abnormalities in gut physiology and visceral sensation (*Am J Gastroenterol* 2013;108:707)

  Fiber: Soluble fiber supplements (i.e., psyllium, methylcellulose,

wheat dextrin, calcium polycarbophil) shown to be effective in ↓ overall IBS sx (*Am J Gastroenterol* 2014;109:1367)

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, with poor-quality evidence overall but best evidence for improvement in IBS sxs w/ *Bifidobacterium infantis;* some evidence for *Bifidobacterium lactis* in treating abdominal distention (*J Clin Gastroenterol* 2015;49:S60)
- **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 NNT is 3.2 to benefit 1 pt (*NEJM* 2003;349:2136) 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:CD003460); ↓ postprandial sxs if given 30 min before meals S/e: dry mouth, dizziness, blurred vision Long-term effects unknown
	Peppermint oil	Safe and well-tolerated, felt to provide

		selective inhibition of GI smooth muscle to reduce colonic motor activity in patients with postprandial pain, gas, bloating, and urgency
Diarrhea	Antidiarrheals	Helpful for sx control, no improvement in global sx
	Eluxadoline	New oral agent with mixed opioid effects, reduced symptoms of IBS-D, can result in constipation, nausea, pancreatitis (*NEJM* 2016;374:242)
	Rifaximin (2-wk course)	Global ↓ in sxs/↓ bloating in IBS-D, recently FDA approved for this indication (*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 Linaclotide: cGMP activator, used for IBS-C

- **When to refer:** Severe/refractory sx, dx uncertain, or presence of alarm sx → GI

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/ **diarrhea** from malabsorption or pancreatic insufficiency, **chronic abd pain,** or **unexplained nutritional deficiencies including iron and fat-soluble vitamins;** testing for celiac is part of complete eval for these sx, & celiac dx 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)

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 ≥1 of the following:** Abd pain/bloating, chronic diarrhea; dermatitis herpetiformis, Fe-deficiency anemia unresponsive to PO supplementation
Mod (4–10%) Test; ⊖ serology adequate to r/o disease	IBS, ↑ LFTs, Fe-deficiency anemia (if 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 excluded	↓ BMD, fibromyalgia, chronic fatigue, GERD, chronic or recurrent pancreatitis, alopecia, myalgias/arthralgias, autoimmune liver disease, personal hx, other skin rashes, HA, mood d/o, ADHD, dementia, epilepsy, RLS

- **Complications:** Osteoporosis, ↓ splenic function, neuropathy, ataxia (rare), infertility/ recurrent miscarriage, ulcerative jejunoileitis, &

small bowel lymphoma (rare, complication of long-standing, untreated celiac disease)

- **Diagnosis:** Generally made by serologic screening, followed by confirmatory bx; avoid starting gluten-free diet prior to testing and consider re-challenge if already on GF-diet (↓ Se of both serology and bx off gluten resulting in FN); additionally, trial of gluten-free diet not Se/Sp or specific as test for celiac disease, so should be avoided (*JAMA* 2011;306:1582)
- **Gluten disease Ddx:** Gluten *allergy* (IgE-mediated food, contact, or asthmatic reactions) & gluten (wheat) *sensitivity* (nonimmune, idiopathic response to gluten, improves on GFD)
- **Serology:** Celiac antibodies include anti-tissue transglutaminase (anti-TTG), anti-endomysial antibody (EMA), and anti-deamidated gliadin peptide (DGP)

Celiac Disease Diagnosis	
Standard	✓ **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; false ⊕ can occur in autoimmune disease → may ✓ IgA EMA if concerned
If initial testing ⊖ but ↑ suspicion	Refer for EGD with SB bx
Borderline results:	✓ IgA EMA

- **Biopsy:** If screening ⊕ → refer for confirmatory small bowel bx (villous atrophy, ↑ intraepithelial lymphocytes, crypt elongation); may obtain if screening ⊖ but ↑ suspicion

Management (*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; sx begin to improve in 2–4 wk & intestines heal by 6–24 mo; even minimal intake can → intestinal damage over time; gluten reintroduction typically → re-injury
- **Screen for complications:** Screen for and treat nutritional deficiencies (✓ Fe, folate, vit D, vit B_{12}); 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

INFLAMMATORY BOWEL DISEASE

Background (*NEJM* 2009;361:2066; *Lancet* 2012;380:9853)

- **Definition:** Syndromes of chronic inflammation which primarily affect the GI tract
  - **Crohn disease (CD):** Systemic, often transmural, and granulomatous intestinal inflammation which can occur throughout the GI tract
  - **Ulcerative colitis (UC):** Inflammatory disorder of the colonic mucosa
- **Pathophysiology:** Both CD & UC are thought to result from dysregulation of immune system response to intestinal microbes; however, much of the genetic predispositions, clinical risk factors, presentation, complications, & tx are distinct
- **Epidemiology** (*Gastroenterology* 2012;142:46)
  - **CD:** Bimodal, w/ peak incidence in 20s & 50s; ♀ > ♂; *risk factors:* smoking, ⊕ FHx, recent gastroenteritis, Ashkenazi Jewish heritage
  - **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

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 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**) <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 or 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:* erythema nodosum, pyoderma gangrenosum; *abd:* RLQ mass/tenderness: 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/B_{12}/folate, vit D
  - *Stool studies:* If diarrhea prominent, consider *C. diff,* stool culture, O+P, fecal leukocyte testing, fecal calprotectin (calprotectin released by activated neutrophils, ↑ in stool has Se/Sp 93/96% for IBD) or lactoferrin (*BMJ* 2010;341:c3369)
- **Imaging:** KUB if ?obstruction, **CT** indicated if ?abscess, colitis, alt dx (diverticulitis)
- **Endoscopy:** Flex sig (UC, distal CD) vs. colonoscopy to establish extent of disease
- **Differential diagnosis:** Extensive: infectious colitis, diverticulitis, CRC, celiac disease, chronic pancreatitis, & IBS

Treatment (*BMJ* 2008;336:1062; *Lancet* 2012;380:1590)

- **When to refer:** If severe disease (unstable VS, clinically ill, inadequate PO, ?abscess, obstruction) → ED; otherwise, if suspect IBD based on eval (above) → gastroenterology

- **Monitor for complications:**
  - *Stricture (CD or UC):* Obstructive sx, usually in terminal ileum if 2/2 CD
  - *Fistula (CD):* Enterovesicular (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 wk (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 in pts w/ colonic 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
- **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 for mild UC induction + maintenance; limited data in CD *Route:* PO for ileal or colonic; PR for distal disease (proctitis → suppository; proctosigmoiditis or L-sided colitis → enema) *Specific agent:* Mesalamine, Pentasa (small intestine + colon); Asacol (terminal ileum + R colon), Lialda (terminal ileum + delays to release throughout colon), sulfasalazine

(colon), olsalazine/balsalazide (colon)
Monitoring/SEs: Annual CBC, LFTs, U/A (risk of interstitial nephritis), BUN/Cr, small proportion (<5% of pts) experience idiosyncratic worsening of sx on tx

Escalated therapies (below) should be used in consultation with gastroenterology

Thiopurines: Used as maintenance in UC & CD
✓ TPMT genotype prior to tx to assess risk of toxicity (leukopenia, ↑ LFTs)
Specific agents: 6-MP, AZA
Monitoring/SEs: CBC w/ diff (BM suppression), LFTs, amylase/lipase (pancreatitis) every 2 wk, then q1–3 mo; metabolites also assessed if concerns for toxicity or nonadherence (6-TG, 6-MMP)

Corticosteroids: Typically used as induction, NOT maintenance
Budesonide: High 1st-pass metabolism → ↓ systemic s/e; used in active ileitis or R-sided colon CD
Prednisone: 40–60 mg/d used as induction, 60–80% of pts respond in 2–3 wk
Monitoring/SEs: Multitude of risks related to immunosuppression and corticosteroid therapy/HPA axis suppression

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: vedolizimab, natalizumab (CD); calcineurin inhibitors
Monitoring/SEs: Related to immunosuppression, infusion reaction, lupus-like syndrome, annual TST or T-SPOT, reactivation HBV, contraindicated in heart failure

ABNORMAL LFTs

Background

- Abnormal liver biochemical ("function") tests (LFTs) extremely common; affect 10–20% of general population; usually mild; among these patients, <5% have severe liver disease (*Eur J Gastroenterol Hepatol* 2015;27:1)
- Testing obtained under variety of circumstances, ranging from severe illness to drug monitoring; correct interpretation requires considering clinical presentation *and* 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 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); also ↓ 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 (https://livertox.nih.gov/),** EtOH use, & careful exam
- **Is it severe or is patient symptomatic?** If asx & <2× ULN, recheck → LFTs will normalize in 30% of pts upon retesting (*Ann Int Med* 2008;148:348)
- **What is pattern of elevation?**

Patterns of LFT Abnormalities	
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, consider Ddx 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	✓ HAV IgM, HBsAg, HBsAb, HBcAb, HCV Ab; see *"HBV" & "HCV"* If recent exposure, reasonable to check viral load
Hemochromatosis	Common in pts of Northern European descent ✓ Fe/TIBC ratio: If >45%, ✓ ferritin → if ferritin >400 ng/mL (♂) or >300 ng/mL (♀), ✓ *HFE* gene mutations 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, BMI ≥30 or DM, any e/o liver synthetic dysfunction, or elevated NAFLD fibrosis score
Autoimmune Hepatitis	♀ > ♂ (4:1), bimodal age distribution; ✓ SPEP (80% have ↑ IgG), consider ANA, anti-SMA, soluble liver antigen (SLA), anti-LKM; refer for liver bx
Celiac Disease	Chronic diarrhea, symptoms of pancreatic insufficiency, long-standing IDA, wt loss, fatigue (see *"Celiac Disease"*)
Other	α-1 Antitrypsin deficiency: Assoc w/ panacinar emphysema; ✓ α1AT level (<80 mg/dL suggestive), SPEP 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 (recalling that bili "lags"; expect some delay of bili peak after injury)
  - *PBC (primary biliary cholangitis, formerly primary biliary cirrhosis):* ♀ > ♂, onset 40–50 y; 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, e.g., 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"*)

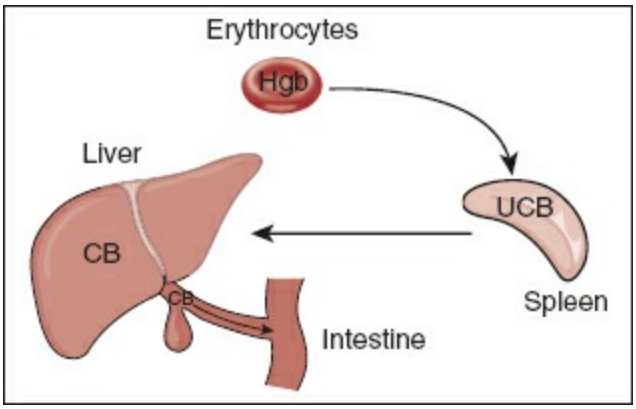
Common Medications Causing Liver Injury, By Pattern (*NEJM* 2006;354:731)

Hepatocellular		Mixed	Cholestatic
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	Enalapril	Erythromycins
Fluoxetine	Rifampin	**Nitrofurantoin**	Estrogens
HAART Rx	Risperidone	Phenobarbital	Irbesartan
Herbals: Kava kava, Germander	Sertraline	Phenytoin	Mirtazapine
INH	**Statins**	Sulfonamides	Phenothiazines
Ketoconazole	Tetracyclines	Trazodone	Terbinafine
Lisinopril	Trazodone	**TMP–SMX**	Tricyclics
	VPA	Verapamil	

Evaluation of Jaundice

Background (*BMJ* 2001;322:33)

- **Definitions: Jaundice:** Yellowish discoloration of the skin, sclera, & mucous membranes due to hyperbilirubinemia (usually appears when total bili >3 mg/dL)
  Hyperbilirubinemia: Accumulation of bili above nl limits (>1.5 mg/dL)
- Etiologies range from benign to life-threatening; full evaluation needed for management
- **Physiology:**



1. Hgb (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 into intestines

- **Pathophysiology:** Excess heme breakdown or defective conjugation → ↑ unconjugated ("indirect") bili; impaired excretion, biliary obstruction, or epithelial damage → ↑ conjugated ("direct") bili

Evaluation (*AFP* 2004;69:299)

- **General approach:** Characterize type of bilirubinemia (predominantly indirect or mixed?) to guide Ddx; 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 "above")
  PMHx: Liver disease, HIV, gallstones, wt loss, autoimmune disease, abd surgery (e.g., CCY), FHx liver disease
- **Exam:** Jaundice (conjunctival, sublingual), 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

Differential Diagnosis (*Best Pract Res Clin Gastroenterol* 2010;24:555)

Selected Causes of Indirect 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; clinical dx; **benign;** can offer reassurance Crigler–Najjar: Conjugation enzyme deficiency, rare
Selected Causes of Direct Hyperbilirubinemia	
Obstruction	*Intrahepatic:* PBC, medications (OCPs, erythromycin) *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

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 of 1970/80s and rising burden of NAFLD (*Gastroenterology* 2010;138:513; *Hepatology* 2016;64(1):73)

- **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; median survival w/ compensated cirrhosis ~9 y, median survival w/ decompensated cirrhosis 1.6 y (*Hepatology* 1987;7:122)
- **Risk factors for decompensation:** (*Hepatology* 2011;54:555; 2012;56:1983)
  - *Clinical:* Obesity, EtOH use, smoking, new viral hepatitis, other hepatic insult incl DILI
  - *Biochemical:* MELD >10, albumin <4 g/dL, HVPG >10 mmHg (*Gastroenterol* 2007;133:481)

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 evidence of/risk factors for progression and undergo regular HCC surveillance
- **History:** Assess for risk factors of liver injury: *PMHx:* HCV, HBV, obesity, HLD, DM; *social hx:* EtOH use, lifetime or ongoing hx of IDU; *Meds:* APAP, NSAIDs (see *"Abnormal LFTs"*)
- **Exam:** Examine for evidence of portal HTN & hepatic insufficiency
  - *HEENT:* Scleral icterus; *chest:* gynecomastia; *GI:* firm, nodular liver, hepatosplenomegaly, **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's nails** (⊕ LR 16), silver-white discoloration of proximal nail bed; *neuro:* **asterixis** (⊕ LR 10)
- **Labs:** Hallmarks of cirrhosis are synthetic dysfunction, evidenced by ↓ alb (⊕ LR 3.5 in alb <3.5 g/dL) and ↑ INR (⊕ LR 5 if abnl); other findings below
  - *CBC:* Neutropenia, anemia, ↓ **PLT** (due to splenomegaly; ⊕ LR for cirrhosis of 6.8 if PLT <160 K)
  - *BMP:* ↓ Na, Cr assoc w/ prognosis (MELD score)
  - *LFTs:* Conjugated hyperbilirubinemia (↑ total bilirubin, ⊕ LR 2.7 if TB >1.2), ↑ Aφ/GGT, often ↑ AST/ALT but correlates poorly w/ disease severity

MELD Score	3 Mo 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** noninvasive measures (Fibroscan or FibroSURE, strongly validated in chronic HBV and HCV), **hepatology referral**
- **Prognosis:** MELD (Model for End-Stage Liver Disease) score: **TB, 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 tx, wt loss; with established cirrhosis, HCV treatment should only be undertaken in consultation with hepatologist given evolving and controversial implications
- **Immunizations:** HAV, HBV, influenza, pneumococcus
- **Counseling**

  Lifestyle: EtOH abstinence, tobacco cessation; limited data suggest 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 med changes or 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 nearly 2x that of

healthy adults (1–1.5 g/kg/d vs. 0.8 g/kg/d); supplement vit A, D, E, & K, selenium, zinc; no CHO restriction (*Clin Gastroenterol Hepatol* 2012;10:117)

- **Screening for Complications of Cirrhosis:** See table below

Screening in Compensated Cirrhosis	
Complication	**Screening Modality**
HCC	RUQ U/S or MRI ± AFP q6–12 mo → ↓ mortality (*Clin Gastroenterol Hepatol* 2007;5:508)
Varices	EGD at time of dx, then q3y if no varices or at new decompensation
Decompensation	Hx/PE at routine visits, CBC, BMP, LFTs, INR q3–6 mo

- **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 for all in this group (see *"Advance Care Planning"*)
- **General approach:** 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, carvedilol, propranolol, goal HR 60) 1° *prevention:* Pts w/ varices 2° *prevention:* βB as above + endoscopic band ligation (↓ mortality > EBL alone) (*Hepatology* 2000;32:461) *Refractory/recurrent:* Consider TIPS *When to discontinue:* History of **SBP**, refractory volume issues, hepatorenal syndrome
SBP	*Concern for current SBP:* Refer to ED *Ppx:* Cipro 500 mg QD or TMP–SMX 1° *prevention:* Pts w/ ascitic TP <1.5 g/dL **and** altered renal function (≥1.2 mg/dL, BUN ≥25 mg/dL, Na ≤130 mEq/L) **or** liver failure (Child–Pugh score ≥9 and a bilirubin ≥3 mg/dL) 2° *prevention:* Indicated in all pts w/ hx SBP

Ascites	*New/worsening ascites:* Refer to ED *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) (preferred ratio for K^+ balance: 50-mg spironolactone:20-mg furosemide), goal loss 2 lb/wk; monitor BUN/Cr, K, Na; reduce/hold diuretics if Cr incr. *Refractory:* Serial LVP + albumin, TIPS
Encephalopathy	*New/worsening encephalopathy:* Refer to ED *Stable:* Diet: at least 1–1.5 g/kg/d protein (no restriction); lactulose 30 mL titrated to 2–3 loose BMs/d; consider adding rifaximin 550 mg BID, can ↓ hospitalizations (*NEJM* 2010;362:1071) *Refractory:* Add rifaximin
Hepatorenal Syndrome	Typically in pts w/ refractory ascites—HRS1 rapidly progressive, ↑ Cr (median survival 2 wk), HRS2 gradual (med survival 6 mo) **Hold diuretics** in any pt w/ ↑ Cr to >1.5 mg/dL or ↑ 1.5× baseline & discuss w/ hepatology/nephrology (*Transp* 1995;59:361) Acute ↑ Cr → ED for albumin challenge & r/o other causes
Transplant eval	1st episode of decompensation, HCC, or MELD ≥14

GALLSTONES

Background (*NEJM* 2008;358:2804; https://www.niddk.nih.gov/; *BMJ* 2007;335:295)

- **Definitions: Gallstones:** Small, crystallized concretions of bile which form in the gallbladder; **cholelithiasis (biliary colic):** development of symptomatic disease due to temporary blockage of biliary tree by gallstones; **cholecystitis:** infection or ischemia of gallbladder (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 altered ratio of components (↑ cholesterol, ↑ bili, ↓ bile salts) or incomplete/infrequent gallbladder emptying
- **Epidemiology:** Majority of US adults have gallstones; 10–15% lifetime prevalence of symptomatic disease
- **Natural history:** *Asx gallstones:* 10% of these pts 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); obesity, rapid wt loss, Native American or Hispanic ethnicity, ⊕ FHx, DM (↑ risk of gallstones & ↑ risk of sx disease/complications), age >60; also TPN, sickle cell, cirrhosis, Crohn disease

- **Pts at increased risk of complications from gallstones:** DM, sickle cell, hereditary spherocytosis, s/p gastric bypass

Evaluation

- Varies by clinical scenario; for those w/ incidentally discovered gallstones, assess for sx or presence of complication risk factors (above); for those in whom etiology of abdominal pain uncertain, see "*Abdominal Pain*"

Classic Presentation of Gallstone Disease	
Cholelithiasis	Episodic RUQ or epigastric pain, can be poorly localized, w/ abrupt onset that typically resolves within hours, often after meals or in the evening; may radiate to scapula, R shoulder/back, ±N/V
Acute Cholecystitis	Often w/ hx of episodes as above; similar sx but persistent, localizes to RUQ, accompanied by fever/systemic sx

- **Exam:** May be normal in pt w/cholelithiasis; in acute cholecystitis, evaluate for fever, RUQ pain, and Murphy sign (pain w/ deep inspiration during palpation of RUQ); should have full abdominal exam; look for jaundice
- **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 of Oddi dysfunction, biliary dyskinesia

Management

- Suspected acute cholecystitis (fever, acute RUQ pain): send to ED for treatment
- **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 indefinite 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 or advanced/functional GB imaging, e.g., HIDA scan
- **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 GB cancer (GB polyps, porcelain GB); these pts and those with increased risk of complications from GB disease may benefit from discussion w/ surgeon re: risks/benefits (*Cochrane Database Syst Rev* 2007;1:CD006230)

PANCREATIC DISEASE

Acute Pancreatitis

Background (*Lancet* 2008;371:143; *NEJM* 2016;375:1972)

- **Definition:** Pancreatic inflammation, ranging from mild/interstitial to extensive necrosis
- **Epidemiology:** Overall incidence increasing in US; higher incidence w/ ↑ age, African–Americans; majority of cases mild but 20% severe (assoc w/ ↑ morbidity/mortality)
- **Risk factors:** Smoking (↑ risk of EtOH-induced & idiopathic pancreatitis); obesity (↑ severity & incidence); DM2 (2–3× ↑ risk), EtOH → 4× ↑ risk of acute pancreatitis and ↑ risk of progression to chronic pancreatitis

Selected Etiologies for Pancreatitis	
Obstructive	**Gallstones** (40% of all cases), cysts, ?pancreatic divisum
Meds/Toxic	**EtOH** (30%; often >5 y heavy consumption), organophosphates *Meds:* Usually mild; many implicated but most commonly azathioprine, 6-MP, valproic acid, ACEI, and mesalamine; also HAART (lamivudine, nelfinavir); ?DPP-4 inhibitors; evidence suggests GLP-4 *not* assoc w/ pancreatitis

Metabolic	**Hyperlipidemia** (2–5%; fasting TG >1000 mg/dL), hypercalcemia
Genetic, Autoimmune	**Autoimmune** (IgG4 disease; more commonly presents as pancreatic mass), SLE, Sjögren
Other	*Post-procedural:* ERCP, abdominal, or cardiac surgery *Infection:* Viral (mumps, CMV, VZV), parasitic (Ascaris, Clonorchis)

- **Complications:** Systemic (AKI, ARDS, DIC), metabolic (↓ Ca, hyperglycemia), acute fluid collection, necrosis with resultant superinfection, pseudocyst

Evaluation (*Ann Intern Med* 2010;153:ITC51; *Gut* 2013;62:102)

- **General approach:** Most pts who p/w acute pancreatitis require inpt tx; dx and etiology can often be made in clinic setting
- **Diagnosis:** based on ≥2 of the following: (1) typical presentation, (2) serum lipase or amylase >3x ULN, and (3) evidence of pancreatitis on imaging (CT or MR)

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 pain w/ or w/o palpation; may radiate to chest, back, flank ± ↓ bowel sounds; pt may bend forward ("knee–chest" position) to ↓ pain if peritonitis present

- **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 (combo 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: CT** in most pts to confirm dx and assess complications (fluid collection, necrosis) RUQ U/S in all pts w/ first episode (visualizes gallstones, not pancreatitis itself)

Urgent ERCP (inpt) indicated for e/o sepsis with gallstone pancreatitis or 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:** No rebound tenderness, nl HCT, & nl serum Cr predicts a nonsevere course w/ 98% accuracy

Treatment (*Gastroenterology* 2007;132:2022)

- Most acute pancreatitis managed in inpt setting (see Red Flags above); mild cases *rarely* 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 Disorder"*); smoking cessation; adherence to diet, lipid-lowering medication if ↑ TG

Chronic Pancreatitis

Background (*Gastroenterology* 1998;115:763; *Pancreas* 2014;43:1143, *AFP* 2007;76:1679)

- **Definition:** Chronic inflammation which leads to progressive fibrosis & destruction of pancreatic cells; can → pain (80–90%), endocrine (>40%) and/or exocrine (10%) insufficiency & ↑ risk of pancreatic CA
- **Etiology:** Toxic-metabolic: **EtOH** (45–65% of cases, risk greatest at >4–5 drinks/d), **smoking;** smoking + EtOH → ↑↑ risk)**;** idiopathic, genetic, recurrent/severe acute pancreatitis, autoimmune (hypergammaglobulinemia, ↑ IgG4), obstructive, idiopathic
- **Epidemiology:** ♂ > ♀, age at dx typically 35–55 y
- **Pathophysiology:** Recurrent acute pancreatitis necessary but not sufficient; "two-hit hypothesis" of preexisting acute pancreatitis RF +

initial acute pancreatitis → immune system activation → progression to chronic pancreatitis

- **Complications:** Pseudocyst/abscess, pancreatic CA (13.3x ↑ risk, up to 4% incidence over 20 y) (*Best Pract Res Clin Gastroenterol* 2010;24:349), pseudoaneurysm of adjacent arteries, portal vein thrombosis, CBD stricture, duodenal stenosis

Evaluation (*Clin Gastroenterol Hepatol* 2012;10:108; *Pancreas* 2014;43:1143)

- **General approach:** Sx develop over years; diagnosed based on imaging + lab findings
- **History:** Intermittent → chronic epigastric pain, often postprandial; e/o pancreatic insufficiency (steatorrhea, weight loss, hyperglycemia), risk factors (alcohol, tobacco, family history)
- **Labs:** Amylase/lipase often nl; may have ↑ AΦ, TB, ↑ glucose, ↑ fecal fat, vit D; consider fecal elastase (↓) or serum trypsin (↓) if ? of exocrine insufficiency
- **Imaging: CT** initial test; classic findings = calcification in combination w/ atrophy or dilated duct; if inconclusive or nondiagnostic → additional testing (below)
- **Additional testing:** Done by specialist; if CT inconclusive or nondiagnostic → EUS, MRI w/ MRCP; if this is unrevealing → pancreatic function testing, ERCP
- **Differential diagnosis:** Pancreatic CA, IPMN, BD/duodenal obstruction

Treatment (*Gastroenterology* 2013;144:1282; *Lancet* 2016;387:1957)

- **General approach:** Management based on slowing progression, managing pain, endocrine/exocrine insufficiency, and potential complications (biliary obstruction, bleeding, malignancy); most pts managed w/ help of GI specialist (below)
- **When to refer:** Consider GI referral in all cases; refer if dx unclear, no clear etiology, or suspect an etiology other than EtOH; if sx persistent/severe, refer for evaluation & consideration of endoscopic/surgical tx; low threshold for inpatient 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, Ca/Vit D supplementation (consider BMD testing)

- **Analgesia:** Consider APAP/NSAID, then tramadol, pregabalin/gabapentin, SSRI/SNRI/TCA (see *"Chronic Pain"*)
- **Exocrine/endocrine treatment:** If insufficient, pancreatic supplementation (e.g., pancrelipase w/ meals; can add PPI, H2RA to ↑ activity); for DM, may use metformin but often poorly tolerated; particularly prone to hypoglycemia when on insulin (see *"Diabetes"*)

Pancreatic Cysts

Background (*Gastroenterology* 2015;148:819; *JAMA* 2016;315:1882)

- **Asymptomatic ("incidental") pancreatic cysts** diagnosed with ↑ frequency 2/2 ↑ frequency of cross-sectional imaging; detected in 2–20% of pts who undergo advanced imaging for unrelated reasons, incidence ↑ w/ age
- **Classification:** Multiple types of cysts; 2 types are precursors for pancreatic adenoCA
  - *Premalignant* (30%): Mucinous cystic neoplasms and intraductal papillary mucinous neoplasms (IPMNs)
  - *Benign:* Serous cystic neoplasms (20%)
  - *Pseudocysts* (30%): Not malignant: assoc w/ pancreatitis (often 4–6 wk after acute attack); "pseudo" b/c lining w/o epithelium; if suspected → GI referral given risk of complications
- **Natural history: Incidental MRI lesions unlikely to be malignant:** (~1 in 10,000 chance of mucinous cystadenoCA, 1.7 in 10,000 chance of ductal adenoCA); malignant transformation rate also very low, ~0.24% annually; **even among lower-risk patients with higher-risk features, mortality from nonpancreatic CA > pancreatic CA** (*Am J Gastroenterol* 2017;112:1330)
- **Higher-risk features:** Cyst size >3 cm (3x ↑ risk of malignancy), solid component (8x ↑ risk), dilated pancreatic duct

Evaluation (*Gastroenterology* 2015;148:819)

- Before embarking on surveillance strategy, consider pt's wishes, risk tolerance, life-expectancy, and pt willingness to consider/appropriateness of surgery if the cyst has/develops high-

risk features (still relatively low absolute CA risk and ~2% mortality rate w/ surgery) (see "*Disease Screening*")

- **Symptomatic cysts, those w/ higher-risk features (see above) or main-duct IPMNs:** GI referral for EUS w/ FNA; high-grade dysplasia or concerning features then → surgery referral
- **Asymptomatic cysts:** Per 2015 AGA guidelines, dedicated MRI/MRCP: if no worrisome/higher-risk features, repeat MRI in 1 y; if stable, repeat MRI in 1–2 y; if stable then, generally d/c surveillance, although may consider extended surveillance in pts at ↑ risk or w/ certain imaging features (*Am J Gastroenterol* 2017;112:1153)

GI BLEEDING

Background (*Essentials of Gastroenterology* 2012:317)

- Hemodynamically significant or acute bleeding episodes warrant ED visit ± admission; however, mild or chronic GIB may be managed as outpatients
- **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 evidenced by ⊕ FOBT or Fe-deficiency anemia
- **Risk factors:** ↑ Age, liver disease, prior hx, NSAID, or anticoagulant/antiplatelet 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 admission warranted (any red flags); if not, proceed w/ evaluation
- **Indications for urgent evaluation:** Concern for hemodynamically significant bleed (HoTN, tachycardia, orthostasis), comorbidities (ESLD, CHF, CAD), or symptomatic anemia → ED
- **Bleeding symptoms:** Hematemesis, "coffee-ground emesis"—dark 2/2 exposure of heme to gastric contents; *melena* (black, tarry, malodorous stool from digested blood), *hematochezia* (maroon-colored stool assoc w/ brisk UGIB vs. LGIB), 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 symptomatic anemia (DOE/SOB, fatigue)
  Alt source of blood: Epistaxis, 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 Lower GI Bleeding	
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 (see *"Diverticular Disease"*)
IBD	Episodes of tenesmus, urgency, fatigue, fevers, diarrhea w/ blood or hematochezia (see *"IBD"*)
Hemorrhoids	Constipation, blood on toilet paper or in bowl, can coat exterior of 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, weight loss, vasculopathy (see *"Diarrhea"*)
Selected Causes of Mild or Occult Upper GI Bleeding	
Esophagitis/Ulcer	Dysphagia, odynophagia; infection, pill-induced, GERD, immunosuppression
Gastritis/GU Duodenitis/DU	Epigastric pain, NSAID use, ASA, EtOH (see *"PUD"*), positive *H. pylori*
Gastric Cancer	Early satiety, abd pain, dyspepsia (*Gut* 1997;41:142)

Angiodysplasia	CKD/ESRD; HHT, GAVE, AS, assoc w/ ASA/NSAID use
Esophageal CA	Wt loss, older ♂, dysphagia, hx of smoking/EtOH use
Celiac	⊕ FHx, steatorrhea, bloating (see *"Celiac"*)

- **Lab studies:** Hgb/HCT (↓ often "delayed" during acute bleed due to hemoconcentration), MCV, Fe studies; consider BMP, coags, LFTs; further labs as directed by hx/PE

Management

- **Occult bleeding:** Referral for colonoscopy ± EGD (dependent on presentation; upper GI source more common in pts **w/o** Fe-deficiency anemia or those with upper GI sx [heartburn, dysphagia, odynophagia, N/V, dyspepsia]) (*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
- **Positive FOBT obtained for colorectal cancer screening:** colonoscopy
- **All pts w/ upper GI or alarm symptoms** (e.g., abd pain, dysphagia, wt loss): EGD
- If hx/PE consistent w/ LGIB of known cause (e.g., hemorrhoids), no e/o iron-deficiency anemia **and** recent colonoscopy, reasonable to treat underlying cause; GI referral if bleeding persists/recurs

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:* above dentate line, viscerally innervated → painless; *external hemorrhoids:* below dentate line, somatic innervation → pain
- **Pathophysiology:** ↑ Intra-abdominal pressure (straining, constipation, pregnancy, ascites) → dilation of submucosal vascular tissue + weakening of supporting connective tissue → descent/prolapse of hemorrhoid

- **Epidemiology:** Prevalence: 4–30%; variable estimates due to wide range in severity & whether mild and/or unreported disease included; one of the 3 most common outpatient GI diagnoses; peak prevalence ~45–65 y
- **Differential diagnosis:** Skin tags (may be hemorrhoidal remnant), anal warts, fistula or perirectal abscess (Crohn's), anal fissure, perianal dermatitis, tumor, polyp, rectal prolapse, rectal ulceration, rectal STI (GC/CT)

Evaluation (*NEJM* 2014;371:944)

- **History:** Ask about onset, bowel habits, straining, fiber and fluid intake, if c/o bleeding, assess severity (see *"GI Bleeding"*); classical sx of hemorrhoids include:
  - *Bleeding:* BRBPR w/ or after defecation, blood on toilet tissue or drops in bowl (60%)
  - *Pruritus:* 2/2 inflammation/hygiene difficulties (55%)
  - *Soiling:* (10%)
  - *Pain:* Distention from engorged vein (20%); thrombosis can → acute discomfort
- **Red flags:** Change in bowel habits, abd pain/bloating, weight loss, blood in stool, ⊕ FHx colorectal CA, overdue for CRC screening
- **Exam:** Abdominal, **perineal,** digital rectal, and anoscopy exam; classical findings: **venous dilation w/ distortion of anal architecture;** *external*: **often dull pink;** *internal:* dilated purple–blue veins; seen on anoscopy or at anus if prolapsed
- **Diagnostics:** FOBT; 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, ⊕ FOBT, or red flag sx

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")*; more research needed on PO bioflavonoids

Rx: Topical steroids (avoid prolonged use, limited efficacy data), anesthetics, astringents, and/or antiseptics*; thrombosed veins:* topical lidocaine cream

- **Surgical management:** Indicated for mod–severe sx (primarily with internal hemorrhoids) 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
- **Gastroenterology 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 tissue or streaking stool surface
- **Exam:** Perineal exam ± anoscopy → visible tear, posterior midline > anterior midline, off midline may suggest 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 2/2 anal canal trauma from hard stool → pain w/ defecation → ↑ involuntary resting internal anal sphincter tone→ more trauma
- **Treatment:** Stool softeners (see *"Constipation"*); for chronic/refractory sx → GI/colorectal surgery for consideration of alt tx (can include topical CCB, botulinum injection); no role for manual sphincter dilatation (sphincter damage → incontinence)
- **When to refer:** Chronic, refractory to stool softeners

DIVERTICULAR DISEASE

Background (*NEJM* 2007;357:2057; *J Clin Gastroenterol* 1999;94:3110)

- **Definitions: Diverticula:** Pouch-like 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 colonic mucosa through weakened areas of the bowel wall (adjacent to vasa recta); *diverticulitis* thought to be 2/2 stasis/obstruction at neck of individual diverticulum → local infection/ischemia
- **Natural history:** Most pts w/ diverticulosis are asx, but some develop diverticular disease: *Diverticular hemorrhage* (~3–5%): responsible for ~23% of all LGIB cases (see *"GI Bleeding"*) *Diverticulitis* (~10–25%): 10–33% of this group 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 typically after age 50
- **Risk factors:** *For diverticular disease:* Low-fiber diet (↑ 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)

Treatment (*Nat Rev Gastroenterol Hepatol* 2015;12:629)

- **Diet:** Fiber data somewhat conflicting but intake may improve sx & ↓ diverticulitis risk; red meat intake may ↑ diverticulitis sx/complications; **not** assoc w/ nuts & popcorn intake
- **Lifestyle:** ↑ Physical activity can ↓ risk of diverticular bleeding & diverticulitis; wt loss & smoking cessation interventions not well-studied; moderate EtOH intake recommended

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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 10 (*Dis Colon Rectum* 2010;53:896)
- **Differential diagnosis:** IBD, PID, ectopic pregnancy, cystitis, infectious colitis, colon CA
- **Labs:** CBC, BMP; consider U/A, β-hCG
- **Imaging:** Indicated if dx uncertain, presentation severe, or refractory; CT preferred
- **Endoscopy:** Not performed in acute setting 2/2 ↑ risk perforation, performed 6–8 weeks after treatment 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; *Aliment Pharmacol Ther* 2015;42(6):664)

- **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 TMP–SMX DS BID **and** metronidazole 500 mg TID–QID *Alt:* Amox/clav 875/125 or 1000/62.5 BID

- **All patients: Colonoscopy** at 6–8 wk unless negative CRC screening within past year; begin high-fiber diet 6–8 wk after resolution of acute sx
- **When to refer: If red flags** (above), e/o complications on imaging, advanced age or multiple comorbidities, PO or outpatient medication intolerance → ED/hospital admission; pts w/ recurrent disease (>2 episodes), complications, or younger age should have surgical eval

ANEMIA

Background (*NEJM* 1999;341:1986; 2005;352:1011; 353:1135; 2015;372:1832; 373:1649)

- **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, ACEI, volume status

Causes of Anemia (*AFP* 2000;62:2255; 2009;79:203; 2010;82:1117; *NEJM* 2014;371:1324)
Microcytic: Iron/copper deficiency, anemia of chronic dz, lead poisoning, congenital/acquired sideroblastic anemias; thalassemias & hemoglobinopathies
Normocytic: Anemia of chronic dz, early iron deficiency, CKD, hypothyroidism, bleeding, hypersplenism, hemolysis (spherocytosis, sickle cell, G6PD, autoimmune, mechanical)
Macrocytic: B_{12}/folate deficiency, ↑ reticulocytes, medications (dozens, inc hydroxyurea, AZT, chemotherapy), EtOH, liver dz, hypothyroidism, myelodysplastic/myeloproliferative dz

- **Pathophysiology:** Erythropoietin produced in kidney stimulates hematopoiesis in the bone marrow; Nl RBC life ~120 d; hemolysis considered when life <120 d; in many pts iron deficiency is multifactorial

Anemias with ↑ Erythrocyte Destruction (*AFP* 2004;69:2599)
DDx: Sickle cell, thalassemia major, hereditary spherocytosis, autoimmune, infectious (malaria, babesia, bartonella), G6PD deficiency, hypersplenism, medications (dapsone), liver dz, autoimmune hemolytic anemia, microangiopathy (i.e., aortic stenosis), pulmonary hemosiderosis. Hemolysis may be intravascular (mechanical trauma, paroxysmal nocturnal or cold hemoglobinurias, cold agglutin dz, infection, complement fixation) or extravascular in liver/spleen (antibody fixation, inability to deform)
Autoimmune: ⊕ direct Coombs; cold agglutinins (IgM, found in mycoplasma PNA, mononucleosis) or warm (IgG, found in autoimmune dz, drug exposure (dozens reported, common culprits include penicillins, NSAIDs)) target RBC surface proteins → destruction;

cold or warm agglutinins found in malignancy (CLL, lymphoma, Waldenstrom)

Evan's syndrome: Warm autoimmune hemolytic anemia + ITP

Fragmentation hemolysis: ↑ Schistocytes (>1%) found in disseminated intravascular coagulation, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, & HELLP syndrome (*Am J Hematol* 2004;75:18); fragmentation may also be seen w/ faulty prosthetic heart valves, malignancy, severe HTN, hypersplenism, & after chemo

Glucose 6-phosphate dehydrogenase (G6PD) deficiency: NADPH produced by G6PD protects RBC from oxidative stress; X-linked; ↑ oxidants from physiologic stress, meds (i.e., acetaminophen, aspirin, chloroquine, colchicine, nitrofurantoin, phenazyopyridine, primaquine, sulfamethoxazole) → ↑ oxidative damage → 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° to ↑ iron

Anemias with Decreased Erythrocyte Production (Low Reticulocyte Count)

DDx: Iron, B_{12}, folate deficiency (Chap X) due to malnutrition, malabsorption (celiac dz, *H. pylori,* atrophic gastritis, gastric bypass); marrow problems (MDS, tumor, aplastic anemia, medications, XRT); ↓ erythropoietin (renal failure), hypothyroidism, hypogonadism; chronic dz (↓ absorption, ↓ macrophage release)

Iron deficiency: Iron deficiency 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 Hgb; iron stores (mg) may be estimated by 8–10 × ferritin (ng/mL); inflammatory dz (i.e., RA), ↑ ferritin by ~3-fold (*Blood* 2003;101:3359; *Semin Hematol* 1982;19:6); ↑ risk in pts with vegetarian/vegan diets & athletes (Fe loss via GIB & exercise-induced hemolysis); pts w/ obesity/CHF may be iron deficient due to subclinical inflammation (*NEJM* 2015;372:1832)

Anemia of chronic disease: ↓ marrow RBC production 2/2 to chronic illness

Elderly: 20–30% of pts have anemia of ? etiology, likely multifactorial & related to ↓ stem cells, hypogonadism, ↓ erythropoietin, & 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

EtOH abuse: ↓ heme synthesis, malnutrition, variceal bleeding; macrocytosis

Acquired pure red cell aplasia: ↓ RBC production, absent retics, & absence of RBC precursors in marrow; most cases idiopathic; may be assoc w/ leukemia, MDS, thymoma, drugs (INH, valproic acid, mycophenolic acid), parvovirus, & autoimmune dz

Aplastic anemia: Hematopoietic stem cell deficiency/failure → pancytopenia w/o splenomegaly → anemia + recurrent infections & bleeding. Congenital (Fanconi anemia), acquired (drugs - chloramphenicol, sulfonamides, phenytoin, carbamazepine, valproic acid, indomethacin; infection - parvovirus, EBV, hepatitis, HIV), & idiopathic (*Lancet* 1995;346:228). Diagnosed by BmBx. 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), diverticular dz, malignancy

Evaluation

- **History:** Duration of sx; exertional dyspnea, fatigue, dizziness, HA, palpitations, ↓ concentration, syncope, menorrhagia, melena, hematochezia, bone pain, diet (vegetarian/vegan); signs of systemic dz (fevers, night sweats, anorexia, wt loss, malaise); meds (esp NSAIDS, aspirin, PPI), EtOH, alternative meds; pica (craving items not suitable as food), geophagia (craving clay/dirt), pagophagia (craving ice); restless leg syndrome (Fe deficiency); ethnicity (i.e., Mediterranean) & FHx of hematologic dz/malignancy or bleeding d/o; blood transfusion/donation hx; sx on cold exposure (cold agglutinin hemolytic anemia); personal hx of *H. pylori*, PUD, sprue, IBD, bariatric surgery/gastrectomy, diverticular dz, hemorrhoids; compliance with oral iron therapy; Mediterranean/north African/south east Asian ancestry (thalassemia)

  Abnormal menstrual bleeding: Changing pads >q3h. >21 pads/cycle, need to change pad at night (*Am J Obstet Gynecol* 2004;190:1216)
- **Exam:** Pallor (skin, palmar creases, oral mucus membranes, nail beds, palpebral conjunctiva), tachycardia, orthostatic VS, systolic flow murmur (↑ CO), atrophic glossitis (Fe, folate, B_{12} def), angular cheilosis, jaundice (hemolysis), splenomegaly, koilonychia (spoon-like fingernails seen in Fe deficiency); lymph node exam
- **Workup:** CBC w/ differential & RBC indices, retic count, peripheral smear (*NEJM* 2005;353:498), Chem-12, stool guaiac. Further w/u based on clinical suspicion: Iron, TIBC, ferritin, folate, B_{12}, Hgb electrophoresis, TSH, erythropoietin, SPEP, *H. pylori*, colonoscopy/EGD, ANA, TTG for celiac dz (Chap X); referral to hematology for BmBx if Dx unclear despite above w/u

  Reticulocyte index: [reticulocyte count × (Pt's HCT/nl HCT)]/maturation factor; maturation factors for given HCT: 45 = 1, 35 = 1.5, 25 = 2, 20 = 2.5. RI >2% = appropriate BM response; RI <2 = inadequate BM response

  Screening: ✓ CBC in pregnant women at first prenatal visit (*USPSTF Ann Int Med 2015;163:529*); CDC recommends ✓

CBC in premenopausal ♀ q5–10 y (*MMWR Morb Mortal Wkly Rep* 1998;47:1); consider CBC q5 y in asx pts >50 y & annually in pts w/ chronic dz (*Curr Med Res Op* 2006;22:385)

Disease	Test & Comments
Iron deficiency	Microcytosis, ↓ Fe, ↓ ferritin, ↓ transferrin sat, ↑ TIBC, ± reactive ↑ PLT; ferritin <41 ng/mL 98% sensitive/specific; cutoff higher in CHF (300 ng/mL) due to inflammation (*Blood* 1997;89:1052); transferrin sat <16% diagnostic (30% in pts w/ CKD)
Anemia of chronic dz	Dx of exclusion; ↓ Fe, nl or ↓ TIBC, nl or ↑ ferritin, ↑ ESR or CRP, ↓ retic index, erythropoietin value not appropriately increased in pts w/ nl renal function (*NEJM* 2014;371:1324)
α- or β-thalassemia minor	Hgb electrophoresis; FHx anemia, nl or ↑ ferritin, Fe
B_{12} or folate deficiency	Macrocytosis + neutrophil hypersegmentation (Chap X)
Hemolysis	↑ LDH, ↓ haptoglobin, ↑ indirect bilirubin, ± ↑ retic; ↑ urine & plasma Hgb & ↑ urine hemosiderin in intravascular hemolysis; Nl LDH + haptoglobin >25 mg/dL 92% sensitive in r/o hemolysis (*JAMA* 1980;243:1909)
Hypersplenism/bleeding	↑ retic count, retic index >2% w/o e/o hemolysis
Autoimmune hemolytic anemia	⊕ *Direct Coombs:* Detects offending Ab bound to pt RBC; washed pt RBCs mixed w/ antiserum or Abs specific to immunoglobulins (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 U packed RBC contains 200 mg iron, ↑ Hgb by 1 g/dL & HCT by 3–4% (*Ann Intern Med* 1994;121:278)
- **Iron deficiency anemia:** Typical Rx is ferrous sulfate 325 mg PO QD; if not tolerated then ferrous gluconate 325 mg PO QD; co-administration of oral iron w/ ascorbic acid, orange juice or meat ↑ Fe absorption & tolerability; Ca supplements/antacids, tea, & soy protein ↓ Fe absorption. 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, celiac dz, *H. pylori,* HD, profound deficiency); treatment may continue until Hgb normalizes, unless profoundly deficient & iron stores need repletion; reticulocytosis ~1 wk & ↑ Hgb ~2 wks after beginning PO iron repletion suggests

response; PO iron produces dark stools but does not produce false positives on stool guaiac tests

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 comorbid dz (i.e., anemia of chronic dz, MDS, RA), B_{12}/folate deficiency, malignancy, thalassemia, compliance issues, ↓ absorption (antacids, s/p bypass), bleeding

Iron Repletion (*Lancet* 2007;369:1502; *NEJM* 2007;357:93; 2014;371:1324; 2015;372:1832)

	Form	Elemental Fe	Comments
Oral	Ferrous fumarate	106 mg/tablet	Highest "concentration" of iron/tablet
	Ferrous sulfate	65 mg/tablet	Least expensive; first line treatment
	Ferrous gluconate	28–38 mg/tablet	↑ GI tolerance due to ↓ Fe, but more pills/day
	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
	Goal dose (mg): Weight in kg × 2.3 × (target Hgb – pt Hgb) + 500–1000 mg to replete iron stores; various calculators available online, i.e., globalrph.com/iron.htm; **General s/e:** Nausea, pruritus, headache, myalgia/arthralgia		
	Iron sucrose	200 mg per 2–90′ infusion	Equal in safety (*Nephrol Dial Transplant* 2006;21:378); test dose not necessary unless pt has reacted previously to iron dextran; pts may
	Ferric gluconate	125 mg/10–60′ infusion	

Intravenous			require multiple infusions to replete
	Ferric carboxymaltose	750 mg/15–30′	Doses must be given 1 wk apart
	Ferumoxytol	510 mg (max)	Rapidly given (30 mg/sec); used in HD
	Iron dextran	50 mg/mL	Highest rate of local or systemic s/e (4.7%), & anaphylactic rxns (1%) (*Am J Kid Dis* 1999;33:464); requires 25 mg test dose & 4–6 h infusion

- **Anemia of chronic disease:** Treat underlying condition; may coincide w/ iron deficiency anemia, which should be treated; consider use of an erythropoiesis-stimulating agent; see Chap X for management in CKD
- **Hemolytic anemias:** Co-management w/ hematology recommended

  Immune: D/c culprit drug; **Warm agglutinins:** Steroids; immunosuppression, cytotoxic meds, IvIg; splenectomy in sev cases (*Am J Hematol* 2002;69:258); **Cold agglutinins:** Avoidance of cold, cytotoxic agents, rituximab, plasmaphresis in severe 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

POLYCYTHEMIA

Background (*Ann Intern Med* 2010;152:300; *Blood* 2007;110:1092; *NEJM* 2007;356:444; 459)

- **Definition:** ↑ RBC mass (Hgb >18.5 g/dL ♂, >16.5 g/dL ♀, or HCT >52% ♂, 48% ♀). Pts w/ thalassemia trait may have ↑ RBC # w/ a nl or ↓ Hgb/HCT &/or ↓ MCV.
- **Pathophysiology:** Relative polycythemia is due to ↓ plasma volume; usually asx. **Secondary polycythemia:** ↑ RBC mass in response to ↓ oxygen (COPD, high altitude, smoking, OSA, chronic CO exposure, R → L shunt). May also be due to erythropoietin secretion secondary to renal-vascular dz, 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 & PLTs in absence of physiologic stimulus; chronic myeloproliferative disorder 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:** H/o 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; daytime somnolence.
- **Exam:** Plethora, splenomegaly, HTN, purpura, engorged retinal veins, cyanosis, normal O_2 sat at rest & w/ activity (i.e., walking).
- **Workup:** CBC w/ diff (repeat testing to confirm ↑ RBC mass), pulse ox; Epo level (↑ in 2° polycythemia; ↓↓ in PCV). Carboxyhemoglobin level (↑ in 2° polycythemia due to CO). *JAK2* mutation analysis (V617F most common, exon 12 mutations rare). CXR if pulm dz suspected. Urinalysis (microscopic hematuria may be seen in Epo-secreting RCC). Other Epo-secreting tumors include HCC, hemangioblastoma, pheochromocytoma, & uterine fibroids.
- **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, CVA, arterial/venous thrombosis.

Treatment (*Blood* 2012;120:275)

- **Secondary polycythemia:** Treat underlying cause (smoking cessation, COPD (Chap X)).
- **Polycythemia vera:** Hematology referral for phlebotomy (goal HCT <45%) (*NEJM* 2013;368:22) & hydroxyurea if ↑ risk thrombosis (age >60 y, h/o thrombosis) or severe sx (pruritus, bone pain, weight loss, splenomegaly) (*Br J Haematol* 2005;130:174); first phlebotomy should remove ½ unit (250 cc) & replace volume lost w/ saline; avoid iron supplementation; allopurinol if ↑ UA; pruritus may be treated w/ antihistamines, avoiding hot showers & starch baths.
- **All pts:** Consider low-dose ASA (75–100 mg/d) unless contraindicated.
- **Patient information:** *AFP* 2004;69:2146

DVT AND PULMONARY EMBOLUS

Evaluation (*AFP* 2012;86:913; *Blood* 2002;99:3102; *NEJM* 2003;349:1227; 2008;358:1037; 2010;363:266)

- **DDx of DVT:** Varicose veins, superficial thrombophlebitis, muscle strain, cellulitis, lymphedema, Baker cyst. See "*Chest Pain*" (Chap X) for DDx of PE.
- **History:** Edema, calf/thigh pain, venous distention, dyspnea, pleuritic chest pain, cough, hemoptysis, syncope, orthopnea or asx; PE found in 1 in 6 pts hospitalized for first episode of syncope (*NEJM* 2016;375:1524); H/o previous thrombosis; OCP or tamoxifen use; fetal losses; cancer hx, incl compliance w/ CA screening; pregnancy; FHx DVT/PE, cancer (*Am J Med* 2007;120:871).

  Risk factors: H/o immobility, surgery, obesity, h/o VTE, LE trauma, malignancy, OCP use, pregnancy, stroke
- **Exam: DVT:** Edema, redness, warmth, palpable cord, ⊕ Homans' sign (calf pain w/ passive foot dorsiflexion), difference in calf diameter; distal DVT → deep calf below the knee; proximal DVT → popliteal, femoral, or iliac veins. **PE:** Tachypnea, tachycardia, ↓ O_2, rales, pleural rub, ↑ JVP, fever; stool guaiac prior to anticoagulation
- **Workup:** Se of LE U/S 94% (proximal DVT), 63% (distal DVT), Sp 94% (both); if clinical suspicion for DVT is high & LE U/S negative,

repeat in 5–7 d; ✓ 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

D-dimer: 96–99% NPV in pts w/ low/intermediate pretest probability; age-adjusted cut-off of 10 ng/mL × age should be used in pts >50 y (*JAMA* 2014;311:1117).

Hypercoagulability w/u: Controversial (*JAMA* 2005;293:2352); consider in idiopathic VTE, FHx VTE, recurrent pregnancy loss, recurrent VTE, unprovoked VTE in pt <50 y, thrombosis in unusual location; factor V Leiden & prothrombin gene mutations, antiphospholipid Ab, & UA (nephrotic syndrome) may be checked during anticoagulation; antithrombin, factor VIII, lupus anticoagulant, protein C/S affected by anticoagulation or acute thrombosis → check once DVT resolves & pt off anticoagulation; role of homocysteine screening unclear

Malignancy w/u: Pts w/ unprovoked VTE should be current w/ routine cancer screening (Chap X), be carefully asked about FHx of CA, & be followed closely; consider CXR & screening for breast/cervical/prostate CA; 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 ? effect on outcome (*NEJM* 1998;338:1169; *NEJM* 2015;373:697).

Dx of PE in pregnant pts: Consider LE U/S first 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 for DVT (points)	Dichotomized Wells Criteria 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)	H/o DVT/PE (1.5)
Pitting edema (1)	Hemoptysis (1)

Active malignancy (1)	Malignancy (1)
Collateral superficial vein (1)	**PE unlikely (≤4 points):**
Alternative dx more likely (subtract 2 points)	D-dimer negative or <500 ng/mL: PE ruled out D-dimer ⊕ or ≥500 ng/mL → ✓ PE-CT **PE likely (>4 points):** ✓ PE-CT
Low (0 points) & mod (1–2 points) risk: D-dimer negative: DVT r/o; D-dimer ⊕ → ✓ LE U/S **High risk (≥3 points):** ✓ LE U/S	
PERC rule: Risk of testing for PE (D-dimer, imaging) outweighs potential benefit if pt meets all of following criteria: (1) Age <50 y, (2) HR <100, (3) Oxyhemoglobin ≥95%, (4) No hemoptysis, (5) No estrogen use, (6) No h/o DVT/PE, (7) No leg swelling, (8) No h/o hospitalization for trauma/surgery in previous 4 wks	
Risk for Recurrent DVT/PE (in pts w/o other risk factors, i.e. cancer, thrombophilia)	
Unprovoked: 1st episode: 10% 1st yr, then 5%/y; **2nd episode:** 15% 1st yr, then 7.5%/y **Provoked: Surgery:** 1% 1st yr, then 0.5%/y; nonsurgical factor: 5% 1st yr, then 2.5%/y	
Estimating Bleeding Risk (*Chest* 2016;149:315)	
Risk factors (1 point each, unless noted): Age >65 y (+2 if >75 y), h/o bleeding, cancer (+2 if metastatic), liver or renal failure, stroke, DM2, anemia, ↓ PLT, anti-PLT or NSAID Rx, poor anticoagulant control, poor performance status, recent surgery, falls, EtOH abuse	
Bleeding risk (%/y): Increases with ↑ risk factors; **low risk (1 factor):** 0.8%; **mod risk (1 factor):** 1.6%; **high risk (≥2 factors):** ≥6.5%	

Management (*AFP* 2011;83:293; 2013;87:556; 2017;95:295; *Ann Intern Med* 2007;146:204; 2008;149:ITC3-1; 2015;162:ITC-1; 2015;163:701; *Blood* 2014;123:1794; *Chest* 2016;149:315; *JAMA* 2011;305:1336; 2014;311:717; 2015;314:72; *Lancet* 2010;375:500; *Mayo Clin Proc* 2013;88:495)

- **Outpatient management of PE/DVT:** Consider in reliable pts w/ good social support, no O_2 requirement, normal VS, no narcotic requirement, no h/o bleeding or serious comorbid disease (esp CKD); scoring systems available to guide pt selection for outpt PE treatment (*Am J Med* 2016;129:974; *Lancet* 2011;378:41)
  - **Anticoagulation:** Apixaban, dabigatran, edoxaban, or rivaroxaban recommended over warfarin in pts w/o malignancy. See Chap X for choice of specific agent.
- **Duration of venous thromboembolism (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 physician subjective assessment (*Am J Med* 2012;125:1095)

Cancer patients: Indefinite (metastatic) or until cancer resolves

Compression stockings: 30–40 mmHg may prevent DVT postthrombotic syndrome.

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); D-dimer has poor NPV for predicting pts at low risk of recurrent VTE (*JAMA* 2015;313:1668)

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); aspirin ↓ risk of recurrent VTE by ~30% compared to ~90% for warfarin (*BMJ* 2013;347:f5133)

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)

ANTICOAGULATION

Anticoagulant	Dose & Monitoring	Reversal/Contraindications/Notes
Warfarin (INR goal 2–3) ~$7/mo Review pt med list for drugs that interfere w/ warfarin Diarrhea, fever may	Initial: 5 mg PO then dose by INR. Use lower starting doses in elderly -Requires bridge for 5 d + INR 2–3 for >24–48 h in DVT/PE -Referral to anticoagulation	↑ risk of bleeding, vascular, and all-cause mortality compared to NOAC in afib (*JACC* 2016;68:2508). ↑ risk of major bleeding compared to NOAC in mild renal insufficiency (CrCl 50–80 mL/min) (*Chest* 2016;149:1516)

potentiate anticoagulation Preferred over NOAC in pts >120 kg	monitoring service (↓ complications, ↑ time in therapeutic range) -Missed doses do not result in subtherapeutic anticoagulation	Preferred for CrCl <30 mL/min **Reversal in asymptomatic pts (INR):** -<4.5: ↓ or hold dose, ↑ freq of monitoring, resume at lower dose -4.5–10: Hold 1–2 dose(s), ↑ freq of monitoring, resume at lower dose ->10: Vitamin K ->20 or bleeding → ER
Dalteparin or **enoxaparin** Superior to warfarin for VTE in cancer (*Arch Intern Med* 2002;162:1729; CLOT, *NEJM* 2003;349:146)	**DVT/PE dosing:** Dalteparin: 100 U/kg q12h or 200 U/kg QD Enoxaparin: 1 mg/kg q12h (preferred in CA, extensive clot, obese) or 1.5 mg/kg QD	Protamine reverses. Anticoagulant of choice in liver disease Contraindications: CrCl <30, HIT. Relative contraindications: Weight <50 kg or >150 kg (consider checking Xa levels) Preferred for outpt anticoagulation in pregnant pts. ↑ risk of osteoporosis if used for years
Fondaparinux (synthetic Xa inhibitor)	<50 kg → 5 mg QD 50–100 kg → 7.5 mg QD >100 kg → 10 mg QD; no monitoring required	No antidote Contraindicated in bacterial endocarditis (↑ risk ICH), weight <50 kg, CrCl <30. Safe in HIT
Apixaban (factor Xa inhibitor) ~$315/mo FDA approved for afib & VTE	Afib: 5 mg BID VTE: 10 mg BID × 10 d → 5 mg BID May be taken with or without food	Safest direct oral anticoagulant in mild–moderate renal insufficiency (CrCl 30–80 mL/min) (*Am J Cardiol* 2015;115:323). No specific antidote 2.5 mg BID dose in pts w/ 2 of the following: Age ≥80 y, weight ≤60 kg, Cr ≥1.5 mg/dL
Dabigatran (direct thrombin inhibitor) ~$315/mo FDA approved for afib & VTE	150 mg BID (afib & VTE) **Requires parenteral bridging for VTE** May be taken with or without food	Reversed with idarucizumab (*NEJM* 2015;373:511) Afib: CrCl 15–30 mL/min: 75 mg BID Noninferior to warfarin for recurrent VTE with ↓ bleeding but ↑ risk of acute coronary syndrome (REMEDY, *NEJM* 2013;368:709)
Edoxaban (factor Xa inhibitor) ~$277/mo FDA approved for afib & VTE	60 mg QD (afib & VTE) **Requires parenteral bridging for VTE** May be taken with or without food	**Once-daily dosing** CrCl 15–50 mL/min or weight ≤60 kg: 30 mg QD Avoid if CrCl >95 mL/min No specific antidote
Rivaroxaban (factor Xa inhibitor)	Afib: 20 mg QD VTE: 15 mg BID × 21d →	**Once-daily dosing** Afib: CrCl 15–50 mL/min: 15 mg QD

~$315/mo FDA approved for afib & VTE	20 mg PO QD	No specific antidote Must be taken with food. For afib, must be taken with the evening meal
Special Patient Populations (*Chest* 2016;149:315)		
Coronary Artery Disease	Avoid dabigatran, which has ↑ risk of coronary events compared to warfarin, apixaban, edoxaban, or rivaroxaban	
Dyspepsia, GIB	Dabigatran ↑ risk of dyspepsia. Warfarin has ↓ risk of GIB vs. NOACs	
Poor Adherence	Warfarin. 1 missed dose of NOAC → subtherapeutic anticoagulation	
Renal Failure	Warfarin preferred for CrCl <30	

(*JAMA* 2014;311:731; 1150; 2015;314:76; 2016;315:2117)

COAGULATION DISORDERS

Background (*AFP* 2009;80:1261; 2016;93:279; *Mayo Clin Proc* 2002;77:181; *NEJM* 2009;361:1887)

- **Cause:** A bleeding disorder may be due to abnormalities in the coagulation cascade, platelets (Chap X), blood vessels, or fibrinolysis.

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 subcutaneous/soft tissue

- **von Willebrand disease (vWD):** Most common inherited bleeding d/o (prevalence ~1%, M:F 7:3) 2° to deficiency or dysfunction of VW factor (vWF) which binds platelets to endothelium → PLT & clotting defect; vWF binds factor VIII & protects it from proteolysis.

  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: Severe (1–5% cases), autosomal recessive; severe or complete vWF deficiency & moderate 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° to ↓ coag factor synthesis, ↓ PLT (splenic sequestration, ↓ thrombopoietin) & ↑ clotting risk (↓ synthesis of protein C, S, antithrombin) (*NEJM* 2011;365:147)
- **Hemophilia:** Factor VIII deficiency (A), factor IX deficiency (B, Christmas dz); X-linked recessive w/ bleeding in joints, muscles, GI tract with varying severity

Evaluation (*AFP* 2008;77:1117; *NEJM* 2008;359:938; 2016;375:76)

- **History:** Bleeding after surgery, dental work, minor trauma, childbirth, h/o palpable lumps, epistaxis (>10 mins), menorrhagia, anemia, melena, BRBPR; how severe was the bleeding? FHx of bleeding; h/o transfusion; medications (esp abx, aspirin, NSAIDs, steroids, SSRIs + aspirin/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); lymphadenopathy, 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** = Patient PT ÷ control PT

  Activated partial thromboplastin time (aPTT): Measures intrinsic (VIII, IX, XI, XII) & common pathways

  Mixing studies: Combine patient & normal plasma to identify factor deficiencies & inhibitors

Thrombin time: Measures conversion of fibrinogen to fibrin & clot formation by thrombin

Diagnosis	PT	aPTT	[Platelet]
Prothrombin, fibrinogen, factor V or X deficiency, liver dz, severe vitamin K deficiency	↑	↑	Nl
Factor VII or mild vitamin K deficiency, liver dz, warfarin	↑	Nl	Nl
Hemophilia A or B, von Willebrand dz, factor XI, XII deficiency	Nl	↑	Nl*
Vasculopathies, connective tissue dz, collagen d/o, PLT dysfunction, scurvy, steroid-induced purpura, vasculitis	Nl	Nl	Nl

*Platelet count may be low in type 2B von Willebrand disease

Treatment (*Blood* 2009;114:1158; 2012;120:275; *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

PLATELET DISORDERS

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 (aspirin, 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 (*Semin Thromb Hemost* 2011;37:267)	

Causes of Thrombocytopenia (***JAMA* 2004;292:2263**)		
Destruction	***Immune-mediated*** **Drugs:** Heparin (HIT-II), indomethacin, thiazides, sulfonamides, quinine (Tonic water), quinidine, (comprehensive listing at ouhsc.edu/platelets) **ITP** (dx of exclusion) **Infxn:** HIV, HCV, *H. pylori* **Rheumatologic:** SLE, APLS, RA, sarcoid **Neoplasm:** CML, Hodgkin, solid tumors **Globulins:** IgA-deficiency, hypogammaglobulinemia	***Nonimmune-mediated*** **Drugs** **Infection:** Sepsis, mononucleosis, CMV, HSV, RMSF, ehrlichiosis, babesiosis **MAHA:** TTP, HUS, DIC, HELLP, vasculitis **Others:** HELLP, DIC, TTP-HUS, giant hemangioma
↓ Production	**Drugs/toxins:** EtOH, thiazides, estrogen, IFN, chemotherapy, many others; **XRT** **Infection:** Sepsis, parvovirus, CMV, HSV, influenza, HIV, rubella, mononucleosis **Cancer:** Leukemia, lymphoma, myeloma, CLL, myelofibrosis, myelodysplasia, CML, aplastic anemia, paroxysmal nocturnal hemoglobinuria **BM infiltration:** Solid tumors, TB, osteopetrosis **Nutritional deficits:** B12 & Folate, rarely iron **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 dz, uremia, multiple myeloma, Waldenström macroglobulinemia		

- **Immune (idiopathic) thrombocytopenic purpura (ITP):** Dx of exclusion for isolated ↓ PLT (*NEJM* 2002;346:995); incidence of 1 in

10,000/y; IgG against PLT membrane proteins or megakaryocytes → ↓ production, ↑ destruction

- **Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome:** ↓ PLT + microangiopathic hemolytic anemia (≥2 schistocytes on 100× HPF) of o/w unexplained etiology ± neurologic/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 alternative therapies, supplements), nutrition, B-sx, FHx of bleeding/leukemia, cancer screening, HIV/TB risk factors, h/o DVT; h/o bleeding w/ minor trauma, dental work, easy bruising, blood transfusions
- **Exam:** Splenomegaly, lymphadenopathy, petechiae, purpura, ecchymoses, stool guaiac
- **Workup:** CBC w/ diff in citrate tube to avoid pseudothrombocytopenia; peripheral smear (*NEJM* 2005;353:498); PLT count of 50–100k w/o bleeding may be rechecked in 1–2 wks before further w/u; consider: Chem-12, CRP, retic, LDH, coags, ferritin, D-dimer, fibrinogen, ANA, *H pylori* testing, direct Coombs, B12/folate, HIV, HepC, AbdUS (splenomegaly); BmBx for severe unexplained ↓ PLT, 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
- **ITP:** Tx depends on bleeding risk/hx, typically Tx begun if PLT <30k or bleeding sx at dx; pts should avoid ASA/NSAIDs, dangerous activities if PLT <50; glucocorticoids 1st-line tx; IvIg & anti-Rh(D) are temporary tx; splenectomy or rituximab may induce remission while Tpo agonists require maintenance dosing
- **Patient information:** *AFP* 2012;85:623

THROMBOCYTOSIS (*JAMA* 2015;314:1171; *NEJM* 2004;350:1211)

Etiology of Thrombocytosis	
Reactive (85%)	**Acute/chronic inflammation: Infectious** (TB, osteomyelitis), **Rheum** (RA, vasculitis, sarcoid), **IBD** (UC, Crohn); **Asplenia** (Chap X), **CKD/nephrotic synd; 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 (MPN):** Essential thrombocytopenia, polycythemia vera, 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 CVA, 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); pts w/ high risk disease & a h/o arterial thrombosis should receive hydroxyurea + ASA 81 mg; pts w/ a h/o venous thrombosis should receive hydroxyurea + anticoagulation; pts aged >60 y should be treated with hydroxyurea + ASA 81 mg
- **Sx of thrombocytosis:** HA, chest pain, sx assoc w/ thrombosis/bleeding, visual disturbances

ABNORMAL WBCs

Leukopenia

Causes of Neutropenia (*Blood* 2014;124:1251; *Hematology ASH Educ* 2004:63; 2012:174)
Infectious: Viral (HIV, HepB, HepC, EBV, CMV), bacterial (Shigella, Brucellosis, TB), parasitic, tick-borne (Ehrlicia, Rickettsial, RMSF)
Medications: Suppress BM or trigger autoimmune rxn; ACE inhibitors, acetaminophen, acyclovir, abx (ampicillin, bactrim, cephalosporins, macrolides, vancomycin), AZT, chemotherapy, clopidogrel, clozapine, digoxin, dipyridamole, fluoxetine, furosemide, ganciclovir, immunosuppressants, methimazole, NSAIDs, prednisone, propranolol, propylthiouracil, ranitidine, spironolactone, sulfasalazine, thiazides, tricyclic antidepressants, 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 synd (rheumatoid arthritis + splenomegaly + neutropenia), sarcoid
Malignancy: Leukemia, myelodysplasia, cancers that metastasize to bone, amyloidosis
Other: Vitamin B12, folate, copper deficiency, EtOH, common variable immune deficiency, 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 synd, glycogen storage dz, cyclic neutropenia (autosomal dominant, occurs q14–35 d) (*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, HepB/C), bacterial (TB, histoplasma, brucella), malaria
Medications: ATG, rituximab, steroids, chemotherapy (fludarabine, cladribine)
Autoimmune: Lupus, rheumatoid arthritis, Sjögren
Malignancy: Lymphoma, cancers that metastasize to bone
Other: EtOH, zinc & vitamin deficiency, physiologic stress (i.e., post-op, sepsis)

- **History:** 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., q3 wks may suggest cyclical neutropenia)
- **Exam:** Lymph nodes, spleen, dental exam to r/o abscesses &

gingivitis

- **Workup:** CBC w/ diff, peripheral smear, viral serologies (HIV, HepB & C, EBV), B12, folate, MMA, homocysteine, copper/ceruloplasmin level, ESR/CRP, ANA, complement, flow cytometry, retic; Lyme, RMSF, & ehrlichia serologies, PPD, RF, & anti-CCP Ab based on clinical suspicion; may need hematology referral for bone marrow biopsy if above w/u unrevealing, neutropenia is persistent, & ANC <1000; role of antineutrophil Ab for autoimmune dz 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:** Infectious risk ↑ w/ ↓ ANC, especially for ANC <500 (*Ann Int Med* 1966;64:328); ANC 1000–1500: Mild; ANC 500–1000: Mod. ANC <500: Sev; recurrent infections usually only seen when ANC <200
  - **Asx:** D/c offending meds, monitor CBC w/ diff q2–12 wks, 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 symptoms; chronic G-CSF use assoc w/ osteoporosis & ? ↑ 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)

LEUKOCYTOSIS (*AFP* 2014;89:731; 2015;92:1004)

- **History:** H/o of recent infection, fevers, chills, night sweats, wt loss; complete medication & supplement hx; allergic reactions & exposures; travel hx; h/o asthma, bronchiectasis, inflammatory bowel disease, anxiety, or exercise; smoking hx
- **Exam:** Lymph nodes, spleen, skin (rash/petechiae)
- **Workup:** CBC w/ diff, peripheral smear, viral serologies (HIV, EBV, CMV), flow cytometry (for CLL & other leukemias), peripheral blood for FISH for BCR-ABL (Philadelphia chromosome – 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 bone marrow bx if above workup 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 blast; tx o/w directed at underlying cause (i.e., withdrawal of offending medication), referral to heme/onc for chronic leukemias, smoking cessation, management 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, multiple myeloma, large cell lung CA (*Cancer* 1987;60:903) **Chronic myelogenous leukemia:** 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, panic attacks), IBD, bronchiectasis, thyroid storm, asplenia, polycythemia vera (in assoc w/ ↑ HCT), post seizure, heatstroke, sickle cell anemia, platelet 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: Sustained absolute lymphocyte count ≥5000 with clonality on flow cytometry (*Blood* 2008;111:5446)
Monoclonal B-cell lymphocytosis: Clonal lymphocyte count ≤5000 w/o cytopenias, LAN, organomegaly, or sx; patients w/ MBL & CLL phenotype cells have a ~1%/y risk of developing CLL requiring treatment (*NEJM* 2008;359:575)

Other: Hyperthyroidism, post-splenectomy, posttransplant lymphoproliferative d/o, cigarette smoking, rheumatoid arthritis, Addison disease, splenomegaly

Causes of Monocytosis

Infectious: Brucellosis, VZV, TB, malaria, bacterial endocarditis, syphilis, trypanosomiasis, typhoid fever.

Malignancy: Leukemia, Hodgkin lymphoma, myelodysplastic syndrome
Chronic myelomonocytic leukemia: Absolute peripheral monocytosis >1000 that persists ≥3 m w/ myelodysplastic/myeloproliferative features in bone marrow; important to r/o CML & PDGF rearrangements (*Am J Hematol* 2012;87:611)

Other: Steroids, pregnancy, asplenia, sarcoidosis, inflammatory bowel disease, lupus

Causes of Eosinophilia

Leukemia (usually CML), lymphoma, polycythemia vera, myelofibrosis, adrenal insufficiency, solid tumors, allergic rxns, RA, lupus, Addison disease; asthma, Churg–Strauss; drug hypersensitivity; infections (HIV, scarlet fever, leprosy, GU, fungi)

Causes of Basophilia

Leukemia (usually CML), myelofibrosis, polycythemia vera, essential thrombocytosis, myelodysplastic syndromes, allergic rxns, ulcerative colitis, RA, hypothyroidism, estrogen supplementation, ovulation, infection (viral, TB, helminth, varicella, chronic sinusitis)

LYMPHADENOPATHY & SPLENIC DISORDERS

Background (*AFP* 1998;58:1313; 2002;66:2103; *Hematol Oncol Clin N Am* 2012;26:395)

- **Definitions:** >600 LN 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 dz 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 towards the nearest LN; typically caused by *Strep pyogenes.*

Lymphadenitis: Inflammation of a LN which may be enlarged, red, or tender

Splenomegaly: Greatest dimension >11–13 cm; size of spleen proportional to height; 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 influenza* type b); Assoc w/ ↑ prevalence of infection (3.2%) & mortality (1.4%), usually due to fulminant *Streptococcal* sepsis in a 7 y observational study (*J Infect* 2001;43:182)

  Hyposplenism: Caused by sickle cell, IBD, celiac dz, Whipple dz, hepatitis, EtOH, cirrhosis, BMT, leukemia, myeloproliferative dz, autoimmune dz, 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, pruritis, new/changing skin lesion or rash, joint pain, weakness, exposures (travel, sick contacts, pets, rabbits [Tularemia], cats [cat scratch dz]), 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 dz, CTD; painful LAN after EtOH (Hodgkin)

  Diagnostic clues: Rate of growth (benign LAN suggested by <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) → 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 interobserver 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 otherwise suspicious; biopsy the most suspicious LN (i.e., largest, most abnormal) 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 *and* 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 treatment:** Steroids not recommended due to effect of glucocorticoid on LN which may complicate pathologic interpretation if bx needed; abx recommended only infection suspected
- **LAN 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 symptoms, duration >4–6 wks, supraclavicular) → bx

Differential Diagnosis of Lymphadenopathy & Splenomegaly	
Splenomegaly (*NEJM* 2008;359:2707)	**Benign:** Portal vein thrombosis/hypertension, 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's), HepB, strep], fungal, bacterial, protozoal, tick borne, toxoplasma), autoimmune (RA, lupus, sarcoid), drug hypersensitivity (allopurinol, atenolol, captopril, carbamazepine, cephalosporins, 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 infxn, 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's Node): abdominal/thoracic/testicular/pelvic malignancy, breast cancer, lymphoma, leukemia; Right: esophageal, lung, breast, thyroid, or laryngeal cancers, lymphoma, leukemia
Epitrochlear	**Benign:** Infxn 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 infxn 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:** STD, 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/Hyposplenic Patient (*Lancet* 2011;378:86; *NEJM* 2014;371:349)

- **Functional asplenia/hyposplenia:** ↓ splenic function seen in sickle cell, chronic GVHD, untreated HIV, celiac dz
- **Pt education:** Pts should seek medical attention *immediately* w/ any fevers or rigors because of ↑↑ mortality in postsplenectomy sepsis related to impaired bacterial clearance from blood, & ↓ humoral immunity
- **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, especially if pt has survived pneumococcal sepsis, have HIV, or are immunosuppressed posttransplant.
- **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, especially to prevent 2° bacterial infections. There is no contraindication to live attenuated vaccines (i.e., shingles); **Tetanus** q10y. One time doses of **diphtheria, *H influenza* type b**

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) varies, 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 dz 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 balances 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 hepatocellular carcinoma (*Gastroenterology* 2003;125:1733); cirrhosis (especially if pts consume >30–60 g EtOH/d), hepatomegaly, abnormal LFTs
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, especially in 2nd & 3rd MCP joints & wrists; osteoporosis
Cardiovascular: Cardiomyopathy/CHF due to iron accumulation; Arrhythmias (SSS, afib)
Dermatology: Hyperpigmentation "bronze diabetes" due to melanin/iron deposition

- **DDx:** Iron overload anemias due to chronic transfusion, hemolytic anemias, liver dz (HepC, NASH, EtOH), dialysis, a1-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. Hep serologies if risk factors present; ECHO if cardiac sx
  - **Iron studies**: Transferrin saturation ([serum iron], µmol/L/TIBC, g/L) ≥50% in ♀ or ≥60% in ♂ &/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 advocates cutoff transferrin saturation >45% in ♀ & ♂; transferrin saturation <45% w/ normal ferritin is 97% specific to r/o hemochromatosis (*AFP* 2013;87:183)
  - **Other causes of ↑ ferritin:** EtOH, HIV, inflammation, malignancy, metabolic syndrome, hepatitis, autoimmune dz, 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 negative (*NEJM* 2004;350:23)

Liver bx: Consider if pt is >40 y & has ↑ LFTs or ferritin >1,000 ng/mL

Liver MRI: Useful to evaluate for hemochromatosis or other iron overload dz in pts who test *negative* for *HFE* mutations but have clinical/laboratory signs of iron overload dz (*Best Pract Res Clin Gastroenterol* 2009;23:171); may help quantify hepatic Fe concentration

- **Screening:**

  Normal population: USPSTF and American Academy of Family Physicians 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 1° ♀ relatives who are also homozygotes for hemochromatosis have dz-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)

  Patients with liver dz: American Association for the Study of Liver Dz 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 mg/L more likely to have sx or liver dz (*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 patients w/ ferritin <1000 µg/L; F/u includes annual H&P, iron studies; these patients should be encouraged to donate blood; screen for hepatocellular CA w/ U/S ±

AFP q6 mos (*Hepatology* 2011;53:1020)

- **Indications to treat:** Sx &/or end-organ damage. Consider in asx pts w/ ferritin >1000 µg/L. Consider in pts at risk for liver dz (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); Hgb & HCT should remain >80% of baseline level during phlebotomy; ✓ ferritin q3mos
  - **Schedule**: Remove 1-unit q1–2 wks 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 q2–6 mos 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 an alternative to phlebotomy in physician's office for some 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; phlebotomy not effective at restoring pituitary/thyroid function, lowering the risk of liver CA or infection; phlebotomy may improve cardiomyopathy, cirrhosis (rarely) & DM (*Ann Intern Med* 1998;129:932)
- **Diet:** Avoid iron & vitamin C supplements (contributes to oxidant damage, iron mobilization) (*Ann Intern Med* 1999;131:475), uncooked seafood (Vibrio vulnificus infxn), & EtOH (due to risk of cirrhosis) (*Gastroenterology* 2002;122:281); otherwise 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

FOLATE & VITAMIN B_{12} DEFICIENCY

Background (*Blood* 2008;112:2214; *J Nutr* 1999;129:779; *Neurology* 1995;45:1435; *NEJM* 2013;368:149)

- **Epidemiology:** Prevalence of B_{12} deficiency = 5–400 per 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

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 (smaller body stores)
Absorbed in terminal ileum	Absorbed in jejunum
↑ homocysteine & ↑ methylmalonic acid	Only homocysteine elevated
B12 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 B_{12} deficiency:** B12 (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; B12 absorption requires: (1) Adequate intake; (2) Gastric acid & pepsin to release B12 from protein & allow it to bind R factor; (3) Pancreatic proteases release B12 from R factors; (4) Intrinsic factor (IF) to bind B12. (5) Functional B12-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 (*NEJM* 2014;370:773); present in up to 2% of pts >60 y (*NEJM* 1997;337:1441); most common cause of severe B_{12} 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, Sjogren

- **Pathophysiology of folate deficiency:** Inadequate intake or EtOH (↓ absorption); folate (= vitamin B9) is the naturally occurring form; folic acid is the therapeutic vitamin

  Risk factors: Conditions that ↑ folate demand (i.e., pregnancy, hemolytic anemia, severe dermatitis) or meds that interfere w/ metabolism (trimethoprim, pyrimethamine, methotrexate, phenytoin); eating d/o, depression → malnutrition; ↓ absorption in celiac dz, IBD, short bowel syndrome, gastric bypass

  Neural tube defects (NTD): Folic acid supplementation ↓ incidence of NTDs

Evaluation (*NEJM* 2013;368:149; 2015;373:1649)

- **History:** Sx of anemia (Chap X); symmetric paresthesias, numbness, gait instability, memory loss, personality or MS Δ (found only in B_{12} deficiency); sx of malabsorption (wt loss, diarrhea); h/o blood clots, incl 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, intestinal surgery, pancreatitis, IBD); EtOH; h/o autoimmune dz (DM1, thyroid, vitiligo)
- **Exam:** Wt; prematurely graying hair; glossitis; gait, peripheral sensation (incl vibratory/position sense; check Romberg), motor strength; MMSE, depression screen; pallor, vitiligo, hyperpigmentation; vaginal atrophy

Common Tests Used to Assess B_12 & 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, multiple myeloma, folate deficiency, excessive vitamin C intake; falsely ↑ in liver dz, 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 (MMA) & homocysteine: Both ↑ in B_{12} deficiency (Se 94%, Sp 99%) (*Am J Med* 1994;96:239); MMA nl & ↑ homocysteine suggestive of folate deficiency (Se 86%, Sp 99%); if both MMA & homocysteine are nl then B_{12} & folate deficiency unlikely; useful for intermediate 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 dz, or homocystinuria; MMA falsely ↑ in renal failure
Anti IF Ab: Se 60–70% for pernicious anemia, Sp >95%; antiparietal cell Ab ↑ Se but ↓ Sp, limiting use; has supplanted Schilling test in dx of pernicious anemia

- **Workup:** Serum B_{12} & folate (& RBC folate if serum folate borderline), CBC w/ diff, MCV, peripheral smear (hypersegmented neutrophils), retic, anemia w/u if anemic (Chap X); consider *H. pylori* testing

Treatment (*AFP* 2011;83:1425; *Blood* 2008;112:2214; *Cochrane* 2005;20:CD004655)

- **B_{12} repletion:** Asx: Cobalamin 1 mg PO QD until serum level normalizes; symptomatic: 1 mg IM QD x 7 d then weekly × 4 wks; prompt recognition & tx needed to prevent permanent neurologic damage; neurologic recovery may take 1.5–3 mos if sx due to B_{12} deficiency
  - **Maintenance:** 1 mg PO QD **or** 1 mg IM qmonth (if neuro sx → 2×/mo × 6 mos then monthly); indefinite IM tx may be needed for pts permanently unable to absorb B_{12} (i.e., as in pernicious anemia, gastrectomy, bariatric surgery)
  - **Monitoring:** CBC 1–2 mos after tx starts (anemia normalizes in ~6–8 wks), then q6–12 mos; follow K in severely B_{12} deficient pts as ↑↑ BM erythropoiesis may lead to ↓ K
- **Pernicious anemia:** IM B_{12} due to poor GI absorption to correct initial deficiency; maintenance IM B_{12} or high dose oral (i.e., 1–2

mg/d) may be used; ✓ TFTs since thyroid dz 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/Hgb normalizes on CBC; test for B_{12} deficiency prior to folate supplementation
- **Bacterial overgrowth:** Poor movement of stool → ↑↑ bacteria; may be 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 → vitamin malabsorption; ✓ stool Cx; Rx appropriate abx/anthelminthic + folic acid + B_{12} (if deficient) (*Dig Dis* 2007;25:237)
- **Prevention:** B_{12} supplementation in vegetarians, pregnant & breast feeding ♀, 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

INFLUENZA

Background (cdc.gov/flu)

- Influenza viruses are common respiratory pathogens, with presentation ranging from asx to common cold to life-threatening lower respiratory infection

  Influenza-like illness (ILI): Syndrome of fever, respiratory sx which may or may not be 2/2 influenza virus

- **Epidemiology:** Influenza affects between 9 and 36M adults annually, with 140–710K requiring hospitalization, and 12–56K deaths (a further ~5M cases and ~71K hospitalizations prevented by flu immunization in 2015–2016 season)
- **Microbiology:** ⊖ ssRNA Orthomyxoviridae; 2 viruses (A & B); A virus undergoes frequent mutations; *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)
- **Transmission:** Primarily spread from person to person via droplets (cough or sneeze); infectious 1 d *prior* and 5–7 d *after* onset of sx; incubation period 1–4 d
- **Natural history:** 33% of pts with influenza are asx; usually resolves after 3–7 d but can → serious/life-threatening complications (bacterial upper or lower respiratory infections, dehydration, worsening of other chronic illnesses)
- **Bacterial pneumonia:** 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)

- **History:** Distinguishing features vs. URI include **high fever & cough,** severe myalgia, exhaustion, sudden-onset; ask about vaccination (although does not rule out influenza), known/suspected

flu exposure; assess for complication risk (below)

- **Exam:** *VS:* high temperature, hemodynamic instability, oxygenation; *HEENT:* coryza; *Pulm:* ↑ work of breathing, rhonchi, scattered rales

High Risk of Influenza Complications (ACIP, *MMWR* 2011;60:1)	
Age ≥65 y	Chronic liver disease
Pregnant or <2 wk postpartum	Diabetes
American Indians/Alaska Natives	Hematologic disorders (sickle cell)
BMI ≥40	Neurologic disorders (epilepsy, cerebral palsy, developmental delay, spinal cord injury)
Nursing home/chronic care residents	Immunosuppressed (including 2/2 medications)
Chronic lung disease (incl asthma)	HIV
ASCVD (not HTN alone)	
CKD	

- **Whom to test: Strategy** varies by clinical scenario (below); do not test asymptomatic persons; generally no need to test if presenting w/ ILI and at average risk of complication (regardless of tx decision)

Whom to Test for Flu (IDSA guidelines: *CID* 2009;48:1003)	
During Flu Season (Locally)	**Outside of Flu Season**
High-risk and sx onset <5 d	Healthcare workers at or residents of institution w/ institutional outbreak
Immunocompromised and still sx (↑ shedding period)	Those w/ known/likely risk in setting of larger outbreak
Recently hospitalized	

- **Testing modality** (*Ann Intern Med* 2012;156:500):
  - *Rapid Ag testing:* Can detect A vs. B or identify presence of either in <20 min but poor test characteristics (sensitivity 62.3% and specificity 98.2%); 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 & B

Treatment (ACIP, *MMWR* 2011;60:1)

- Pts who are severely ill or hypoxemic → inpatient admission (see *"Pneumonia"*); for those considering outpatient treatment, see below
- **General approach:** Treatment most effective when started ASAP and w/in 48 h of sx onset (data limited on effectiveness if >48 h); if high clinical suspicion, start Rx immediately (do *not* wait for test

results, if ordered)

- **Whom to treat:** *Those with suspected or confirmed influenza, regardless of testing decision and results*
  (1) all pts w/ ↑ risk of complications
  (2) progressive or severe disease
  (3) consider in pts at avg risk who present w/in 48 h of sx onset
- **Prophylaxis indications**
  (1) Pts at ↑ risk pts of complications or healthcare workers <48 h after contact w/ infectious individual
  (2) SNF residents in an outbreak (>2 lab confirmed cases in <72 h), regardless of pt vaccination status
  (3) Consider in exposed, unvaccinated pregnant women
- **Neuraminidase inhibitors:** ↓ Duration of illness 1–3 d if given <48 h of sx onset

  Oseltamavir first-line; *alt:* **Zanamivir** (inh, avoid in COPD/asthma/pregnancy) & **peramivir** (IV only, $$$); do not use rimantadine or amantadine (resistance)
  Tx dose: Oseltamavir 75 mg BID × 5 d (30 mg BID if CrCl <30 mL/min)
  Ppx dose: Oseltamivir 75 mg QD × 7 d (30 mg QD if CrCl <30 mL/min)
  Institutional outbreak ppx duration: 2 wk or 1 wk after last case diagnosed, whichever is longer
- **Prevention:** Hand-washing, avoid touching mucous membranes, masks; smoking cessation (*NEJM* 2003;348:1256); annual **influenza vaccination** (see *"Immunizations"*)

PNEUMONIA

Background (*Natl Vital Stat Rep* 2012;60:1; *Am J Manag Care* 2012;18:380)

- **Classification:** *Community-acquired pneumonia (CAP):* Bacterial pneumonia acquired in community setting; *Healthcare-associated PNA (HCAP):* PNA acquired in hospital, SNF, HD facility, or within 90 d of hospitalization; HCAP assoc w/ ↑ drug resistance and

different organisms

- **Epidemiology:** >2.5M annual visits to PCPs (*Vital Health Stat* 2011;13:1), prevalence of PNA among pts presenting w/ acute cough to primary care is 5–7% (*Ann Intern Med* 2003;138:109)
- **Microbiology:** No pathogen detected in ~60% of cases; among identified pathogens, viral etiology most common (22%; rhinovirus > influenza > metapneumovirus > RSV > parainfluenza > coronavirus > adenovirus) followed by bacterial (11%; *Streptococcus pneumoniae* > *M. pneumonia* > *S. aureus and L. pneumophila*) (*NEJM* 2015;373:415)
- Other etiologies: **Fungal** (*Histoplasma, Coccidioides, Cryptococcus, Pneumocystis*), **zoonotic** (psittacosis, Q fever, tularemia)
- **Pneumonia 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)
- **Drug-resistant *S. pneumoniae* (DRSP) risk factors:** Age >65, abx w/in past 3 mos, EtOH, comorbid illness (chronic heart, lung, liver, or renal disease, DM, 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:S27)
- 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;** assess for HCAP criteria (above) or drug-resistant *S. pneumoniae* risk factors (above)
- **History:** Assess for cough, 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: 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: CRP shows promise in prediction rules & ↑ procalcitonin may help rule in bacterial illness; optimal use of both tests not yet clear: Further study needed
- **Microbiologic testing** (sputum culture ± serology, urinary Ag, PCR) **optional** in outpts; identifies causative organism <½ the time & empiric Rx usually effective (*JAMA* 2000;283:749; *Ann Intern Med* 2005;142:165); pursue if:

  (1) ↑ Suspicion for epidemiologically important organism (influenza (see *"Influenza"*), *Legionella,* TB (see *"Tuberculosis"*), CA-MRSA)
  (2) Cavitary lesion, pleural effusion, severe underlying lung disease
  (3) Failure to respond to tx
  (4) Unusual presentation

Treatment

- **First decision for outpatient provider is whether or not to hospitalize:**

  HCAP: Usually requires admission for IV antibiotics
  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	Outpt
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:** Empiric regimen based on drug-resistant *S. pneumoniae* risk (see "DRSP risk factors," above); treat for minimum 5 d or until afebrile 48–72 h; if ↑ suspicion for unusual organism, may alter diagnostics & tx coverage

Empiric Antibiotic Regimens (***CID* 2007;44:S27**)

Risk	Antibiotic Choice
Low DRSP risk	**Azithromycin 500 mg × 1, then 250 mg QD × 4 (preferred)** **Alt:** Azithro 500 mg QD × 3, azithro 2 g × 1, or clarithromycin 1 g QD × 5 Assoc w/ ↑ QTc & ↑ CV mortality; use alt or monitor in ↑ risk pts • If adherence concerns, consider short course w/ single dose or 3 d course of azithro (long $t_{½}$) (*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) • 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)** **Levofloxacin 750 mg QD × 5–7 d, moxifloxacin, or gemifloxacin** • If possible TB, avoid FQ use (2nd-line tx for TB)
	(**Macrolide** or doxy) & (**amox/clav 2 g BID** or amox 1 g TID or 2nd-gen

	ceph) • Amox or amox/clav preferred over cephalosporins; cefpodoxime preferred over cefuroxime (*CID* 2003;37:230)

- **Follow-up:** Sxs should improve soon after abx, but some sxs (cough, fatigue) can linger up to 30 d; repeat CXR usually unnecessary; consider if smoker or ? of malignancy
- **Symptomatic treatment:** Cough suppressants and expectorants do not affectoutcomes
- **Smoking cessation:** Screen all pts, advise to quit, & offer assistance (see "*Tobacco*")
- **Prevention:** Administer pneumococcal vaccines per guidelines (see *"Immunizations"*) to prevent invasive pneumococcal disease (*Cochrane Database Syst Rev* 2013;1:CD000422; *NEJM* 2003;348:1747)

SEXUALLY TRANSMITTED INFECTIONS

Background (*CDC: STD Surveillance* 2016; *Sex Transm Infect* 2011;87:183)

- **Epidemiology:** 110 M Americans have current (new/existing) infections; half of new dx in pts <24 y
- **Microbiology:** HPV most common (~14M/y); *C. trachomatis* most common bacterial infection (~1.4M cases in US in 2015, majority asx → importance of screening, see below), followed by *N. gonorrhoeae* (~700,000 cases/y)
- **Risk Factors: Young age** (15–24 yo), unmarried, **MSM** (esp ↑ RR of syphilis), new partner in past 60 d, multiple sex partners, hx prior STI, HIV ⊕, illicit drug use, imprisoned, contact w/ sex workers, hx exchanging sex for payment, inconsistent condom use
- **Screening:** Screen or consider testing in groups with risk factors (above) at least annually, be aware of local prevalence patterns and recommendations; complete sexual history helps to identify those at ↑ risk; for specific testing modality see *Individual pathogens* below

Specific STI Screening Recommendations (***CDC 2015 guidelines***; ***MMWR* 2015;64:1**)	
Gonorrhea, Chlamydia	Sexually active ♀ <25 y MSM annually at site(s) of contact, q3–6mos if ↑ risk HIV⊕ at first visit, subsequently if ↑risk

Syphilis	MSM annually, q3–6mos if ↑ risk HIV⊕ pts at first visit, subsequently if ↑risk
HIV	**All adults 13–64 once** MSM annually if pt/partner have had any partners since last test; more frequently in those at ↑ risk **Anyone seeking evaluation for STIs** ("STD check") More frequently in those at ↑ risk

General Approach (*CDC: STD Treatment Guidelines* 2015)

- **History:** Cannot screen/test accurately without obtaining sexual history; respectful, nonjudgmental attitude key to obtaining accurate history; ask about 5P's (below); "Is there anything else I need to know?"; see "*Patient Visit*"

Sexual History	
Partners	"Tell me about any new sex partners you've had since your last visit" "Is it possible any of your sex partners in past 12 mos had sex with someone else while still in a sexual relationship with you?"
Sexual practices	"To understand your risks for STDs, I need to understand the kind of sex you have had recently" "When you have sex, who puts what where?"
Pregnancy	"What are you doing to prevent pregnancy?"
Protection	"What are you doing to protect yourself from HIV/STDs?" "When you have [ ] sex, do you use condoms always, sometimes, or never?" If sometimes: "In what situations do you use condoms?" "Some of my patients have difficulty using a condom every time. How is it for you?"
Prior STIs	"Have you ever had a sore or scab on your penis?" "Have you ever had an STD? Has your partner?

- **STI symptoms:** Recall that many STIs are asx
  - *Urethritis*: Dysuria > pruritus, burning, or discharge
  - *Cervicitis:* Pelvic pain, dyspareunia, discharge; early sign of PID (see *"PID"*)
  - *Epididymitis:* Pain, swelling, inflammation of the epididymis; may extended to testes
  - *Proctitis:* Anorectal pain, tenesmus, rectal discharge or bleeding
  - *Ulcer:* Oral, anal, vaginal, perineal; for hx rash, consider HSV (see *"HSV"*)

- **Exam:** Skin, LN exam (cervical, inguinal), OP exam
  Perineal: Rash, ulcer (*Painless:* Syphilis, LGV, granuloma inguinale; *Painful:* HSV, chancroid),
  Rectal: Discharge (proctitis)
  Male exam: Urethra: Purulent/mucopurulent discharge (urethritis); epididymal/testicular tenderness (epididymitis)
  Female exam: Cervicitis: Purulent/mucopurulent d/c, bleeding/friable cervix w/ minor trauma (e.g., specimen swab in os, also see "Vaginitis")
- **Testing:** By symptoms; see specific disease processes below; for urethritis and cervicitis, test (& empirically treat) for GC/CT

Causative Organism by Presentation	
Urethritis	*N. gonorrhoeae* or *C. trachomatis* > *M. genitalium* > *T. vaginalis;* also possibly HSV, rarely *T. pallidum* *Dx:* GC/CT testing on urethral swab or first-void urine
Cervicitis	*N. gonorrhoeae* or *C. trachomatis* >> *T. vaginalis* or bacterial vaginosis See *"Vaginitis"* and *"Pelvic Inflammatory Disease"* *Dx:* GC/CT testing on cervical swab or first-void urine
Epididymitis	*Age <35: N. gonorrhoeae* or *C. trachomatis* > *E. coli* (insertive anal intercourse) *Age ≥35:* more likely non-STD (bacteriuria, instrumentation)
Ulcer	*Painless:* Syphilis, LGV (esp if assoc w/ painful LAN), granuloma inguinale; *Painful:* HSV, chancroid
Proctitis	*N. gonorrhoeae, C. trachomatis* (including LGV serovars), *T. pallidum,* HSV

Treatment

- **Treatment by organism below;** empiric GC/CT treatment for pts presenting w/ urethritis & cervicitis, empiric tx for all women w/ suspected PID (see *"PID"*)
- **For all patients who test positive for an STI:**
  Partner Rx: Recent partners of pts w/ STI should be referred for treatment & testing, EPT (expedited partner testing) or PDPT (partner-delivered partner therapy); local dept of public health can do anonymous partner tracing
  Reporting: GC, CT, syphilis, HIV all reportable to local health dept
  Advise rescreening in 3 mos (*Ann Intern Med* 2006;145:564)

- **· For all patients in whom STI diagnosis being considered or at ↑ risk:**

  Immunization: HPV vaccine for ♀ & ♂ ages 9–26; HAV & HBV vaccines for MSM, injection drug users, & HIV-infected pts; consider HBV vaccine all pts being eval for an STI (see *"Immunizations"*)

  Evaluate if appropriate for PrEP (see "HIV")

  Education: Encourage condom use as an effective way to ↓risk; for pts w/ ambivalence, consider motivational interviewing (see *"Counseling Pts"*) (*Ann Intern Med* 2008;149:497)
- **When to refer:** Diagnosis uncertain, treatment-resistant disease, 3° syphilis, co-mgmt in HIV ⊕, multiple STIs → infectious disease specialist and/or STI clinic

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Specific Disease Management (CDC: *MMWR* 2015;64:1)

Chlamydia (*Annals Int Med* 2013;158:ITC2)

- **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
- **Testing (screening and dx):** NAAT (nucleic acid amplification test) most sensitive/preferred; culture also available (but ↓ Se); recommend test all sites of sexual contact to ↑Se; (rectal, oropharyngeal NAAT testing not yet FDA-approved, available at some labs, check cdc.gov/std for ongoing testing updates)

  ♀: First-catch urine, cervical, or vaginal swab; ♂: First-catch urine, or urethral swab; may perform (not FDA-approved) for eval of rectal infection to ↑Se
- **Treatment:** Urine, urethral, cervical, vaginal: Azithromycin 1 g PO ×

1; Rectal, or azithro allergy: Doxycycline 100 mg BID × 7 d (use alt 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)

- **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
- **Testing (screening and dx):** NAAT as above; culture if concern for resistance, inoculate on appropriate growth media (culture Se for GC > CT)
- **Treatment:** Dual therapy: Ceftriaxone 250 mg IM × 1 and (azithromycin 1 g PO × 1 **or** doxycycline 100 mg PO BID × 7 d) *Alt:* If ceftriaxone unavailable → PO cefixime (not first-line 2/2 ↑ resistance); *Cephalosporin allergy:* azithromycin 2 g PO × 1 **&** gentamicin 240 mg IM × 1 **or** gemifloxacin 320 mg PO × 1
- **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 also "*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 wk; only 30–60% of cases dx at this stage as may be subtle or difficult to visualize (vaginal, rectal)
  - **Secondary:** Occur 2–8 wk 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; classified as early (<1 y) or late (>1 y)
  - **Tertiary:** Years after 1°infection: May include CV, neuro, ophtho, granulomatous disease
  - **Neuro:** Any stage disease, various presentations; cog dysfunction, motor/sensory deficit, ophthalmic sxs (uveitis, optic neuritis), auditory sxs, CN palsy, meningitis, stroke s/sxs
- **Testing:** Multiple modalities available
  - *Screening:* Direct antitreponemal preferred for pts w/o hx infection; if ⊕ may be 2/2 prior infection (treated or not) or current infection, false ⊕ in pts w/ low likelihood also possible; typically confirmed w/ RPR
  - *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°), but not on oral lesions (other spirochetes are nl oral flora)
  - *3°:* As above & CSF testing if neuro sx (LP w/ ↑ lymphocytes, TP; 50% ⊕ VDRL)

Syphilis Testing (*AFP* 2012;86:433)	
Testing Modality	**Notes**
Indirect/nontreponemal: (Measures marker of immune response to syphilis infection) **VDRL, RPR**	False ⊕ in other infections, pregnancy False ⊖ early in disease or in immunocompromised Follow titers to track tx response; 4× ↑ in titers can indicate reinfection
Direct antitreponemal: **FTA-ABS, TP-EIA, TPPA**	More specific; more costly; false ⊖ early in disease Remains ⊕ for years after tx → cannot be used to dx reinfection
Direct visualization of organism: **Darkfield microscopy**	⊕ In early disease; requires technical experience ↑Sp/↓Se

- **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 (less effective)
  - **Late latent/3°:** Co-mgmt w/ specialist; PCN as above IM weekly × 3 wk, or doxycycline × 4 wk
  - **Neuro/Ophthalmic: IV** PCN 4 × 10^6 q4h or ceftriaxone 2 g IV QD (↓ effective) × 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 g 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

URINARY TRACT INFECTION

Background (*NEJM* 1996;335:468; 2012;366:1028; *J Urol* 1993;149:1046; *Ann Epidemiol* 2000;10:509)

- **Classification:** *Uncomplicated cystitis:* Acute (<14 d) infection of the lower urinary tract in an otherwise healthy, nonpregnant woman

Complicated cystitis/UTI: Acute UTI in anyone else (see "Red Flags" below)

Pyelonephritis: Infection of the kidneys, usually extension of lower urinary tract infection

- **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* causes 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, GU tract surgery/recent instrumentation, bladder dystonia, indwelling catheter

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; altered mental status or incontinence in the elderly; elicit sexual hx (i.e., new partners) to evaluate for STIs; see "*STIs*"
- **Criteria for 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
- **Differential diagnosis:** Gonococcal or chlamydial urethritis, interstitial cystitis (bladder pain related to filling/emptying w/ frequent voids occurring over mos), irritants (tampons, condoms, detergents), pyelonephritis, vaginal infections (trichomonas, candidiasis), PID; in ♂: Prostatitis, BPH, or epididymitis
- **Exam:** VS; GU exam: suprapubic tenderness or fullness (urinary retention), CVA tenderness; pelvic exam if sx suggestive of vaginitis (including atrophic vaginitis) or urinary source unclear
- **Diagnostics:** Uncomplicated UTI may be diagnosed based on sx; telephone diagnosis using established protocols is safe & effective (*Wisc Med J* 2007;106:326; *Am J Med* 1999;106:636; *Arch Intern Med* 2004;164:1026); for those w/ complicating features or pyelonephritis, must obtain

urinalysis (midstream) and **urine culture**

Laboratory Testing in Urinary Tract Infection		
Urine Dipstick	**Urinalysis**	**Urine Culture**
Leukocyte esterase (Se 75–96%/Sp 94–98% for WBC); nitrite detects Enterobacteriaceae (which incl *E. coli*) only (*Med Clin North Am* 1991;75:313)	Pyuria (>10 neutrophils/HPF [95% Se, 71% Sp]) + bacteriuria ± hematuria (>5 RBC/hpf); pH >6.5 suggests urea-splitting organism such as *Proteus*	>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

- **Imaging:** Not needed for diagnosis of UTI or pyelonephritis; generally only ordered if suspicion of alternative/precipitating etiology (stones, abscess); consider in pts w/ pyelonephritis and: ♂ Gender, DM, renal colic, or no response to abx after 72 h

Treatment (*AFP* 2000;61:713; *AFP* 2010;82:638; *CID* 2011;52:e103; *NEJM* 2003;349:259)

- **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)
- **Uncomplicated UTI: Multiple regimens available; note duration varies by Rx**
- **Complicated UTI:** Preferred regimen varies by case; **review prior culture data;** do *not* use moxifloxacin (even if spectrum appropriate, GU drug concentration is too low to be effective); avoid nitrofurantoin or b-lactams in ♂, as they do not treat occult prostatitis

Uncomplicated UTI Regimens		
Antibiotic	**Duration**	**Notes**
Nitrofurantoin 100 mg PO BID	5 d	Preferred 1st-line agent
TMP-SMX DS 1 tab BID Fosfomycin 3 g PO	3 d ×1	Use if no abx use in the past 3 mos, no recent hospitalization and local resistance <20%

Amoxicillin/clavulanate 500/125 mg	7 d	2nd-line agent
Not Fluoroquinolones	Save for complicated UTI – ↑ resistance	

Complicated UTI regimens		
Antibiotic	**Duration**	**Notes**
Ciprofloxacin 500 mg BID Levofloxacin 500–750 mg daily	7–14 d	For patients who have not recently received an FQ and are not from a long-term care facility
TMP-SMX 160/800 mg (DS) one PO BID	7 d	Phenazopyridine 200 mg PO TID × 2 d; avoid in pts w/ G6PD deficiency

- For dysuria/symptom management: May add phenazopyridine 200 mg PO TID × 2–3 d; avoid in pts w/ G6PD deficiency; caution pts can → orange urine
- **Pyelonephritis: Dx of UTI** + **CVA tenderness and/or systemic sx:** If pt does not meet ED referral criteria (below), tx guided by local FQ resistance patterns
  - *Empiric if E. coli FQ resistance <10%:* Ciprofloxacin 500 mg PO BID × 7 d: Noninferior to 14 d and ↓s/e (*Lancet* 2012;380:484)
  - *Empiric if E. coli FQ resistance >10%:* Consider first-dose IV w/ CTX 1 g or cipro 400 mg IV × 1, then empiric cipro 500 mg BID
  - *Culture-guided subsequent treatment:* Narrow regimen if possible; if narrow to TMP-SMX or B-lactam (2nd-line), extend to 14-d course (*NEJM* 2003;349:259); do not use nitrofurantoin (does not penetrate renal parenchyma); do not use moxifloxacin (ineffective 2/2 low [GU])
- **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
- **When to refer:** Complicated pyelonephritis: Pts w/ severe systemic sx, hemodynamic instability, altered mental status, pregnant, unable to tolerate PO, inability to confirm close outpatient f/u → ED/inpatient admission

Recurrent UTI

- **Definition:** >2 UTI in 12 mos
- **Pt counseling:** Avoid spermicides; unclear whether hydration, postcoital voids, methenamine hippurate, probiotic vaginal suppositories, wiping urethra front-to-back are effective; cranberry juice ineffective (*JAMA* 2016;316:1879)
- **Self-treatment:** Depends on prior susceptibilities; consider TMP-SMX; instruct pt to call if sx persist >48 h
- **Postmenopausal:** Consider intravaginal estrogen cream
- **Postcoital ppx:** Nitrofurantoin 50–100 mg PO **or** cephalexin 250 mg PO × 1 postcoitally; TMP-SMX ½ SS tab (40/200 mg) PO **if** pt has high-efficacy birth control regimen
- **Prophylaxis:** 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)
  - *Duration:* >12 mos duration not evaluated; not recommended in pts at risk for complicated UTIs; chronic nitrofurantoin associated w/ hepatitis, neuropathy, pulm complications—counsel pt; advise risk & sx of *C. diff* infection
  - *Regimens*: TMP-SMX ½ SS tab (40/200 mg) PO QHS if local *E. coli* resistance <20%, **or** nitrofurantoin 100 mg PO QHS; may also use cefaclor, cephalexin; FQs & TMP-SMX **contraindicated** in pts who could become pregnant

C. DIFFICILE

Background (www.cdc.gov; *CID* 2008;46:S19; *Infect Control Hosp Epi* 2010;31:431)

- ***Clostridium Difficile* Infection case definition:** Clinically significant diarrhea or toxic megacolon without other etiology with (1) stool with positive toxin A- or B-producing organism; (2) pseudomembranes seen on endoscopy; (3) pseudomembranous colitis on histopathology
- Rapidly increasing incidence in US, including community-acquired infections and community-based recurrence; 500K cases in 2011; most common hospital-acquired infection in US; increasing severity

→ higher hospital mortality (*CID* 2012;55:S88)

- **Microbiology:** Spore-forming, toxin-producing, anaerobic gram-positive rod; **resistant to alcohol disinfectants;** spores are ingested, colonization occurs → protective colonic flora disturbed → *C. diff* releases toxin A/B which mediates mucosal inflammation and damage → necrosis/pseudomembranes
- **Risk factors:** Recent antibiotic use: Fluoroquinolones, clindamycin, penicillins/cephalosporins assoc w/↑ risk, but all abs implicated (*CID* 2008;46:S19); antacids (*Am J Gastro* 2012;107:1011), age, chemotherapy, immunosuppression, hospital exposure

Evaluation (*CID* 2012;55:S88)

- **Hx/PE:** Assess for risk factors (above) and **red flags** (suggest fulminant colitis): Fever or hemodynamic instability, severe or systemic symptoms, lower or diffuse abd pain, ileus, distention
- **Labs:** CBC, BMP (WBC and Cre used to assess disease severity)
- If diarrhea and risk factors, send stool for EIA testing (glutamate dehydrogenase [GDH] antigen test + toxin A/B test); GDH enzyme is present in all *C. diff* isolates; toxin confirms strain is pathogenic; if indeterminate → PCR for tcdB and tcdC genes to confirm disease; False ⊕ seen in asx carrier or s/p tx
- **KUB:** Typically obtained in setting of ED eval; colonic distention (>7 cm) = emergency

Treatment (*CID* 2012;55:S88; *Inf Cont & Hosp Epi* 2010)

- **General approach:** Treatment determined by severity: No consensus guidelines for classification of mild, mod, severe illness, relies on clinician judgment; proposed stratification by IDSA/SHEA below
- Asx colonization: Toxin or PCR ⊕ and no symptoms → no treatment required
- Acute diarrhea w/ colitis: Watery, rarely bloody ±mucus; spectrum of systemic sxs; only mild and some moderate disease appropriate for outpatient treatment
- Mild–moderate disease criteria: T <38.5, WBC <15K, no peritoneal signs, no evidence of sepsis, age <65 y; all others → ED
- **Treatment regimen:** For mild–mod disease, **metronidazole 500 mg PO TID ë 10–14 d**

Other meds: D/c all antiperistaltics

Other antibiotics: If on antibiotics to treat a different infection, d/c if not essential; if must continue, *C. diff* tx course should extend 7 d beyond last dose of other abx

Reassess: If no improvement after 2–3 d, change to vancomycin 125–500 mg PO QID

- **Recurrence:** 1st – Same regimen as original; 2nd – vancomycin in tapered or pulsed regimen (vanco 125 mg PO q6h for 10–14 d, then 125 mg PO q12h for 1 wk, 125 mg PO QD for 1 week, 125 mg PO every 2 or 3 d for 2–8 wk)
- **Refractory disease:** Fecal transplant appears safe and effective (*NEJM* 2013;368:407; *Open Forum Infect Dis* 2015; 2: ofv005)
- **When to refer:** Severe disease, red flags → ED; recurrent or persistent disease or for guidance on continuing preceding antibiotics → ID

SKIN & SOFT TISSUE INFECTIONS

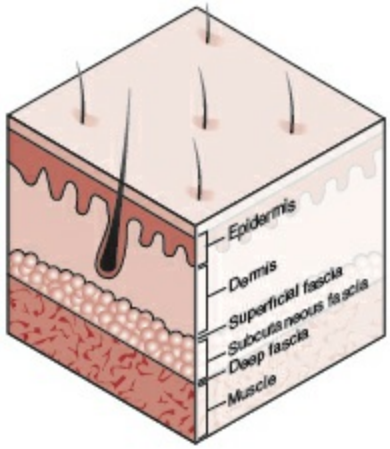
Background (*JAMA* 2016;317:3; *NEJM* 2004;350:904; *BMJ* 2012;345:e4955)

- **Definition:** Acute, pyogenic inflammation of dermis & subcutaneous tissue 2/2 bacterial infection; ranges from mild infections of the epidermis (impetigo, erysipelas), or hair follicles (folliculitis, furuncles, carbuncles), deeper involvement of the dermis (cellulitis), abscesses or life-threatening infection (necrotizing soft-tissue infection [NSTI])
- **Presentation:** May occur on any part of epidermis, but legs common, followed by face, feet, hands, torso, neck, & buttocks (*AFP* 2002;66:119)
- **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, atopic dermatitis, trauma, IDU); disruption of vascular/lymphatic system (PAD, venous stasis, prior surgery/trauma), or depressed immune function (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)

Syndromes (*Chest* 1996;110(1): 219)

Infection by Cutaneous Layer



Skin/Soft Tissue Layer	Infection
Epidermis	Erysipelas Impetigo
Hair follicle	Folliculitis Furunculosis (deep) Carbunculosis (deep)
Dermis/superficial fascia	Cellulitis
Subcutaneous and below	Necrotizing STI

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
- **History 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 (common pathogens still common, but consider 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 healthcare 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 venous stasis), 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
- **Labs:** Typically not needed; obtain CBC, BMP 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 or planned abx use
- **Imaging:** Typically not needed but may obtain if concern for osteomyelitis or NSTI
- **Differential diagnosis:** Up to 1/3 of LE "cellulitis" cases are actually due to another cause: *Vascular* (DVT, superficial thrombophlebitis, calciphylaxis, stasis dermatitis), *inflammatory* (drug reactions, contact dermatitis, gout, erythema nodosum), *other infections* (erythema migrans, zoster), *miscellaneous* (insect bites/stings); 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 (*CID* 2014;59:2; *AFP* 2015;92:474)

- Management based on whether infection is purulent vs. nonpurulent
- **General approach to purulent STI:** I&D if large enough to drain, with cultures sent from abscess if considering antibiotics; mild SSTI do not require further treatment; for moderate infection, abx as below; for sever infection → inpt/ED
- **Red flags:** Abscess requiring extensive I&D, in cosmetic/sensitive area (face, neck, groin), suspect extension near/into deeper structures, systemically ill, immunocompromise
- **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 if drainable fluid collection +/- abx (see below)
- **Antibiotic indications: 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
- **Antibiotic choices:** Empiric coverage for MRSA generally recommended—susceptibilities vary by region & even by hospital; do not use FQ for MRSA even if reported susceptible

Antibiotic Regimens for Moderate Purulent SSTI	
Empiric tx	**Targeted tx**
• TMP-SMX 1–2 DS tabs BID • Doxycycline/minocycline 100 mg BID • Clindamycin 300—450 mg PO QID	• MRSA: See empiric • MSSA: Dicloxacillin 500 mg QID or cephalexin 500 mg QID

- **General approach to nonpurulent STI:** For mild infection, topical abx, for others coverage of strep infection and MSSA most important; if culture data available, use to guide (but typically none available)
- **Red flags:** Periorbital cellulitis, concern for NSTI (see above), e/o

systemic infection, immunocompromised

- **Impetigo:** Most superficial infection, affects face & limbs, red w/ "honey crust." 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
- **Folliculitis:** Inflammation follows hair follicles; usually spontaneously resolves; warm compresses, avoid shaving affected area; consider mupirocin (*AFP* 2002;66:119)
- **Erysipelas:** Well-demarcated, brightly erythematous; rare in adults but may cause sepsis or deeper infection if not treated early, esp in elderly: → Hospitalize if febrile as may progress quickly
- **Cellulitis:** No e/o better outcomes 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 ↓ recurrence

  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

  Recurrent cellulitis: For patient with 2 or more episodes of nonpurulent cellulitis in the past 3 y, consider PCN VK 250 mg PO BID for oral suppressive therapy (*NEJM* 2013;368:1695)

Empiric Antibiotic Regimens for Mild-Mod Nonpurulent SSTI
• PCN VK 250–500 mg PO QID • Cephalexin 500 mg QID • Dicloxacillin 500 mg QID • Clindamycin 300–450 mg PO QID

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

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
- **Ulcer risk factors:** ⊕ PAD or ↓ sensation in affected limb, CKD, hx walking barefoot; risk of progression to osteomyelitis if ulcer present >30 d, prior LE amputation
- **Classification:** Acute (<2 wk); chronic (>3 wk); *Mild:* Limited to SC tissue, *Moderate:* Extending to deeper structures including bone, joints, fascia; *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 history (onset, duration), systemic sx
- **Exam:** Assess for ulcer, local inflammation, vascular exam, neuropathy, tinea; for ulcers, probe for communication to bone
- **Diagnostics: Probe-to-bone test:** If ulcer probes to bone, then assume osteomyelitis (no imaging needed); if chronic deep ulcer, eval for osteomyelitis with plain radiograph → insensitive in early infection; if XR ⊖, serial radiograph vs. MRI
- **Culture:** Recommended; 1st cleanse & debride to decrease contamination with wound colonizers, then culture based on ulcer w/ sterile instruments or obtain bone biopsy; if pt stable/minimal inflammation, complete biopsy/debridement *prior to abx;* **no role for superficial wound swab or specimen from clinically uninfected**

wound

Management

- **All patients:** *Behavioral:* Offload wt bearing, wound care, glycemic control, proper footwear; also needs vascular evaluation as osteomyelitis not curable in absence of vascular sufficiency to allow healing of overlying skin; *Referral:* Co-mgmt w/ ID, orthopedics, wound specialists, vascular services optimal
- **Wound Care:** see *"Wound Care"*
- **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

Management of Selected DFI		
Severity	**Antibiotic**	**Notes/Precautions**
Mild	Cephalexin Amoxicillin/Clavulanate	Consider adding *Pseudomonas* and anaerobic coverage if chronic; treat 1–3 wk with final duration determined by clinical response
Mild + RF for MRSA	Doxycycline TMP–SMX	
Moderate +/- RF for MRSA	ID and surgical consult for management of associated osteomyelitis, abscess, or septic arthritis	Consider for outpatient IV antibiotic therapy if not meeting criteria for admission

- **Follow-up:** If not improving at 3–5 d follow-up, re-eval abx, consider surgical referral

HERPES SIMPLEX VIRUS

Background (*JAMA* 2006;296:964; 2011;305:1441; 2011;305:1441; *JAAD* 2007;57:737)

- **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 & 10–20% of new genital infections in US; can also → skin (e.g., eczema herpeticum), eye (keratitis), & CNS disease (encephalitis) (*JAAD* 2007;57:737; *CID* 2013;56:344; *JAMA* 2016;316:23)

- **HSV-2:** Responsible for anogenital lesions but can also infect oral mucosa; infection in ♀→ ↑ risk of neonatal HSV; can also cause CNS disease (meningitis, including recurrent, assoc w/ Mollaret's)
- **Epidemiology:** 23.6 million new cases/y in persons aged 15–49 y; US seroprevalence of HSV-1/HSV-2 ~58/17%; of these people, only 10–25% have ever had clinical disease; acquisition rates higher in ♀ (HSV-2), prior STI (HSV-2), ↑ number of lifetime sexual partners (HSV-2), uncircumcised men (♂ circumcision ↓ HSV-2 acquisition by 25%) (*NEJM* 2009;360:1298); African-American (HSV-1 & 2), early acquisition assoc w/ ↓ SES
- **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 CN V ganglia (orofacial) or sacral (genital) → **reactivation:** usually 1–6 episodes/y, milder, shorter in duration than primary episode
- **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)

- **Anogenital:** 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; **herpes gladiatorum** (multiple lesions) in contact sports; HSV can also be assoc w/ **erythema multiforme**
- **Diagnosis:** If dx uncertain, unroof vesicle w/scalpel and then swab lesion → direct fluorescent Ab (result 24–48 h), Tzanck smear (most rapid), viral culture (gold std), skin bx
- **Serologic testing:** Given high seroprevalence of HSV-1, ⊕ test not very useful in dx of specific lesion; **cannot** distinguish between oral & genital HSV-1; HSV-2 Ab test has low specificity and not recommended for routine screening including during pregnancy (*JAMA* 2016;316:23); 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 periods (*J Infect Dis* 2006;194:420; *BMJ* 2007;334:1048)
- **Pregnancy:** Routine screening is *not* recommended; for women with recurrent genital HSV, offer suppressive therapy at 36 wk gestation;

for outbreak at the time of delivery, consider C-section

- **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; dose adjustment and consideration of alternate agents in the immunosuppressed

Treatment of HSV in Immunocompetent Patients (*JAAD* 2007;57:737; *MMWR* 2015;64:1)		
Medication	**Clinical Context**	**Dose**
Acyclovir	Primary oral or genital	400 mg PO TID × 7–10 d
	Recurrent genital	400 mg PO TID × 5 d; or 800 mg PO BID × 5 d; or 800 mg PO TID × 2 d;
	Suppressive therapy	400 mg PO BID
	Herpes labialis (*Arch Intern Med* 2008;168:1137)	200–400 mg 5×/d × 5 d 5% crm—apply 5×/d × 4 d
Valacyclovir – ↑ bioavailability – FDA-approved for Rx of HSV in HIV	Primary oral or genital	1 g PO BID × 7–10 d
	Recurrent genital	500 mg BID × 3 d; or 1000 PO QD × 5 d
	Herpes labialis	2 g PO BID q12h × 2 doses
	Suppressive therapy	500 mg PO daily

VARICELLA 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," usually primary infection acquired in childhood) & herpes zoster ("shingles," reactivation from the sensory ganglia → typically dermatomal distribution)
- **Shingles risk factors: Age >50 yo, immunosuppression** (s/p transplant, autoimmune disease, immunosuppressive medications esp MMF, malignancy, HIV ⊕), ♀ gender, trauma, stress
- **Complications: Postherpetic neuralgia** (pain present >90 d; 5% in

pts <60 yo, 20% in pts >80 yo) that may last mos–y; bacterial superinfection of the skin (2.3%); ocular complications (1–2%); meningitis/encephalitis (0.5%); motor neuropathy (1–3%); GBS (0.03%); stroke syndromes due to cerebral artery involvement (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, allodynia** often in dermatome where the eruption later develops
- **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; can occur without rash (**zoster sine herpete**)
- **Diagnosis:** Determined by morphology & distribution; confirmatory tests are best done in vesicular phase: Unroof vesicle w/scalpel and then swab lesion → 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 × 7–10 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); consider addition of prednisone taper
- **Antivirals in immunocompromised hosts:** Treat all pts even if they present after 72 h; if disseminated, will need urgent ED referral

for admission & IV acyclovir

- **Postherpetic Neuralgia:** See table

Treatment of Postherpetic Neuralgia		
Medication Class	**Examples**	**Considerations**
Anticonvulsants	Gabapentin, pregabalin, divalproex sodium	Dizziness, somnolence, dry mouth, edema, wt gain reported Abrupt d/c may → withdrawal sx
TCAs	Nortriptyline, amitriptyline, desipramine	Anticholinergic effects & lag time (up to 3 wk), can ↑ QTc
Opioids	Codeine, tramadol, oxycodone, morphine	Use cautiously; potential for addiction & diversion
Topical Agents	Capsaicin, lidocaine patch	Topicals not tolerated by up to 1/3 of pts

(*Neurology* 2004;63:959; *Cochrane Database Syst Rev 20*11 :CD006866; *Ann Pharmacother* 2011;45:1483; *Clin Pharmacol Ther* 1988;43:363; *Pain* 1988;33:333)

- **Recurrence prevention:** Shingles vaccine may ↓ risk of recurrence; is well-tolerated; offer to pts ≥3 mos after zoster episode (booster effect may be greater if further out from zoster episode); see *"Immunizations"* (*JID* 2013;208:559)

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; assoc w/ **vesicles & erosions on nasal tip** (Hutchinson sign); 71% have ocular complications including **keratitis**, conjunctivitis, episcleritis, corneal scarring, iritis, **vision loss in 15%;** also can → acute retinal necrosis or progressive outer retinal necrosis (immunocompromised); **requires urgent ophthalmologic eval** (*JAAD* 2007;57:S136; *Am J Med* 2017;130:1)
- **Herpes zoster oticus (Ramsay Hunt syndrome):** Reactivation of VZV in CN VII dermatome, geniculate ganglion; presents 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; requires admission → IV acyclovir

HEPATITIS B

Background (www.who.int; *Hepatology* 2009;50:661; *NEJM* 2008;359:1486)

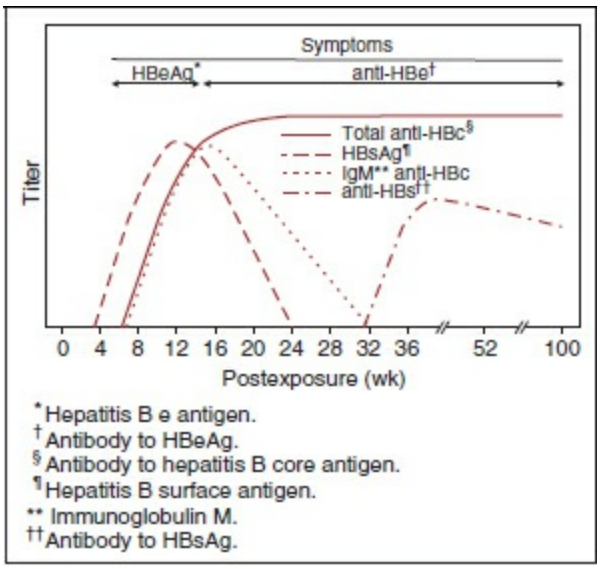
- **Epidemiology:** >240 million people worldwide chronically infected with hepatitis B virus (HBV); 850K–2M carriers in US (most asx)
- **Complications of chronic infection:** 15–40% will develop serious sequelae (cirrhosis, ESLD, HCC) over their lifetime; **HBV → 100× ↑ risk of HCC, even without cirrhosis**
- **Microbiology:** HBV is a partially dsDNA retrovirus, primarily infects hepatocytes, difficult to eradicate, transmitted by bloodborne exposure, sexual contact, vertical transmission
- **HBV Risk factors:** Birth in endemic area (Africa, Asia, S. Pacific, due to perinatal transmission); adult transmission: Sexual/household contacts, PWID, MSM, prisoners, ESRD on HD
- **Risk factors for chronic infection:** Progression to chronic HBV (vs. clearance) assoc w/ ↓ age at acquisition: 90% for perinatal, 20–50% for age 1–5; <5% for adult
- **Natural history of chronic infection:** Highly variable, several potential phases, all of which may last several years
  - (1) *Replicative phase:* High HBV viral load, active liver disease/necroinflammation (transaminitis, inflammation on liver biopsies)
  - (2) *Low-replication phase:* Lower viral load (with or without immune tolerance; can have liver inflammation)
  - (3) *Remission phase:* Carrier state (remains in hepatocytes)
  - (4) *Reactivation phase:* Chronic hepatitis
- **Risk factors for reactivation: HbSAg positive,** immune suppression (anti-CD20 agents > cytotoxic chemo+prednisone, anti-TNF agents > methotrexate, azathioprine, glucocorticoids)

Evaluation (*MMWR* 2008;57:1)

- **Screening:** Those at ↑ risk of infection or complications, including

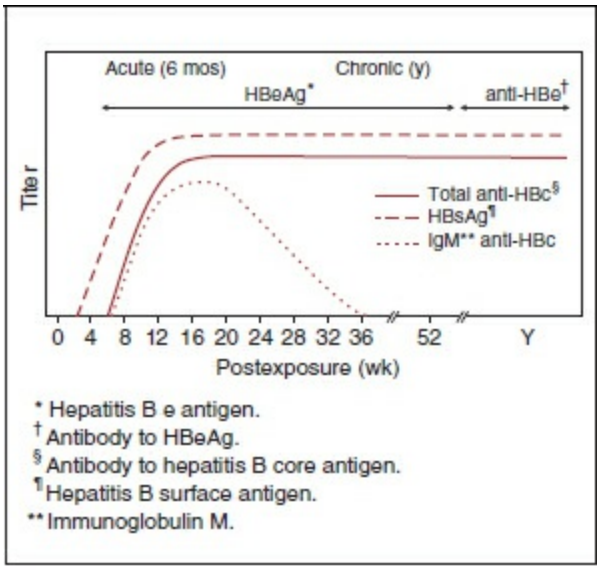
pregnant ♀, HCV ⊕, HIV ⊕, pts starting immunosuppressants, chemotherapy, chronic ↑ ALT/AST, DM

- **Diagnosis:** *Acute infection:* HbsAg, Anti-Hbc IgM;
  Screening for chronic infection: Anti-HBs, HBsAg, anti-Hbc



(*MMWR* 2008; 57:1)

Figure 7-1. Typical serologic course of acute hepatitis B virus infection with recovery.



(*MMWR* 2008; 57:1)

Figure 7-2. Typical serologic course of acute hepatitis B virus (HBV) infection

with progression to chronic HBV infection.

Diagnosis	HbsAg	anti-HBs	anti-HBc	HBeAg	anti-HBe	HBV DNA
Acute hepatitis	⊕	⊖	IgM	⊕	⊖	⊕
Window period	⊖	⊖	IgM	±	±	⊕
Recovery	⊖	⊕	IgG	⊖	±	⊖
Immunization	⊖	⊕	⊖	⊖	⊖	⊖
Chronic hepatitis *HBeAg* ⊕	⊕	⊖	IgG	⊕	⊖	⊕
Chronic hepatitis *HBeAg* ⊖	⊕	⊖	IgG	⊖	⊕	±*

***Precore mutant**: HBeAg not generated, but anti-HBe can develop due to cross-reactivity w/ HBcAg; assoc w/ high serum HBV DNA levels
(From Sabatine MS, ed., Pocket Medicine, 6th ed., 2017)

Prevention

- **Counseling:** Immunization of sexual partners, condom 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 wk apart
- **Postexposure prophylaxis:** 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)

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 to 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
- **Treatment:** Supportive care for mild cases; suspicion of acute lever failure warrants emergent referral → ED, consider antiviral therapy; reportable to CDC/local health dept; IFN gamma NOT indicated as increases mortality

Chronic Infection (*NEJM* 2004;350:1118; *Liver Intl* 2017;37:59; cdc.gov; *Hepatology* 2009;50:661)

- **Background:** Leading cause of cirrhosis and HCC
- **Risk factors for complications:**
  - *Cirrhosis:* ↑ Age, genotype C, ↑ HBV DNA, ♂, EtOH, HCV, HDV, HIV⊕
  - *HCC:* ↑ Age, EtOH, HCV ⊕, smoking, ♂, ⊕ FHx, cirrhosis
- **Diagnosis:** Chronic HBV defined by ⊕ HBsAg for >6 mos
- **Hx/PE:** Should assess for complication risk factors, s/sx of cirrhosis (see “Cirrhosis”)
- **Initial Studies:** To establish disease activity, hepatic function, and screen for comorbidities & HCC: LFTs, CBC, PT/INR, HBV DNA, HBeAg/anti-HBe, HCV, HIV, HDV for those at ↑ risk, AFP (U/S in ↑ risk pts)
- **Treatment:** Includes both risk reduction and consideration of direct tx (below)
- **Immunization:** HAV in all nonimmune pts
- **HCC screening: U/S (preferred) w/ or w/o AFP q6–12mos**
  - **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	q3–6mos ALT q6–12mos HbeAg	**ALT nl, HBV DNA <2000**	q3mos ALT × 3, then q6–12mos if still nl

ALT 1–2× ULN	q3mos ALT, q6mos HbeAg Consider bx if >40; if ↑ ALT persistent, consider bx/Rx	**ALT 1–2× ULN** **HBV DNA 2000–20,000**	q3mos ALT & HBV DNA; consider bx or Rx if persistent
ALT >2× ULN	q1–3mos ALT, q3mos HbeAg Tx if persistent or if ↓ liver function	**ALT >2× ULN** **HBV DNA >20,000**	Tx if persistent, bx optional

(*Hepatology* 2009;50:661)

- **Pharmacologic HBV treatment: Rx'ed by specialists;** regimens include tenofovir, entecavir, pegylated IFN-α
  - *Goal:* ↓ Complications 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; liver bx may be used if ALT 1–2× ULN & HBV >2000 IU/mL to help guide mgmt
- **When to refer:** Consideration of initiating tx; persistent ↑ of LFTs or HBV DNA; abnl liver bx; evidence of complications (HCC, cirrhosis)

HEPATITIS C

Background (*Hepatology* 2015;62:932; *J Hepatol* 2014;61:S58; *WJG* 2014;20:2876; cdc.gov)

- **Microbiology:** ⊕ ssRNA flavivirus, 6 major genotypes w/ assoc subtypes; in US, genotype 1 most common (70% of cases) >>2 (15–20%) >3 (10–12%) (*J Med Virol* 2012;84:1744)
- **Transmission:** Via direct blood contact (IDU, transfusions, needlestick); vertical transmission; sexual transmission exceedingly rare except HIV ⊕ MSM; **no vaccine,** prevention only by ↓ exposure
- **Incubation:** Typically 8–12 wk; range 2 wk–6 mos
- **Natural history:** Acute infection typically asx; **for those infected → ~80% chronic carrier** state; if untreated → **~20% cirrhosis over 20–30 y → 1–5% annual risk of dying from HCC or ESLD**

Epidemiology and Risk Factors (cdc.gov; *Hepatology* 2015;62:932)

- **Prevalence:** Estimated 2.2–3.2M people anti-HCV ⊕ in US; 75% of them born btw 1945 and 1965; leading cause of death from liver disease & leading cause for liver transplantation in US
- **Risk factors for infection: IDU** (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; www.hcvguidelines.org)

- **Screening:** Those w/ risk factors for infection (above) & **one-time screening of all adults born between 1945 and 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 asx but fatigue common, later may develop sxs due to hepatitis or cirrhosis; extrahepatic manifestations can include hematologic (cryoglobulinemia), dermatologic (porphyria cutanea tarda), renal (MPGN), endocrine (thyroiditis, DM)
- **Diagnostic labs**
  - *Anti-HCV:* Current **or** past infection, ⊕ 1–3 mos postinfection, 97% sens after 6 mos
  - *HCV RNA:* Active disease; can be quantitative, ⊕ 2–3 wks postinfection; obtain if ⊕ Anti-HCV (often reflexively ordered); may also be ordered to diagnose despite negative Anti-HCV to dx acute infection (before Ab ⊕) or for w/u of ↑ LFTs in immunocompromised pt
- **Studies in anticipation of Rx: In addition to HCV Ab and RNA**
  - *Labs:* ✓ LFTs (incl albumin), INR, PLT, **genotype**
  - *Fibrosis assessment:* Indirect: Serum-based commercial fibrosis score (FibroSURE) or vibration-based transient liver

elastography; indirect measures ↓ need for liver bx

- **Management of acute hepatitis:** Supportive care (can consider early antivirals); if concern for acute liver failure (rare) → **prompt ED referral**

Chronic HCV Management (www.hcvguidelines.org; *Hepatology* 2015;62:932; *Ann Intern Med* 2010;152:36)

- **Immunization:** HAV, HBV (if not infected), Tdap, influenza annually, PPSV23
- **Screen for coinfections:** HIV, HBV, sexually transmitted infections
- **HCC screening: Indicated only in pts w/ cirrhosis** (unlike HBV): U/S every 6 mos
- **Pt Education:**
  - *Prevent 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
  - *Prevent disease progression:* Avoid other RFs for liver fibrosis (**EtOH,** tob, obesity), avoid NSAIDs, limit APAP (<2 g in 24 h), vertical transmission in ♀; coffee is protective
- **Pharmacologic Treatment: All pts w/ life expectancy long enough to expect benefit should be offered treatment for HCV; Rx'ed by provider trained in HCV treatment**

Treating Hepatitis C (www.hcvguidelines.org)	
Regimen	Selected based on genotype, fibrosis score, and, if ESLD, compensated vs. decompensated; also by prior exposure to antiviral therapy; algorithms constantly being updated
Duration	Generally 12 wk Rx if no cirrhosis, 12–24 wk for cirrhosis, often combination of agents
Side effects	*Direct acting antivirals:* Very well-tolerated, excellent safety profile; mild–mod s/e: Headache, fatigue, nausea, insomnia; occ pruritus, rash *Ribavirin:* May be used as adjunct; s/e fatigue, flu-like sx, depression, N/V, anemia
Safety Monitoring	**Check for drug–drug interactions,** especially HIV antiretrovirals; screen for and **monitor HBV activity** (curing HCV can cause HBV flare); safety labs for more toxic med regimens (CBC for ribavirin)

Treatment Monitoring	**HCV viral load at 4 wk into treatment** to ensure efficacy (should be undetectable) and **12 wk after cessation:** If undetectable, sustained viral resistance "SVR12" (>99% cure)
Efficacy	>95% cure rates, incl all genotypes, lower rates for cirrhosis

- **When to refer:** Refer to HCV provider for consideration of treatment; refer to GI/ID provider w/ medical expertise, ideally at liver transplant center, if decompensated cirrhosis or infection w/ multiple genotypes

HIV/AIDS

Background (www.unaids.org; cdc.gov/hiv)

- **Microbiology:** Human immunodeficiency virus (HIV) is a ssRNA lentivirus; retrovirus (inserts itself into host genome); 2 types: HIV-1 most common; HIV-2 infections (limited primarily to W. Africa)
- **Epidemiology and risk factors:** 37M people infected worldwide, 1.2M in US; 13% are unaware; sexual contact most common transmission route in US; HIV disproportionately affects MSM, PWID, as well as people of African-American > Hispanic race/ethnicity; however, significant transmission occurs among all demographic groups
- **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
- **Acquired immunodeficiency syndrome (AIDS):** HIV infection *and* CD4+ T-lymphocyte count <200 cells/mm^3 (normal CD4 count is 500–1600 cells/mm^3) *or* CD4% <14% *or* an AIDS-defining opportunistic infection or malignancy (see below)

Acute Retroviral Syndrome (ARS) (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 wk after viral transmission

- **Presentation:** "Mono-like illness," w/ fever, viral exanthem (erythematous maculopapular lesions, face, & trunk), LAN, nonexudative pharyngitis, myalgia/arthralgia; often **mimics other viral infections** and can be easily missed
- **Diagnosis:** HIV RNA (viral load) is most sensitive for acute retroviral syndrome
- **Treatment:** Supportive; prompt referral for 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

Diagnosis (cdc.gov/hiv/guidelines/testing.html)

- **Diagnostic criteria:** Presence of any of the following: (1) ⊕ HIV Abs by ELISA w/ confirmation by Western blot; (2) ⊕ 4th generation immunoassay w/ confirmatory testing by HIV-1 and HIV-2 differentiation assay **or** (3) detectable plasma HIV RNA
- **Lab tests:**
  - *Antibody/antigen testing:* 4th generation immunoassay detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen; p24 antigen positive 2–3 wk after infection; confirmatory testing performed w/ HIV-1 and HIV-2 differentiation assay; alternative algorithm at some centers includes western blot as confirmatory test.
  - *Discordant results: If ⊕ screen* with negative differentiation assay check HIV-1 VL for acute infection; can consider HIV-2 VL if risk factors (travel to/from W. Africa)
  - *Rapid test:* Uses oral fluid (also available as home test kit: OraQuick), blood, plasma, or serum; result in 10–20 min; Se & Sp 98.4–100%; must confirm by 4th generation test above (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 (other tests may be ⊖)**
- **Delivering diagnosis:** See "Breaking Bad News" section of *"Counseling Pts"*); can set this conversation up to be more successful w/ counseling prior to testing

(1) Arrange for in-person meeting (avoid disclosing results over the phone)
(2) Assess pt's understanding of likelihood of HIV dx & their level of anxiety
(3) Disclose diagnosis; allow time for pt response
(4) Emphasize HIV's transformation to a chronic, manageable disease
(5) Set up plan for next steps in mgmt; offer access to counselor/peer group/social work
Consider initiation of ART on day of diagnosis: Safe, ↓ time to viral suppression, may ↑ retention in care (*J AIDS* 2017;74:44)

- **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 Evaluation of HIV ⊕ Patient

- **History:** Full PMHx, including HLD, CAD, DM, CKD, neuropathy, depression, anxiety, PTSD, TB, hx hepatitis, HSV, VZV, immunizations, prior CA screening

  HIV staging: Current viral load, current & nadir CD4, date of dx (& route/date exposure)
  HIV treatment hx: Prior regimens (including adverse effects), resistance testing (obtain medical records whenever possible), current/prior adherence
  Substance use: Tobacco, EtOH, IVDU, illicit 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?"), assess sexual practices (vaginal, oral, anal) & condom use, hx other STIs
- **Exam:** Full PE, including weight, skin exam, OP exam, LN exam

Initial Labs/Studies (***CID*** **2014;58:e1)**	
HIV-specific	CD4 cell count, HIV-1 viral load, HIV genotype, HLA B*5701 (predicts hypersensitivity to abacavir)
Medical/Screening	CBC w/ diff, BMP, LFTs, lipids, glucose/HbA1c, U/A, G6PD (for

	dapsone use), cervical and/or anal pap test based on risk, consider baseline CXR
Other ID	STI: GC/CT (rectal + pharyngeal if risk factors), syphilis, trichomonas in ♀ Hepatitis: HAV IgG, HBV sAb/sAg, HCV Ab (HCV VL if ⊕) TB, CMV + VZV IgG, Toxoplasma IgG (*see "STIs," "TB," "Hep B," "Hep C"*)

HIV Primary Care

- Health maintenance is an important component of HIV care; HIV ⊕ pts are at increased risk of cardiovascular, metabolic, infectious, neoplastic, and psychiatric disease and careful monitoring, prevention, and treatment of these complications is key to their primary care
- **Cardiovascular risk:** ↑ CAD mortality, and stroke risk in HIV pts; multifactorial and due to (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) (*JAMA Intern Med* 2013;173:614; *AIDS* 2013;27:973; *Neurology* 2015;84:1933)
  - **Prevention:** Aggressive management of risk factors (BP control, smoking cessation; see "*Coronary Artery Disease"*) recognize that ASCVD calculators likely underestimate risk in HIV ⊕ patients; monitor closely for development of ↑glucose or ↑lipids, esp in setting of starting or changing antiretroviral therapy regimen
  - **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)
- **Osteoporosis:** ↑ Prevalence; screen postmenopausal women (same as general population) *and* men ≥50 (considered insufficient evidence in general population)
- **Cervical cancer screening:** ↑ risk for cytologic progression and ↑ infection with high-risk HPV; however, if receive appropriate screening, risk of invasive cervical CA = to general population; as of 10/2016 ACOG guidelines; pt should continue screening for lifetime per life expectancy (not stop at 65); baseline recommendation is

annual screening

Women <30 y: If 3 annual cytology screens nl → can go to q3y
Women ≥30 y: As above **or may cotest w/ HPV;** if ⊖ co-test (cytology and HPV nl) → can go to q3y (*Obstet Gynecol* 2016;128:e89)

- **Anal cancer:** Yearly anal pap testing in MSM, pts with anogenital condylomas, woman with abnl cervical histology
- **Breast, prostate, colon cancer screening:** HIV pts at avg risk; recommendations the same as HIV-negative (see "Screening")
- **Mental health/trauma:** ↑ Prevalence of depression, PTSD; ♀ esp have↑ hx of IPV, childhood trauma; assess at initial visit and periodic mental health assessment thereafter
- **Sexually transmitted infections:** See "Sexually Transmitted Infections"; GC/CT and syphilis if ongoing risk (q3–6mos), Hep C Ab q12mos in pts at risk (MSM, IDU, multiple sex partners)
- **Immunization:** CD4 cells affect vaccine efficacy: Defer vaccination in pts w/ CD4 <200 who will soon start ART; **live-virus vaccines contraindicated when CD4 <200** (*MMWR* 2013;62:2); *see "Immunizations"*
- **HIV monitoring:** Frequency depends on CD4 and duration/degree of viral suppression; once suppressed, viral Load q6mos once suppressed

  CD4 yearly (optional if CD4 >500 and VL suppressed >2 y)
  CBC, BUN/Cr, LFTs q6–12mos

Immunization Recommendations for HIV ⊕ Patients

Vaccine		Schedule
Inactived	Inactivated Influenza	Yearly (do not use intranasal)
	Tdap	Substitute 1-time dose of Tdap for Td booster, then boost with Td every 10 y
	Pneumococcal 13-valent (PCV13)	1 dose; preferred before PPSV23 (if PPSV23 given first must wait >1 y before PCV13)
	Pneumococcal polysaccharide (PPSV23)	1 dose followed by booster at 5 y (if PCV13 given wait >8 wk)
	HPV series	3 doses up to age 26
	Hepatitis B	3 dose series

	Hepatitis A	If MSM, or other risk factor
	Meningococcal conjugate	2 doses of MenACWY-D or MenACWY-CRM, 8–12 wk apart; booster q5y (*MMWR* 2016;65:1189)
Live*	MMR	1 or 2 doses
	VZV	2 doses
	Zoster	No recommendation
	Yellow Fever	Based on travel risk
	Intranasal Influenza	Do not use

*Live vaccines are contraindicated if CD4 <200

Antiretroviral Therapy (aidsinfo.nih.gov 7/2016)

- Antiretroviral therapy (ART) should be initiated & managed by a clinician experienced in HIV care; all pts should have HIV genotyping to assess for pre-existing resistance
- **Indications for ART initiation:** Recommended for **ALL** HIV-infected individuals regardless of CD4 count; ↓ risk of serious events and death when compared to waiting for CD4 <350 or other indication (INSIGHT START, *NEJM* 2015;373:795)

Common 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; ✓ HLA B*5701 before starting)
	Emtricitabine (FTC; Emtriva)	HA, nausea, insomnia, palm/sole hyperpigmentation
	Lamivudine (3TC; Epivir)	HA, dry mouth; also active against HBV
	Tenofovir disoproxil fumarate (TDF; Viread)	AKI, Fanconi syndrome, CKD, osteomalacia, GI sx
	Tenofovir alafenamide (TAF; Vemlidy)	Pro-drug of TDF with fewer bone/kidney side effects; can be used in CKD (CrCl >30).
	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
Protease Inhibitor	Atazanavir (ATZ; Reyataz); also coformulated with cobicistat (ATZ/c; Evotaz)	↑Bili, ↑ LFTs, ↑ PR interval, rash, contraindicated w/ PPI, causes less hyperlipidemia than other PIs
	Darunavir (DRV; Prezista); also coformulated with cobicistat (DRV/r; Prezcobix)	↑LFTs, risk for rash in pt w/ sulfa allergy ↑ statin levels except atorvastatin
	Lopinavir/ritonavir (LPV/r; Kaletra)	GI sx, HA, fatigue, dyslipidemia, ↑ LFTs, pancreatitis; med interactions
	Ritonavir (RTV; Norvir)	Med interactions,↑LFTs, GI sx
Integrase Inhibitor (INSTI)	Raltegravir (RAL; Isentress)	GI sx, ↑ LFTs & amylase, CNS sx, myalgia, rash/pruritus/SJS; generally well tolerated
	Dolutegravir (DTG; Tivicay)	GI sx, insomnia, fatigue, HA.; ↑ metformin levels (↓ metformin dose by ~50%)
	Elvitegravir/Cobi (EVG/c; Vitekta)	Drug–drug interactions due to Cobi; must take w/ food
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
Recommended Initial ART Regimens in Treatment-Naive Patients please refer to source for updated tx regimens (aidsinfo.nih.gov 7/2016)		
INSTI + 2 NRTI	DTG and either TDF/FTC or TAF/FTC EVG/c/TAF/FTC or EVG/c/TDF/FTC DTG/ABC/3TC if HLA-B*5701 RAL and either TDF/FTC or TAF/FTC	
PI + 2 NRTI	DRV/r and either TDF/FTC or TAF/FTC	

*FI, Fusion inhibitor; EI, Entry inhibitor

Infectious and Malignant Complications of HIV/AIDS (aidsinfo.nih.gov

11/2016)

- **General approach:** Pts w/ HIV/AIDS are at ↑ risk of both common and unusual infections ("opportunistic infections," OI); low threshold for eval of new/persistent complaints; **if red flags present, prompt consultation w/ ID specialist vs. ED eval** depending on chronicity/severity; all OIs below considered "AIDS-defining conditions" (*MMWR Recomm Rep* 2014;63:1)
- **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 "VZV," "HSV"; 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	**Opportunistic Infections or Malignancies**	**Recommended 1° Ppx (if none listed, only preventive therapy is ART)**
<500 (cells/mm3)	Recurrent **bacterial** PNA/infections, MTb infection, mucocutaneous candidiasis (oral **thrush**, vaginitis) Kaposi sarcoma, oral hairy leukoplakia, cervical CA	If ⊕ latent **TB** screen (see "*Tuberculosis*" for Latent Tx regimens) Vaccination as per above (see *"Immunizations"*)
<100–200 (cells/mm3)	**PCP, Toxoplasma** *gondii* encephalitis, HSV, VZV, *Histoplasma capsulatum* infection, *Cryptosporidium* enteritis, ***Cryptococcus*** *neoformans* encephalitis, isosporiasis Visceral Kaposi sarcoma, non-Hodgkin lymphoma, PML	For **PCP** (when **CD4 <200 or CD4% <14**): TMP–SMX DS or SS daily or DS 3×/wk (see *"PCP prophylaxis"* for alternatives) For **Toxo** (if **IgG+** & **CD4 <100**): TMP–SMX **DS** daily For **histoplasmosis** (in hyperendemic areas when CD4 <150): Itraconazole 200 mg daily
<50–100 (cells/mm3)	Invasive candidiasis/aspergillosis, disseminated MAC, CMV (retinitis, esophagitis, colitis), penicilliosis, CNS	For **MAC** (when CD4 <50): Azithromycin 1200 mg weekly *or* Clarithromycin 500

	lymphoma	mg BID *or* Azithromycin 600 mg 2×/wk For **Penicilliosis** (in **SE Asia**): Fluconazole 400 mg qwk

Discontinuing OI Prophylaxis:

- **PCP:** D/c ppx in pts who respond to ART w/ CD4 counts >200 **and** CD4% >14% for >3 mos; discontinuation *may* be safe at CD4+ counts 101–200 cells/μL if suppressed VL, but not currently recommended
- **MAC:** D/c ppx in pts who respond to ART w/ CD4 >100 for >3 mos

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HIV Prevention

Background

- **Prevention:** HIV prevention takes multiple forms, including; post-exposure prophylaxis (PEP), pre-exposure prophylaxis (PrEP), decreases transmission by ~93%; **treatment = prevention of transmission to others** (~0% transmission rate if stably suppressed; (*NEJM* 2016;375:830), safe sex practices
- **Risk of transmission** (*AIDS* 2014;28:1509)**:** Sexual (vaginal insertive/receptive ~0.04/0.08% risk per sexual act, anal insertive/receptive ~0.1/1.4%), IDU (0.7%), vertical transmission (10–40% w/o ARVs, ↓↓ if suppressed viral load), transfusion (now in US <1/2,000,000), occupational (needlestick ~0.3%); **all dependent on viral load (approximates 0% if VL undetectable)**

Screening (*MMWR* 2006;55:1; *Ann Intern Med* 2013;159:51)

- **Universal one-time screening:** Screen all pts aged 13–64 y once
- **Repeat screening:** Pts initiating tx for TB, pts seeking tx for STIs, all pregnant women; see *"Screening" "STIs"*
- **Serial screening:** Screen at least annually in pts w/ ongoing risk (tailor based on individual risk); typically annually for MSM, IDU

Pre-Exposure Prophylaxis (PrEP) (cdc.gov/hiv/pdf/prepguidelines2014.pdf)

- Available for sexually active adult MSM or heterosexually active men or women at substantial risk for HIV acquisition such as HIV ⊕

partner, multiple sex partners, recent bacterial STI, IDU with needle sharing, or recent need for nPEP (below)
- Document negative HIV test, normal CrCl, negative Hepatitis B status
- Follow-up **every 3 mos** for HIV test, bacterial STIs (including rectal and pharyngeal GC/Chlamydia), renal function, pregnancy test
- Once daily TDF/FTC shown to reduce HIV transmission by 44% (by 92% for those who were adherent (*NEJM* 2010;363:2587;) must take daily, regardless of timing of sexual exposure; on-demand PrEP not currently recommended by CDC (2017)

Non-Occupational Post-Exposure Prophylaxis (nPEP)

- Latest guidelines (2016) at cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf
- Indications: High-risk sexual exposure, sharing of IV drug equipment, or other high-risk exposures, esp when source is known HIV ⊕ and pt presents **w/in 72 h of exposure**
- Dosing: Full nPEP course is **28 d of TDF/FTC QD** + **either Dolutegravir QD or Raltegravir BID;** practices vary by location; often starter pack of 3–7 d given with expedited f/u
- Referral: Consult with ID if starting; ED eval may be preferable if allows for earlier start of Rx, as **earlier = ↑ effective;** if occupational exposure, occupational health services should eval & document agents, or other immunosuppressive meds (*Mayo Clin Proc* 1996;71:5)
- Other infections: Consider other bloodborne diseases: HCV, HBV (see respective chapters); if sexual exposure, consider other STI prophylaxis with ceftriaxone 250 mg IM, Azithromycin 1 g PO, metronidazole 2 g x 1
- Follow-up: Ongoing f/u needed for safety labs and repeat HIV testing; **consider PrEP after completion of PEP based on individual risk assessment**
- Pt education: Counsel pt about need for risk-reduction measures until testing excludes HIV

PNEUMOCYSTIS PROPHYLAXIS

Background (*Emerg Infect Dis* 2002;8:891; aidsinfo.nih.gov; *BMC Infect Dis* 2004;4:42)

- Pneumocystis pneumonia (PJP/PCP) is clinical infection w/ *P. jirovecii;* clinical disease typically limited to those w/ immunodeficiency, although subclinical infection/colonization likely widespread (*Emerg Infect Dis* 2005;11:245)
- **Microbiology:** *Pneumocystis jirovecii* is a fungal organism 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
- **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 antibodies to PCP (*J Immunol* 1988;140:2023)
- **Epidemiology:** 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, Oropharyngeal candidiasis *Consider:* CD4 <14% of total T cells, Hx of AIDS-defining illness (see "HIV/AIDS"), CD4 200–250 & unable to monitor q1–3mos	>20 mg of prednisone daily (or equivalent) for >1 mo plus another cause of immunocompromise (Rx or disease) 1° immunodeficiency (e.g., hyper-IgM, SCID) Allogeneic SCT, solid organ tx, selected auto-SCT *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 is effective:** In HIV ⊕ w/ CD4 <200, to prevent 1 case,

NNT ≈ 2 (*BMJ Clinical Evidence* 2010;8:908; *JAMA* 1988;259:1185); In HIV ⊖, to prevent 1 case, NNT = 15–19 (*Cochrane Database Syst Rev* 2007;18:CD005590; 2014;10:CD005590)

PCP Prophylaxis Regimens (aidsinfo.nih.gov 2015 guidelines)		
Drug	**Dosage**	**Adverse Effects**
TMP–SMX (1st line)	**1 ds tab daily** (preferred in HIV⊕) or 1 ss tab daily	Fever, rash, **neutropenia,** GI upset, ↑ LFTs
Alternative Regimens (inferior to above)		
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 (**must 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; *CID* 2010;51:1114; aidsinfo.nih.gov)

- **HIV ⊕:** D/c ppx in pts who respond to ART w/ CD4 counts >200 cells/μL and CD4% >14% for >3 mos; discontinuation *may* be safe at CD4+ counts 101–200 cells/μL if suppressed VL, but not currently recommended
- **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)

TUBERCULOSIS

Background (cdc.gov/tb; who.int; *MMWR* 2012;61:11; *NEJM* 2013;368:745)

- Tuberculosis (TB) infection affects >1/3 of the world's population, range of disease from lifelong asx infection, to pulmonary or, more

rarely, myriad extrapulmonary manifestations (Pleural > lymphatic > bone + joint disease > GU tract > miliary disease, meningitis, peritonitis)

- **Microbiology:** Causative organism *Mycobacterium tuberculosis (MTb);* aerobic, slow-growing rod, acquired via aerosolized transmission of infected **droplets**, often from close contacts of infected pts (household members, etc.); casual contacts at low risk for infection
- **Classification:** *Latent TB:* Infection present but no clinical illness, no evidence of active disease, **not infectious**

  Active TB: Illness present, infectious (degree varies by site)
  1° disease: Illness occurs <24 mos after infection
  2° disease: Occurs >24 mos after infection
- **Natural history:** Once infected, 5% develop 1° disease; 90% have lifelong asx infection (LTBI); 5% go on to develop 2° disease ("reactivation")

Epidemiology (cdc.gov; *MMWR* 2012;61:11; *Am J Resp Crit Care Med* 2000;161:S221)

- **Incidence/Prevalence:** Estimated 4% of US population (up to 13M) has latent TB infection; 9.5K new cases active TB in 2015, annual incidence of 3/100,000 persons
- **Demographics:** 66.4% active TB cases in US in 2015 were among foreign-born people (13× ↑ rate than US-born population; particularly ↑ among immigrants 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, TNF alpha inhibitors
  Medical hx: DM, ESRD, gastrectomy/bypass, CA, silicosis, >10% underwt
  Recent acquisition: Within last 2 y; risk of active TB ↓ w/ time since

infected

Other: EtOH use d/o, IDU; ↓ BMI; healed TB on CXR, inadequate/incomplete prior tx

- **HIV:** 6% of 2014 US cases of TB w/ known HIV test result were coinfected w/ HIV

Screening (ATS/IDSA/CDC guidelines; *CID* 2017;64:e1)

- **Indications:** Pts w/ risk factors for acquisition or for developing active infection (above), frequency depends on nature of exposure (e.g., ongoing or one-time), pt-specific risk of infection; screening of those at low risk of infection/low risk of active disease not recommended; **healthcare providers screened annually**
- **Prior BCG vaccination:** (Given to young children in endemic countries to ↓TB risk) 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 (1) likely to be infected and at low-intermediate risk of disease progression, (2) hx BCG vaccination or (3) unlikely to return to have TST read
- **Tuberculin skin test (TST):** Uses Mantoux intracutaneous tuberculin (PPD); dependent on cell-mediated immunity; can be ⊖ in up to 25% of active disease (more common in pts w/ immunosuppression)

  Administration: Should be performed by trained personnel; 0.1 mL (5 tuberculin units) injected intradermally on volar surface of forearm

  Reading: Reaction size determined at 48–72 h; if >72 h, cannot interpret (*MMWR Recomm Rep* 2005;54:1); based on **induration (not redness);** cutoff for positive test depends on

  (1) Pretest probability of being infected (e.g., household contacts: ↑ prob, so ↓cutoff)

  (2) If infected, probability of developing active disease (e.g., HIV ⊕: ↑ prob, so ↓ cutoff)

"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)

Evaluation (*CID* 2016;64:e1)

- **General approach:** In patients with positive TB testing, **first step in evaluation is to assess for active TB;** critical to exclude 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 wk, 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

Management

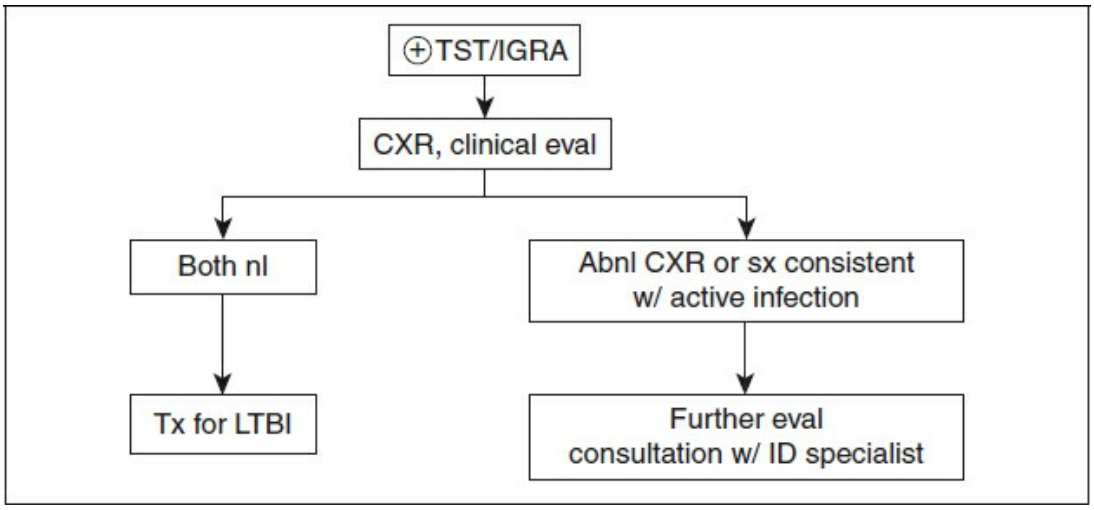

Figure 7-3. Management following positive TST/IGRA

- **General approach:** 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
- **Latent TB Infection (LTBI):** See subsection below
- **Active TB Tx:** Initial empiric tx, Rx'ed by experienced clinician, consists of 4-drug regimen (INH, rifampin, PZA, EMB) + B_6; see 2016 ATS/CDC/IDSA guidelines
- **When to refer:** If any of the above w/u equivocal, high suspicion, or pt pregnant or immunocompromised (including all HIV pts) → ID and/or public health consultation/mgmt
- **Reporting:** Public health dept must be **notified of all new dx of TB** (latent or active)

Latent TB Infection (LTBI) Management

Evaluation

- **General approach:** Confirm pt does not have active TB (above) or complicating factors, then assess risks/benefits of tx for the individual pt; decision to tx and choice of Rx influenced by pt factors/decisions; pts who undergo tx require regular monitoring to ensure safety/efficacy
- **Appropriateness for PCP management:** Exclude active TB (above); pts w/ LTBI who have known exposure to drug-resistant TB, those who are pregnant, immunocompromised, or have HIV should be evaluated by a specialist
- **Risks/benefits of treatment:** Not all pts with LTBI require or desire treatment; calculator such as **tstin3d.com/en/calc.html** can help assess risk of reactivation & risk of treatment; in general **treatment is recommended (benefits > risk) for pts at ↑ risk of reactivation** (see above)
- **Shared decision making:** Given duration of most regimens & level

of adherence required to eradicate, pt buy-in is key to successful tx; review of risks/benefits, pt & provider assessment of potential barriers to adherence, & assessment of pt commitment should be initiated prior to starting tx

- **Factors which may ↓ adherence:** ↓ Perceived personal risk of progressing to active TB (incl doubts re: LTBI dx), concerns re: frequent venipuncture, cultural, language, or logistical barriers (*AJRCCM* 2006;174:717)

Treatment (cdc.gov)

- Isoniazid (INH) monotherapy (300 mg QD × 9 mos) considered 1st-line
  - *S/e:* GI upset (common), hepatotoxicity (avoid EtOH), neuropathy
  - *Vit B_6:* add **50 mg QD pyridoxine** while on INH for pts at risk for neuropathy (DM, EtOH, malnutrition, HIV)
  - *Labs:* Not always required; 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
- **Monthly visits:** Recommended for assessing s/e, monitoring adherence

LTBI Therapy		
Drug	**Duration**	**Notes**
INH 300 mg QD (± 50 mg Vit B_6 QD)	**9 mos** (6 mos)	**1st-line** 6 mos ↓ efficacy, but ↓ cost & may ↑ adherence
INH/Rifapentine weekly wt-based dosing: for pts ≥60 kg: INH 900 mg qwk & Rifapentine 900 mg qwk	12 wk	Recommended *only* as directly-observed therapy (DOT) 1.2–1.9× ↑ rate of completing tx compared to std INH regimen (*NEJM* 2011;365:2155; *CID* 2016;62:53) S/e: Lightheadedness/orthostasis, flu-like illness
Rifampin 600 mg QD	4 mos	*S/e:* Orange urine/sweat/tears GI upset, hepatotoxicity, drug interactions (incl warfarin & HIV meds), rash

- **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; there is *no* role for future TST screening (will be ⊕ and can develop severe reaction)
- **Patient information:** Including 1-page fact sheets on LTBI medication regimens at cdc.gov/tb/publications/factsheets/treatment.htm

INFECTIOUS ENDOCARDITIS PROPHYLAXIS

Background (*Arch Intern Med* 1992;152:1869; *Lancet* 1992;339:135)

- **Incidence:** Estimated at 3–9 cases/100,000 persons annually; significantly ↑ risk in pts w/ valvular disease or IDU (*NEJM* 2013;368:1425)
- **Rationale for ppx:** Bacteremia can → IE if diseased valves; abx ↓ bacterial load → ↓ IE risk
- **Historical context:** Preprocedure ppx used to be recommended more widely, now limited (as of 2007 AHA guidelines) to those at highest risk, as procedures account for very small proportion of IE cases (*CID* 2006;42:e102); bacteremia likely occurring more w/ daily activities (eating, brushing); poor oral hygiene may contribute more than procedures (*Am J Cardiol* 1984;54:797; *Pediatr Cardiol* 1999;20:317)
- **Adverse effects of ppx:** GI upset, diarrhea, allergic reactions, ↑ 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/ACC 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 (meet 1 criterion from each → ppx)	
Conditions	**Procedures**

• Prior IE • Prosthetic cardiac valve or prosthetic material used for cardiac valve repair • Congenital heart disease if: (1) Unrepaired cyanotic CHD (may have palliative shunts & conduits) (2) Repaired w/ prosthetic material or device w/in past 6 mos (3) Repaired but w/ residual defects near a prosthetic patch or device • Cardiac transplantation recipients who develop cardiac valvulopathy • Native valve disease **not** an indication for ppx	• Dental procedures w/ manipulation of gingival tissue/periapical region of teeth, perforation of oral mucosa • Surgical procedures of **infected** skin, skin structures, or MSK tissue* • Respiratory tract procedures that involve incision or bx of the respiratory mucosa (such as tonsillectomy or adenoidectomy) • GI & GU procedures (including EGD & colonoscopy) **during active GI/GU infection only** (Note: These pts should receive *antienterococcal* abx [e.g., amoxicillin]; any GI/GU procedures w/o active infection do not require ppx)

*These pts should receive regimen active against GAS and *S. Aureus*.

Prophylactic Antibiotic Regimens (*Circulation* 2007;116:1747; *Surg Infect* 2013;14:73)

- **Antibiotic should be given as a single dose 60 min prior to procedure**
- Do not use cephalosporins if hx of anaphylaxis, angioedema, or urticaria to penicillin

Prophylactic Regimens for Dental Procedures	
Scenario	**Regimen (all are single doses)**
Standard	Amoxicillin 2 g PO
Unable to take oral meds	Ampicillin 2 g IM/IV **or** (Cefazolin or Cftx) 1 g 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 g IM/IV **or** Clindamycin 600 mg IM/IV or Vancomycin 15 mg/kg max 2 g (vanco should be 120 min before procedure)

FEVER OF UNKNOWN ORIGIN

Background (*Arch Int Med* 2003;163:545; *Medicine* 2007;86:26)

- **Definition:** (1) Illness of >3 wk 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 uncommon presentation of 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 has different Ddx and different considerations

Etiologies of FUO (***Arch Int Med* 2003;163:545; *Am J Med* 2015;128:1138**)	
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) **Abscess:** Usually abd or pelvic (e.g., liver, splenic, renal, prostatic); also retroperitoneal, dental, paraspinal; risk factors include ESLD, immunosuppressants, recent surgery, DM **Osteomyelitis:** E.g., vertebral, mandibular, DFI; local sx may be min **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"* **Adult Still's:** (Adult JRA, younger adults) fever + macular truncal rash often precede arthritis Also PAN, Takayasu arteritis, RA, SLE, granulomatosis w/ polyangiitis, mixed cryoglobulinemia (*Clin Rheumatol* 2012;31:1649)
Neoplastic	**Leukemia, Lymphoma** (esp non-Hodgkin) **Renal cell CA:** 15–20% of cases have fever (*Lancet* 1997;350:575) HCC or liver metastases (*Heart Lung* 2013;42:67) **Atrial myxomas:** Rare cause, but 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) **Endocrine:** Hyperthyroidism, thyroiditis, pheo, adrenal insufficiency **Other:** Hereditary periodic fever syndromes (Familiar Mediterranean Fever); **clot** (PE, DVT, hematoma); factitious fever

Diagnosis (*Infect Dis Clin North Am* 2007;21:867; *Am J Med* 2015;128:1138.e1)

- **Detailed history:** Travel, sick contacts, animal exposure, outdoor exposure (forest, lake, ocean), immunosuppression, med & toxin hx unusual foods, localizing symptoms; review of systems could give clues to category of illness (wt loss/early anorexia is hallmark of malignancy)
- **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

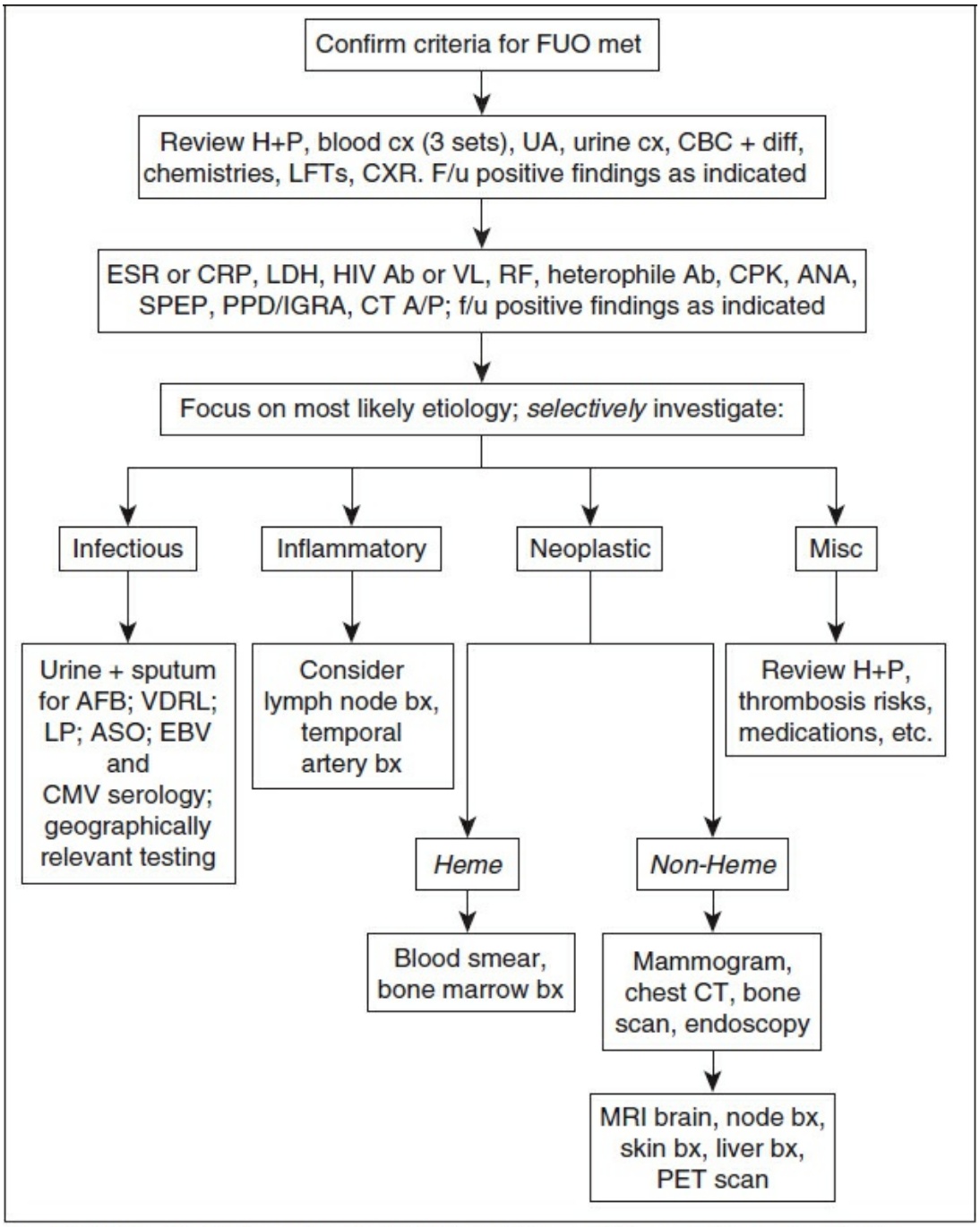

Figure 7-4. Diagnostic Approach to FUO

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
- **When to Refer:** As needed per dx; if dx uncertain, ID consultation

TICK-BORNE ILLNESS

Background (cdc.gov/niosh/topics/tick-borne; niaid.nih.gov/topics/tickborne)

- Tick-borne disease can be caused by bacteria, viruses, or parasites; most common in Northeast, but found throughout US; specific pathogens usually have geographic restriction
- **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
- **Prevention:** Counsel those at ↑ risk to **reduce exposure** by wearing light-colored long-sleeved shirts & pants, socks & hat when possible; using **insect repellent**, & performing **daily tick checks,** including axillae, groin, & scalp; adult tick size ≈ sesame seed, nymphal tick size ≈ poppy seed
- **Counseling:** If tick is found, **promptly remove** 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; *JAMA* 2016;315:16)

- **Microbiology:** Pathogen *B. burgdorferi,* a spirochete bacterium; vector is *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 summer; *Where:* NE, Midwest; 96% of cases in CT, DE, MA, ME,

MI, NH, NJ, NY, PA, VT, & WI; *Who:* Adult distribution peaks ~40–50 y; reinfection can occur

- **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

Presentation (*NEJM* 2001;345:115; *JAMA* 2016;315:16)

- **Erythema migrans:** Occurs in 70% of pts w/ Lyme disease: Classical appearance is warm, erythematous, nonpruritic/nonpainful 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 classically 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)	*Derm;* Erythema migrans (EM) (70–80%) *Constitutional:* Fevers, myalgias, fatigue, LAD
Early disseminated (days–weeks)	*CNS* (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 (weeks–months)	*CNS* (5%): Polyneuropathy, subtle cognitive deficits (5%); *Arthritis* (60%): Recurrent, inflammatory

Diagnosis (*JAMA* 2016;315:16)

- **Serology: ELISA & confirmatory Western blot only approved diagnostic tests per IDSA & CDC;** Western blot ⊕ if 2 bands for IgM or 5 bands for IgG
- **Early localized disease (EM):** Diagnosed clinically by exam & hx; serology <40% sensitive so not recommended; if suspect early disease, treat
- **Disseminated disease:** ELISA → if ⊕, confirmatory Western blot; if >4 wk of sx, send IgG only (not IgM); serology can remain ⊕ after tx

(even IgM, in some cases)

Treatment (*CID* 2006;43:1089)

- **Treatment:** Determined by site/severity of manifestations (below)

Treatment of Lyme Disease (*CID* 2006;43:1089)		
Manifestation/Indication	**Antibiotics (alternates)**	**Course**
Erythema Migrans Bell palsy 1st-degree heart block	**Doxycycline 100 mg PO BID** (amoxicillin 500 mg PO TID, cefuroxime 500 mg PO BID)	14–21 d
Arthritis (w/o CNS disease)	**Doxycycline 100 mg PO BID** (amoxicillin 500 mg PO TID, cefuroxime 500 mg PO BID)	28 d
Meningitis Radiculopathy 2nd-/3rd-degree AV block	**Ceftriaxone 2 g IV QD** (PCN G 4 million U IV q4h, cefotaxime 2 g IV q8h) Meningitis sx warrant LP; arrhythmia mgmt	14–28 d

- Persistent arthritis after PO tx → additional 4 wk of PO abx or 2–4 wk of IV abx
- **Posttreatment 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)

Other Tickborne Illnesses

Anaplasmosis/Ehrlichiosis (*CID* 2006;43:1089; *JAMA* 2016;315:16)

- **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 wk after exposure

Labs: Leucopenia, thrombocytopenia, elevated LFTs

- **Diagnosis:** Peripheral blood smear showing inclusions, PCR
- **Treatment:** Doxycycline 100 mg PO BID × 10 d; *Alt:* Rifampin 300 mg PO BID × 10 d

Babesiosis (*CID* 2006;43:1089; *NEJM* 366:2397; *JAMA* 2016;315:16)

- **Microbiology:** Intracellular protozoan, infect **RBCs;** *Babesia microti;* transmitted by *I. scapularis* ticks; **often co-transmitted w/ Lyme;** can be transmitted by blood transfusion
- **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 *Dermacentor* "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; rash present in 90% (but absent in 10%, and absent in 50% in first 3 d of illness (when pts often present); petechial = more severe
- **Diagnosis:** Often made clinically; can also see rise in Ab (2 titers 2–4 wk apart)
- **Treatment:** Doxycycline 100 mg PO BID × 7–14 d

Other (cdc.gov/ticks/diseases)

- **Other *Rickettsia* species:** *R. parkeri* in SE US and species 364D on W Coast, both cause fever with eschar at site of tick attachment
- **Tularemia:** Gram ⊖ coccobacillus *Francisella tularensis* transmitted throughout US (more common in south-central US); can also be transmitted by handling infected animal carcass or inhaling aerosolized ("lawn mower" exposure); 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
- **Other *Borrelia* species:** *B. miyamotoi* in NE, causes fever but rarely rash; *B. mayonii* in Midwest, similar presentation to *B. burgdorferi*
- **Viral tick-borne illnesses:** Incl Colorado tick fever reovirus in Western US; Powassan virus in NE, N-central US; Heartland virus in central US
- **Tick paralysis:** Thought 2/2 tick saliva, not infection; tx is removing tick

When to Refer

- 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 (tinet.ita.doc.gov; *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 seek travel advice are most likely to present to PCP
- Travelers can be exposed to many health risks, including infection (GI, STI), accidents (incl MVCs), & 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; *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": Pretravel counseling for risk reduction**
- **Immunizations:** Routine & area-appropriate; **referral** to travel clinic as appropriate
- **Past medical history:** Pts w/ complex or significant hx should carry summary incl meds, allergies, ± ECG; assess for CV/pulm risk factors (see "Preflight Medical Assessment" below)

Air Travel

- **Hydration/activity:** Caution w/ EtOH on flights (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
- Thromboembolic disease: 2–4× ↑ risk w/ prolonged air travel (↑ in flights >4 h): ↑ venous stasis ± hemoconcentration, coagulopathy (*Ann Intern Med* 2009;151:180);

All patients: Frequent movement, adequate hydration, ankle/knee exercises

High-risk pts: Fitted compression stockings or single dose of LMWH; ASA alone ineffective (*Chest* 2004;126:338; *JGIM* 2007;22:107)

- **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
- **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 min before local bedtime, helpful to try "test dose" in advance

Safety Counseling (*Ann Intern Med* 2012;156:ITC6; *AFP* 2009;80:583; cdc.gov/travel)

- Indicated for all patients; attention to each topic will vary based on pt & nature of travel
- **Emergency preparedness:** Know where to find health care (ASTMH, State Dept, embassies have lists); consider evacuation insurance & medical alert tag if indicated
- **Transportation: MVC the leading cause of preventable death in 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 ↑ risky sexual behavior abroad; contacts may have ↑ prevalence of STIs; always use barrier protection (may need to pack)
- **Food and water:** Specific to 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
- **Zika exposure:** See cdc.gov/zika for updated maps; territories include Mexico, Caribbean, much of Central/S. America, sub-Saharan Africa, and SE Asia); primary risk is for men or women pregnant or desiring pregnancy

  Women: Avoid travel if pregnant or planning pregnancy; avoid pregnancy and use condoms for 8 wk *after* leaving Zika area

  Men: Use condoms during travel and for 6 mos after leaving Zika area

  Prevention: DEET (~30% concentration) or picaridin (20%) on skin, permethrin on clothing
- **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; see "Sunscreen Pearls" in Prevention/Treatment section of "*Melanoma*"
- **Animal avoidance:** Steer clear of animals unknown to traveler; urgent care for any bites
- **Altitude:** For rapid ascents to >9000 ft (including via flight), acetazolamide 125 mg BID, starting 1 d before ascent; *S/e:* Paresthesias, urinary frequency (*NEJM* 2001;345:107)
- **Scuba diving:** Wait 12–24 h prior to flying if one dive per day, 24–28 h if multiple dives per day (*Aviat Space Environ Med* 1990;61:1130).

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 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 or CDC (*MMWR* 2015;64:23); check country requirements: www.cdc.gov/travel

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, or 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, booster q5y; live vaccine; not while on abx or immunocompromised)

Polio: Previously vaccinated adults need single lifetime inactivated 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" and "HBV"*

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, camping, animal exposure or staying >1 mo in endemic area (India, SE Asia, Africa) w/o available postexposure Ig (*CMAJ* 2008;178:567)

- **No civilian indications** 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 wk of travel in much of S. Asia, Africa, Middle East, Mexico, Central/S. America; nearly all benign, self-limited (3–5 d); most common etiology is enterotoxigenic *E. coli* (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 (counsel pts may cause temporary darkening of tongue/stool) (*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 tx; 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** Cipro 500 mg BID × 1–3 d (↑ resistance in SE Asia; avoid in pregnancy) *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:** See cdc.gov/malaria/map and who.int/malaria/travellers for areas w/ regional endemicity; risk also depends on type of accommodation, season, elevation, & duration of exposure; ↑ risk among pregnant women, military, or immigrants VFR
- **Self-protection** (also ↓ other vector-borne diseases): Insect

repellent (DEET 20–30% or picaridin >20%; reapply q8h), long sleeves, pants; screens + permethrin-treated clothing and bednet if sleeping w/o A/C (open windows)

Malaria Prophylaxis for Travelers (*CID* 2006;43:1499)			
Medication (Cost)	**Dose**	**Duration**	**Notes**
Atovaquone/Proguanil (Malarone) ($$$-$$$$)	1 tab QD	1–2 d before trip – 1 wk after	*Resistance:* N/a *S/e:* GI, HA *CI:* Coumadin, pregnancy (relative)
Doxycycline ($)	100 mg QD	1–2 d before trip – 4 wk after	*Resistance:* N/a *S/e:* Photosensitivity, GI, candida *CI:* Pregnancy
Mefloquine* (Lariam) ($$$)	228 mg QWk	2 wk before trip – 4 wk after	*Resistance:* SE Asia *S/e:* **Neuropsych** (black box warning), GI, cardiac *CI:* ψ Disease, cardiac conduction abnormalities
Primaquine ($$$)	30 mg QD	1–2 d before – 1 wk after	*Resistance:* Used for *P. vivax* **only** *S/e:* GI *CI:* G6PD deficiency, pregnancy
Chloroquine ($$)	300 mg QWk	1–2 wk before – 4 wk after	*Resistance:* Widespread *S/e:* GI, HA, visual, insomnia, pruritus *CI:* Psoriasis (relative)

*Recommended for pregnant travelers

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,** chikungunya, Zika, **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 × 3
- **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
- **Posttravel illness:** Travel/ID if significantly ill or any uncertainty in dx/mgmt

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Pre-Flight Medical Assessment

- **General Approach:** For travel advice re: medical conditions below, much based on expert opinion rather than wealth of evidence; for patients with significant medical conditions, involve their specialists in advising pt on their specific travel risks & measures to ↓ risk

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

- **Contraindications:** Recent ACS/PCI (<3 wk), unstable angina, decompensated HF, symptomatic 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/ and w/o magnet) and recent office visit note with summary of medical history (prior interventions etc.).
- **CV indications for in-flight oxygen:** NYHA class III CHF, angina, cyanotic congenital heart disease, pulm HTN/right heart failure (*Can J Cardiol* 2004;20:1314)

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

- **Contraindications:** Recent PTX, severe hypoxia

Indications for in-flight oxygen (*Thorax* 2002;57:289)	
SaO_2 at Rest on Room Air	**Recommendation**
>95%	Supplemental O_2 not indicated
<92%	Supplemental O_2 indicated
92–95%	With risk factors,* supplemental O_2 not indicated
92–95%	Without risk factors,* supplemental O_2 indicated
***Risk factors:** Hypercapnia, FEV_1 <50%, severe cardiopulmonary disease, pulm HTN, recent hospitalization for pulm disease, inability to walk <50 m, cerebrovascular disease	

- **Home O_2:** ↑ Flow rate 1–2 L/min (*Chest* 2008;133:1002)
- **Asthma:** Carry-on β-agonist rescue inhalers, bring a course of steroids
- **Cystic fibrosis and bronchiectasis:** May need abx and secretion-clearing medications; stay well hydrated

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

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

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

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

Other

- **Pregnancy:** Air travel safe for uncomplicated pregnancies <36 wk gestation; pts at ↑ risk for DVT → preventive measures (above) recommended (*Obstet Gynecol* 2009;114:954)
- **Procedures:** Wait 2 wk after open surgery, 1 d for uncomplicated laparoscopic procedures or colonoscopy (*Am Fam Physician* 1999;60:801)

JOINT PAIN AND MONOARTICULAR ARTHRITIS

Background (*AFP* 2003;68:83; 2011;84:653; 2016;94:810; *JAMA* 2007;297:1478)

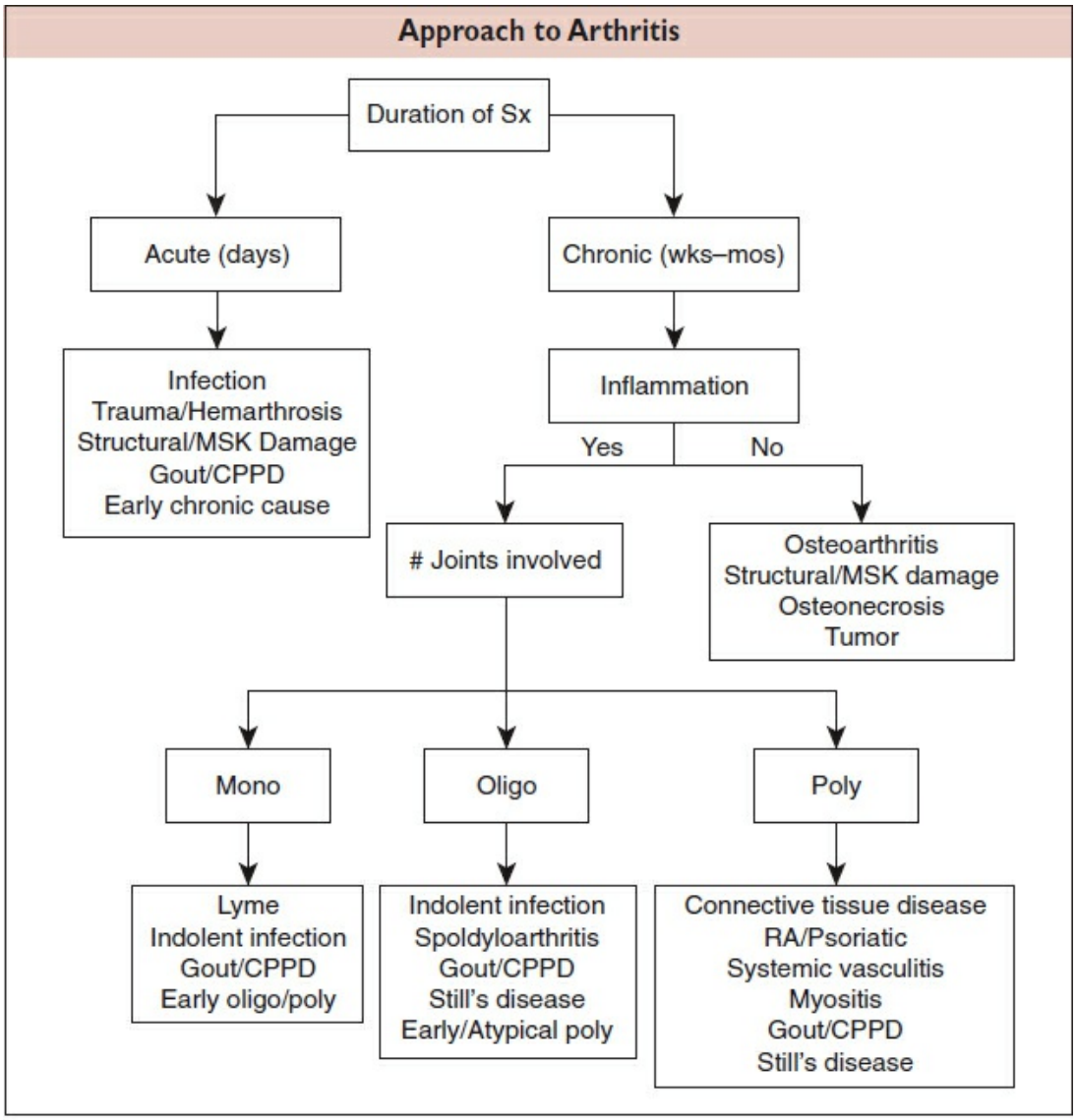
- **Definitions:** Monoarticular (1 joint) vs. oligoarticular (2–4 joints) vs. polyarticular (>4).
- **History:** H&P critical to clarify type of joint pain (e.g., inflammatory monoarticular, noninflammatory polyarticular); h/o trauma or prior joint pain/swelling; sexual hx (gonococcal); EtOH/diuretic use/shellfish intake (gout); IVDU, immunosuppression, prosthetic joints, DM, steroid injection, ↑ age, cellulitis (septic); renal failure (tx considerations, gout); travel, tick exposure (Lyme); anticoagulant use, bleeding d/o (↑ risk of hemarthrosis); chronicity acute (days) vs. chronic (>2 wks)
  - **Inflammatory pain:** Redness in specific joint, prolonged morning stiffness (>30 min), improvement of pain/stiffness w/ motion/exercise
  - **Articular vs. periarticular** (bursitis, tendinitis): Passive ROM < painful than active ROM in periarticular process
  - **Noninflammatory, polyarticular/soft-tissue pain:** Consider fibromyalgia (see "*Fibromyalgia*")
  - **Extra-articular manifestations:** Fevers/chills (septic arthritis), GI illness (reactive arthritis, IBD-assoc arthritis), genital pain/lesions (gonococcal), rash (psoriasis, SLE, viral exanthems, erythema migrans), mucocutaneous ulcers (SLE), inflammatory eye disease (seronegative spondyloarthropathies, RA)
- **Differential diagnosis: Noninflammatory:** OA, mechanical (ligament injury), hemarthrosis, AVN, malignancy. **Inflammatory:**

Crystalline dz (gout), septic arthritis, immune-mediated, spondyloarthropathy (psoriasis), SLE, sarcoid

Evaluation

- **Exam:** Assess for warmth, redness, effusion, joint line tenderness, bony crepitation w/ flexion, rash or skin break, soft tissue swelling, tophi, extra-articular disease (above)

  Range of motion: ↓ active ROM w/ preserved passive ROM suggests soft tissue (periarticular) cause; limited active & passive ROM more likely joint involvement; significant pain w/ minimal ROM concerning for septic arthritis



(Adapted from Sabatine MS. *Pocket Medicine: The Massachusetts General Hospital Handbook of Internal Medicine*. 6th ed. Philadelphia, PA: Wolters Kluwer, 2017. With permission.)

- **Arthrocentesis:** If effusion present; cell count w/ diff, gram stain, crystals, gram stain & Cx); also appropriate to aspirate bursa in the setting of bursitis; see discussion in "*Gout*"

Synovial Fluid Analysis

Measure	Norm	Noninflammatory	Inflammatory	Septic
Color	Clear	Yellow	Yellow	Yellow/green
Clarity	Clear	Clear	Clear-opaque	Opaque

WBC/mm^3	<200	<2000	>2000	>2000 (usually >50 K)
PMNs (%)	<25	<25	>50	>75
Cx	⊖	⊖	⊖	Often ⊕
Crystals	⊕ or ⊖ *May find MSU or CPPD crystals extracellularly*		⊕ *Intracellular if crystalline*	⊕ or ⊖

(Adapted from *JAMA* 2007;297:1478)

- **Imaging**: Radiographs useful to assess for fracture (h/o trauma), degenerative changes (OA) chondrocalcinosis (CPDD), erosions (RA, gout, osteomyelitis); other imaging depending on clinical setting
- **Laboratory:** BCx if septic arthritis suspected; Lyme Ab testing if suspected; ESR, CRP in inflammatory arthritis; uric acid if suspicion for gout; RF & CCP if polyarticular or monoarticular w/o other explanation
- **Common monoarticular conditions:**
  - **Bursitis:** Inflammation/injury of bursa (protect bony prominences) 2/2 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
    - **Treatment**: Avoid activities that ↑ pain, joint protection, NSAIDs, ice, heat, PT; intrabursal steroid injection in refractory cases
  - **Bacterial: Risk factors:** Previous joint pathology (RA, OA, gout, prosthetic joints), immunosuppressed, cutaneous infection, IVDU, prior intra-articular steroid injection (*Lancet* 2010;375:846)
    - **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*"

Hemarthrosis: Analgesics, aspiration/injection, compression sleeve to prevent reaccumulation, assessment for bleeding d/o

See "*Gout*," "*Lyme,*" "*Polyarticular Arthritis,*" respective joint section (e.g., "Hip")

- **Patient information:** *JAMA* 2007;297:1510

POLYARTICULAR ARTHRITIS

Background (*AFP* 2003;68:1151; 2015;92:35)

- **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 sx (e.g., IBD, rash, mouth ulcers)
- **Workup:** RF, CCP (for RA, below), ESR, CRP; acute-onset (<6 wks), consider parvovirus B_{19}, HBV, HCV, Lyme serologies
- **Differential diagnosis:** In addition to specific disease below: OA (noninflammatory); gout/pseudogout; lupus; PMR; sarcoidosis/Lofgren's (assoc w/ hilar adenopathy, erythema nodosum); adult-onset Still's disease (assoc w/ high fevers, rash, ↑ ferritin); systemic vasculitides (e.g., granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis); hemochromatosis (esp w/ MCP &/or wrist involvement); antisynthetase syndrome; serum sickness; paraneoplastic or chemotherapy related (specifically checkpoint inhibitors)

RHEUMATOID ARTHRITIS (*AFP* 2011;84:1245; *Ann Intern Med* 2010;153:ITC1; *Lancet* 2010;376:1094)

- **Definition:** Symmetric, inflammatory arthritis affecting multiple peripheral joints
- **Epidemiology:** 0.5–1% of Caucasian adults; peak incidence 50–60

y

- **Risk factors:** ↑ age, ♀>♂, FHx; HLA-DRB1 locus; smoking
- **Extra-articular 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, Felty syndrome (RA + neutropenia + splenomegaly + recurrent infections)
- **Complications:** ↑ risk of infection; cervical subluxation → pain, neuro deficit, instability; increased risk of CVD

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) • 2–10 medium/large joints (shoulder, elbows, hips, knees) (1) • 1–3 small joints (i.e., MCP, PIP) (2) • 4–10 small joints (3) • >10 joints (including ≥1 small joint) (5)
Serology	• ⊖ RF &⊖ anti-CCP (0) • Low- ⊕ RF or low- ⊕ anti-CCP (2) • High- ⊕ RF or high- ⊕ anti-CCP (3)
Acute-phase reactants	• Nl CRP & nl ESR (0) • 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	

- **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; also can be ⊕ in Sjögren's, cryoglobulinemia
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:** 1° goal is remission w/o active disease, requiring early & aggressive comanagement w/ rheumatology (*BMJ* 2011;343:4027; *Arthritis Rheum* 2005;52:3381); initial control & acute flares 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/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 (see *"Side Effects and Monitoring of Common DMARDs"*)
  - **Nonbiologic:** MTX (1° tx for most RA pts), hydroxychloroquine, sulfasalazine, leflunomide; "Triple therapy" (MTX, hydroxychloroquine, sulfasalazine) may be noninferior to etanercept + MTX (*NEJM* 2013;369:307); tofacitinib
  - **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)
  - **Supportive care:** PT, OT, pt education, exercise, smoking cessation
  - **Surgery:** Consider joint replacement in pts w/ uncontrolled pain or severe disability despite optimal medical Rx
- **Patient information:** *JAMA* 2011;305:1824

Viral Arthritis

- **Background:** Nonerosive usually managed symptomatically (*Infec Dis Clin N Am* 2005;19:963)
  - **Parvovirus B_{19}:** 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-B_{19}± PCR
  - **Hepatitis: HCV** assoc w/ chronic arthritis in 2–4% (± cryoglobulinemia syndrome), many w/ ⊕ RF, usually – anti-CCP; acute **HBV** assoc w/ transient RA-like arthritis
  - **HIV:** ↑ risk of septic arthritis, arthralgias common, ↑ risk of spondyloarthropathies (esp reactive/psoriatic arthritis, may be severe but ↓ frequency in HAART era)
  - **Chikungunya:** Often bilateral, symmetric, small joints; suspect if other manifestations such as fever, rash with appropriate travel history; can be more chronic

Seronegative Spondyloarthropathies (*AFP* 2004;69:2853)

- **Background:** Umbrella term that includes four diagnoses: ankylosing spondylitis, reactive arthritis, psoriatic arthritis, IBD associated arthritis; often with axial involvement, 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 & 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:** Characterized by prominent inflammatory back pain; extra-articular manifestations include iritis, tendonitis, aortic insufficiency; +HLA-B27 in 90% of pts; MRI detects SI joint

inflammation earlier than radiograph; tx w/ **NSAIDs** (first-line treatment), TNF inhibitors, secukinumab (IL-17A antagonist) (*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 3–6 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 h/o psoriasis (psoriasis vulgaris most common); 20% w/ +HLA-B27; leads to joint deformity/erosive disease if untreated; DMARDs, TNF inhibitors effective, ustekinumab (IL-12/23 inhibitor) (*Lancet* 2013;382:780), secukinumab (*NEJM* 2015;73:1329; 2017;376:957) (see *"Psoriasis"*)
- **Inflammatory bowel disease:** (a) axial arthritis resembling ankylosing spondylitis or isolated sacroiliitis; (b) Type I peripheral arthritis affects large joints (oligo-) of LE & acutely assoc w/ IBD flare; (c) Type II peripheral arthritis affects small joints (poly-) in a symmetrical manner & persists regardless of IBD activity (see *"IBD"*)

RHEUMATOLOGIC TESTS

Inflammatory Markers (*JAMA* 2015;314:827; *Mod Rheumatol* 2009;19:469)

- **C-reactive protein:** Produced by liver; rapidly δs, direct measure of inflammation
- **Erythrocyte sedimentation rate:** Slowly δs; indirect measure of inflammation; ↑ ESR suggests acute-phase proteins (e.g., fibrinogen, globulin) in plasma causing RBC aggregation; also ↑ by pregnancy, ↑ age, certain medications (e.g., OCPs), anemia

Antinuclear Ab (*AFP* 2002;65:1073; *Arthritis Rheum* 2002;47:434; *Autoimmun Rev* 2006;5:10; 2016;15:162)

- **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, pregnancy; may be ⊕ in systemic (e.g., SLE) or single-organ autoimmune disease (e.g., autoimmune hepatitis)

- **Titer:** 1:40 (seen in 25–30% of healthy pts); 1:80 (seen in 1–15% of healthy pts); 1:160 (⊕ in 5% of healthy pts); If >1:160, less likely see in healthy pts; ⊕ titer may precede sx by several years (*Arthritis Res Ther* 2011;13:1; *NEJM* 2003;349:1526); titer significance must be considered in the clinical context
- **Staining pattern:** 40+ patterns; somewhat 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 so not very helpful

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.

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

Rheumatic Conditions with Specific Antibodies (*Clin Chem Lab* 2001;39:189)

Disease	Antibodies	Notes
SLE	Anti-dsDNA, Anti-Sm Anti-Ro, Anti-La, Anti-RNP, Anti-histone	Anti-Ro/La assoc w/ neonatal lupus incl congenital heart block Antihistone assoc w/ drug-induced LE

DM/PM	Anti-Jo-1, consider add'l myositis Ab testing	Myositis specific- & associated-antibodies may prognosticate
Systemic sclerosis (SSc)*	Anti-Scl-70, Anti-centromere, RNA polymerase III	Anti-Scl-70 assoc w/ dSSc >lSSc; Anti-centromere assoc w/ lSSc>dSSc; RNA pol III assoc w/ ↑ risk of renal crisis
Sjogren's	Anti-Ro, Anti-La	
MCTD	Anti-RNP	
Rheumatoid Arthritis (RA)	RF & CCP	See "*Polyarticular Arthritis*" section

SSc includes both diffuse (dSSc) and limited (lSSc) scleroderma; limited also known as CREST = **C**alcinosis, **R**aynaud's, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasias syndrome

Antineutrophil Cytoplasmic Antigen (ANCA) (*Clin Chem Lab* 2001;39:189)

- **p-ANCA:** Perinuclear pattern; target is usually myeloperoxidase (MPO); assoc w/ systemic vasculitis esp. microscopic polyangiitis & eosinophilic granulomatosis with polyangiitis-EGPA (formerly Churg–Strauss); ↑titer, consider drug- or levamisole (cocaine)-induced
- **c-ANCA:** cytoplasmic pattern; targets PR-3 = major autoAg in granulomatosis w/ polyangiitis (GPA, previously Wegener granulomatosis); 10–30% of pts w/ GPA are cANCA ⊖; ↑ titer may be assoc w/ relapse

Cryoglobulins (*Lancet* 2012;379:348)

- **Background:** Precipitate in cold, dissolve w/ rewarming, if ⊕, type & % (cryocrit) reported
  - **Type1:** 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 & autoimmune disease; can lead to immune-complex–mediated vasculitis
  - **Type 3:** Mixed cryoglobulin (polyclonal IgM & IgG) assoc w/ autoimmune disease (e.g., SLE, SS), infection (HBV, HCV, HIV), & malignancy (hematologic >> solid)
- **Interpretation:** ⊕ or % of cryo is not necessarily diagnostic, % does

not always correlate w/ active dz; if ⊖ test but ↑ clinical suspicion, test should be repeated; high false- ⊖ rate

OSTEOARTHRITIS

Background (*Ann Int Med* 2014;161:ITC1; *Best Pract Res Clin Rheumatol* 2006;20:3)

- **Epidemiology:** Most common joint d/o (21 million pts in US); prevalence ↑↑ >40 y
- **Common risk factors:** Age, obesity, trauma, repetitive use, ♀, genetics/FHx, neuropathy
- **Pathophysiology:** Slow, progressive loss of articular cartilage assoc w/ bone hypertrophy (osteophytes) & sclerosis; usually 1° (idiopathic) but may also be 2/2 trauma, deformity, or inflammatory process
- **Affected joints:** Often affects multiple joints; typically hands/feet (DIP, thumb base/CMC, 1st MTP), knees, hips, spine (esp cervical/lumbar), shoulders (AC, glenohumeral joint)

Evaluation and Prognosis (*AFP* 2011;84:2012; 2011;85:49; *JAMA* 2003;289:1016; *NEJM* 2007;357:1413)

- **History:** Highly variable & depends on affected joint(s); pain worsened by activity, relieved by rest; gelling/stiffness w/ inactivity; slowly progressive; limitation in ROM; bony swelling, morning stiffness that resolves in <30 min; joint locking, popping, or instability; pt may report trauma/repetitive injury
  - **Noninflammatory OA:** Most common; pain/disability is 1° sx
  - **Erosive OA:** Subset of hand OA w/ prolonged morning pain/stiffness, effusion
- **Exam:** Depends on joint; ↓ ROM w/ pain at end of range, typically w/o warmth; ± swelling (± tenderness) around joint line; crepitus; periarticular muscle weakness/wasting or bursitis/tendinitis
- **Workup:** Advanced imaging (e.g., CT or MRI) is rarely necessary unless suspicion for alt dx (e.g., meniscal injury in the knee); x-ray 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

Consider further eval or referral to rheum: Younger pts, atypical sx or signs (e.g., atypical location, significant rest or night pain), wt loss/constitutional sx, rapidly progressive pain or when dx is in question

- **Prognosis:** Slowly progressive, may stabilize esp w/ risk factor reduction (e.g., wt loss), PT/exercise; no disease-modifying pharmacologic therapy

ACR Criteria for Diagnosis of Osteoarthritis	
Hand	Hand aching, pain, or stiffness & 3 of 4 of the following: (1) Hard tissue enlargement of 2 or more of 10 selected joints*; (2) Hard tissue enlargement of 2 or more DIP joints; (3) <3 swollen MCP joints; (4) Deformity of at least 1 of 10 selected joints*. *10 selected joints include 2nd & 3rd DIP, 2nd & 3rd PIP, & 1st CMP joints of both hands (94% Se, 87% Sp) (*Arthritis Rheum* 1990;33:1601)
Hip	Hip pain & ≥2 of 3 of: (1) ESR <20 mm/h; (2) Radiographic femoral or acetabular osteophytes; (3) Radiographic joint space narrowing (89% Se, 91% Sp) (*Arthritis Rheum* 1991;34:505)
Knee	**Clinical:** Knee pain & ≥3 of 6 of: (1) Age >50 y; (2) Stiffness <30 min; (3) Crepitus; (4) Bony tenderness; (5) Bony enlargement; (6) No palpable warmth (95% Se, 69% Sp)
	Clinical and radiographic: Knee pain, osteophytes on radiographs & ≥1 of 3 of: (1) Age >50 y; (2) Stiffness <30 min; (3) Crepitus (91% Se, 86% Sp)
	Clinical and laboratory: Knee pain & ≥5 of 9 of: (1) Age >50 y; (2) Stiffness <30 min; (3) Crepitus; (4) Bony tenderness; (5) Bony enlargement; (6) No palpable warmth; (7) ESR <40 mm/h; (8) RF <1:40; (9) Synovial fluid OA (clear, viscous, or WBC <2,000/mm^3) (92% Se, 75% Sp) (*Arthritis Rheum* 1986;29:1039)

Management (*AFP* 2011;83:1287; 2012;85:49; 2015;92:774; *NEJM* 2006;354:841; *Osteoarthritis Cartilage* 2008;16:137)

- **Nonpharmacologic:** Pt education, exercise (esp non wt-bearing), 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 (effectiveness unclear)→

standing → NSAIDs (evaluate comorbidities); **Erosive OA:** NSAIDs PRN → standing (if persistent pain), colchicine, hydroxychloroquine

Osteoarthritis Medications

Drug	Dosing	Adverse Reactions	Additional Info
NSAIDS	Lowest effective dose; do not combine NSAIDs	- Contraindicated in PUD & ASA sensitivity - ↑ r/o CVD - ↑ r/o bleeding w/ warfarin - Avoid in CKD, CHF, cirrhosis, diuretics - may ↑ BP - Add PPI/H2 blocker 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) CV risk similar to ibuprofen or naproxen (*NEJM* 2016:375:2519), no effect on PLT function
Duloxetine (SNRI)	Start 30 mg/d, ↑ to 60 mg/d	Nausea, dry mouth, somnolence, fatigue	Duloxetine added to oral NSAIDs improved knee OA pain (*Curr Med Res Opin* 2011;27:2361)
Capsaicin & Topical NSAIDs (i.e., diclofenac)	Can apply up to QID	Minimal systemic absorption	May be of only minimal benefit; capsaicin may be irritating
Tramadol	50–100 mg q4–6h PRN	**Opioid use (other than tramadol) not recommended by American College of Rheumatology**	Tramadol may be synergistic w/ APAP (*Cochrane Database Syst Rev* 2006;CD005522)
Hydroxy-Chloroquine	0.5 mg/kg/d (200–400 mg/d)	Upset GI; retinal toxicity	Consider in pts w/ erosive OA unresponsive to NSAIDs; reduce dose of colchicine in renal failure (e.g., 0.3 mg/d)
Colchicine	0.6 QD-BID	N/V, diarrhea (↑ w/ ↑ dose); ↓ dose in CKD (however, not nephrotoxic); BM supp, myopathy, neuropathy	

- **Glucosamine & chondroitin:** Controversial but multiple negative

trials, esp in advanced arthritis (*NEJM* 2006;354:795); glucosamine contraindicated in shellfish allergy

- **Intraarticular injections:** Glucocorticoids (1–2 mos) may be useful in pts w/ pain refractory/contraindication to NSAIDs. Hyaluronate-related injectable agents are FDA-approved for treatment of OA of the knee, but efficacy is unclear & use is controversial (*NEJM* 2015;372:1040); *Ineffective treatments*: Intra-articular triamcinolone injections (*JAMA* 2017;317:1967); vitamin D supplementation (*JAMA* 2016;315:1005); lateral wedge shoe inserts (*JAMA* 2013;310:722); glucosamine/chondroitin supplements (*AFP* 2015;92:875)
- **Surgical:** Consider joint replacement (esp knee/hip) in pts w/ severe 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

BACK PAIN

Background (*Ann Int Med* 2014;160:ITC6-1; *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

Evaluation (*Ann Intern Med* 2007;147:478; *AFP* 2007;75:1181; 2015;91:708)

- **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 hx, 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:** Spine flexibility & palpation; 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); exam of hip joint (youtube.com/watch?v=q1gX9hORtLY)
  - **Straight-leg test:** 91% sensitive, 26% specific for detecting herniated discs (*Spine* 2000;25:1140); w/ 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)
  - **Labs:** Guided by clinical scenario: Consider ESR/CRP, CBC, BCx, AlkPhos, HLA-B27); for pts on chronic opioids, random drug testing to assess for presence of opioids to detect substance use d/o (*JAMA* 2013;309:919)
  - **Radiographs:** Useful in diagnosing compression fractures, ankylosing spondylitis
  - **MRI:** ~2/3rds of healthy adults w/o 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

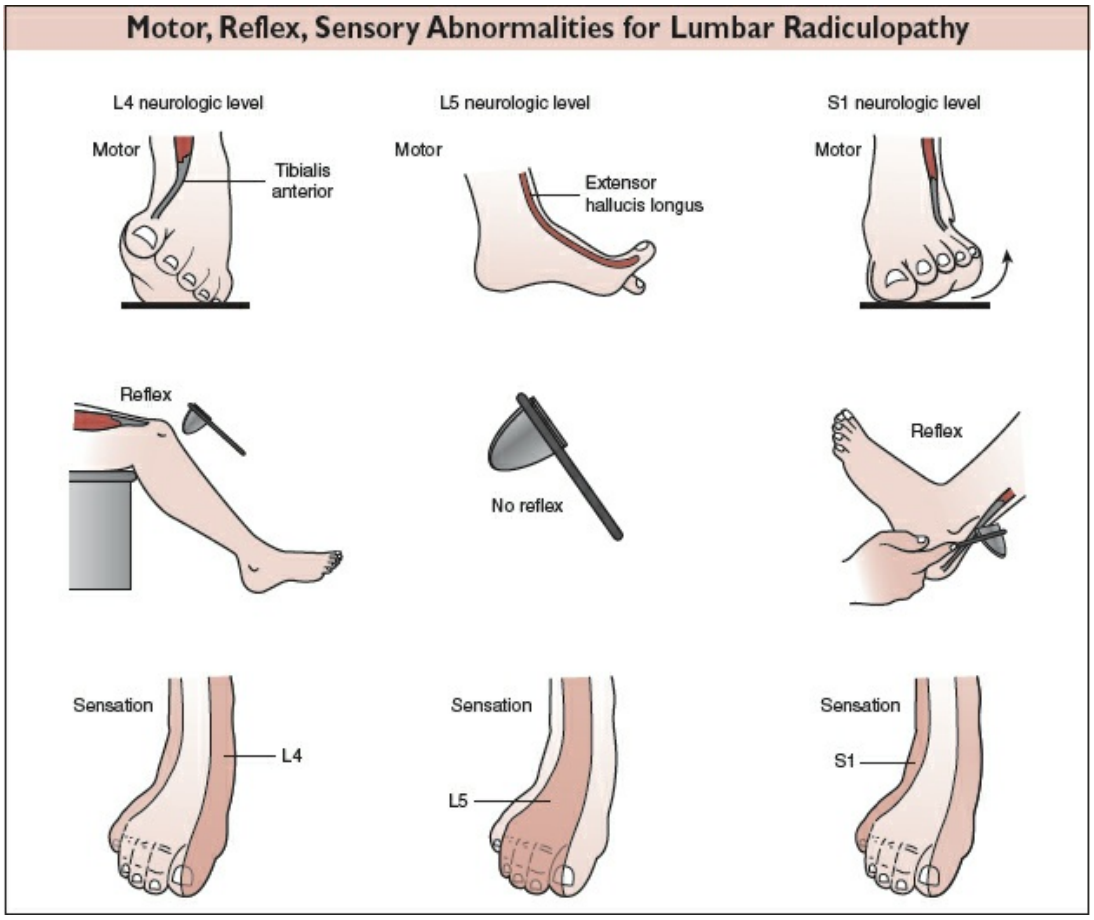
Etiologies of Back Pain and Common Presenting Symptoms

Suggestive History and Exam Findings	Etiology of Back Pain
Sudden onset, often w/ precipitating movement, may radiate to buttock, upper thigh; feeling of "something giving way"	Muscle or ligament injury (70%)
Chronic, subacute pain often assoc w/ osteoarthritis	Degenerative joint disease (10%)
L5–S1 most common; ⊕ straight leg test; worse w/ coughing, straining; sciatic pain (sharp/burning, radiating down buttock, thigh, or leg) in dermatomal distribution	Disk herniation (4%)
Sudden onset of pain in pt w/ risk factors for fracture (i.e., osteoporosis, steroid use, malignancy, elderly) after coughing,	Compression fracture (4%)

bending, lifting, or minor trauma; loss of height, point tenderness; may be presenting sign of osteoporosis	
Pain in lower back, buttocks (pseudoclaudication), wide gait, paresthesias (often bilateral), worsened by standing, walking (downhill > uphill, in contrast to claudication) & ↓ by sitting/bending/leaning forward (*JAMA* 2010;304:2628; *NEJM* 2008;358:818)	Spinal stenosis (3%)
Forward subluxation of vertebrae causes chronic ligamentous pain worse w/ activity, relieved by rest	Spondylolisthesis (2%)

Rare Causes of Back Pain

Suggestive History and Exam Findings	Etiology of Back Pain
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	Malignancy (<1%)
Fever, back pain, neuro deficit in minority of pts; risk factors include instrumentation, HIV, IVDU, TB, & hematogenous seeding from a UTI, catheter, or abscess (*NEJM* 2006;355:2012; 2010;362:1022)	Epidural abscess, vertebral osteomyelitis, discitis (0.01%)
Inflammatory back pain: onset of pain insidious, improves w/ motion, worse in the morning/better at night, improves w/ NSAIDs, typically in pts 20–45 y	Spondyloarthropathies (<1%)
Referred pain from hip, SI joint; AAA/TAA, endometriosis, fibroids, nephrolithiasis, pancreatitis, cholecystitis, pyelonephritis, neuropathy, claudication	Extraspinal (2%)



Red Flags to Prompt Imaging

(Adapted from the American College of Radiology Appropriateness Criteria www.acr.org)

Red Flag	Possible Underlying Condition
Unexplained fevers or wt loss H/o cancer Immunosuppression Indwelling catheter, recent UTI or cellulitis IVDU Prolonged steroid use Back pain not improved w/ conservative tx	Cancer or infection
H/o significant trauma Minor fall or heavy lifting in elderly individual or osteoporosis Prolonged steroid use	Spinal fracture
Acute onset urinary retention or incontinence Loss of anal sphincter tone or fecal	Cauda equina syndrome or severe neurologic compromise

incontinence Saddle anesthesia Global or progressive motor weakness	

Treatment

Acute/Subacute (<12 wks)

Urgent surgical eval: Indicated for cauda equina, motor weakness, cord compression

Nonpharmacologic Therapy: 1st-Line Therapy

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); role of early PT referral unclear (*JAMA* 2015;314:1459)

Reassurance: 90% of pts w/ acute, nonspecific back pain improve in <2 wks w/o intervention (*BMJ* 1994;308:577)

CAM: Physical therapy, yoga (chronic low back pain), acupuncture, chiropractic, aquatherapy, massage tx; heat; cold compresses (acute back pain); spinal manipulation assoc w/ improvements in pain & function (*JAMA* 2017;317:1451)

Self-care: Education books (e.g., *The Back Book*); back braces or abdominal binders

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

Pharmacologic: 2nd-Line Therapy

APAP no longer recommended (*Ann Intern Med* 2017;166:480; *Lancet* 2014;384:1586)

NSAIDs: 1st-line, scheduled for short course (*JAMA* 2017;317:2327)

Topicals: Lidocaine, capsaicin

Muscle Relaxants: Cyclobenzaprine, baclofen, tizanidine, 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)

Opioids: Not recommended (*JAMA Int Med* 2016;176:958)

Steroids: Oral steroids for herniated disc did not improve pain compared to placebo but did improve function somewhat (*JAMA* 2015;313:1915)

Bisphosphonates: Consider in pts w/ osteoporotic compression fractures & pain unrelieved by PO meds

Chronic (>12 wks)

Epidural steroid injections: Consider for chronic radicular pain from disk herniation; insufficient evidence, but certain subgroups 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 (*JAMA* 2016;315:1240), 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)

HIP PAIN

- **General principles:** Hip pain is one of the most common musculoskeletal complaints. A patient's report of "hip pain," however, is often misleading since there are many causes of pain in the area of the hip, several of which do not arise from the true hip joint (where the femoral head articulates with the acetabulum).
- **Anatomy:** Hip joint comprised of femoral head articulated with 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 Pain in the Hip Region (*AFP* 2014;89:27)

Diagnosis	Symptoms	Demographics
Osteoarthritis (*NEJM* 2007;357:1413)	*Groin pain* w/ movement, better w/ rest, ↓ ROM	Common in the elderly
Trochanteric bursitis	*Lateral hip pain* w/ point tenderness over greater trochanteric bursa, exacerbated by	Middle-aged women,

	gait impairment, walking & direct pressure	younger pts, runners
Meralgia paresthetica	Paresthesias (esp burning) over *upper outer thigh* (due to lateral femoral cutaneous nerve entrapment)	Obese or pregnant pts; DM patients; tight clothing
Referred pain & spinal stenosis	*Back, hip & buttock pain* 2° to lumbosacral disc & facet joint dz	Middle-aged & elderly
Occult hip fracture (*AFP* 2003;67:537)	Severe pain in "hip area" 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 use, EtOH, sickle cell, SLE, trauma
Gluteus medius tendinopathy	*Buttock pain* w/ hip abduction & rotation, pain above the greater trochanter, ⊕ Trendelenburg sign	More common in women (wider pelvis)
Piriformis syndrome	*SI joint or sciatic notch pain → foot*, w/o numbness/weakness; ↑on hard surface, ↓ w/ walking	Anatomic variation in sciatic nerve or piriformis muscle
Labral tear	*Anterior hip/groin pain*, clicking/locking of the hip	Pts w/ OA, athletes
Femoroacetabular impingement (*AFP* 2009;80:1429)	*Chronic antero/lateral hip/groin pain* worse w/ turning, ↓ ROM, ↑risk of early OA	Athletes

- **Less common causes of hip pain to consider:** Malignancy (wt loss, nocturnal pain), septic arthritis (fevers, h/o IVDU, unable to bear wt), Leriche syndrome due to PAD (claudication sx)

Evaluation (*Clin J Sport Med* 2003;13:152; *Orthop Relat Res* 2009;467:638)

- **History:** Location 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), medications (steroids, EtOH)
- **Exam:** Natural gait & heel-to-toe; look for Trendelenburg/antalgic gait, & short leg limp (youtube.com/watch?v=yluzGVcWEsg; youtube.com/watch?v=iTfDvFCPZ_w)

  Squatting: Will be limited by mod-to-severe OA, bursitis, or

muscle weakness

FABER: Flexed, **AB**ducted, And **E**xternally **R**otated hip may identify SI joint dysfunction

Internal & external rotation: ↓ rotation in pts w/ severe OA or septic arthritis

Palpation of trochanteric bursa: w/ hip 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)

- **Diagnostics:**

  Plain film: Assess for fracture if 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/injections & can also demonstrate bursitis; hip aspiration indicated if infection is suspected (should be image-guided)

Treatment

- **Osteoarthritis:** Limit high impact activities, NSAIDs/APAP, rest, heat, stretching (see *"Osteoarthritis"*); Hip arthroplasty if failure of conservative Rx or significant disability. Meta-analysis shows diclofenac 150 mg QD more effective compared to other NSAIDs (*Lancet* 2016;387:2093); role of PT unclear (*JAMA* 2014;311:1987)
- **Bursitis:** Avoid pressure over hip, bending & stairs; stretching, heat, NSAIDs/APAP, PT (for orthotic & gait eval); consider steroid injections if conservative measures fail
- **Femoroacetabular impingement:** Rest, PT, NSAIDs/APAP, ortho referral if refractory
- **Labral tear:** PT; ±arthroscopic surgery (*Curr Rev Musculoskelet Med* 2009;2:105)

- **Meralgia paresthetica:** Self-limited; reassurance, avoid tight garments, wt loss; if persistent consider gabapentin, carbamazepine, or phenytoin
- **Osteonecrosis:** Rest, wt-bearing as tolerated, pain control; referral to ortho for progressive dz or failure of conservative mgmt
- **Piriformis syndrome:** PT, stretching, NSAIDs; consider gabapentin, TCA, steroid injection
- **Patient information:** *AFP* 2009;80:1439; *JAMA* 2007;298:2442 (hip fx)

KNEE PAIN

Background (*AFP* 2003;68:917; 2015;92:875; *JAMA* 2001;286:1610; *NEJM* 2006;354:841; 2010;363:e5)

Differential Diagnosis of Knee Pain by Location
Anterior: Injury to quadriceps, patella, or patellar tendon; patellofemoral syndrome; OA; Inflammatory arthritis (e.g., gout)
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
Posterior: Effusion (e.g., 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, acutely disabling pain
- **Exam:** Examine both knees (asx knee as a control if unilateral), hip, & ankle; observe gait, squat, duck waddle (pt squats & moves forward); test quadriceps, hamstring strength (youtube.com/watch?v=JWQ_a-k8qqM; youtube.com/watch?v=wlLfNls75RY)

Inspection: Joint architecture, erythema, swelling/effusion

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), swelling/effusion

Range of motion: Active & passive extension, (0–135° nl), varus & valgus instability at 0° for LCL & 30° for MCL; crepitus

- **Workup:** Start w/ radiograph; consider U/S or MRI to evaluate meniscal, ligament tear, or other etiology if dx unclear; if effusion present, aspirate to assess for cell count, crystals, & infection

  Ottawa knee rule: Plain films after acute injury to r/o fracture if any of the following: ≥55 yo, 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)

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 (Meniscal injury) 53–97% Sp	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; Tai chi as effective as PT (*Ann Int Med* 2016;165:77)

  Treatment: Wt loss (if overweight), PT, APAP, NSAIDs; in surgery candidates, unilateral total knee replacement followed by nonsurgical treatment superior to nonsurgical treatment in improving pain & QOL at 1 y in pts w/ mod–sev OA (*NEJM* 2015;373:1597). Hyaluronate-related injectable agents are FDA-approved for treatment of OA of the knee, but efficacy is unclear & use is controversial (*NEJM* 2015;372:1040)

  Ineffective treatments: Intra-articular triamcinolone injections (*JAMA* 2017;317:1967); vitamin D supplementation (*JAMA* 2016;315:1005); lateral wedge shoe inserts (*JAMA* 2013;310:722); ? glucosamine/chondroitin supplements (*AFP* 2015;92:875)

- **Anterior cruciate ligament injury:** Trauma → "pop," immediate pain; swelling (may be delayed), 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/knee pads (protection), 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
  - **Treatment:** Rest, 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:** Typically injured after twisting or hyperextension of leg; medial knee pain, pain w/ walking, twisting, pivoting
  - **Treatment:** Rest, ice, compression; NSAIDs, early mobilization as tolerated; 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; exercise therapy as effective as arthroscopic partial meniscectomy for degenerative tears (*BMJ* 2016;354:1); arthroscopic partial meniscectomy showed no benefit compared to sham surgery for mechanical sx in pts w/ degenerative meniscus tears (*Ann Int Med* 2016;165:449).
- **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°. May consider arthrocentesis/steroid injection
- **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, NSAID, 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

SHOULDER PAIN

Background (*AFP* 2016;94:119; *Ann Int Med* 2015;162:ITC1-15; *BMJ* 2005;331:1124)

- **Epidemiology:** 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

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 w/ abduction &/or reaching, typically in context of repetitive activity at or above level of shoulder
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)
Biceps tendinitis	Gradual onset anterior shoulder pain typically w/ heavy lifting
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
AC or GH Joint	>50 y, pain w/ activity, stiffness, ↓ ROM, crepitus w/ arm elevation;

Osteoarthritis (*AFP* 2008;78:605)	may affect AC (pain w/ elevation of arm >90°) or GH joint (pain w/ external/internal rotation when arm is in neutral position)
GH joint instability	Shoulder pain in throwing athletes
Other (*AFP* 2004;70:1947)	Sternoclavicular pain; fracture; MI; inflammatory/septic arthritis; UE DVT; lung malignancy; avascular necrosis; PMR
RC, rotator cuff; GH, glenohumeral; AC, acromioclavicular	

- **Exam:** Examine C-spine; palpate AC, SC, & GH joints, biceps tendon, subacromial bursa, trapezius muscles (youtube.com/watch?v=g8xtOqZFTwo; youtube.com/watch?v=GxswYxiUdzI)
  - 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 from 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:** Imaging (beginning with radiograph) may be useful if hx, sx, or exam *inconsistent* with RC tendinopathy (w/o tear). In pts w/ persistent shoulder pain attributed to RC tendinopathy despite w/ 2–3 mos of conservative Rx, obtain 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; may 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/atrophy, or infection, initial trial of NSAIDS/APAP±PT (if↓ ROM or strength) for 2–4 wks; consider steroid injection; if no improvement, consider ortho referral
- **Shoulder impingement:** Ice, rest, PT, glucocorticoid injection in refractory cases
- **Adhesive capsulitis:** PT; glucocorticoid injection; surgery referral for manipulation under anesthesia or release in refractory/severe cases
- **Osteoarthritis:** NSAIDs/APAP, PT, glucocorticoid injections
- **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
- **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

ELBOW PAIN

Background (*AFP* 2014;89:649)

Etiologies of Elbow Pain
Lateral elbow: Lateral epicondylitis ("tennis elbow") is caused by damage to extensor carpi radialis brevis & longus tendons; worsened by repetitious use of forearm/wrist, hand shaking; referred pain worsened by movement of shoulder/neck
Medial elbow: Medial epicondylitis ("golf elbow") is caused by damage to flexor carpi radialis tendon; worsened by contraction of wrist flexors (i.e., lifting); injury to ulnar collateral ligament (often due to throwing injury); ulnar neuropathy or entrapment
Elbow joint pain: Pain w/ supination/pronation as well as extension
Olecranon bursitis: Swelling/fullness over the olecranon as opposed to in the humeroulnar or humeroradial joint
Throwing injury: Ulnar collateral ligament injury

Evaluation

- **History:** "Popping" sound or immediate swelling suggests a soft tissue injury or bleeding into the joint; locking, catching, or joint instability; numbness or tingling; prior injury; hobbies involving joint (i.e., pitching, golf); nocturnal awakening
- **Exam:** Flexion, extension, supination, pronation of joint (youtube.com/watch?v=rNXZlbamJuY); percussion of ulnar nerve at ulnar groove, cubital tunnel, & Guyon canal to test for ulnar neuropathy
- **Workup:** Elbow radiographs (AP, lateral, oblique); MRI if soft tissue injury or ulnar neuropathy suspected; musculoskeletal U/S; EMG if ulnar neuropathy suspected

Treatment

- **Epicondylitis:** NSAIDs (systemic or topical), counterforce bracing, physical therapy; splinting generally not effective & may worsen sx; steroid injections may temporarily improve sx but do not lead to improved long-term outcomes (*JAMA* 2013;309:461; *Lancet* 2002;359:657;

2010;376:1751); benefit of autologous blood injection unclear (*PM R* 2016;8:780); orthopedic referral for refractory sx

- **Olecranon bursitis:** Joint protection; fluid aspiration along w/ an elbow orthosis; surgical excision of bursa if chronic
- **Ulnar neuropathy at elbow:** Splinting to limit flexion beyond 45, foam elbow pads, activity modification, avoidance of provocative factors (leaning on elbows, prolonged elbow flexion), ulnar nerve decompression

HAND DISORDERS

Evaluation

- **History:** Characteristic of given condition (below); hx injuries; systemic dz
- **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

Common Nontraumatic Hand Disorders

Disorder	Description	Presentation	Treatment Options
Osteoarthritis (*Arthritis Rheum* 1990;33:1601) (see *"Osteoarthritis"*)	Hand pain, characteristically involving PIP, DIP & CMC joints 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	Heat; splinting for CMC OA Topical NSAIDs, topical capsaicin, oral NSAIDs (if no contraindication); consider Tramadol (*Arthitis Care Res* 2012; 64:465)
Dupuytren Contracture	Genetic fibroproliferative	Painless palmar skin nodules or	**Nonoperative:** Observation of isolated

	disease (autosomal dominant, incomplete penetrance); collagen within palmar fascia proliferates, thickens, & contracts	cords, which sometimes cause flexion contracture (inability to straighten finger)	nodules; percutaneous needle fasciotomy, or injectable collagenase for substantial contractures **Surgery:** Excision of diseased palmar fascia (fasciectomy)
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	**Nonoperative:** NSAIDs, splinting; corticosteroid injection into the tendon sheath (works ~50% of the time, can take 2 mos to show efficacy) **Surgery:** Release of digital A1 pulley
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)	**Nonoperative:** NSAIDS, thumb spica wrist splint, corticosteroid injection in the 1st dorsal compartment **Surgery:** Release of 1st extensor compartment
Ganglion cyst	Mucin-filled synovial cyst	Painless mass, Δ in size, characteristic locations: dorsal & volar-radial wrist; dorsal DIP (assoc w/ OA); over A1 pulley (retinacular ganglion cyst)	**Nonoperative:** Observation, as many spontaneously resolve; avoid aspiration (clear, gelatinous fluid) on volar surface as often abuts radial artery **Surgery:** Excision (5–10% recurrence rate)
Carpal tunnel syndrome (idiopathic median neuropathy in carpal tunnel)	- Compression of median nerve → sensory & motor neuropathy - Indications for Electrodiagnostic testing debated: Used to (1) R/o CTS in reports of paresthesias where	- Transient numbness in median nerve distribution w/ wrist flexion (sleeping, driving) → eventual constant numbness, thenar atrophy, &	**Nonoperative:** **Splinting:** holds wrist in neutral position; steroid injection into carpal tunnel; NSAID trial. **Surgery:** Indicated if failure of nonoperative Rx or median nerve denervation demonstrated on clinical or electrodiagnostic

	it is a possible but less likely dx, (2) Provide objective data to manage postoperative expectations in pts w/ severe dz	weakness - Provocative factors: Wrists flexion/extension; nocturnal worsening since wrist often flexed during sleep - Provocative maneuvers: see below	testing (*JAAOS* 2009;17:389). Severe dz w/ constant numbness & atrophy is permanent; the sx from moderate disease usually disappear
Cubital tunnel syndrome (idiopathic ulnar neuropathy in cubital tunnel)	Compression of ulnar nerve at elbow → neuropathy	Initially transient then constant numbness of 4th & 5th digits; weakness & atrophy of 1st dorsal interosseous muscle; medial elbow pain	**Nonoperative:** Brace or pillow to limit elbow flexion at night; avoid leaning on elbow **Surgery:** Mod to sev neuropathy; progressive symptoms & signs less than 6 months duration despite conservative measures. Benefit may be less for patients with chronic involvement

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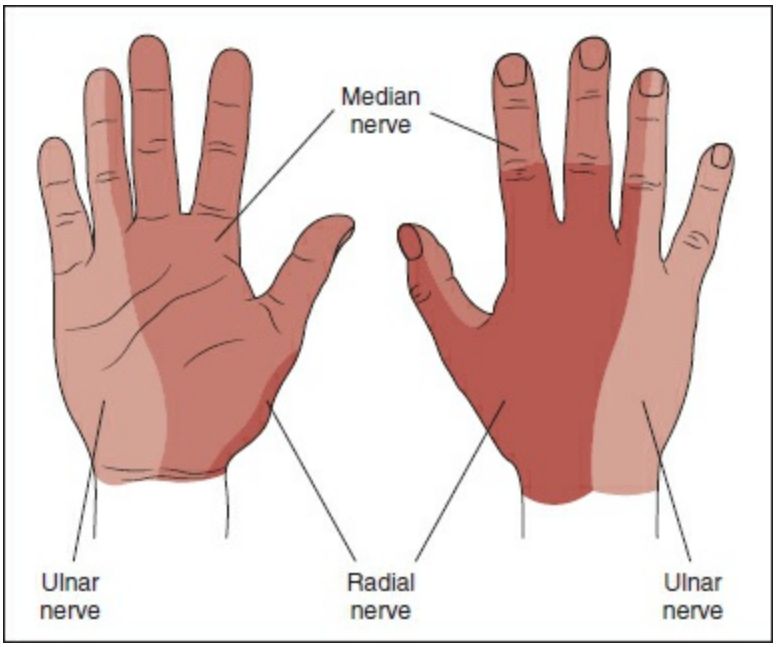
CARPAL TUNNEL SYNDROME (*AFP* 2011;83:952; 2016;94:993; *Ann Int Med* 2015;163:ITC1; *BMJ* 2007;335:343; *JAMA* 2000;283:3110)



- **Definition:** Peripheral mononeuropathy of median nerve at level of wrist
- **Anatomy:** The carpal tunnel, made up of the carpal bones & the transverse carpal ligamment, 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 dz, ↑ risk w/ age; many pts don't seek medical attention
- **Risk factors:** Evidence that it is related to environmental factors is low quality & inconsistent.
- **DDx:** Cubital tunnel syndrome, neuropathy, cervical radiculopathy
- **History:** Intermittent numbness & tingling of the thumb, index, middle, ring finger (patient may describe as the "entire hand"); Classic: Awakens patient from sleep or present on waking; not a painful condition except that the numbness can be very intense & experienced as pain; patients 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; results reflect likelihood of syndrome
- **Exam:** (*J Am Acad Orthop Surg* 2009;17:389)
  - **Sensory:** Affects threshold sensibility initially (light touch measured w/ Semmes–Weinstein) then discriminatory sensibility later (measure with two-point discrimination)
  - **Motor:** In severe dz 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 increase Se/Sp

Provocative Tests for Carpal Tunnel Syndrome (*J Hand Ther* 2004;17:309)

Test	Maneuver	Se	Sp
Phalen	Wrists flexed for 30 s	68%	73%
Tinel	Tap on median n. 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 dz; 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); 85% sensitive, >95% specific
  - **Electromyography (EMG):** Excludes other peripheral neuropathies
- **Treatment:**

Preferred Nonsurgical Treatment Modalities

Modality	Description
Splinting	Brace at night holds wrist neutral to prevent waking w/ numbness; improvement usually occurs within 2 wks
Steroid inj	Single injection into carpal tunnel; methylprednisolone injections ↓ pain at 10 wks & risk of surgery at 1 y compared to placebo (*Ann Int Med* 2013;159:309)

Modalities w/ insufficient evidence: Carpal bone mobilization; nerve gliding; yoga; ergonomic keyboard; oral steroids, ultrasound

Modalities w/ no significant benefit: Diuretics, vitamin B6, magnet therapy, 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 rare but problematic; incomplete release of transverse carpal ligament very uncommon & difficult to distinguish persistent from recurrent sx
  - **Prognosis:** Severe dz w/ constant numbness & atrophy is permanent; the sx from mod disease usually disappear, but the NCV/EMG don't return to nl
- **Patient information:** *AFP* 2011;83:965; *JAMA* 2011;306:2283

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:** Nonoperative mgmt insufficient; constant numbness, weakness, atrophy

FOOT & ANKLE DISORDERS

Evaluation (*BMJ* 2003;326:1)

- **History:** Inciting injuries, specific location of pain, functional impairment, chronicity of sx, exacerbating conditions; medical hx incl DM, arthropathies, vascular dz, neuropathy
- **Exam:** Assess gait, ability to toe rise; look at ankle alignment from behind; assess hindfoot alignment & arch (cavus vs. neutral vs. planus); assess for swelling & bruising; 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, incl tibialis anterior (ankle dorsiflexion), gastrocsoleus (plantarflexion), inversion w/ the foot plantar-flexed (posterior tibialis), eversion w/ the foot dorsiflexed (peroneals); check tenderness & passive ROM of tibiotalar (ankle) joint (dorsi & plantarflexion), subtalar joint (hindfoot inversion & eversion), 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 (Semmes–Weinstein 5.07 monofilament)
- **Imaging:** Radiograph of ankle should include AP, lateral, mortise; radiograph of feet should include AP, lateral, oblique; all x-rays should be wt-bearing unless assessing for fracture or pt unable to bear wt; 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 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, boot, NSAIDs, ice
- **Hallux rigidus:** OA of the 1st MTP joint; **Dx:** Sx include ↓ motion, crepitation, tenderness, ✓ radiographs; **Tx:** Orthotic w/ a Morton's extension to shield the 1st MTP joint, stiff sole or rocker sole shoe; 1st MTP injection, surgery
- **Morton (interdigital) neuroma:** Irritation of digital nerve usually in 3rd or 4th web space; burning pain in webspace ± numbness of involved 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, MTP synovitis; **Tx:** Metatarsal pad to shield forefoot; steroid injection or surgical excision 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: Middle-aged; ♀ gender, obesity, tight gastrocnemius

  Dx: Tenderness at plantar fascia origin from calcaneus; **DDx:** Tibial nerve compression aka tarsal tunnel syndrome (Tinel sign behind medial malleolus & plantar numbness), Baxter's neuropathy (pain more medial & less plantar), insertional Achilles tendinitis, calcaneal stress fracture (squeeze test), heel pad pain (pain more posteriorly at center of heel pad), posterior tibial tendinitis (palpate tendon behind medial malleolus), plantar fibromatosis

  Tx: NSAIDs, ice, dorsiflexion night splint, Achilles & plantar fascia stretches, silicone gel heel cups, PT; steroid injection usually avoided; wt loss; surgery in refractory cases
- **Cysts/ganglions:** Pain w/ wt bearing, friction; **Dx:** Clinical, transillumination, U/S, MRI; **Tx:** If painful – aspiration (~50% recurrence), surgical excision (~10% recurrence)

- **Bunions:** 1st MTP joint w/ medial prominence; pain onset gradual, progressive, ↑ w/ ROM, weight-bearing, shoe pressure; assoc w/ RA, female, ↑ age, FHx, shoewear w/ narrow toe box; **Tx:** APAP/NSAID's, shoewear modification (wide toe box), shoe stretching (ball & ring shoe stretcher), bunion brace, toe spacers, surgical correction only for refractory pain or deformity severe enough to prevent reasonable shoewear (i.e., not for cosmesis)
- **Pes planus (flat foot) Dx:** Clinical, plain films, hindfoot valgus & low arch, unable to single leg rise. Often have medial ankle pain →suspect adult-acquired flat foot 2/2 posterior tibialis pathology; **Tx:** Boot for acute PTT tendinitis then orthotic w/ medial arch support (off the shelf vs. custom), PT for PTT conditioning; surgical correction vs. fusions if assoc w/ arthritis
- **Pes cavus (high arch): Dx:** Clinical – high arch ± varus hindfoot, plain films; often assoc w/ neuromuscular disease (CMT); can lead to recurrent ankle sprains, peroneal tendon tears, 5th MT fx's; **Tx:** Lateral posting orthotics; surgery in refractory cases
- **Plantar fibromatosis:** Foot manifestation of Dupuytren disease; genetic (autosomal dominant; British Isles & Scandinavia); firm, palpable SC plantar nodules, continuous w/ plantar fascia; can be painful; most pts do not bring this problem to the attention of a doctor; **Tx:** Accommodative orthotics; surgery doesn't work well

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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 assoc 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 assoc 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;2016;93:183)

- **Achilles tendon rupture:** "Popping" & sudden onset of posterior ankle pain

  Dx: Ecchymosis & palpable deficit at Achilles tendon, Thompson test ⊕ (no plantarflexion of foot w/ calf squeeze – compare to

other side), check resting dorsiflexion of both feet when prone w/ legs in the air; MRI or U/S rarely needed

Tx: Referral to ortho, in the interim splint in 20° of plantar flexion (not neutral): Non-op vs. surgery

- **Fractures:** High index of suspicion if pain onset acute, ↑ age, osteopenia, neuropathy, hx Fx, smoking, ± trauma; **Dx:** Tenderness, difficulty w/ weight-bearing, edema, ecchymosis, plain films (if ⊖, could still be stress Fx).

  Ankle fracture: Key is the stability of the ankle joint. If stable, can be managed nonoperatively w/ splint/boot, elevation, APAP; if joint unstable usually requires surgery; weight-bearing radiographs help determine joint stability

  Indications for orthopedic referral for metatarsal fractures: Open fractures, fracture + dislocation, multiple metatarsal fractures, 2nd–5th metatarsal fracture w/ ≥3 mm displacement, ≥10° angulation in dorsoplantar plane; first metatarsal fracture w/ any displacement or angulation

  5th Metatarsal: Often reported as an ankle sprain because it occurs w/ ankle inversion; 3 zones of proximal 5th MT fx's: Zone 1 – tuberosity avulsion Fx from peroneus brevis; Tx: WBAT in boot; Zone 2 aka "Jones Fx" involves the articulation at the base of the 4th & 5th MT's; notoriously slow to heal; Tx: NWB in boot or cast; Zone 3 – Often proximal shaft stress fractures; Tx: NWB in boot; distal 5th MT fx aka "Dancer's Fx," acute Tx: WBAT in boot; check all patients for Vit D deficiency; check radiograph to document healing

  Metatarsals other than 5th: If acute injury, suspect a Lisfranc fracture/dislocation injury (see below); o/w often stress fractures; Tx: WBAT in boot; check for Vit D deficiency; healing time 4–6 wks; check radiograph to document healing

  Sesamoid: Pain under 1st MTP joint; Tx: WBAT in boot then orthotic w/ 1st metatarsal head recession

  Calcaneus: Heel pain ± deformity s/p fall/jump; pain w/ lateral squeeze, Mondor sign (ecchymosis extending to sole); assoc w/ lumbar spine fx's; Tx: bulky jones splint & ortho referral for possible surgery; stress Fx may present like plantar fasciitis, however unlike plantar fasciitis, tenderness on sides of

calcaneus present (+ squeeze test)

Toes: Toe alignment & joint involvement are key

Tx: Boot or post-op shoe; buddy toe taping × 4–6 wks for lesser toe fractures; if big toe, intra-articular or toe malaligned then Podiatry/Ortho eval

- **Lisfranc fracture/dislocation:** Often high energy injury → damage to Lisfranc ligament (between medial cuneiform & base of 2nd MT) → midfoot pain/swelling, plantar ecchymoses; 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 1–2 wks when pt able to wt bear; if missed can lead to midfoot collapse & arthritis; **Dx:** Widening of space between medial cuneiform & base of 2nd MT (compare to other side), 2nd metatarsal step off, fleck sign (bony fragment at base of 2nd metatarsal), ± metatarsal fracture on plain films, CT, MRI; **Tx:** NWB, splint, 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, 1st MTP arthritis; **Dx:** Clinical, MRI; **Tx:** Cast or boot, Podiatry/Orthopedic referral (*Am J Sports Med* 2011;29:1)

Ankle Pain (*AFP* 2009;80:1107; 2012;85:1170)

- **Achilles tendinitis:** Can be insertional or noninsertional, assoc w/ fluoroquinolone use, may have a bump on Achilles tendon; pain w/ exercise, relieved by rest, radiograph may show insertional calcification (spur); **Tx:** Rest, ice, APAP/NSAID's, dorsiflexion night splint, heel lift, Achilles stretching, PT for eccentric stretching protocol; surgery for refractory cases
- **Ankle sprain:** Low ankle sprain—inversion injury; high ankle sprain – eversion injury; limited wt bearing, swelling, ecchymoses; Tx: Rest, Ice, Compression, Elevation; NSAID's; period of rest & immobilization in boot or brace (1–2 wks) then start PT for peroneal strengthening & proprioception. If no improvement after PT consider MRI

- **Patient information:** *AFP* 2011;84:686; *JAMA* 2003;290:1542 (plantar fasciitis); *JAMA* 2010;303:188 (Achilles tendinopathy); www.AOFAS.org/footcareMD

FIBROMYALGIA

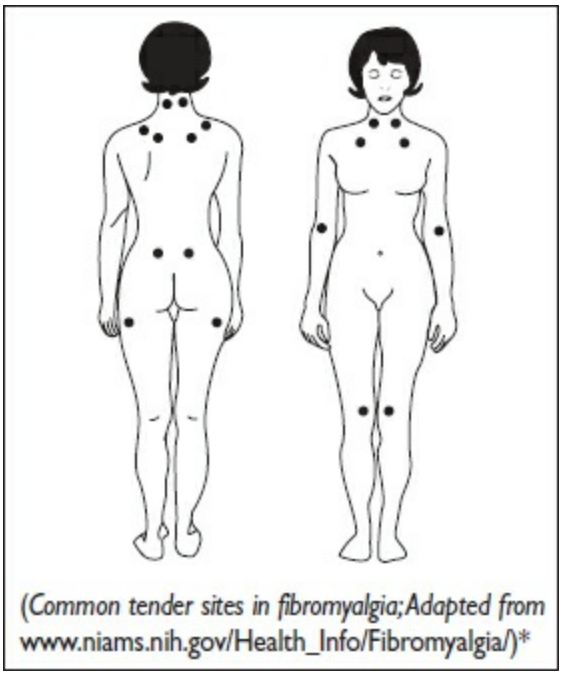
Background (*Arthritis Care Res* 2010;62:600; *JAMA* 2014;311:1547; *J Rheumatol* 2007;34:1415)

- **Definition:** Generalized pain amplification w/ widespread musculoskeletal pain & fatigue, thought due in part to aberrant central pain processing; sleep disturbance, anxiety, & depression contribute/exacerbate sx
- **Epidemiology:** Affects 2–5% US adults, ♂:♀, 7:1; common comorbidity of rheumatic dz (e.g., RA, SLE)
- **Differential diagnosis:** Rheum dz (SLE, RA, Sjögren, spondyloarthritis, PMR), malignancy, drug toxicity (i.e., statins), OSA, hypothyroidism, small fiber neuropathy

Evaluation (*Arthritis Rheum* 2010;62:3101; *Mayo Clin Proc* 2011;86:457)

- **History:** Diffuse (bilateral, upper/lower body) migratory pain, often affecting joints & soft tissue between joints that may be worsened w/ touch/tight clothes; fatigue, sleep disturbance, anxiety, depression, cognitive difficulties, stiffness, HA, pelvic, abdominal wall & chest wall pain; sx of neuropathy; hyperresponsiveness to light, odor, noise; screen for depression, anxiety, sleep apnea, other sleep disturbance
- **Exam:** Often w/ diffuse tenderness, especially in certain trigger points
- **Findings *inconsistent* w/ fibromyalgia:** Synovitis, rash, abnl labs (e.g.,↑ESR/CRP), focal neuro findings (numbness, weakness)
- **Workup:** Labs not necessary to confirm dx, but useful to r/o other dz; consider ESR, CRP, Chem-12, TFTs, CBC, vit D; consider iron studies, B_{12} (based on hx & PE)
- **Not recommended:** ANA, RF, CCP unless H&P suggestive or if ↑ ESR/CRP
- **Prognosis:** Important to acknowledge the pain may not completely

resolve



(Common tender sites in fibromyalgia; Adapted from www.niams.nih.gov/Health_Info/Fibromyalgia/)*

Treatment (*AFP* 2015;91:472; *Ann Rheum Dis* 2017;76:318)

- **First Line:**
  1. **Education:** About dx, tx, prognosis, reassure about benign nature, validate pain/sx; education may need to occur over several visits
  2. **Address comorbidities:** Sleep disturbance/insomnia (see *"Insomnia"*), anxiety (see *"Anxiety"*), depression (see *"Depression"*); consider cognitive behavioral therapy for comorbidities
  3. **Physical activity:** Tai Chi more effective than wellness education + stretching (*NEJM* 2010;363:743); consider acupuncture, massage, yoga; cognitive behavioral therapy
  - **When to refer to rheumatology:** Uncertain dx, unusual sx, abnl labs
- **Pharmacologic:** If persistent/sev sx despite first-line tx; no clear guidance for one agent over another; *Fibromyalgia should never be treated w/ opioids*, which can amplify pain; consider starting w/

amitriptyline or cyclobenzaprine; consider combination therapy; among antiepileptics, only pregabalin assoc w/ meaningful reduction in pain (*JAMA* 2014;312:182)

Prominent fatigue: Consider duloxetine or milnacipran in AM
Sleep disturbance: TCA or pregabalin at night helpful

- **Patient information:** cfidsselfhelp.org; treatcfsfm.org, *JAMA* 2014;311:1577

Fibromyalgia Treatments

Drug	Dosing	Particular Benefit	Adverse Reactions
Amitriptyline (TCA)	Start 5–10 mg QHS, ↑ to 25–50 mg QHS	Sleep disturbance	Constipation, dry mouth, ↑ wt ↓ concentration. QHS dosing may improve tolerability
Cyclobenzaprine	Start 10 mg QHS, ↑ to 10 mg QAM & 20–30 mg QHS	Sleep disturbance, myalgia	
Pregabalin	Start 75 mg BID, ↑ to 150–225 mg BID	↓ Pain 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	May be easier to get coverage for than pregabalin	Sedation, dizziness, lightheadedness, ↑ wt

GOUT AND PSEUDOGOUT

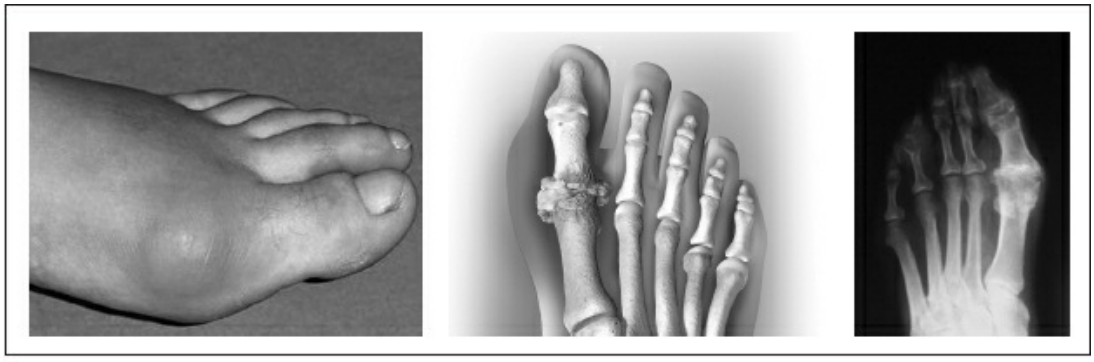
Gout

Background (*AFP* 2007;76:801; *Arthritis Care Res* 2012;64:1431; *Lancet* 2016;22:2039)

- **Pathophysiology:** Acute gout attacks are due to deposition of monosodium urate (MSU) crystals in joints, bones, & soft tissue which can precipitate intermittent inflammation. Asx hyperuricemia → Acute intermittent gout → Increased frequency of attacks → Chronic tophaceous gout; tophi (collections of MSU deposits) are a pathognomonic feature of gout; common areas include the pinna, olecranon bursa, Achilles, & joints
- **Anatomy:** Typical joints include 1st MTP ("podagra"), other MTP joints, ankles, knees, & sometimes fingers, but may be anywhere
- **DDx** includes septic arthritis, OA, RA, cellulitis, psoriatic arthritis, sarcoidosis; low threshold to aspirate (see *"Joint Pain"*)
- **Risk factors:**↑ age, M > F (7–9:1); consumption of red meat, shellfish, EtOH; meds (ASA, thiazide & loop diuretics), trauma/surgery, hospitalization
- **Asymptomatic hyperuricemia:** Pts should be assessed for gouty arthritis, urolithiasis (see *"Kidney Stones"*), & kidney damage (see *"Chronic Kidney Disease"*); pts w/ asx hyperuricemia do not require tx

Evaluation (*AFP* 2014;90:831; *JAMA* 2003;289:2857; 2012;308:2133; *NEJM* 2003;349:1647)

- **History:** Intermittent, acute onset of painful, erythematous, warm, swollen joint; w/ time, episodes often evolve from monoarticular → polyarticular flares; w/o active Rx, almost always resolves in days to weeks
- **Exam:** Synovitis (erythema, swelling, tende, reduced ROM), inspect for tophi (*NEJM* 2012;366:e6)



From left to right: Acute podagra; MSU deposition at 1st MTP; XR of chronic tophaceous gout

- **Workup:** Joint fluid w/ *3 C's: C*ell count (WBCs often 2K–60K/μL, but can be >100K), *Cx* (⊖), & crystal analysis w/ strongly *negatively* birefringent needle-shaped crystals (monosodium urate crystals, see below); ideally, Dx will be made based on joint aspirate, however clinical criteria exist (*Ann Int Med* 2017;166:52; *JAMA* 2012;308:2133)
  - **Imaging:** Radiographs to evaluate for erosions; *Ultrasound* findings (e.g., double-contour sign) may be observed by skilled ultrasonographer & can assist w/ dx; *Dual-Energy CT (DECT)* reveals MSU crystal deposition (*Ann Rheum Dis* 2015;74:1868)
  - **Serum uric acid:**↑ UA is supportive but not diagnostic; during acute flares, UA can be falsely low; 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* 2016;165:ITC-1*;* 2017;166:37; 58; *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; no tx is clearly superior, consider comorbidities when choosing tx
  - **Colchicine:** 1.2 mg at onset, → 0.6 mg an h later → 0.6 mg BID (various regimens exist); continue for 2–3 d after attack ends
  - **Prednisone:** Consider if multiple joints involved; many options for dosing, but often treat for total 1–2 wks, tapering quickly; pts can re-flare if prednisone tapered too quickly
  - **Steroid injection (if monoarticular):** Aspirate to verify crystals & r/o infection
  - **NSAIDS:** Naproxen, indomethacin (*JAMA* 2015;313:2276); continue 1–2 d after attack; use cautiously in pts w/ CKD, hx GIB, CVD, CHF, anticoagulant Rx
  - **IL-1 Inhibition (e.g., Anakinra):** Not FDA-approved; may be useful in the setting of contraindications to other options (*Curr Rheumatol Rep* 2014;16:398)
- **Uric acid lowering therapy (Long-term therapy):** May begin during or after acute flare; **Indications:** ≥2 attacks/y, erosive dz on radiograph, nephrolithiasis, gout & CKD ≥ stage 2, tophi, or urinary

UA >1.1 g/d

Goals: Serum UA <6; <5 mg/dL if tophaceous dz; no recurrent flares (though may occur while uric acid is being lowered by uric acid-lowering therapy)

Diet/Lifestyle:↓ meat, seafood, high-purine vegetables, **EtOH**, high-fructose corn syrup; avoid HCTZ & loop diuretics; cherry juice may prevent or ↓ attacks

Allopurinol: 1st-line agent; xanthine oxidase inhibitor; start 100 mg QD (50 mg/d in CKD stage IV or higher) × 2 wks, then ↑ by 100 mg QD q 2–4 wks; titrate to UA goal every 2–4 weeks (monitor UA, CBC, creatinine q 2–4 wks); typical dose 300–800 mg/d; monitor for toxicities (i.e., acute gouty attack, rash, diarrhea, cytopenia, fever); *avoid discontinuation during acute hospitalizations (↑ risk of gout flare)*

Risk of Allopurinol Hypersensitivity Syndrome: Life-threatening drug reaction similar to DRESS; pts of Han Chinese, Thai, & Korean pts w/ stage 3 CKD ancestry are at ↑↑↑ risk (screen for HLA-B*5801 & avoid if +) (*Pharmacogenomics* 2011;12:1741)

Febuxostat: Xanthine oxidase inhibitor; 40 mg/d starting dose, up to 80 mg/d after 2 wks if UA not at goal; s/e include abnl LFTs, nausea, rash, arthralgias

Probenecid: Promotes UA secretion (uricosuric); appropriate for pts w/ ↓ renal UA secretion (verified by 24 h urine UA); contraindications include CKD, nephrolithiasis, tophi; 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; should be used w/ advice from rheumatologist, high risk of infusion reaction/neutralizing Ab

- **Prophylactic medications:** Administer during initiation of urate-lowering Rx to ↓ risk of triggering a flare as uric acid is lowered; **Options:** Colchicine (0.6 mg QD-BID, ↓ frequency in CKD); low-dose NSAIDs or prednisone (≤7.5 mg/d);

Duration: Continue for at least 6 mos **or** 3 mos after achieving target serum UA (no tophi) **or** 6 mos after achieving target

serum UA & tophi resolution (tophi present)

- **Patient information:** *AFP* 2007;76:811; *JAMA* 2012;308:2161

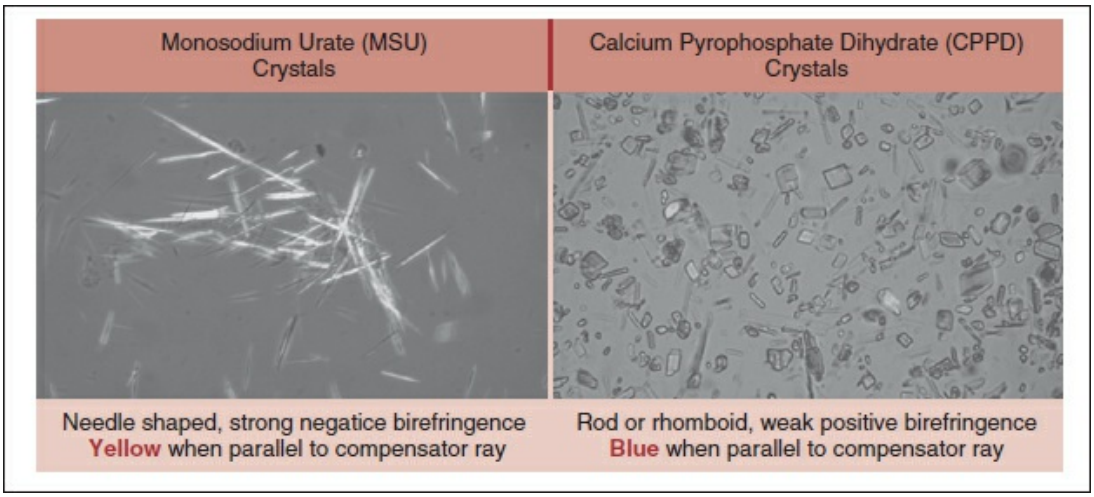
Pseudogout (Calcium Pyrophosphate Deposition Disease)

Background (*NEJM* 2016;374:2575)

- **Pathophysiology:** Mono- or oligoarthritis typically of knee (>50%), wrist, ankle but can occur nearly anywhere; compared to gout, less predilection for 1st MTP
- **Risk factors:** ↑ age, hemochromatosis (see *"Hemochromatosis"*), hyperparathyroidism, hypo-Mg, hypophosphatasia (congenital syndrome)

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:** Arthrocentesis to r/o gout, infection, other inflammatory arthritis; fluid shows crystals are rectangular/rod/rhomboid shaped w/ **weak, ⊕ birefringence**
  - **Imaging:** Radiograph can show chondrocalcinosis (calcifications within the joint space/cartilage) though this is not specific to pseudogout; U/S may show characteristic changes in tendons/joints
  - **Metabolic Disease Workup:** Recommended in those <60 y; iron studies, PTH, Mg, Phos



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:** Low-dose colchicine (0.6 mg PO BID-QOD), NSAID, or MTX
- **Patient information:** mayoclinic.com/health/pseudogout/DS00717; arthritis.org

MYALGIAS

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* or muscle ache/pain is nonspecific & may be a feature of many conditions; *myositis* refers to inflamed/damaged muscle (see "*Myositis*") in which *pain is not typically a prominent feature (as opposed to weakness) when due to immune-mediated causes* (e.g., dermatomyositis, polymyositis); *polymyalgia rheumatica* (see "*PMR*") is assoc w/ aches in the muscle & soft tissue around the shoulders, hips, & neck, often assoc w/ prominent stiffness & ↓ ROM

Differential Diagnosis of Generalized Myalgias

Category	Examples
Infectious	Viral (enterovirus, hepatitis B/C, influenza, dengue, HIV), spirochetal (see *"Tick-Borne Illness"*)
Pain syndromes	Fibromyalgia (see *"Fibromyalgia"*)
Rheumatologic	PMR, polymyositis/dermatomyositis, RA, SLE, spondyloarthropathy, vasculitis
Metabolic	Scurvy, metabolic myopathy, vit D deficiency
Endocrine	Adrenal insufficiency, hypothyroidism
Medications	Statins, antipsychotics, fibrates, colchicine, AZT, bisphosphonates, aromatase inhibitors, withdrawal from antidepressants
Leg cramps (*AFP* 2012;86:350)	Flat feet, dialysis, pregnancy, spinal stenosis, radiculopathy, claudication, ↓ Mg, ↓ Ca, neuropathy
Differential of localized myalgia: Exercise/overuse (strain/sprain), pyomyositis, infarction (e.g., diabetic muscle infarction), compartment syndrome, bursitis	

Distinguishing Features of Myalgias (*AFP* 2002;65:907; *NEJM* 2010;363:e17)

Presenting Features	Potential Diagnosis
Pain out of proportion to exam	Necrotizing fasciitis/cellulitis/myositis, compartment synd
Sudden onset ± fever	Acute bacterial (systemic or focal) or viral
Gradual onset	Med, chronic infx, endocrinopathy, fibromyalgia, PM/DM
Shoulder/hip girdle	PMR, RA
Weakness (see *"Weakness"*)	PM/DM, hypothyroidism, statin-induced
Dysphagia, dyspnea	PM/DM
Red/brown urine + weakness	Rhabdomyolysis
Redness, swelling, asymmetry	Pyomyositis, compartment syndrome
Delayed reflexes	Hypothyroidism
Statin exposure	May cause myalgia or inflammatory myositis
Hyperpigmentation	Adrenal insuff
Malar rash	SLE
Erythema migrans	Lyme dz

Gottron papules (occur on dorsal MCP & IP joints), heliotrope eruption on upper eyelids, shawl or V-sign→ Dermatomyositis

- **General myalgia workup:** CBC, U/A, CMP (±Mg, Phos), TSH, Vit D, HIV, HBV, HCV; consider CK, aldolase, LDH if weak; depending on level of suspicion for certain explanations, consider add'l testing (e.g., ESR/CRP, auto-antibodytesing, imaging)
  - **Myopathy:** EMG/NCS, bx, neuro c/s
  - **Dermatomyositis/polymyositis:** ↑CK, aldolase, LDH; ⊕ ANA, ⊕ anti-Jo-1, or other myositis Ab (see "*Myositis*"); EMG &/or MRI; muscle or skin biopsy
  - **Pyomyositis:** CT or MRI, BCx, biopsy/fluid aspiration

Management

- **Medication-induced:** D/c medication, may take wks to mos for sx to resolve
- See specific sections "*Fibromyalgia*," "*Myositis*," "*PMR*," "*Thyroid Disease*"
- **Chronic fatigue syndrome:** Cognitive behavioral therapy & graded exercise therapy (no evidence for medications or dietary changes)
- **Dermatomyositis/polymyositis:** See below
- **Pyomyositis:** Abx &/or drainage, ID c/s

MYOSITIS

Background (*JAMA* 2011;305:183; *Lancet* 2003;362:971; *NEJM* 2015;372:1734)

- **Four primary immune-mediated myositis syndromes:** Dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), necrotizing autoimmune myositis (NAM, often assoc w/ statin exposure); may be feature of another systemic connective tissue dz (overlap)
- **Epidemiology:** Incidence 1.2–19/1,000,000/y; peaks in presentation during childhood (DM) & adulthood (DM & PM); IBM generally consider a dz of older men
- **Differential Diagnosis:** See "*Muscle Pain*"

Disease Specific Features of Myositis
Dermatomyositis & polymyositis: Insidious onset of symmetric proximal weakness ± dysphagia; extramuscular manifestations such as ILD, polyarthritis; skin changes seen in DM but not PM; DM maybe amyopathic; DM ↑ risk of cancer 3–5 years after onset (ovarian, breast, colon, melanoma, NHL, nasopharyngeal [Asian patients]); *overlap*: DM/PM features above + features of a connective tissue dz (systemic sclerosis, SLE, MCTD)
Inclusion body myositis: Most common myopathy after age 50; slow-onset of distal & proximal weakness (maybe asymmetric); mild facial muscle weakness; 50% dysphagia, autophagic vacuoles on bx; poor response to steroids & other immunosuppression
Necrotizing autoimmune myositis: Acute or subacute proximal weakness w/ very high CK, ++ dysphagia; *necrosis* on bx (*Curr Rheumatol Rep* 2015;17:72). Associations: Postviral infection, CTD, cancer, statins; *most will have anti-HMG-CoA* Ab (in statin exposure) or anti-SRP Ab

Evaluation

- **History:** Painless, symmetric proximal weakness (DM/PM); ⊕ rash (DM); asymmetric, proximal & distal (IBM); symmetric proximal weakness ± pain (NAM); all w/ ↑ muscle enzymes (e.g., CPK); syndromes often assoc w/ other organ involvement (e.g., anti-synthetase syndrome)
- **Laboratory:** CBC, Cr, LFTs, TSH, ANA. *Muscle enzymes*: CPK, aldolase, LDH; ESR & CRP (may be normal despite intense inflammatory myositis)
  - **Auto-antibody testing:** Myositis specific & associated antibody testing may support dx, suggest etiology (e.g., statin, malignancy), & prognosticate (other organ involvement, outcomes); consult w/ local neurologist/rheumatologist/lab regarding advanced myositis antibody testing availability
- **Imaging and neuro testing:** MRI shows *muscle edema*, vs. atrophy, fibrosis; helpful for dz activity, localizing muscle bx; EMG demonstrates *myopathic potentials*; useful for active vs. chronic & r/o neurogenic cause
- **Biopsy:** Dx can be made w/o bx; if necessary, consider EMG or MRI to increase yield of bx; findings not always specific; NAM typically w/o 1° inflammation (>>>necrosis)
- **Malignancy evaluation:** In DM & NAM; age-appropriate cancer screen + CT C/A/P + mammogram/TVUS (↑ incidence of ovarian Ca); or PET-CT; consider cancer-specific biomarker screening;

repeat screening for >2 years since may present after diagnosis

- **Swallow evaluation:** If sx of dysphagia are present
- **Respiratory Involvement:** PFTs (lung volumes, DLCO, 6 minute walk test), high-resolution chest CT

Management

- **DM/PM/NAM:** Steroids (e.g., prednisone 1 mg/kg [max dose = 100 mg/QD] → taper after 4–6 wks; ±DMARD [MTX, AZA, MMF, RTX]); NAM often requires *aggressive* therapy; co-management w/ rheum &/or neuro ± derm if DM
- **Cutaneous manifestations of DM:** Consider topical therapy
- **IBM:** Resistant to immunosuppressive therapies
- **Intravenous immunoglobulin (IVIG):** May be helpful if oropharyngeal involvement
- **Physical therapy/occupational therapy:** Once inflammation somewhat controlled

POLYMYALGIA RHEUMATICA

Background (*AFP* 2013;88:676; *Lancet* 2013;381:63; *NEJM* 2014;371:50)

- **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 &/or pelvic girdle), rapid response to mod dose (~20 mg/d) 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
  - **Muscle weakness:** Not characteristic of the dz (exam may be limited by pain)
- **Epidemiology:** 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, inflammatory myositis, infection (e.g., viral syndrome, SBE), endocrinopathy (e.g., hypo- or hyperthyroidism), OA, rotator cuff d/o,

fibromyalgia, malignancy (MM)

- **Association w/ giant cell arteritis (GCA):**Large- to medium-sized arteritis (e.g., branches of the aorta). *Key Features*: New or different headache, jaw claudication, scalp tenderness, blurred vision; PMR & GCA hypothesized to be different manifestations of one dz process; 16–30% of pts w/ PMR have GCA; 40–60% of pts w/ GCA have PMR. *Diagnosis*: Temporal artery (TA) biopsy (may be false ⊖), consider bilateral; cross-sectional imaging suggestive of aortitis (large vessel vasculitis)

Evaluation (*JAMA* 2016;315:2442)

- **Exam:** ↓ active & passive ROM in shoulders, neck, &/or hips; ± swelling of hands/feet; nonerosive peripheral arthritis; assess tenderness in scalp & TA
- **Workup:** ✓ESR & CRP; ✓TFTs, Chem-12, CBC w/ diff; RF & anti-CCP typically ⊖; assoc w/ anemia of chronic dz; muscle enzymes (e.g., CK) should be nl; nl ESR does **not** exclude PMR (ESR <50 mm/h seen in 10%) (*BMJ* 2012;344:e1408)
  - **Radiographs:** Rarely helpful; may aid dx if nl ESR; MRI or U/S can demonstrate periarticular inflammation; joint erosions are not assoc w/ PMR
- **Giant cell arteritis:** Screen for in PMR pts; temporal artery bx if GCA sx present

Management (*Ann Int Med* 2017;166:ITC65; *JAMA* 2016;315:2442)

- **Steroids:** Mainstay of Rx w/ initial dose of 20 mg/d (maximum 30 mg/d) of prednisone or equivalent; anticipate initial improvement within 24–48h & continued improvement over subsequent wks; failure to respond to steroids should raise suspicion for alt dx
  - **Duration:** Steroid Rx often continues for ~12 mos w/ slow taper guided by sx and labs; 50% of pts relapse & require steroids; flares may be managed by raising steroids by 10–20% & retapering; pts should be evaluated for osteoporosis
- **Steroid-sparing agents:** Methotrexate (*Arthritis Rheum* 2007;56:2789) may be useful in pts who cannot take steroids; tocilizumab (IL-6 blockade) recently demonstrated effective (*NEJM* 2017;377:317)
- **Patient information:** *AFP* 2006;74:1557

SYSTEMIC LUPUS ERYTHEMATOSUS

Background (*AFP* 2016;94:284; *Ann Int Med* 2013;159:ITC4-1; *Arthritis Rheum* 2007;56:2092; *NEJM* 2011;365:2110)

- **Definition:** Chronic inflammatory dz 2/2 Ab formation & immune complex deposition, w/ notoriously varied presentation that can affect nearly every organ
- **Epidemiology:** 10–150/100,000; 8:1 ♀:♂ ratio; 65% of pts w/ onset 16–55 y
- **Pathophysiology:** Combination of genetic (complement deficiency), hormonal (estrogen), immunologic (autoantibodies), & environmental factors
- **Clinical course:** Variable; periods of acute flares, remission, & chronic; common manifestations affect skin/mucosa, joints, kidneys, pleura/pericardium, central nervous system, & blood elements; for cutaneous lupus, see *"Rheumatologic Skin Disease"*
  - **Precipitating factors:** *Sun exposure*, infections, stress, surgery, pregnancy

Clinical Manifestations (*Arthritis Rheum* 1982;25:1271; 2012;64:2677)

	1982 ACR Classification 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 (acute cutaneous lupus)** **2. Discoid rash** (chronic cutaneous lupus, erythematous plaques w/ keratosis & plugging) **3. Photosensitivity** **4. Oral/nasopharyngeal ulcers**	Raynaud's, alopecia Malar "butterfly" rash: facial erythema sparing nasolabial folds & exacerbated by UV light (photosensitivity) Many other types of rashes assoc w/ SLE (e.g., subacute cutaneous lupus) Ulcers usually painless & on hard palate
Msk > 90%	**5. Arthritis** (nonerosive, ≥2 peripheral joints)	Myalgias, arthritis (migratory & symmetric involving hands, typically nonerosive)

CV & Pulm	**6. Pleuritis** or **pericarditis**	Also myocarditis, 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) (**May be asx – need screening UA**)
Neuro 10–80%	**8. Seizures** *or* **psychosis**	Cognitive dysfunction, stroke, neuropathy, transverse myelitis, HA, delirium, depression, psychosis
Heme 36%	**9. Hemolytic anemia** (⊕ Coombs) *or* **leukopenia** *or* **lymphopenia** *or* ↓ **PLT**	Anemia of chronic dz; LAD; **Antiphospholipid syndrome (APLS):** Thrombocytopenia, venous & arterial thrombosis, recurrent miscarriages
Serologies	**10.** + **Anti-DNA** *or* + **Anti-Sm** *or* **antiphospholipid Ab** **11.** + **ANA**	
GI 25–40%		Dysphagia, abdominal pain, nausea, mesenteric vasculitis, pancreatitis, gastritis
Misc		Sicca (dry eyes or mouth) symptoms

*Updated criteria (SLICC, *Arthritis Rheum* 2012;64:2677) similar but we present original criteria given ease of presentation; ***Note that classification criteria are meant for clinical trial enrollment, not diagnosis***

Evaluation and Prognosis (*AFP* 2003;68:2179)

- **Diagnosis:** Based on sx, exam findings, & lab testing; ACR & SLICC criteria are useful but meant for use in clinical trials (some SLE patients will not meet criteria)
- **History:** Presence of sx described above; precipitating events for lupus flare
- **Exam:** Full exam, incl CV (pericardial rub, murmurs), **skin**, joints, liver/spleen, LN
- **Workup & monitoring disease activity:** CBC (cytopenias), Chem-12, ESR, CRP, UA (proteinuria, RBC); complement testing (C3, C4 frequently low in active dz); (see *"Rheumatologic tests"*); dsDNA (other ENA testing not typically repeated serially)

Autoantibody Testings in SLE (*Arthritis Rheum* 2002;47:546; 2004;51:1030)	

Test	Notes
ANA	*1st-line test;* ⊕ at high titer (1:160 or higher) in virtually all pts w/ active SLE; if ⊕, proceed w/ additional autoantibody testing
Anti-dsDNA	Especially correlated with renal activity in some pts; Se 57%, Sp 97.4% for SLE
Anti-Smith (Sm)	Low Se (24%) but high Sp (98%) for SLE
Antiphospholipid	Includes lupus anticoagulant, anti-cardiolipin, & anti-b2-glycoprotein (not b2 microglobulin)

- **Imaging:** Not required, but may confirm clinical sx & guided by sx/signs
- **Other:** Bx may be warranted for confirmation of specific organ involvement (i.e., skin, kidney); crucial to review meds for drug-induced lupus (see below)
- **Prognosis:** Course varies btw pts, ranging from relatively quiescent dz to rapidly progressive organ damage; 5 y survival >90%; active dz the most common cause of death, along w/ **premature CVD** & immunosuppression complications (infection)
  - **Poor prognostic factors:** Renal dz, HTN, ♂, extremes of age at presentation, African ancestry, APLS, ↓ socioeconomic status

Treatment (*Arthritis Rheum* 1999;42:1785)

- **General approach:** Avoid sun, smoking, & estrogen (OCPs, caution with pregnancy during active dz); Rheum referral if dz suspected & for continuing co-mgmt; **hydroxychloroquine for most pts** & immunosuppressive Rx based on organ involvement; med tx requires 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 dz; requires optho monitoring for eye toxicity (baseline & q5 years).
  - **Glucocorticoids:** Used for flares; low/mod dose for joints, serositis sx & high dose for nephritis, CNS sx; topical steroids for skin lesions (see *"Rheumatologic Skin Disease"*)
  - **Steroid-sparing agents:** Targeted for specific organ involvement;

MTX, azathioprine, mycophenolate (often used as remission induction & maintenance for lupus nephritis rather than CYC), & belimumab (esp cutaneous/MSK manifestations)

Cyclophosphamide (CYC) for sev (e.g., renal, neuro) sx (*NEJM* 2013;368:1528)

- **Monitoring:** Follow clinical manifestations; serologic studies useful in some pts (anti-dsDNA titers, C3, C4, ESR, CRP); periodic CBC, CMP, & UA for protein/blood
- **Patient information:** rheumatology.org; lupus.org

Drug-Induced Lupus

- **Background:** Mechanism unclear; related to drug-induced autoantibodies (particularly antihistone, & ANA, but *not* dsDNA except in anti-TNF mediated DLE); 1:1 ♂:♀ ratio
- **Associated medications:** Procainamide, hydralazine, minocycline, penicillamine, INH, anti-TNF drugs, IFN, methyldopa, chlorpromazine, diltiazem; others implicated: anticonvulsants, antimicrobials, & βB
- **History:** Fever, rash, myalgias, arthritis, serositis; many anti-TNF treated patients developed +dsDNA of no clinical significance
- **Treatment:** Withdrawal of offending medication; sx should resolve within several mos; symptomatic tx w/ NSAIDs & steroids may be considered

GLUCOCORTICOIDS AND DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Evaluation and Management (*NEJM* 2013;369:307; *Semin Neurol* 2014;34:467)

- **General principles:** With few exceptions (e.g., hydroxychloroquine), DMARDs are immunosuppressants that ↑ the risk of infection (*Curr Opin Rheumatol* 2014;26:404); screening, appropriate vaccination, and PPx mitigate these risks (*Rheum Dis Clin North Am* 2017;43:1)
- **Women of child-bearing age**: Discussion of potential

teratogenicity, contraception and pregnancy planning critical; consult rheumatologist, pharmacist; consider high-risk OB if pregnant; male fertility may be affected by certain agents (*Arthritis Care Res* 2015;67:313)

Pre-Treatment Infection Screening, Vaccination, & Prophylaxis
(*MMWR* 1993;42:RR-4)

Infection	Screening	Prevention/Treatment
Tuberculosis (TB)	PPD, T-Spot, or QuantiFERON Gold	If ⊕, delay DMARD initiation & evaluate latent vs. active TB
Hepatitis B (HBV)	HBV core Ab, HBV surface Ab, HBV surface Ag	If c/w prior exposure or active dz ✓ VL, c/s with ID/hepatology re tx or PPX; consider DMARD delay
Hepatitis C (HCV)	HCV Ab, ±HCV VL	
Varicella Zoster Virus (VZV)	VZV IgG and IgM	Do not administer live vaccine* while on biologic DMARD or prednisone ≥20 mg/d; delay treatment by 4 wks
Measles, Mumps, Rubella (MMR)	MMR IgG and IgM	
Influenza	Killed vaccines are safe to administer while on tx; efficacy may be reduced	
S. pneumonia		

Ab, antibody; Ag, antigen; VL, viral load; *If inadvertent vaccination with VZV, c/s with ID and consider empiric several week course of appropriate antiviral therapy

- **Glucocorticoid side-effects (GC):** GC are critical for swiftly controlling immune-mediated conditions, but goal is to minimize GC exposure by early introduction of DMARD (aka steroid-sparing agents) (*Curr Rheumatol Rep 2015;17:513*)
  - **Glucocorticoid-induced osteoporosis (GIOP):** Baseline DXA, consider bisphosphonate (esp if ≥3 mo of tx ≥7.5 mg/d prednisone equivalent), Calcium/Vitamin D
  - **PCP pneumonia:** Consider PPX for prolonged GC ≥ equivalent 20 mg/day of prednisone
  - **Endocrine:** Wt gain; DM (✓baseline A1c, consider insulin and/or dose Δ)
  - **Neuro-psych:** Sleep-wake cycle Δ; depression, psychosis, mania,

anxiety

Gastritis: Consider PPI for GI protection with ↑dose, h/o gastritis, prolonged tx

Adrenal insufficiency: May require *stress-dose steroids* for shock or perioperatively

Others: Ophthalmic (e.g., glaucoma, cataract), Derm (thin skin, bruising), Myopathy

- **Conventional DMARDs:** First-line treatment in RA, other types of inflammatory arthritis, and connective tissue dz (e.g., SLE)

Common Conventional DMARDs, Side Effects, Monitoring
(*Ann Rheum Dis* 2014;73:529)

DMARD	Unique Side Effects	Monitoring
Hydroxychloroquine (HCQ, PO)	GI upset, retinal toxicity, rarely myo- or neurotoxicity	Baseline eye exam (then q5 y)
Methotrexate (MTX, SC or PO)*	Fatigue, GI upset, oral ulcers, hair loss, ↑LFT, BM suppression	q1 mo CBC, creatinine, LFT until stable dose than q3 mo
Sulfasalazine (SSZ, PO)	GI upset, drug rash, sun Se	
Leflunomide (PO)**	Diarrhea, ↑ LFT, ↓wt	
Azathioprine (AZA, PO)	GI upset, BM suppress (esp if ↓TPMT activity), pancreatitis, ↑LFT	✓TPMT activity prior to tx; CBC, Cr, LFT q1m initially then q3 m
Mycophenolate mofetil (MMF, PO)	BM suppression, GI upset (often dose-limiting)	CBC, Cr, LFT q1 m initially then q3 mo
Cyclophosphamide (CYC, PO or IV)	BM suppression, permanent infertility, hemorrhagic cystitis (HC), malignancy	Depending on IV vs PO route, frequent CBC; monthly UA (HC), Cr, LFT; routine UA/cytology after tx to monitor for bladder cancer

*EtOH should be avoided while on MTX due to risk of hepatotoxicity

**hepato-enteric recirculation which may require special tx to completely remove from body in presence of toxicity or pregnancy

- **Biologic DMARDs:** Often used as the second-line tx in

inflammatory arthritis & other rheumatologic conditions; all are assoc w/ ↑ risk of infection though, risk may vary (*Lancet* 2015;386:258)

Common Biologic DMARDs (*Cochrane Database Syst Rev* 2011;2:CD008794)

Representative DMARD (Target)	Unique Side Effects	Monitoring
Adalimumab (TNF)	Rare neutropenia, infusion reaction (IV route), drug-induced lupus	Periodic CBC, LFT
Tocilizumab (IL-6)	Cytopenias, ↑ LFT, bowel perforation (avoid if h/o diverticulitis)	CBC, Creatinine, LFT q1 m initially then q3 m; lipid q6 m*
Anakinra (IL-1)	Injection-site reaction	Periodic CBC, LFT
Abatacept (CTLA-4)	IV may cause false ↑ glucose on test-strips day of tx	
Rituximab (CD20)	Infusion reaction, flu-like illness, hypo-IgG, late-onset neutropenia	CBC, IgG; may monitor peripheral blood CD20 levels to guide retreatment
Tofacitinib (JAK)**	Cytopenias, possible increased VZV infection	CBC, Creatinine, LFT q1 m initially then q3 m
Belimumab (BLyS)	Cytopenias, infusion reaction	Periodic CBC, LFT
Other agents: Secukinumab (IL-17), Ustekinumab (IL-12/23), Apremilast (PDE4)		

*Lipid change on IL-6 blockade of unclear significance

**PO (all others IV or SQ); biologics should not be combined with one another, in general

- **Perioperative DMARDs:** Continuing tx ↑ risk of infection; holding or discontinuing tx ↑ risk of flare pre-/post-op which can also require GC therapy (*Arthritis Rheum* 2008;59:762)
- **Methotrexate and other conventional DMARDs:** Generally considered safe to continue through the perioperative period (esp arthroplasty) though evidence is controversial (*Seminars Arthritis Rheum* 2015;44:627)
- **Hydroxychloroquine:** Safe to continue through the perioperative period (does not increase the risk of infection)
- **Biologics:** Hold perioperatively, often 1.5 × half-life; most evidence based on TNF-inhibitors; review risks/benefits with patient and

providers

- **Patient Resources:** www.rheumatology.org; www.arthritis.org

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 mo; ♀ > ♂ 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 headache:* Syndromes not due to another cause: E.g., tension, migraine, cluster; *Secondary headache*: Syndromes due to systemic illness or structural neuro abnormalities; primary HA syndromes often chronic conditions, established in early adulthood; new HA "pattern" should raise suspicion for secondary cause

Evaluation

- **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, frequency
  - *Location:* Unilateral (if so, always on same side?), retro-orbital
  - *Triggers/alleviating factors:* Trauma, position change (worse w/ supine → suggestive of ↑ 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 & frequency of use (med overuse HA), 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 for CT & further evaluation

Indications for Imaging
• New HA in pt age >50, or new persistent daily HA
• Unexplained change in HA character/freq
• New cluster-type HA/TAC (*Arch Neurol* 2007;64:25)
• HA awakening pt from sleep
• HA ↑ w/ Valsalva or exertion
• Trigeminal neuralgia w/ CNV deficit or b/l neuralgia (*Neurology* 2008;71:1183)
• Atypical/new migraine aura (other than visual)
• New HA assoc w/ vomiting
• Abnormal neuro exam unexplained by known dx

(*BMJ* 2010;341:c4113; *JAMA* 2006;296:1274; AAN US Headache Consortium 2000 guidelines, aan.com)

- **Red flags: (any of these should prompt ED referral)** *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)

Chronic Headache Management

- **Headache diary:** To identify triggers, pattern, freq, assoc sx, & response to tx; sample at americanheadachesociety.org
- **Medication:** PRN abortive med for all pts, **initiate ppx** if >1 debilitating HA/mo
- **Counseling:** Avoid triggers when possible, caution: re: use of abortive tx >2–3×/wk, may → 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 headache foundation at

www.headaches.org, under “My Headache”

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 age 30–39 y; vast majority (>90%) have onset prior to age 40; ⊕ FHx present in 80% of pts; HAs often interfere w/ work & QoL; most pts have 1–4 migraines/mo

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* (pain w/nonpainful stimulus, e.g., brushing hair, wearing a hat)
- **Chronic migraine:** Migraine present for ≥15 d/mo
- **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; progestin-only OCPs ok*
- **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 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; sole 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
- **Triptans:** 5-HT 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 min
  - *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	1st-line for mild–mod HA, OTC	PUD, AKI, ↑ risk of med overuse HA
ASA/APAP/Caffeine	1st-line for mild–mod HA, OTC	*ASA*: bleeding, *APAP*: hepatotoxicity; *All*: ↑ risk of overuse HA
Compazine	Antiemetic properties	Antidopaminergic (i.e., restlessness, akathisia, dystonia), ↑ QTc
Metoclopramide	Antiemetic properties	Antidopaminergic (see above)
Magnesium	Adjunct for photophobia	Diarrhea

- Opioids not recommended; ↑ risk of rebound & misuse potential; (*Headache* 2012;S1:3)

Prevention

- **Indications:** Should be considered for pts w/ >1–2 episodes/wk or when less frequent but prolonged or debilitating; consider other potential indications for individual ppx agents
- **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: (1) **acupuncture** for ↓ frequency, # days & intensity of migraine w/o aura (*JAMA Intern Med* 2017;177:508); (2) magnesium citrate for ↓ severity & frequency of migraine (600 mg/d; s/e GI upset, diarrhea; *Pain Physician* 2016;19:E97), (3) Coenzyme Q10 for ↓ migraine frequency (100 mg TID; no s/e); (4) Riboflavin (400 mg/d for >3 mo; no s/e); Butterbur may ↓

migraine but not recommended 2/2 concerns for hepatotoxicity; Feverfew 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;30:804)

Migraine: Preventive Medications		
Medication	**Additional 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, ↑ NH_3, 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)

Tension Headaches

- **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:** The most prevalent headache disorder; may be seen in migraine pts
- **History:** Onset typically over hours, *does not require change in daily activity*
- **Triggers:** Sleep deprivation, dehydration, hunger; assoc w/ myofascial sensitivity of head
- **Counseling:** Identify stressors, comorbid contributors (e.g.,

depression)

- **Abortive treatment:** See table: NSAIDs, APAP, ASA, analgesics (but risk of med overuse HA); tx cervicalgia if present
- **Ppx treatment:** See table: TCAs (nortriptyline), biofeedback (*Continuum* 2012;18:823); some data for trigger point injections w/ lidocaine in ↓ HA frequency and thus analgesic use (*J Headache Pain* 2013;14:44); no support for Botulinum toxin (*JAMA* 2012;307:1736)

Medication Overuse (Rebound) Headaches

- **Definition:** Subtype of secondary headaches in pts w/ a primary headache syndrome
- **Triggers:** Use of ergots, opiates, triptans, or combined analgesics >10 days/month or plain analgesics >15 days/month
- **History:** HA worse after starting meds & improves after cessation of meds
- **Treatment:** Multiple approaches: 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)

Other Headache Syndromes

- **Trigeminal autonomic cephalgias (TAC)** (*Continuum* 2012;18:883; *JNNP* 2002;72:ii19): Characterized by autonomic sx (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 min–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 mo; *Tx:* Indomethacin
  - **Paroxysmal hemicrania:** ♀>♂, 2–45 min attacks; *Tx:*

Indomethacin

Short-lasting unilateral neuralgiform headache with conjunctival injection & tearing (SUNCT): Incidence ♂>♀, prevalence ↑ >50 y; *Definition:* Stabbing orbital pain, 15 s–5 min, may occur many times/d, often ⊕ by cutaneous stimulation; *Tx:* Few proven tx; 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 frequency/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 "*Polymyalgia Rheumatica*")

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), vascular causes (stroke, aneurysm/AVM, venous sinus thrombosis), posttrauma (concussion, ICH), meningeal irritation (meningitis, SAH), posterior reversible encephalopathy syndrome (PRES), TMJ syndrome, glaucoma

DIPLOPIA

Background (*Emerg Med Clin North Am* 1997;15:649; *Continuum* 2014;20:942)

- **Definition:** "double vision"; the duplicated visual image of a single object (noncongruence of the 2 images may be horizontal, vertical, diagonal, or torsional)
- **Binocular diplopia** (resolves if 1 eye closed): most common; due to

misalignment of the visual axes, most likely due to cranial nerve pathology

- **Monocular diplopia** (persists if 1 eye closed) can be thought of as a form of "blurred vision"—due to intraocular cause (macular edema, corneal or lens pathology), or central cause (CNS visual pathways)
- **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), neuromuscular junction disorder (myasthenia gravis); can also be due to pathology of the extraocular muscles themselves (trauma, orbital mass, muscular atrophy); 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 (below)

Key Historical Features to Localize 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 toward *affected* side)
Sx worse w/ near focus (e.g., reading)	CNIII
Sx worse w/ distant focus	CNVI
Sx worse at end of day	Myasthenia gravis
HA, N/V, weakness, numbness, dyscoordination	Intracranial pathology

Pain with eye movement	Myopathy

- **Exam:** Full eye & CN exam: Assess for proptosis (Graves disease), ptosis (CNIII, Horner's syndrome), lid lag (hyperthyroidism); fundoscopic exam for papilledema, pupil asymmetries (dilated pupil w/ compressive CNIII lesion; spared/normal pupil w/ ischemic CN III lesion) & response to light (see "*Vision Loss" & "Ophthalmic Evaluation"*)
- **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) (youtube.com/watch?v=yylA-dl49Lg)
  EOM testing: Track examiner's finger in an "H" shape; check for dysconjugate gaze (& note any worsening of diplopia) in each quadrant

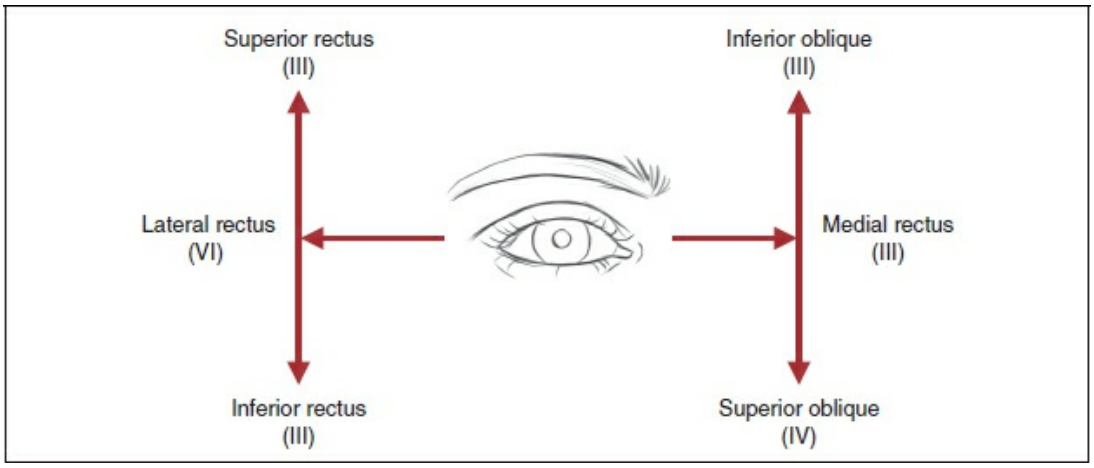


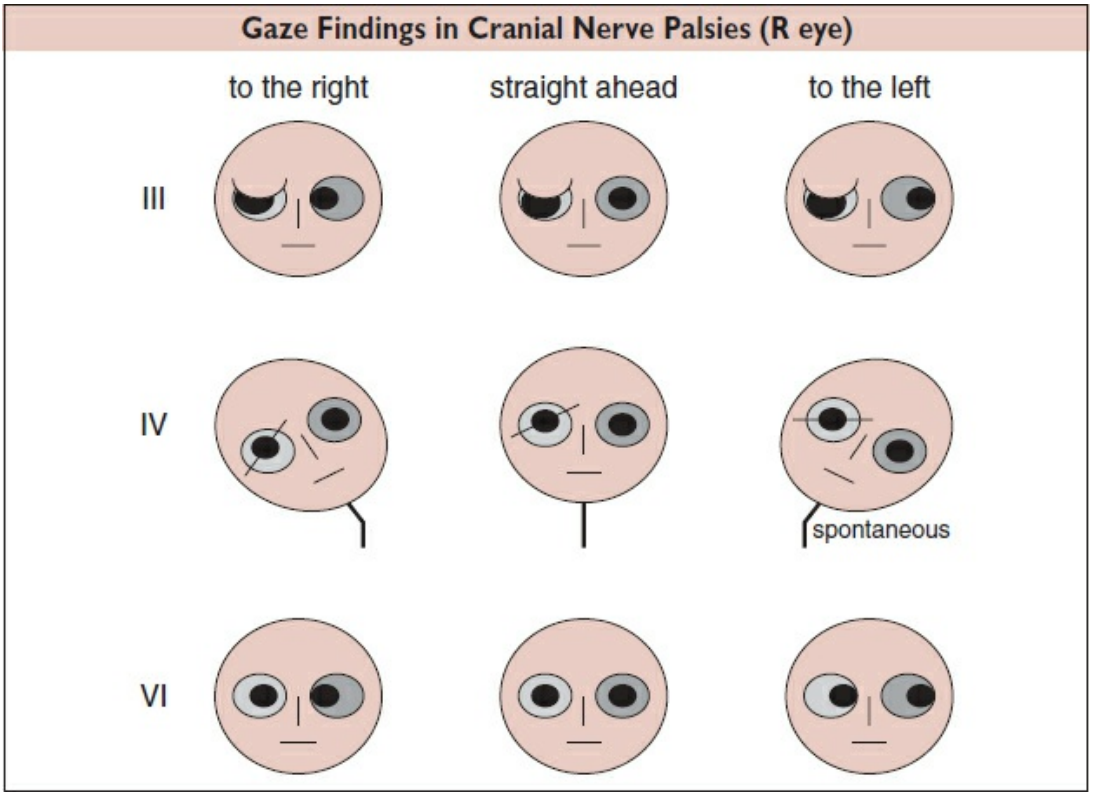
Figure 9-1. The muscles and innervation of extraocular movements (L eye)

- If concern for myasthenia, perform repetitive strength testing (expect decremental response) & check sustained upgaze for fatigable ptosis or diplopia; check neck flexion (surrogate for diaphragmatic function)
- **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 palsies:** III, IV, and VI control extraocular movement



- **Cranial nerve III palsy:** Horizontal or "diagonal" diplopia
  Findings: Impaired eye "down & out" when pt looks straight ahead, diplopia most severe when pt looks superiorly & toward unaffected side ("up & in"); ptosis ± dilated pupil
  Etiology: Most frequently **intracranial compression** by aneurysm (posterior communicating artery) 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 w/ pain over eyebrow
- **Cranial nerve IV palsy:** Vertical diplopia, relatively rare as isolated

finding

Findings: Most severe when pt looks "down & in" (toward unaffected side); **pt will naturally tilt head toward unaffected side** to compensate (worsened by head tilt toward affected side)

Etiology: Traumatic (majority of cases—can occur even w/ very mild trauma), postsurgical, idiopathic, ischemic (*Neurology* 1993;43:2439; *Neurology* 2009;72:e93)

- **Cranial nerve VI palsy:** Horizontal diplopia; most common CN palsy (*JNNP* 2004;75:iv24)

  Findings: Most severe w/ lateral gaze toward affected side "out"

  Etiology: Idiopathic, ischemic microvascular disease (typically in poorly controlled **DM**), traumatic, ↑ ICP (6th nerve is most susceptible 2/2 long intracranial course)
- **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/ reading, watching T.V. or at end of day & 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 diplopia 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) Lightheadedness/presyncope (2/2 cerebral hypoperfusion)
  (3) Disequilibrium (sense of imbalance, can accompany vertigo or be distinct)
  (4) Symptoms assoc w/ anxiety disorders
- **Epidemiology:** Vertigo lifetime prevalence 20–30%, accounts for 1.7% of US ambulatory visits (*Otolaryngol Clin N Am* 2012;45:925)
- **Vestibular system physiology:** Angular acceleration detected by fluid movement in the **3 semicircular canals** (1 in each axis; see figures below); 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

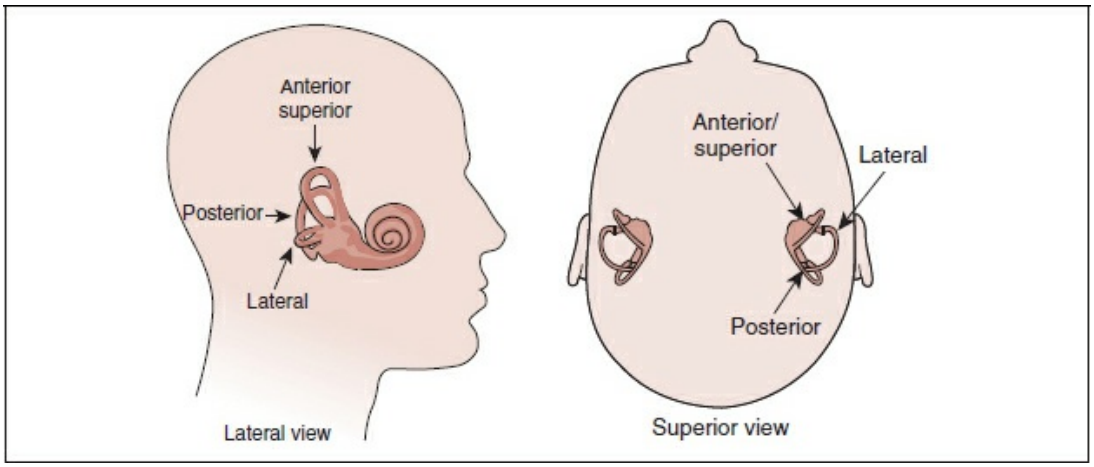


Figure 9-2. Semicircular canal orientation (enlarged, R ear)

- **Classification:** Etiologies divided into peripheral causes of vertigo (inner ear dysfunction: BPPV, Ménière's, vestibular neuronopathy) and central causes (brainstem, cerebellum lesions)
- Peripheral etiologies are more common and generally benign; some central lesions require emergent tx, so important to determine if

peripheral or central cause

Evaluation (*AFP* 2005;71:1115)

- **General approach:** First, establish pt is experiencing vertigo & not other cause of dizziness; next determine central or peripheral cause using history/PE
- **History:**
  - *Establish vertigo as cause of sx:* Ask pt to describe dizziness; 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's
  - *Duration:* Brief episodes (<1 min) suggest BPPV, long
  - *Aggravating factors:* Precipitated by changing head position (BPPV), motion (peripheral)
  - *Peripheral process assoc sx:* HA, prominent N/V, assoc tinnitus
  - *Nonvestibular process assoc sx*: CP, palpitations
  - CNS sx: **Diplopia, other neuro sx, gait instability, N/V** (central)
  - *Other:* Hx trauma (carotid dissection), **stroke risk factors**, **medication list**
- **Exam:** VS (assess for orthostasis if ? of presyncope), otoscopic exam
  - *Cranial nerves;* complete exam, looking for nystagmus, diplopia, Horner's
  - *Cerebellar exam:* Assess for dysmetria, ataxia, wide-based gait, Romberg's
  - *Hearing:* Assess for sensorineural hearing loss w/ Weber & Rinne tests (see "*Hearing Loss*")
- **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); caution in pts w/ severe neck or vascular disease
  - **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)

Skew deviation: Vertical ocular misalignment; indicates central (brainstem) locus; Look for vertical displacement of eye w/ alternating cover of each eye

Features of Central versus Peripheral Vertigo		
	Peripheral	**Central**
Head-impulse test	⊕ Saccades	Absent (normal)
Nystagmus		
Direction w/ head in fixed position *Direction variability* *Effect of visual fixation* *Reversal of head position*	Often horizontal, but can be mixed horizontal/rotational or vertical/rotational **Unidirectional—never Δs direction** Inhibits Can Δ direction of nystagmus	Pure horizontal, pure vertical, or pure torsional **Δ direction w/ gaze** No effect No effect
Skew	Absent	Present
Other	Pronounced **nausea** Deafness/tinnitus	Postural instability/**falls** 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)

- **Benign paroxysmal positional vertigo:** Common, ♀ > ♂, ↑ w/ age

  Etiology: Peripheral; dislodged otoliths in semicircular canals (**90% posterior canal**, tx w/ Epley, below)

  S/sx: Recurrent, transient & **episodic** last **<1 min**, can be triggered by specific head position Δs (lying on 1 side, turning over) (*Semin Neuro* 2009;29:500)

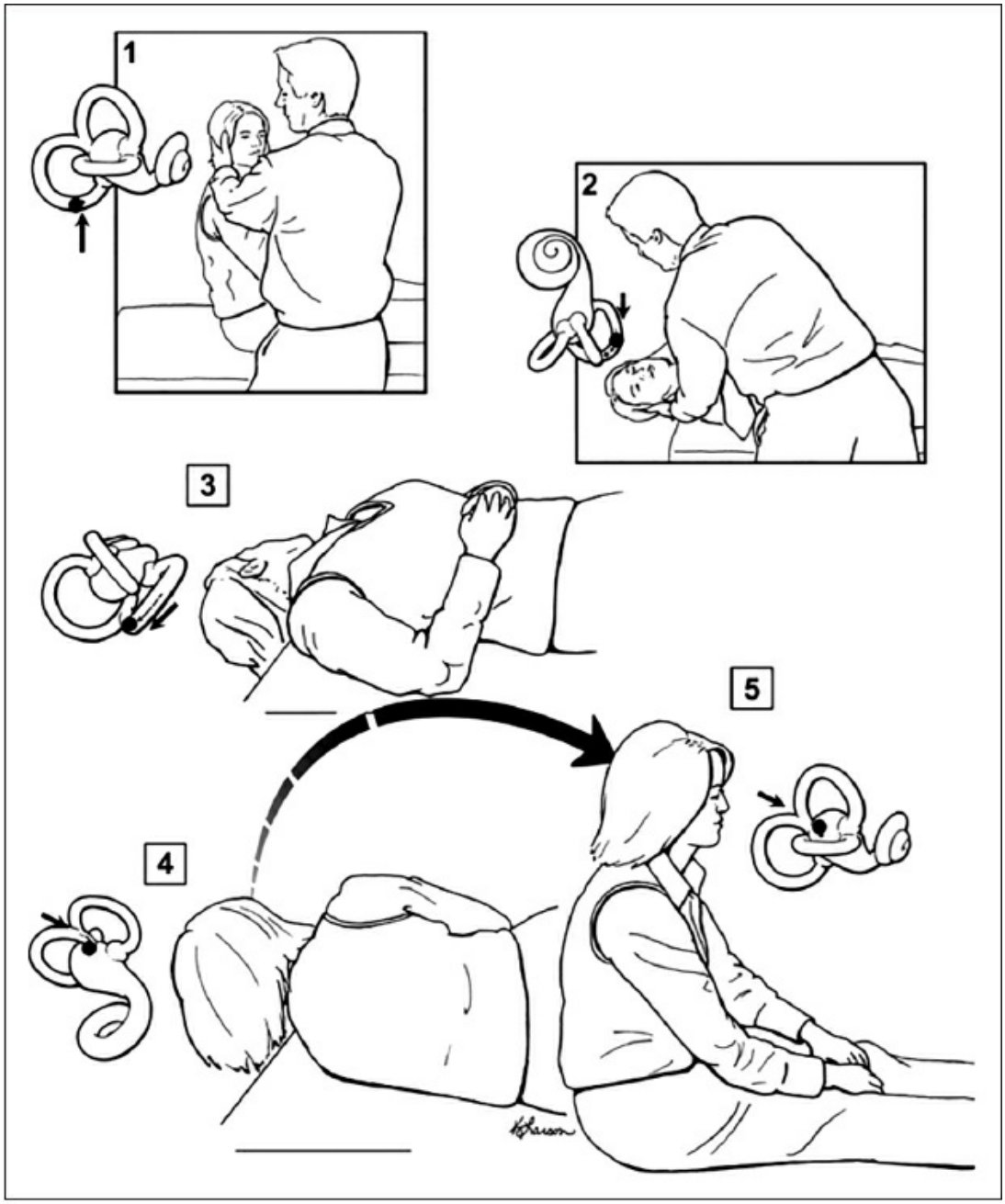
  Dix–Hallpike: Evaluates for posterior canal otolith; attempt on both sides; ⊕ test = nystagmus & vertigo, often after 2–5 s delay, w/ *affected* ear down → BPPV; however relatively ↓ Se (⊖ test doesn't definitively r/o BPPV)

  (1) Examiner holds pt head, rotates 45° toward one side

  (2) Tip pt backward to supine position w/ head overhanging edge

of table, still rotated to the side (45°)

Tx: Otolith repositioning maneuvers (Epley, Semont, Brandt–Daroff); caution: 36% of posted videos inaccurate (*Neurology* 2012;79:376)



From Fife T. Dizziness in the outpatient care setting. *Continuum* 2017;23(2):359–395. With permission.

Epley: Repositioning maneuver for posterior canal otolith; see AAN video at: youtube.com/watch?v=hq-IQWSrAtM; consists of Dix–Hallpike + 2 more steps
(1, 2) Start w/ Dix–Hallpike to affected side & maintain for 1–2 min
(3) Turn head 90° to unaffected side, hold add'l 1–2 min
(4) Roll body to unaffected side so head facing obliquely downward (add'l 90°), hold 1–2 min more
(5) Keeping head toward unaffected side, 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: Peripheral: 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 **min–h**
  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" (*Neurol Clin* 2012;30:61)
  Etiology: Peripheral; presumed viral; can occur post-URI
  S/sx: Persistent sx lasting days-weeks, typically worst in 1st d with gradual resolution; subacute onset, ⊕ head-impulse test
  Tx: Supportive (PT), no e/o improved sx 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 sx; 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 unres ponsive to Epley; may also consider vestibular PT for BPPV & Ménière's

BELL'S PALSY

Background (*NEJM* 2004;351:1323; *AFP* 2007;76:997; *Otolaryngol Head Neck* 2013;149:S1)

- **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, provides some taste to anterior 2/3 of tongue
- **Epidemiology:** 0.2–0.3% annual risk; incidence peaks in 40s, ↑ risk assoc w/ DM, HTN, pregnancy, HIV (*CID* 2007;44:e27)
- **Natural history:** Most pts (71%) w/o tx fully recover (full recovery seen in 94% w/ partial palsy, 61% w/ full palsy); recurrence in 7–15%; *Poor prognosis:* Elderly, 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; *Otolaryngol Head Neck* 2013;149:S1)

- **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 Bell's Palsy	

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

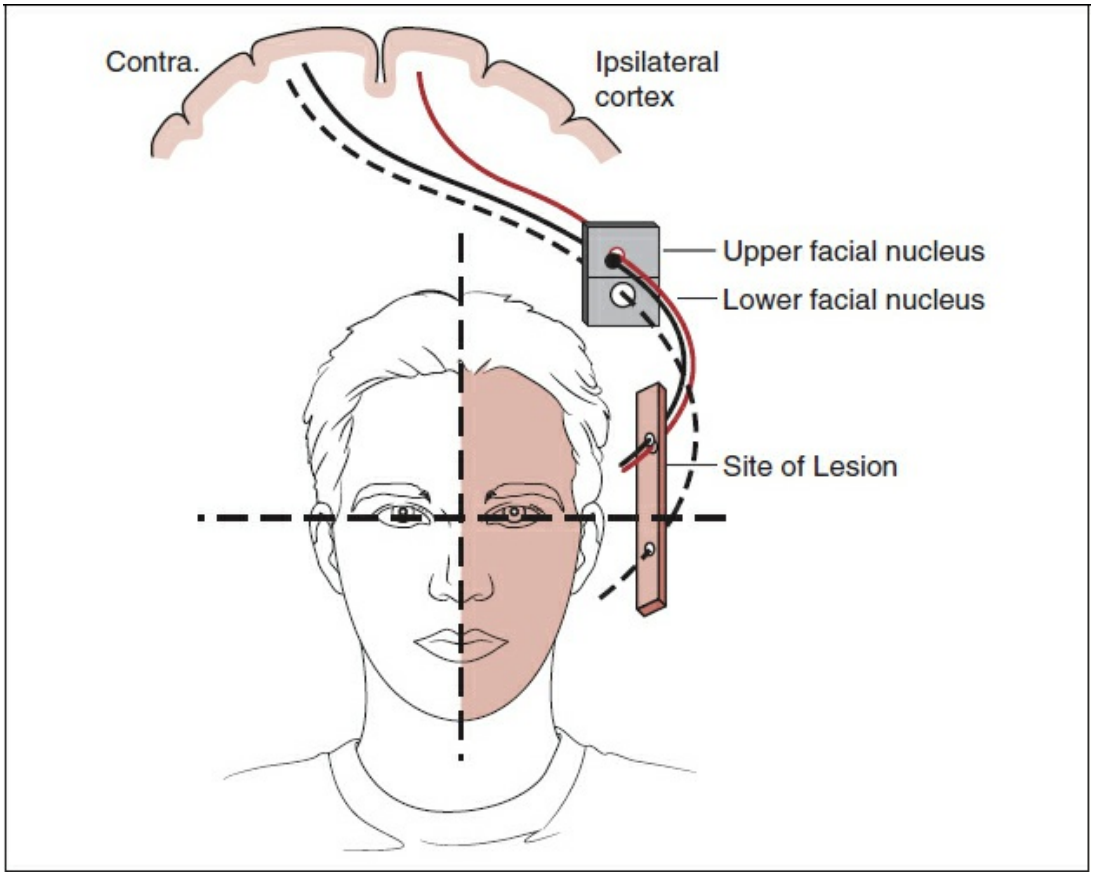


Figure 9-3. Bell's palsy. Lesion distal to facial nucleus → complete ipsilateral facial paralysis

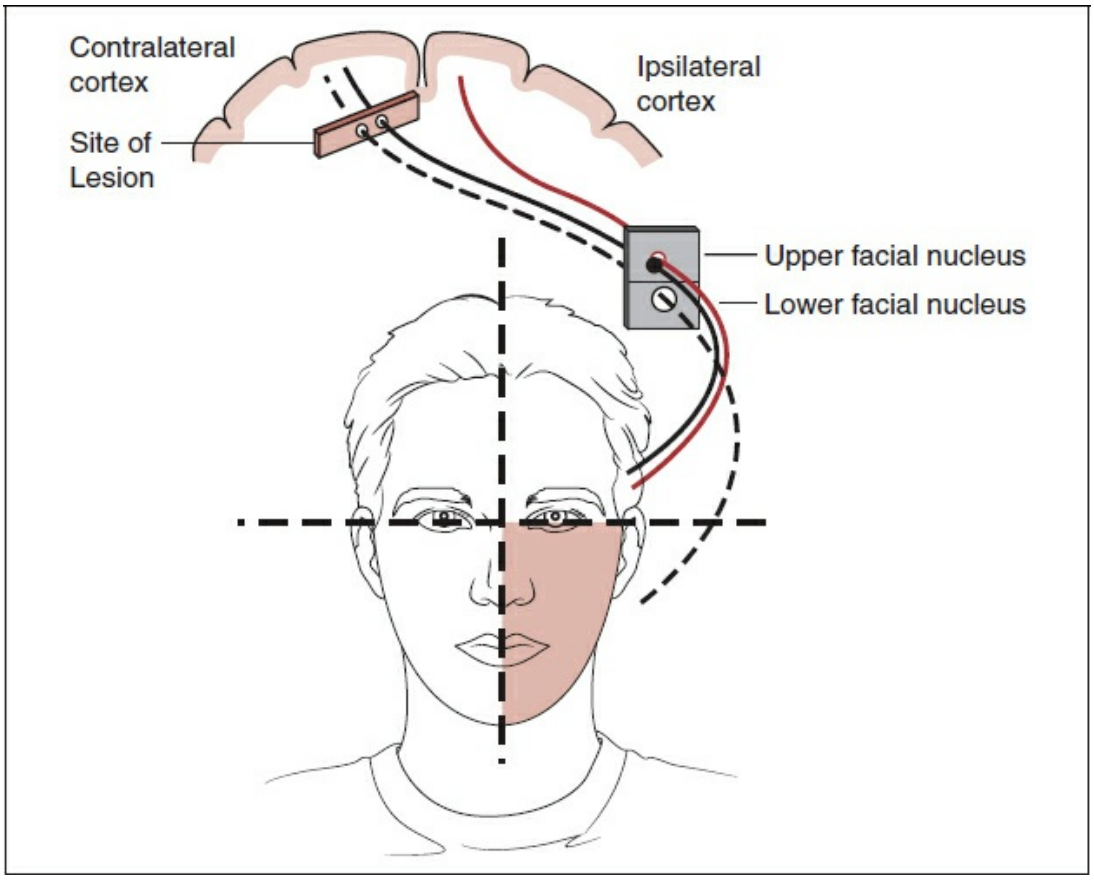


Figure 9-4. Supranuclear palsy (stroke). Lesion proximal to facial nucleus preserves upper facial innervation via intact ipsilateral cortex → forehead spared

- **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** (e.g., Lyme, HIV, sarcoid, GBS), 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), head & neck tumor, ear lesion (otitis media, cholesteatoma), sarcoid, Sjögren's

- **Labs:** None 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:** Typically none indicated; if gradual onset, suspicious HA but no suggestion of acute central process requiring ED referral → neuroimaging; LP if suspect neuro Lyme
- **Other: Nerve conduction studies (NCS)** may be useful for prognosis in complete paralysis, but not routinely recommended; not recommended in incomplete paralysis

Treatment (*Neurology* 2012;79:2209; *NEJM* 2007;357:1598)

- **Corticosteroids:** 40–60 mg prednisone QD × 7 d, started **ASAP**, ideally within 48 h of sx onset (prompt tx → 40% ↑ RR of complete recovery of motor function at 6 mo vs. placebo; NNT 6–8) (*Cochrane Database System Rev* 2016:CD001942)
- **Other:** Antivirals (for presumed HSV) not shown to be effective in most RCTs (*NEJM* 2007; 357:1598) but ? of small benefit & may be offered; valacyclovir & famciclovir preferred 2/2 ↑ adherence; PT not shown to be beneficial or harmful; evidence lacking for acupuncture (*BMJ* 2009;339:b3354; *Cochrane Database System Rev* 2012:CD006283 & 2010:CD002914)
- **Early complications:** Incomplete eye closure can → corneal abrasion; artificial tears q1h; eye ointment; eye patch at night, ophtho referral if any sx
- **When to refer:** New or worsening neurologic findings → neurology/ENT, development of ocular symptoms → ophtho; incomplete facial recovery 3 mo after initial sx onset → neurology/ENT

- **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;** atypical presentation → **Neurology**; no improvement in 6-12 weeks or late complications → **Plastic Surgery**

DEMENTIA

Background

- **Definition:** Clinical diagnosis defined (DSM-5) by e/o significant cognitive decline in ≥1 cognitive domain (learning & memory, language, executive function, complex attention, perceptual-motor, social cognition) & ADL/IADL difficulties
- **Mild cognitive impairment:** Cognitive or memory problem worse than nl aging, but w/ preserved function so not meeting dementia definition (*JAMA* 2007;297:2391; 2008;300:1566; *NEJM* 2011;364:2227); progression to dementia ~6–25%/y
- **Epidemiology:** Incidence ↓ in high-income countries, perhaps 2/2 ↑ educational. attainment in older adults (*JAMA Intern Med* 2017;177:51), yet ~5.5M pts in US in 2017, expected to triple by 2050; costly ($259 billion/y) & burdensome (caregiver stress), **affects 30% of >65 y**
- **Risk factors:**
  - **Definite: Age** (strongest RF for all dementia); CV risk factors (HTN, DM, HLD), hx stroke, FHx, hx head trauma, hx delirium (8x ↑ in incident dementia + accelerated decline in cognition, *Brain* 2012;135:2809), hx SUD, Down syndrome (<1% for early AD, ~50% for FTD)
  - **Possible:** Fewer years of formal education (*JAMA Intern Med* 2017;177:51)
  - **Protective:** No strong data beyond lifestyle modification; unclear evidence for intellectual/social activity, exercise, antioxidants (e.g., Curcumin), statins, ω-3 fatty acids, Mediterranean diet, Ginkgo biloba (*JAMA* 2008;300:2253)
- **Ddx: Important to r/o potentially reversible causes of cognitive**

impairment: Chronic SDH, delirium, depression, NPH, hypothyroidism, malignancy (systemic vs. brain tumor), meds, infections (neurosyphilis, encephalitis, meningitis, Lyme), electrolyte imbalances and toxic metabolic etiologies, vit $B1_2$, folate or thiamine deficiency, heavy metal poisoning

Dementia Subtypes	
Type	**Symptoms**
Alzheimer (AD) (50–80%) (*Lancet* 2011;377:1019)	Memory deficit prominent; language, visual–spatial disturbances, indifference, neuropsych sx; parkinsonian sx = late manifestation; often anognosomic (unaware of deficits)
Vascular (VD) (10–20%) (*Lancet Neurol* 2003;2:89)	Abrupt onset, stepwise deterioration, fluctuating course, executive dysfunction may be prominent, hx stroke/stroke risk factors, focal neuro s/sx
Mixed (50% of AD) (*JAMA* 2004;292:2901)	Abnormalities characteristic of >1 dementia syndrome simultaneously (most commonly AD & VD together)
Lewy body (5–10%) **(LBD)** (*AFP* 2006;73:1223)	Dementia onset concurrent w/onset of parkinsonian sx (in PD dementia onset >1 y after motor sx); visual hallucinations, delusions, fluctuating cognition, sleep d/o, autonomic dysfunction (falls, orthostasis)
Frontotemporal (FTD) (12–25%) (*AFP* 2010;82:1372)	Personality/social/language/behavior problems prominent early sx, incl disinhibition; memory less affected; onset late 50s–early 60s; often anognosomic
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
Other:	EtOH, Creutzfeldt–Jakob disease, cerebral amyloid angiopathy, HIV-associated dementia

Evaluation and Prognosis (*AFP* 2005;71:1745; 2011;84:895; *JAMA* 2007;297:2391)

- **Screening:** USPSTF—insufficient evidence for/against routine screening
- **History:** Important to talk to family members/caregivers about changes from baseline and difficulties w/ ADLs (grooming, managing finances, difficulty w/ learning/memory/language, driving, getting lost); timeline/progression (to distinguish from delirium); meds; r/o depression ("pseudodementia"); assess pt insight on deficits
- **Exam:** Neuro exam, including gait/balance, (see "*Falls*") cogwheel

rigidity, tremors

Screening tests: Montreal cognitive assessment (MoCA) and MMSE are brief screening tests for various domains of cognitive impairment (*BMC Geriatrics* 2015;15:107) and can help monitor disease progression over time; less sensitive (more false ⊖) in pts w/ ↑ baseline cog function; consider formal neuropsych testing if no clear deficit captured on MoCA or MMSE but persistent sx; consider language barriers when testing as can ↓ score

- **Workup:** Dx primarily **clinical**; focus of labs/imaging is to r/o reversible causes: CBC, CMP, $B1_2$, TFTs, ± RPR (based on suspicion)
- **Brain imaging:** Not always required if confident of clinical dx/will not change mgmt, but can be useful to exclude structural etiologies at initial eval, identify dementia subtype based on atrophy pattern
- **Neuropsychological testing:** If available, can quantify domain & degree of impairment (*AFP* 2010;82:495); may guide safety eval; *best if family/friend can also attend*
- **Prognosis:** Highly variable as diagnosed at different stages; etiology- and age-based, dependent on comorbidities; 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) esp early, to help pt & family define GOC

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; sleep hygiene; monitor for medical illness (i.e., UTI, PNA) & med toxicity; identify triggers for behavioral problems
- **Medication toxicity:** underappreciated source of ↓ cognitive function; avoid deliriogenic (BZDs, opioids), anticholinergic (antihistamines, TCAs, antipsychotics) (*BMJ* 2006;332:455)
- **Medications**: Currently no tx reverse or stop disease progression; some evidence that cholinesterase inhibitors and memantine can slow pace of decline *Cholinesterase inhibitors (CI):* Donepezil ≈

galantamine ≈ rivastigmine in mild–mod AD (MMSE 10–26); consider combination of galantamine & donepezil in severe AD (MMSE<10); after 8–12 wk trial of tx, reassess clinical status & continue if improvement noted; restart if clinical deterioration after d/c; may help w/ neuropsychiatric sx in AD (*JAMA* 2003;289:210)

Pharmacotherapy of Dementia	
Drug & Dose	**Side-effects/Comments**
Donepezil 5 mg PO QD × 4 wk → 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 4 mg PO BID × 4 wk, up titrate qmo 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 1.5 mg PO BID, uptitrate q2wk to 6 mg BID; Transdermal available	CI; efficacious in PD dementia (*NEJM* 2004;351:2509), LBD (Lancet 2000;356:2031); ↑ severe nausea, anorexia c/w donepezil; HA; take w/ food; may worsen tremor in PD; significantly less GI s/e w/ transdermal patch; patch may cause rash
Memantine 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)

- **Antipsychotics:** Both typical & atypical antipsychotics ↑ **risk of death** (*NEJM* 2005;353:2335); frank discussion of risks/benefits w/ caregivers & shared decision-makingre: possible Rx; preferable to dx/address underlying etiology of agitation whenever possible; if behavioral sx cannot be managed by other means, reassessment & documentation necessary (*JAMA* 2005;294:1963)
  - *Typical antipsychotics:* No benefit in improving neuropsych sx (*JAMA* 2005;293:596);
  - *Atypical antipsychotics:* When compared w/ placebo for pts w/AD and psychosis, no significant benefit but significantly more s/e (*NEJM* 2006;355:1525)
- **Nutrition:** Most advanced dementia pts will experience eating problems and weight loss in final stages; **tube feeding not recommended** (*J Am Geriatr Soc* 2014;62:1590); **no** evidence of benefit

(*Cochrane Database Syst Rev* 2009;2:CD007209)

- **Mood stabilizers:** Conflicting data to support use (e.g., valproic acid, (ox)carbamazepine, gabapentin, topiramate, lamotrigine); unclear benefit w/ potential for SES; consider psych/neuro c/s before initiating, discuss risks/benefits w/ pt's surrogate decision maker
- **Driving:** Clinical Dementia Rating (CDR) can be useful in assessing driving safety (*Neurology* 1993;43:2412); pts w/ CDR ≥2 are unsafe to drive; pts w/ CDR 0.5–1 should be evaluated for driving ability if 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, meds that affect CNS, sleep d/o, hx falls, or hearing/visual/mobility impairment (*Neurology* 2010;74:1316); pts may be referred for road-test driving assessment; **document** that recommendations conferred to family/pt/caregiver; mandatory reporting of unsafe drivers varies by state
- **Home safety evaluation**: (PT, OT) Work with caregivers and families to assess need for placement in a more supervised setting; may ↓ mortality (JAGS 2006;54:950)
- **Wandering:** Alzheimer's organization offers (for $55, then $35/y) 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)
- **Advance care planning: Start early;** involve pt as much as able; see *"Advance Care Planning"*
- **Patient information:** MCI (*JAMA* 2009;302:452); dementia (*AFP* 2010;304:1972); *Alzheimer's:* alz.org; theaftd.org, *AFP* 2011;83:1415; *FTD* (*AFP* 2010;82:1378); behavioral problems (*AFP* 2006;73:653); caregiver support (*AFP* 2000;62:2621); driving w/ dementia (*AFP* 2006;73:1035); finances (*AFP* 2011;305:1610)

CONCUSSION

Background (*AFP* 2012;85:123; *Neurology* 2013;80:2250)

- **Definition:** Trauma-induced head injury with transient AMS (± LOC); consider mild TBI w/ *functional* impairment (no structural correlate on neuroimaging)
- **Natural history:** Symptoms typically resolve spontaneously 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); in some cases recovery is more prolonged
- **Epidemiology:** 1.6–3.8 million sports concussions annually (*J Head Trauma Rehabil* 2006;21:375); elderly also at ↑ risk (see "*Fall Prevention"*)

Evaluation (*NEJM* 2007;356:166; *AFP* 2012;85:123; *Neurology* 2013;80:2250)

- **History:** Obtain detailed history of mechanism of injury; any anticoagulation use; most common acute sx are **HA** (87%), **dizziness** (65%), & **confusion** (57%); can also present w/ postural instability, amnesia (typically of the event and immediately before and/or after), incoherent speech, diplopia, seizures, drowsiness, nausea, photo-/phonophobia, anxiety, irritability; LOC in only 10%; may be assoc w/ convulsions immediately after injury (*J Neurotrauma* 2009;26:2365)
- **Postconcussive symptoms:** HA, dizziness, & difficulty concentrating, cognitive deficits; can last days-weeks, occasionally months; no evidence that a single concussion → permanent neuro impairment; research ongoing on effects of *multiple* head injuries on cognitive function (*JNNP* 2010;81:1116); ↑ risk of seizures w/in 5 y from event (80% within 2 y); *Risk factors for postconcussive sx*: low socioeconomic status, previous TBI, coexisting injury, ongoing court case, ♀ > ♂ (*Neurology* 1995;45(7):1253), **h/o depression/anxiety**
- **Physical:** Neuro exam, focusing on attention, memory, balance; C-spine eval; consider assessment tools such as the Standardized Assessment of Concussion (most commonly used for athletes: concussioncorps.org/wp-content/uploads/2013/04/SAC.pdf)
- **Red flags:** Any focal neuro deficits, coagulopathy, e/o basilar skull fracture (hemotympanum, raccoon eyes, Battle sign), vomiting, dangerous mechanism of injury, persistent AMS (GCS <15), clinical deterioration → ED
- **Imaging:** Normal in concussion; consider noncontrast head CT to r/o more serious TBI if: age ≥65, coagulopathy, vomiting, severe HA;

the other indications for imaging are red flags (above) which should → ED evaluation; if neuroimaging indicated and cannot be obtained urgently (same-day) as an outpatient with proper f/u → ED (*Ann Emergency Med* 2008;52:713; *Neurology* 2013;80(24):2250)

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)
- **Return to work/school/activities:** Variety of approaches, emphasis on:
  (1) Brief period of physical/cognitive rest; counsel pts that sx might initially persist
  (2) Graded stepwise return to cognitive/physical activities as tolerated; if sx return, fall back to lower level of activity
  (3) Athletes: may **not** return to play while sx (↑ risk of re-injury w/ ↑ sequelae)
- **Symptom management:** See table

Postconcussive Symptom Management	
Symptom	**Recommended Management**
Dizziness/nausea	Meclizine & antiemetics
Headache	Mild PRN analgesics; if prolonged → standard migraine tx (see "*Headache*")
Seizures	No need for AEDs unless seizures persist/recur
Cognitive dysfunction	Consider cognitive eval/OT/SLP referrals, depending on occupation
Anxiety, posttraumatic symptoms, impaired coping, persistent sx	Cognitive behavioral therapy

- **When to refer:** If sx persist >1–2 wk, including HA not responsive to 1st-line agents or persistent cognitive complaints, seizures → **Neurology**
- **Patient information:** cdc.gov/traumaticbraininjury/pdf/tbi_patient_instructions-a.pdf

WEAKNESS

Background

- **Definition**: A loss of muscle power and may be due to injury to the brain, spinal cord, nerve roots, peripheral nerves, neuromuscular junction, or muscle; however, the term "weakness" is often used nonspecifically by the patient & can be used to describe fatigue, pain, joint dysfunction/injury, psychosomatic or "functional" weakness
- Appropriate evaluation of muscle strength is important to determine if true weakness is present & help determine etiology; "weakness" may be presenting complaint for wide range of diseases (e.g., acute illness, depression, anemia, OA); so precise hx/PE important

Evaluation (*Continuum* 2011;17:1040; *AFP* 2005;71:1327)

- **History:**
  - *Onset:* Acute (vascular), subacute (meds, rheumatologic, infectious), or chronic (metabolic)
  - *Precipitants:* Stress (functional), trauma, fever/infection
  - *Distribution* (localizes deficit): Focal, segmental, unilateral, or diffuse? Symmetric? Proximal, distal?
  - *PMHx:* DM, 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 sx, HAs (complex migraines, stroke/ICH)
- **Red flags:** Acute onset, rapid progression, SOB (esp w/ sitting up) or resp involvement, bulbar sx (difficulty speaking, chewing, swallowing); urinary retention → ED referral
- **Exam:** Investigate any other systemic sx as directed by hx; examine for muscle atrophy & tone, assess symmetry; eval muscle strength, clonus, DTRs, sensory exam (✓ for sensory level if concern for cord lesion)
- **Muscle strength assessment:** Verbally encourage pt to offer

maximum effort for 1–2 seconds “Push hard, hard!”

Grading of Muscle Strength	
0	No muscle contraction
1	Muscle contraction without movement at joint
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

Upper (UMN) vs. lower motor neuron (LMN) weakness (see table):
UMN (cortex, corticospinal tracts to spinal cord): Often affects UE extensors/LE flexors → posture of UE flexion/LE extension
LMN (anterior horn cells, nerve roots, peripheral nerves, NMJ, muscle): Distribution varies based on lesion; segmental (anterior horn cell, nerve root), focal (mononeuropathy), diffuse (peripheral nerve, NMJ, myopathy); to determine nerve root vs. peripheral nerve (see “*Peripheral Neuropathy”*)
Sensory sx can be present or absent in either LMN or UMN (nonspecific)

- **If strength impaired, localize the lesion:**

Upper Motor Neuron versus Lower Motor Neuron Signs on Exam		
	UMN	**LMN**
Strength	↓	↓
Tone	↑	↓ or Normal
Muscle Bulk	Normal	↓
Fasciculations	No	Yes
Reflexes	↑	↓
Plantar response (Babinski sign)	↑	↓

- **Labs:** Consider Na, K, Phos, Mg, Ca, CK, TSH, $B1_2$, LDH, LFTs, acetylcholine receptor antibodies, neuropathy w/u (see *“Peripheral Neuropathy”*)

- **Imaging:**
  Head CT: If concern for acute intracranial process w/ UMN weakness (stroke/ICH)
  Spinal MRI: Appropriate with subacute to chronic UMN pattern weakness; consider appropriate spine imaging if UMN or LMN weakness & associated symptoms of trauma (complete spine), neck pain (cervical spine), low back pain (lumbar spine)
- **Other:**
  EMG/NCS: An extension of the neuromuscular exam; helpful to localize and characterize severity & temporal stage of nerve root, peripheral nerve, NMJ, or muscle disease
  Muscle bx: Helpful in assessing etiology of myopathy/myositis

Differential Diagnosis (*Semin Neurol* 2011;31:115)

Selected Differential Diagnosis of Muscle Weakness	
Diagnosis	**Clinical Features**
Stroke, ICH	Acute onset UMN pattern weakness
Spinal cord lesion	Sensory level, crossed sensory sx (e.g., absent ipsilateral light touch, absent pain & temp contralateral), bowel or bladder dysfunction
Motor neuron disease (ALS)	Distal segmental painless weakness & atrophy; UMN + LMN signs (may be later in clinical course)
Myasthenia gravis	Fatigable weakness, often w/ ptosis, diplopia, dyspnea, or generalized weakness
Myositis (PMR, DM)	Proximal symmetric weakness, ± muscle pain, can be assoc w/ heliotropic rash in DM, often ↑CK
Mononeuropathy (see "*Peripheral Neuropathy*")	Focal weakness (e.g., foot drop) w/ sensory loss

Treatment

- As per underlying disorder; 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

PERIPHERAL NEUROPATHY

Background (*Continuum* 2012;18:13; *Neurology* 1993;43:817)

- **Definition:** *Peripheral nervous system:* nervous system outside of CNS (brain & spinal cord); consists of somatic (sensory & motor) & autonomic nerves

  Peripheral neuropathy: Diseases affecting cell body or processes of the lower motor neuron (motor) or dorsal root ganglia (sensory) or paraverterbral/preverterbral ganglia (autonomic)
- **Pathophysiology:** Pattern of nerve injury varies with mechanism; peripheral neuropathy may affect single or multiple *types* of nerve
- **Epidemiology:** Peripheral neuropathy affects ~2–8% of US adults & 21% of DM pts presenting to PCP office
- **Etiology:** Damage to nerves may be inflammatory, vasculitic, traumatic, toxic, metabolic, or infectious—careful hx & exam determining pattern of lesions can help w/Ddx

Classification of Peripheral Neuropathies		
Class	**Site of Damage**	**Example** (w/ example etiology)
Radiculopathy	Nerve root (e.g., C7)	C7 radiculopathy (Spinal DJD)
Mononeuropathy	Individual nerve (e.g., median nerve)	Carpal tunnel syndrome (Trauma/pressure)
Mononeuropathy multiplex	Multiple individual nerves	Foot drop & wrist drop (Vasculitis)
Polyneuropathy	Diffuse, typically symmetric, often length-dependent	Burning/dysesthesia in feet (EtOH)

Evaluation (*Continuum* 2012;18:139)

- **General approach:** First, characterize pattern of neuropathy (sx, onset, distribution); second, look for etiologic 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 when no/low ambient light or when no visual clues)

Predominantly sensory etiologies: DM, B_{12} 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, vitamin deficiency, neoplastic, metabolic, CIDP)

Distribution: Peripheral or proximal? Symmetric or asymmetric?

- **Etiologic 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, malabsorption syndrome (celiac, IBD, gastric bypass), HCV (seen in cryoglobulinemia), thyroid disease, amyloid; consider leprosy, Chagas in appropriate populations (*Continuum* 2012;18:126)

Social hx: EtOH use (known toxic if >7 drinks/d, diet (vegan [B_{12} def]), carnivorous fish (ciguatera toxin), solvent use/abuse ("huffing")

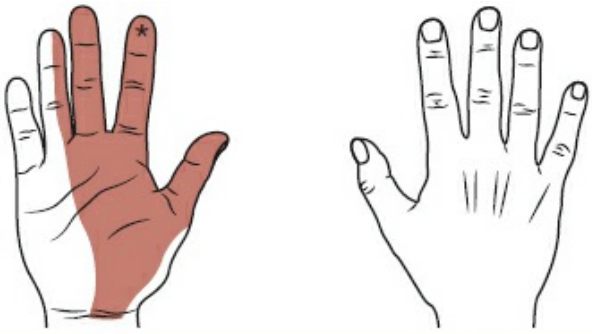
Meds/toxins: Generally cumulative; a dose- and/or time-dependent process (see below)

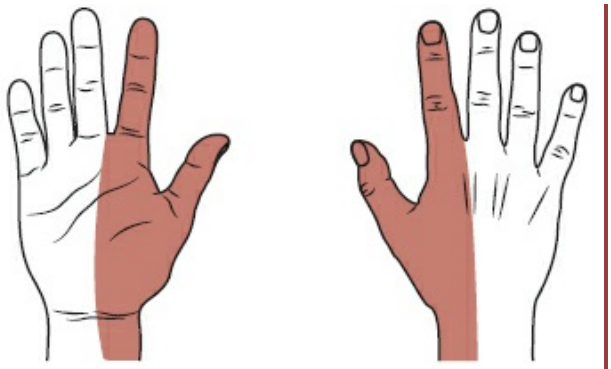
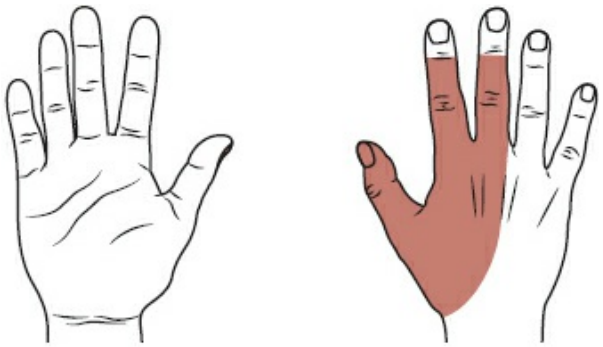
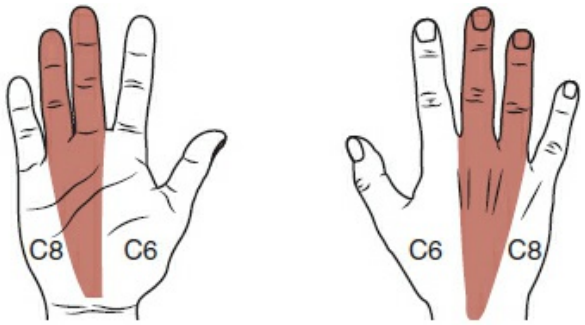
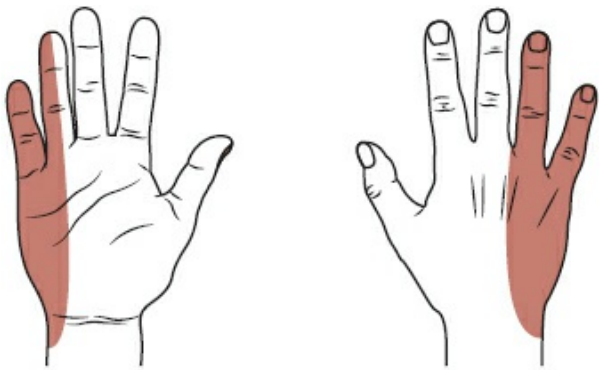
Other: Occupational hx (lead, solvent, grout exposure), **FHx**

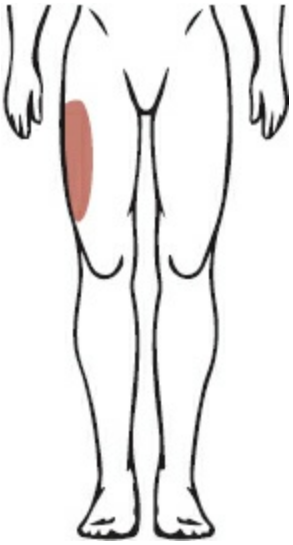
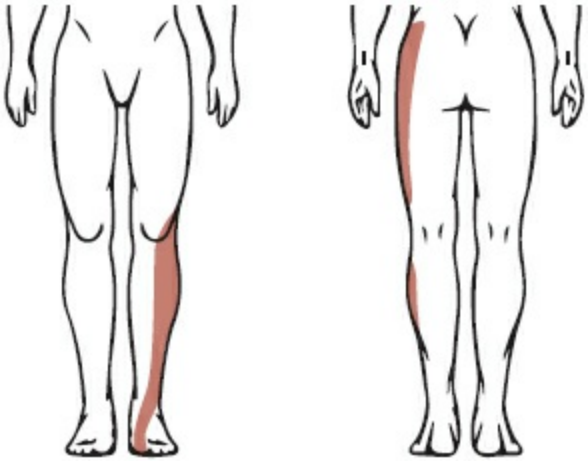
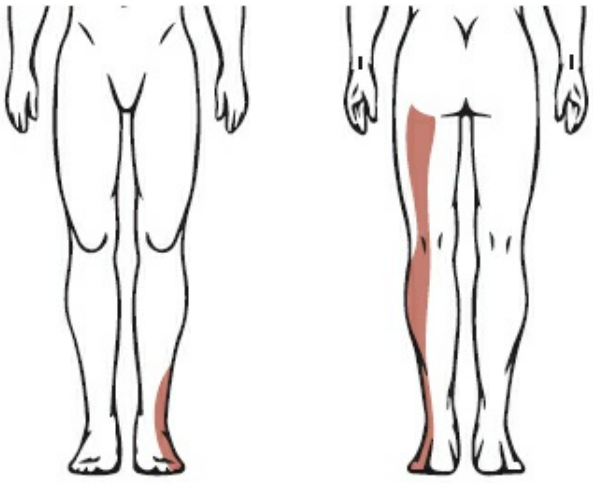
Medications/Toxins/Vitamins Associated with Neuropathy (*Continuum* 2012;18:139)	
Anti-infective	INH, MNZ, nitrofurantoin, chloroquine, FQs, ethambutol
Immunosuppressants	Etanercept, infliximab, leflunomide, tacrolimus
Other	Colchicine, disulfiram, thalidomide, dapsone, phenytoin
Toxins	Arsenic, gold, lead
HAART	Didanosine, stavudine, zalcitabine

Cardiovascular	Amiodarone, hydralazine, ?statins
Oncologic	Cisplatin, docetaxel, paclitaxel, suramin, vincristine (vinblastine)
Vitamins	Vit B1 deficiency, vit B_6 (deficiency or excess), vit B_{12} deficiency, vit E deficiency (malabsorption syndromes), Copper deficiency, Zinc excess

- **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, proprioception (large fiber sensory involvement); **gait** for foot drop
- **Provocative tests:** Test which provokes or exacerbates pt symptoms; suggestive of nerve entrapment or compression
  - *Tinel*: For mononeuropathy; lightly percuss over the nerve
  - *Phalen's:* For median neuropathy (CTS); pt holds dorsum of hands pressed together w/wrist flexion
  - *Spurling:* For cervical radiculopathy: have pt extend neck and tilt toward affected side, then provide axial pressure → worsening symptoms (*Clin Orthop Relat Res* 2012;470:2566)
  - *Straight leg raise:* For lumbosacral radiculopathy: pt supine, knee extended, and provider passively lifts straight leg raise (hip flexion) → radicular pain (not hamstring discomfort) in ipsilateral or contralateral leg

Common Upper Extremity Neuropathies	
Site of Injury & Distinguishing Features	**Sensory Distribution**
Median Nerve (Carpal Tunnel Syndrome) *Hx:* Occupational wrist overuse *Motor:* Thenar eminence wasting *Tests:* Tinel's over volar wrist, Phalen's CTS may spare palm (palmar branch does not go in carpal tunnel)	
C6 Root *Motor:* Primary nerve root for supination	

(biceps, brachioradialis) *Tests:* ⊕ Spurling's *DTR:* Biceps, brachioradialis C6 dermatome includes radial aspect of forearm	
Radial Nerve *Hx:* "Saturday night palsy"; compression in spiral groove of humerus due to sleeping position (arm over chair or pt/companion's weight on arm), often assoc w/ deep sleep of intoxication *Motor:* Wrist/finger extension	
C7 Root *Motor:* Primary nerve root for **elbow extension,** also pronation, wrist/finger flexion *Tests:* ⊕ Spurling's *DTR:* Triceps C7 dermatome includes posterior arm, forearm	
Ulnar Nerve (elbow > wrist) *Hx:* Elbow pain, elbows resting on hard surface (WC, desk); handlebars (wrist) *Motor:* Usually mild hand weakness; → "claw hand" *Tests:* For elbow compression (most common), ⊕ Tinel's over medial cubital tunnel (btw olecranon & medial epicondyle)	
Common Lower Extremity Neuropathies	
Lateral Femoral Cutaneous Nerve Neuropathy (Meralgia Paresthetica) *Hx:*Tight pants/belts, pregnancy, obesity (compression as exits pelvis to lateral thigh)	

Sensory only; can be anterior thigh as well	
L5 Root *Motor:* Hip abduct, ankle dorsiflex, 1st toe ext, foot inversion + eversion Gait: Trendelenburg gait (2/2 weak hip abductors), foot “slap” (2/2 poor dorsiflexion) *DTR:* ± Achilles *Tests:* ⊕ Straight leg raise *Sensory:* First dorsal webspace and lateral calf most consistent	
Site of Injury & Distinguishing Features	**Sensory Distribution**
S1 Root *Motor:* Ankle plantarflex, knee flex *Gait:* heel slap gait (2/2 weak plantarflexion) *DTR:* Achilles *Tests:* ⊕ Straight leg raise *Sensory:* Lateral heel, posterolateral calf most consistent	
Peroneal/fibular Nerve (proximal fibular head > foot) *Hx:* Crossing legs at knee, injury at	

ankle/tight shoes (for deep branch)
Motor: Foot drop (impaired ankle eversion/dorsiflexion)
Sensory: dorsum of foot/lateral ankle; if distal injury, only dorsal webspace between 1st-2nd digits

- **Labs:** For polyneuropathy or idiopathic mononeuropathy: CBC, Cr, HbA1c/fasting glucose, B_{12} (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 tests depending on clinical picture
- **EMG/NCS:** Usually w/ neurology guidance, not needed for all pts; used to assess disease severity, assist in localization, or further characterize type of neuropathy (demyelinating vs. axonal neuropathy)
- **Imaging:** MRI if concern for radiculopathy or plexopathy
- **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; *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:* GBS, CIDP, Lyme, HIV, sarcoid, amyloid, paraneoplastic, genetic d/o
- **Autonomic neuropathy:** DM, 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 & nerve conduction studies; due to DM, autoimmune, paraneoplastic, Celiac disease; may be confirmed w/skin biopsy
- **Mononeuritis multiplex:** Multiple nerves affected, often in stepwise, asymmetric fashion; *Etiology:* Vasculitis, Sjögren's, sarcoid, DM, Lyme
- **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 in severe/refractory/idiopathic cases; consider w/u for DM, thyroid, arthropathies; *Tx:* Reduce external compression as able (ergonomics/behavioral changes, wrist splints at night for CTS); if severe, refractory, involves motor function, consider surgical referral
- **Radiculopathy:** Majority 2/2 nerve root compression due to DJD spine, also DM, Lyme, zoster, sarcoid, tumor infiltration; sx often assoc w/ or preceded by **neck** (cervical) or low **back** (lumbar) **pain** which may then radiate into limb, numbness in dermatome(s) and weakness in myotome(s); see table for most common; *Eval:* EMG/NCS to localize/characterize injury; MRI of appropriate spine region; consider w/u for nondegnerative cause if hx suggests; *Tx:* Neuropathic pain Rx, rest, & exercise therapy; limited data for epidural steroid injections; surgical referral for refractory pain & weakness w/ evidence of structural cause on MRI
- **Diabetic neuropathy** (*NEJM* 2005;353:392; *AFP* 2008;78:835; *Med Clin N Am* 2009;93:285)
- Half of pts w/ DM will develop neuropathic complications; distal symmetric polyneuropathy most common; counsel pts re: ulcer avoidance (7× ↑ risk if neuropathy); see *"Diabetes"*
- *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 sx or severe wt loss; resolves over several mo; 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)

- **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**	**Notes**
TCAs	Amitriptyline 10–25 mg QHS (max 150 mg QD) Nortriptyline 10–25 mg QHS (max 100 mg QD)	*Evidence:* Level A for DM, postherpetic neuralgias *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 *S/e:* Nausea, ↑ BP; caution if liver dz, HTN
Ca channel α-2-δ ligands	Gabapentin 300 mg QD; max 1200 mg TID Pregabalin 25–75 mg QD; max 300 mg BID	*Evidence:* Level A for DM, postherpetic neuralgia, cancer pain (gabapentin) *S/e:* Sedation, dizziness, edema, wt gain Renally cleared, caution if ↓ GFR
Lidocaine patch	1–3 patches; Apply 12 h on, 12 h off	*Evidence:* Level A for postherpetic neuralgia *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 wk)	*Evidence:* Level A for HIV, postherpetic neuralgia

	Alt: Topical anesthetic, then 1–4 patches × 60 min q3mo	*S/e:* Pain, erythema (↓ w/ ongoing use)
Tramadol	50 mg QD; max 400 mg QD (ER)	*Evidence:* Level A: DM, phantom pain *S/e:* N/V, constipation, dizziness, sedation; avoid if substance use d/o, suicide risk

- **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

RESTLESS LEGS SYNDROME

Background (*AASM ICSD-2* 2005; *Neurol Clin* 2012;30:1137)

- **Definition:** Disorder characterized by (1) Urge to move limbs assoc w/ paresthesias, (2) Sx worse at rest, (3) Sx worse at night, (4) Physical activity provides partial relief (*Sleep Med* 2003;4:10):
- **Etiology:** Often idiopathic but can be assoc w/ systemic disease, pathophysiology 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)
- **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 (occurs in 80–90% of pts w/RLS); ⊕ FHx
- Single question w/ Se/Sp 100/96% for dx of RLS: (*Eur J Neurol* 2007;14:1016)

"**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?"**

- **Medications/Toxins:** Agents can induce/worsen RLS: Antidopaminergic (antipsychotics), 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 2° causes when possible (OSA, Fe deficiency); offer nonpharmacologic tx 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 <75 ng/mL), ✓ ferritin after 3 mo, can then follow every 3–6 mo
- **Nonpharmacologic treatment;** cognitive/behavioral tx & exercise may ↓ RLS sx; avoid aggravating factors/exacerbating meds/toxins as able; trial of brief walking, hot baths, or leg massage before bedtime (*BMJ* 2012;344:e3056); counsel pts on sleep hygiene; no strong evidence for efficacy of LE compression devices
- **Dopamine agonists:** Pramipexole, ropinirole are **1st-line,** effective, well-tolerated (lower risk of complications than Levodopa)
  - *S/e:* Nausea, dizziness, somnolence, nasopharyngitis; ↓ impulse control, vivid dreams
  - *Dosing:* Either agent should be taken ~2 h prior to sx onset, renal dosing adjustments
  - *Example Rx:* Ropinirole 0.25 mg QHS; may ↑ by 0.25 q2–3d as needed (max 4 mg) or
  - Pramipexole 0.125 mg QHS; may ↑ by 0.125 q2–3d until relief obtained (max 2 mg)
- **Gabapentin/Pregabalin:** 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 treatments:** 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 rarely used

- **When to refer:** Refractory disease or dx unclear → neurology
- **Patient information:** ninds.nih.gov/disorders/restless_legs/detail_restless_legs.htm

TREMOR

Background (*JAMA* 2003;289:347; *Continuum* 2016;22:1143)

- **Definition:** Rhythmic, oscillatory, involuntary movement with a constant frequency; usually classified into resting vs. action tremor (below)
- **Resting tremor:** Evident when affected body part not voluntarily activated & remains *supported against gravity* (e.g., hand on lap; 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
- **History:** Should include age of onset, evolution of sx over time, body regions involved, maneuvers that elicit or suppress tremor, review of tremor-exacerbating substances (caffeine, tobacco, EtOH w/d), hyperthyroid sx, medication list (bronchodilators, SSRI, SNRI, antipsychotics, stimulants, lithium, VPA, prednisone), ⊕ FHx
- **Exam**: *Postural:* Assess w/ sustained arm extension
  - *Kinetic:* Assess with finger-nose-finger, asking pt to draw spirals or write their name, drink from a cup; ⊕ intentional component if tremor worsens as approaches target (e.g., as finger approaches nose in finger-nose-finger)
  - *Resting tremor:* Evaluate while pt seated & standing; look for tremor of head, jaw, tongue, and voice (sustained phonation)
  - *Psychogenic:* Look for distractability (finger tapping w/ opposite hand), entrainment (tremor → line with specific rhythm),

suggestibility

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:* Usually bilateral (but may be slightly asymmetric), ~4–8 Hz postural action tremor; 50% are intentional; most frequently starts in hands/arms (~95% of pts), usually progressive; can also affect head ("yes-yes" or "no-no" sign= "titubation"), jaw, voice, rarely legs (*Neurology* 2005;64:2008); can improve after 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: Lightheadedness, 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:**

  Parkinson disease: Asymmetric resting tremor affecting UE, LE, or both (if both, typically on same side); wrist pronation–supination common; can affect jaw (closed/resting > open/talking); can also have emergent postural/kinetic tremor, if present, generally ↑ amplitude than essential tremor; see *"Parkinson Disease"*

  Dystonic tremor: Assoc w/ dystonia (sustained abnormal posture), can improve by touching affected region

  Orthostatic tremor: Rare; limited to legs & trunk, occurs exclusively while standing (e.g., legs giving out while waiting in line)

  Psychogenic tremor: Contains rest, postural, & action components; inconsistent features, may have variable frequency or change direction; may be paradoxically worse with "loading" (pressing down on affected extremity); see "*Somatoform Disorders"*

  Drug-induced: Can be resting (antipsychotics) or action tremor (bronchodilators, stimulants); trial off offending agent as able to confirm etiology; may consider propranolol for action tremor or DA for resting tremor if very bothersome but cannot d/c med; (*Continuum* 2016;22:1143) continue neurology c/s prior to tx

PARKINSON'S DISEASE

Background

- **Definition:** Movement disorder syndrome characterized by "TRAP": Tremor, Rigidity, Akinesia/bradykinesia, & Postural instability
- **Pathophysiology:** Progressive neurodegenerative d/o; idiopathic, thought 2/2 ↓ DA in substantia nigra (*Lancet* 2009;373:2055)
- **Epidemiology:** 2nd most common neurodegenerative disease, 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
- **Natural history:** Average pt → disability (not independent w/ ADLs) ~7 y after dx, but variable; 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 sx predict more rapid disease progression (*Mov Disord* 1996;11:236)
- **Other parkinsonian syndromes** (*Neurol Clin* 2001;19:607): *Less responsive to dopaminergic therapy and more rapid progression*; syndromes include:

  Progressive supranuclear palsy (early falls, axial rigidity, vertical gaze palsies); Multiple system atrophy (prominent autonomic sx & cerebellar signs), dementia with Lewy bodies (visual hallucinations), corticobasal degeneration
- **Secondary causes of parkinsonism** (*Lancet* 2009;373:2055)

  Medications: Metoclopramide, compazine, antipsychotics, CCBs, possibly SSRIs
  Toxins: CO, cyanide, manganese, MPTP (street opioid contaminant)
  Vascular: small vessel strokes
  Other: Infection (encephalitis, HIV), metabolic (Wilson, hypoparathyroid), head trauma

Evaluation (*JAMA* 2003;289:347; *NEJM* 2005;353:1021)

- **Diagnosis:** Clinical **diagnosis**: eval w/ careful hx & neuro exam

(including gait assessment)

- **History:** Determine onset and progression of sx; PMHx; HIV, stroke risk factors (vascular parkinsonism); medication list (drug-induced parkinsonism)

Typical Presentation of Parkinson's Disease	
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% Se, 81.4% Sp for predicting eventual dx of PD (*Mov Disord* 2002;17:795)
- **Features which suggest an alternative diagnosis at onset:** ↑ **falls** and ↓ **tremor,** symmetric onset, rapid progression, poor response to dopaminergic therapy

Treatment (*Neurology* 2006;66:983)

- **Referrals:** All pts w/ suspected parkinsonism should be referred to neurology or a movement d/o specialist; PT, OT & home safety assessment usually indicated
- **Pharmacologic Rx:** No current tx options to slow progression; Rx below intended to ↓ sx & to ↑ function; all typically prescribed by neurologist/specialist

  Dopaminergic agents: Dopamine (levodopa/carbidopa) or dopamine agonists (ropinirole, pramipexole) typically 1st-line; tolerance & disease progression → ↑ doses over time

S/e: GI sx (N/V, abdominal pain), dizziness, orthostatic HoTN, hallucinations, impulsive behavior (e.g., pathologic gambling), vivid dreams, insomnia, dystonia, dyskinesias

Other agents: Catechol-*O*-methyltransferase inhibitors (entacapone), MAOI (selegiline, rasagiline), anticholinergics (frequent s/e), amantadine

- **On–off phenomenon:** (motor fluctuations) "On" effect immediately after taking med → excessive movements, dyskinesias; "Off" effect ~4 h later, as dopaminergic effect wears off → freezing, prominent rigidity; often managed w/ adjunctive tx (rasagiline, entacapone, pramipexole, & ropinirole all shown to ↓ "off" time, at expense of ↑ "on" sx)
- **Deep brain stimulation:** 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 sx

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Management of Comorbidities

(*Mov Disord* 2005;20:958; *Biol Psych* 2002;17:1031)

- **Assessment of home safety** & safety w/ activities (driving, ambulating) crucial as functional status ↓: involve PT/OT, low threshold for SLP swallowing eval/ speech therapy, consider aspiration precautions
- **Counseling and support:** Given disease course, recommend for spouse as well; review advance directives (see *"Advance Care Planning"*)
- **Depression:** 40–50% of PD pts; consider TCAs, paroxetine, venlafaxine; SSRI contraindicated if using MAOI (*Cochrane Database Syst Rev* 2003;3:CD003465)
- **Sleep disturbance:** Many manifestations, including insomnia, daytime hypersomnolence w/ sleep attacks, restless legs syndrome (see *"Restless Legs Syndrome"*), excessive limb movements during sleep, REM sleep d/o; provide counseling about sleep hygiene to pt and spouse, identify causes of poor nocturnal sleep (see

"*Insomnia*"), can consider modafinil for daytime hypersomnolence (limited evidence)

- **Psychotic sx:** Can be 2/2 PD or dopaminergic tx; paranoia & hallucinations in ~40% of PD pts, frequently 2/2 PD meds or underlying dementia, consider antipsychotics only after r/o toxic/metabolic cause & ? trial of ↓ dopaminergic med dose; avoid typical antipsychotics (DA antagonists worsen motor sx); quetiapine or clozapine preferred, should be comanaged *w/ neurologist*; see *"Dementia"*
- **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
- **Sialorrhea:** ↑ drooling 2/2 dysautonomia & ↓ motor control, chewing gum use might help in mild cases, for severe sx consider anticholinergic Rx or referral for *Botulinum* injections
- **Orthostasis:** Common in late stage PD, can be worsened w/ levodopa; 1st remove other offenders (βBs), encourage fluid/salt intake, try compression stockings; may consider fludrocortisone ± midodrine
- **Patient information:** parkinsons.org.uk/?page=10495w

SEIZURE

Background (*Neurology* 2011;77:1005; *Epilepsia* 1975;16:1)

- **Definitions: Seizure:** Symptomatic 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:** Seizure disorder; ≥2 unprovoked seizures; **Status epilepticus:** Seizure lasting >5 min or multiple seizures over >5 min period w/o interval return to baseline
- **Epidemiology:** ~6% of population will experience a seizure in their

lifetime; epilepsy affects ~2 million in US

- **Risk factors:** ⊕ FHx, perinatal injury, childhood febrile seizures, head trauma, CNS infection, stroke, brain tumor, ICH
- **Provoked seizure:** Due to discrete, temporary trigger rather than underlying seizure d/o
- **Etiologies:** Idiopathic/unknown, structural, metabolic, genetic, perinatal, infection (encephalitis, meningitis, cysticercosis), neoplasm, stroke, ICH, trauma, EtOH or BZD withdrawal
- **Differential dx:** Syncope (up to 90% pts w/ syncope have myoclonic jerks during event), physiologic sleep myoclonus ("jerk" when asleep/falling asleep), sleep d/o, complex migraines, movement d/o, limb shaking TIA, transient global amnesia, & nonepileptic seizures (aka pseudoseizures; frequently coexist w/ epilepsy, in up to 10–30%)

Evaluation (*AFP* 2007;75:1342; *Postgrad Med* J 2009;85:667; *BMJ* 2012;345:e4576)

- **General approach:** For 1st-time seizure, determine (1) was it a true seizure and if so (2) was it provoked; for recurrent/worsening epilepsy, attempt to determine cause of worsening
- **History:** *Was it a seizure?:* From pt/witness: preceding aura (epigastric sensation, bad smell), focal vs. generalized onset, duration, tonic and/or clonic movements

  Features suggesting seizure: Tongue biting, head turning, cyanosis, postictal confusion, incontinence, eyes open during event w/ forced gaze deviation
- **History:** *Was it provoked? Why now?*

  PMHx: Seizure RF: TBI, febrile seizures, metabolic d/o (hyponatremia, hypoglycemia/DM on hypoglycemic agents), SLE, developmental delay

  Meds: Can ↓ seizure threshold; *Anti-infectives:* FQs, high-dose β-lactams, INH, MNZ, chloroquine, mefloquine; *Analgesics:* Tramadol, opiates, meperidine; *Psych:* Bupropion, clozapine

  Associated symptoms/processes: Current illness, liver or renal dysfunction, UTI; ↓ sleep

  Features suggesting provoked seizure: EtOH or BZD w/d, cocaine/methamphetamine use, head injury, CNS infection, stroke, eclampsia; n.b. seizure after sleep deprivation

considered *un*provoked

- **Exam:** Full neuro exam (frequently nl); tongue & extremities for ictal injuries; skin exam for e/o neurocutaneous d/o (tuberous sclerosis, neurofibromatosis, Sturge–Weber)
- **Studies:** CBC, lytes, glucose, tox, pregnancy test; (note that GTCs may transiently ↑ lactate, CK, & WBC); ✓ ECG to exclude arrhythmia **EEG:** All pts w/ new seizure; 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
- **Pt w/ known epilepsy:** Ask about typical seizure presentation, frequency of seizures, current AED/prior AED regimens, triggers for prior seizures (e.g., ↓ sleep)

  Pt w/ epilepsy reporting ↓ control of disease from baseline (recurrent seizure/↑ seizure frequency): Are episodes(s) similar to prior seizures? Adherence to AED regimen? New meds started or current toxic/metabolic process? ✓ AED levels if applicable; unless new seizure type, new neuro sx, or known brain mass/infectious etiology (e.g., neurocysticercosis), no imaging required

Management (*Continuum* 2010;16(3):105)

- If provoked single seizure → treat underlying cause
- **All pts**: Avoid meds/processes that ↓ seizure threshold (above)
- **Antiepileptic drugs:** Initiated & managed by neurology

  Indications: For all pts w/ >1 seizure or structural abnormalities, abnl EEG or neuro exam

  Relative indication: Pts w/ 1 seizure and no structural/neuro abnormalities, but ↑ 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

  Regimen/agent: Monotherapy is goal; AED chosen based on sz type, age, comorbidities, **med interactions** (review prior to PCP initiation of new meds, esp if pt on carbamazepine, phenytoin, valproic acid) & 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 mo; some states require providers to report directly to DMV (CA, DE, NV, NJ, OR, & PA), list at: http://www.epilepsy.com/driving-laws

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 nonadherence, including missed doses

Antiepileptic Medications (*Continuum* 2010;16(3):121)

Medication	Monitoring	Side Effects
Carbamazepine	✓CBC, LFT, lytes; CYP450 inducer (↓ concentration of other Rx such as warfarin, OCPs); avoid w/ MAOI, ↑ SJS incidence in pts of Asian descent	↓ 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; dose adjust w/ CKD	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 sz, pts on >1 AED, or no response to meds; pts w/ diagnosis of epilepsy should be established with neurologist; if not → refer
- **Emergency department:** If suspicion of CNS infection, fever or immunocompromised → ED for LP; if new neuro deficits or not back to baseline (? of status epilepticus) → ED for urgent imaging (r/o ICH, stroke, tumor)

STROKE, TIA, & POSTSTROKE CARE

Background (*Circulation* 2012;125:e2; *MMWR Weekly* 2012;61:379; *Circulation* 2016;133:e388)

- **Definitions: Stroke:** Loss of brain function 2/2 disruption of cerebral blood supply; can be *ischemic* (occluded blood vessel; 87% of all strokes), or *hemorrhagic* (disrupted/ruptured blood vessel; 13% of strokes)
  - **Transient Ischemic Attack (TIA):** *Transient* (<24 h) episode of neurologic dysfunction 2/2 temporary occlusion of blood vessel, w/ no lesions seen on MRI (*Stroke* 2009;40:2276)
- **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
- **Epidemiology:** 2.7% of US adults report hx of stroke and 2.3% have hx of TIA; ↑ w/age: 8.3% of US adults ≥65 y report hx stroke; mean age at 1st stroke is 71–75 y; ↑ in African-American & Native American; major cause of mortality & disability
- **TIA** is a "warning sign" for stroke; → 10–17% risk of stroke w/in 90 d, w/ half 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

Evaluation (*Stroke* 2009;40:2276; *Lancet Neurol* 2005;4:727; *Lancet* 2007;369:283)

- **General approach: For pts w/new, current focal findings → ED; for pts reporting recent TIA sx, risk-stratify w/ABCD2 score to determine management**
- **History: Acute onset of focal neurologic finding** should prompt consideration of stroke; most commonly unilateral weakness or speech disturbance (dysarthria, aphasia), but can also present w/parasthesias, vertigo, ataxia, visual field defects
- **Exam:** Complete, succinct neurologic exam: presence of facial hemiparesis (forehead spared – see "Bell's palsy," pronator drift, or abnormal speech → ⊕LR 5.5 for stroke)
- **All pts with suspected** current **TIA or stroke → ED STAT; document "last seen well" time** to help ED team determine if pt candidate for IV tPA (4.5 h from sx onset) or endovascular therapy (up to 24 h from sx onset)
- **Recent TIA symptoms: if red flags → ED, otherwise risk stratify (below)**

  Red flags: Suggest increased risk of stroke; *PMHx:* hypercoaguable state, prior stroke, hx Afib & not anticoagulated, mechanical valve; *Sx:* basilar TIA symptoms (vertigo/nausea, diplopia, tinnitus: up to 59% risk of subsequent stroke) → ED

  Risk stratification: ABCD2 score (Age, BP, Clinical features of TIA, Duration of sx, DM) predicts short-term stroke risk; available at mdcalc.com/abcd2-score-for-tia/

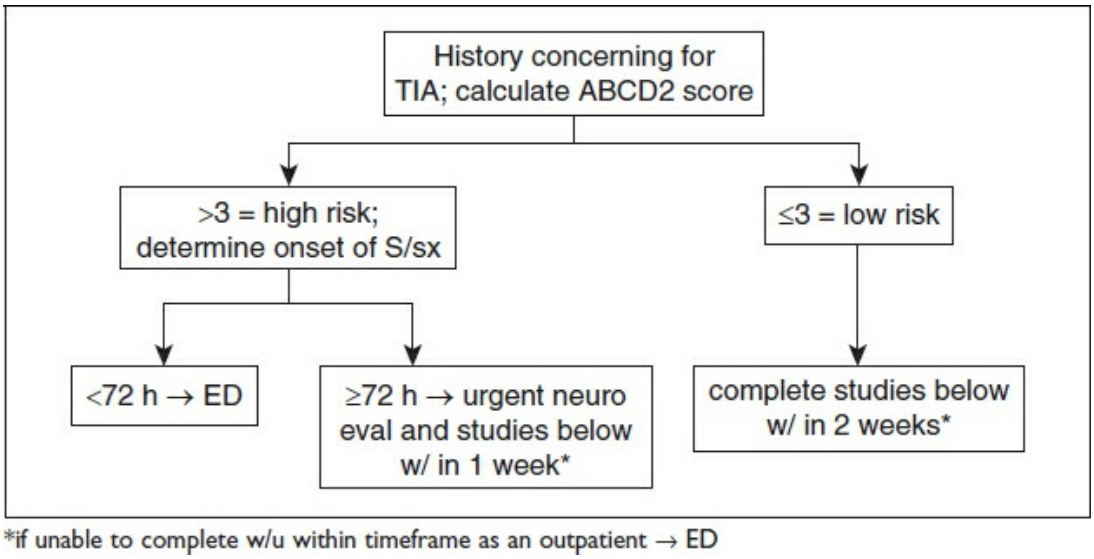


Figure 9-5. Management algorithm for history of TIA-like symptoms

- **Labs***:* CBC, BMP, HbA1c, coags, lipids
- **Imaging***:* Should be of brain *and* cervical vessels; *Brain*: MRI w/diffusion-weighted imaging preferred (may be able to determine ischemia as well as infarction); CT acceptable; *Cervical vessels*: MRA, CT-A, or u/s; one approach is MRI/MRA of head & neck
- **Cardiac studies:** to evaluate for cardioembolic etiology: ECG, rhythm strip, if no e/o carotid disease → Holter, TTE
- Additional studies: If above unrevealing/per clinical suspicion, may consider endocarditis or hypercoagulability w/u, cardiac event monitor (*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/ischemic 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 significant difference vs. ASA/dipyridamole (*NEJM* 2008;359:1238)	Higher cost

- **Dual antiplatelets:** CHANCE trial demonstrated ↓ risk of recurrent stroke (8.2% vs. 11.7%) in pts w/ *TIA/minor stroke* & *no cardioembolic source* who were on 3 mo of dual anti-PLTs (ASA/clopidogrel) vs. ASA alone (*NEJM* 2013;369:11–19)
- **Anticoagulation:** Indications listed in "special populations" below, refer to *"Anticoagulation"* chapter for selection of anticoagulant (warfarin vs. direct oral anticoagulants) & consideration of bridging; if concern for cerebral amyloid angiopathy (CAA, microhemorrhages on MRI) **no anticoag** 2/2 ↑ risk ICH
- **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 in all patients (*Stroke* 2014;45:2160)
- **SSRIs:** FLAME trial showed ↑ motor recovery at 3 mo in stroke pts w/ mod–sev motor deficits, effect independent of hx depression (*Lancet Neurol* 2011;10:123–30)
- **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 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 1–4 wks poststroke to start anticoag depending on stroke size and location, 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 mo (*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; 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), most studies with no significant benefit of PFO closure vs. med tx alone for 2° prevention (CLOSURE, I *NEJM* 2012;366:991; PC TRIAL, *NEJM* 2013;368:1083; RESPECT, *NEJM* 2013;368:1092) 2 newer trials suggest ↓ risk of recurrent stroke in carefully selected pts (NNT 28 at 2 y, NNT 20 at 5 y) (Gore_REDUCE & CLOSE, *NEJM* 2017;377:1033 & 377:1011); Reasonable to start pts on antiplatelet agents (*Stroke* 2011;42:227); obtain LE U/S to r/o DVT (risk of paradoxical embolus) → start anticoag if ⊕ DVT

OPHTHALMIC EVALUATION

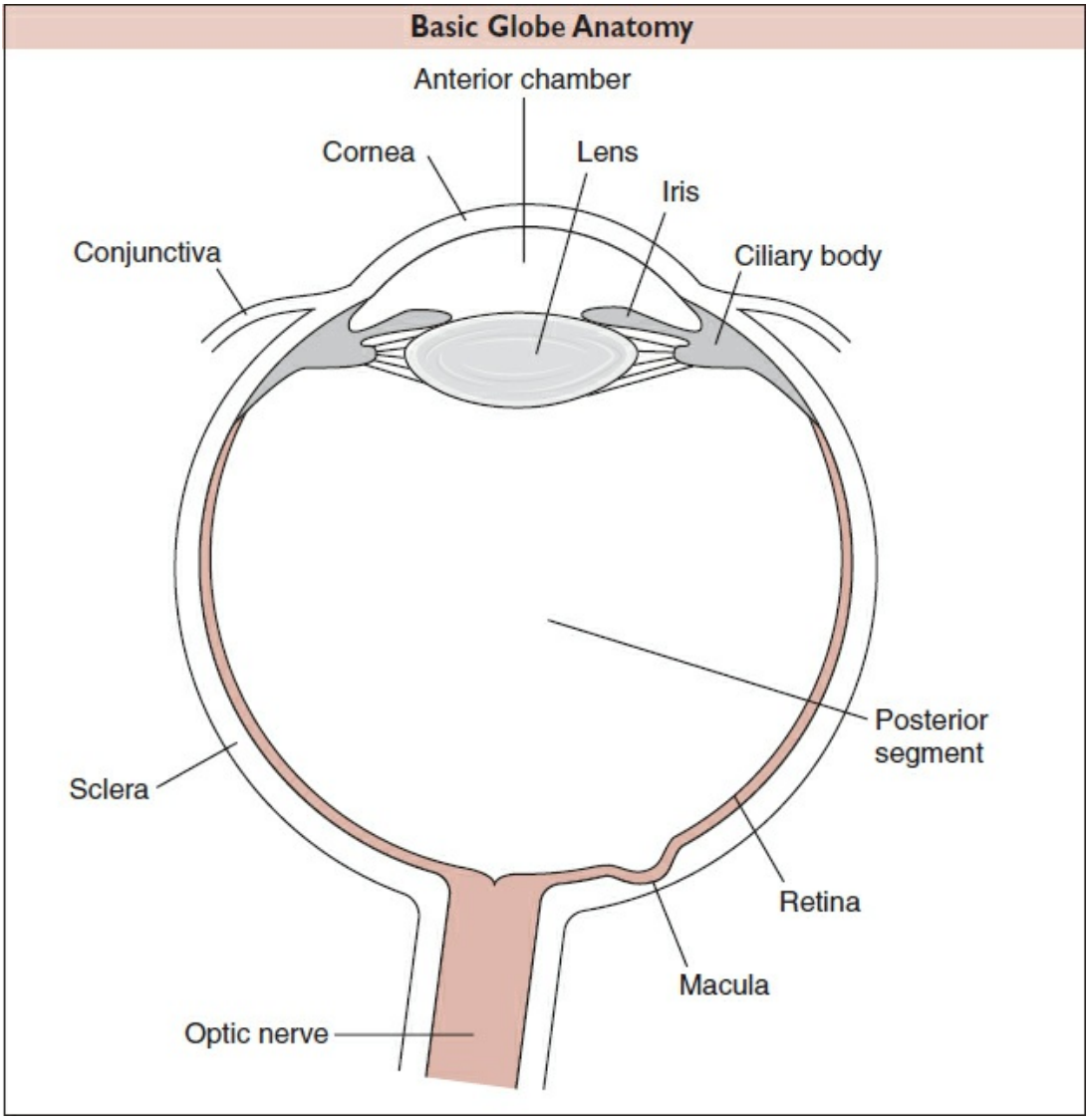
Background (*JAMA* 2004;291:1487)

- 40% of vision loss is preventable; careful hx/PE can establish dx and distinguish between urgent and routine ophtho referrals
- **Definitions: Legal blindness:** Corrected VA ≤20/200 ***or*** visual field <20° diameter *in better eye;* **Visual impairment:** Corrected VA worse than 20/40 in better eye
- **Screening** (See AAO PPP Guidelines 2015; aao.org/ppp)
  - *If no RF, comprehensive eye exam:* Age 40–54 q2–4y, 55–64 q1–3y, & ≥65 q1–2y
  - *If glaucoma RF (see "Vision Loss"):* Age 40–54 q1–3y, 55–64 q1–2y, & ≥65 q1–2y
  - *If DM:* Dilated exam at time of diagnosis (DM2) or 5 y s/p dx (DM1), then yearly

Basic Eye Anatomy

- **Anterior segment contents**
  - **Cornea:** Dome-shaped transparent outermost layer of front of eye
  - **Limbus:** Circular ring of transition between cornea & sclera
  - **Sclerae:** White (opaque) outermost layer of the rest of the eye; continuous w/cornea
  - **Conjunctiva:** Covers the sclerae (bulbar portion) and inner aspect of eyelids (palpebral portion), does *not* cover cornea
  - **Anterior chamber:** Fluid (aqueous humor)-filled space between lens and cornea
  - **Iris/Ciliary body:** Iris is anterior extension of ciliary body, which holds the lens and adjusts it for near/far distances (*accommodation*); pupil is the opening at center of iris
- **Posterior segment contents**
  - **Retina:** Inner lining of eye, vascular, contains photoreceptor cells (rods/cones)

Macula: Pigmented area near center of retina; contains *fovea* (highest concentration of cones)
Choroid: Pigmented layer between retina & sclerae, vascular (supplies macula)
Optic nerve: Axons from retinal ganglion cells in retina; transmits images → brain
Vitreous cavity: viscous fluid (vitreous humor)-filled space behind lens



History

- Complete history below; may be narrowed based on nature of complaint
  - *Age:* Relevant in narrowing Ddx (e.g., GCA unlikely if <50 yo)
  - *Ocular history:* Hx trauma, eye surgery, contact lens use (incl sleeping in lens, failure to change regularly), eye drop use, family ocular hx
  - *Symptoms:* Gradual vs. sudden onset, monocular vs. binocular, duration, quality, similar prior episodes, painful vs. painless vision change, irritation, pruritus, FB sensation, discharge (severity & quality), photophobia
  - *Associated systemic Sx:* HA, fever, rash, arthralgia, GI sx, environmental allergies

Ocular Side Effects of Systemic Medications		
Medication/Class	**Ocular Side Effects & Toxicities**	**Notes & Mgmt Guidelines**
Amiodarone	Glare, colored halos, dry eye; possible optic neuropathy	Refer for eye exam if ⊕ sx, D/c if possible
Bisphosphonates	Red eye or ocular discomfort due to dryness; uveitis, scleritis	Refer urgently (<1 wk) if acute, painful, or ↓ vision; may need to d/c
Corticosteroids	Cataract, glaucoma, central serous retinopathy (→ blurred vision)	Annual eye exam if long-term use, refer more urgently (1–2 wk) if acute or subacute vision ð
Hydroxychloroquine/Chloroquine	Ocular irritation, contact lens intolerance (drug crystals in tear film may aggravate ocular surface); can → irreversible central vision loss due to retinal (macular) toxicity	At dose of 5.0 mg/kg, risk of toxicity is <1% at 5 y, <2% at 10 y; almost 20% after 20 y Baseline eye exam to r/o pre-existing maculopathy Annual screening after 5 y in pts on <5 mg/kg & w/o other RF (CKD, concurrent tamoxifen, Stargardt's disease)

Ethambutol	Bilateral optic neuropathy causing irreversible central VA loss, ↓ color VA, & central scotomas	Onset w/in 2–5 mo of starting tx 1% risk with daily dose ≤15 mg/kg, 5–6% at 25 mg/kg, 50% at 100 mg/kg Baseline ophthal exam then q1mo for high doses or RF (DM, CKD, EtOH, old age, other eye d/o, neuropathy)
Fluoroquinolones	Probable: Diplopia (EOM tendonitis), myasthenia exacerbations, ?uveitis	Sx resolve with drug withdrawal
Isoniazid	Optic neuritis (blurred vision, pain w/ EOM)	Refer if suspicion, d/c Rx if able
Niacin	Blurred or ↓ vision due to cystoid macular edema	Refer for eye evaluation if suspicion
Rifabutin	Uni- or bilateral ocular pain, redness, photophobia due to uveitis	Urgent referral (<1 wk); most cases resolve w/in 1–2 mo of d/c'ing agent
Scopolamine (incl patch)	↓ near vision due to accommodative impairment, pupil dilation	Dose- and proximity-related; may last several days after drug discontinuation
Sildenafil and other PDE5 inhibitors	Δ in color perception, blurred vision, conjunctival hyperemia, ocular pain, photophobia Common, dose-dependent, appears to be fully reversible	3% risk at doses of 50 mg, 10% at 100 mg, 40–50% at 200 mg; s/e start 15–30 min after ingestion, peak at 60 min; Avoid use if prior hx of nonarteritic anterior ischemic optic neuropathy (NAION)
Statins	Probable: diplopia, ptosis, ↓ EOM 2/2 to localized myositis	Reversible upon d/c, similar to known statin-induced myopathy
Sulfa- (incl. thiazide diuretics, acetazolamide, topiramate)	Acute angle closure glaucoma, choroidal effusions, acute or subacute transient blurred vision due to	Urgent referral to ophthalmology Usually reversed if d/c agent Patients with primary

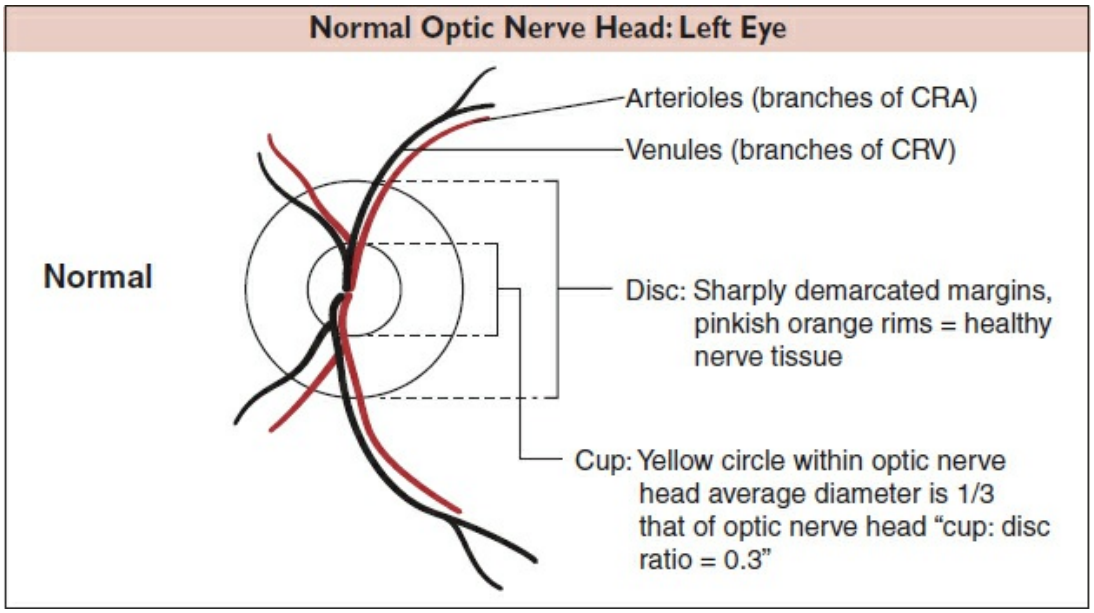
	myopia	*open-angle* glaucoma are not at ↑ risk
Tamoxifen	↓ vision due to crystalline retinopathy, cystoid macular edema, retinal hemorrhages, ? cataracts	Baseline eye exam then q4–6mo; d/c'ing drug may halt further ↓ VA but reversal is rare; raloxifene ↓ likely to cause SE
Tamsulosin and other alpha-adrenergic antagonists	Intraoperative floppy iris syndrome (IFIS) may complicate cataract surgery (highest risk w/ tamsulosin)	Alpha-1A blocking affects iris dilator muscle → atrophy from disuse; risk of IFIS persists yrs beyond d/c of drug
Vit A & derivatives (retinoids, Accutane)	↓ vision, transient obscurations assoc. w papilledema, ↑ ICP (vs. night blindness, dry eye if vit A deficient)	Risk occurs at ↑ doses

Drugs 2007; eyedrugregistry.com/aao-syllabus.html; aao.org

Exam

- **Visual acuity (VA):** Measure each eye separately w/ glasses if worn; standard Snellen chart at 20′ distance preferred; near card held at 14″ also OK; if VA 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); *SC:* without correction, *CC:* with correction
- **Color perception:** Unilateral "red desaturation" (red object appears "washed out") suggestive of optic nerve disease
- **Confrontational visual field:** Assess all 4 peripheral quadrants in each eye separately; field loss can suggest optic nerve pathology (often bitemporal), retinal detachment (RD; unilateral), advanced glaucoma, or neurological disease (e.g., homonymous hemianopsia)
- **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); previous ocular surgery or topical eye gtts can affect pupil exam

- **Extraocular movements:** Should be full & conjugate
- **Anterior segment exam:** Eval w/ penlight for lid changes, conjunctival hyperemia or hemorrhage, corneal opacity or epithelial defect (+ fluorescein staining with Wood lamp, see Figure in "Vision Loss"), anterior chamber (hypopyon, hyphema), iris (irregular shape, obvious defects), lens (visible opacity)
- **Direct ophthalmoscopy:** Allows provider to assess vitreous clarity (e.g., able to visualize nerve?) & evaluate for optic nerve edema, cotton wool spots, peripapillary/retinal hemorrhage; dilated exam provides for ↑ field of view and views of ↑ areas of retina



VISION LOSS

Overview (cdc.gov/visionhealth)

- Visual deficits affect >40 million adults in US; 16% of adults >40 y have cataracts, and 2% have glaucoma; visual loss affects 23.5% of US adults w/diabetes >50 y; only half of the 61 million adults at risk for vision loss have visited an eye specialist in the past year
- Important to recognize common causes of vision loss and those that require urgent referral; differential should be guided by acuity and

absence/presence of pain

Acute Painless Vision Loss

- **General approach: Requires same-day ophthalmology evaluation;** usually unilateral
- **DDx: GCA/temporal arteritis** (suspect if >50 y w/ new HA or diplopia; ⊕ systemic sx): amaurosis fugax, diplopia, jaw claudication, scalp tenderness, PMR; check ESR/CRP/PLT
  - **Nonarteritic ischemic optic neuropathy** (Mean age 60, ↑ in vasculopath, PDE5 use): painless ↓ vision, ⊕ RAPD, "altitudinal" (in horizontal plane) visual field defect, sectoral optic disc edema
  - **Central retinal artery occlusion** (Vasculopath, postcardiac surgery, 5–10% assoc w/ GCA)—presents w/ sudden profound ↓ VA, ⊕ RAPD, ± amaurosis fugax → ED for stroke w/u
  - **Central retinal vein occlusion** (hx HTN, DM, hypercoagulability, hyperviscosity, glaucoma, OCPs): variably ↓ VA, ± RAPD, + diffuse intraretinal hemorrhages
  - **Vitreous hemorrhage:** Commonly due to DM or RD/retinal tear; VA variable
  - **Retinal detachment:** Photopsias (flashes of light), floaters, variable ↓ VA/visual field; ± abnl red reflex
  - **Pseudosudden vision loss:** Gradual monocular vision loss may be perceived as "sudden" due to inadvertent occlusion of other eye; obtain careful hx

Acute Painful Vision Loss

- **General approach:** See "Painful Red Eye" in "*Eye Compllaints*" for further discussion
- **Optic neuritis:** Typically unilateral w/ age <50 y; ♀ > ♂; Etiologies include MS, idiopathic, infectious (e.g., postviral, Lyme), & granulomatous (e.g., sarcoidosis); *Sx:* Blurred vision, pain w/ EOM; photopsia, scotoma *Exam:* Variably ↓ VA, red desaturation, + RAPD, ± optic disc edema; **Refer w/in 24 h**

Gradual Painless Decreased Vision

- **General approach:** Determine if uni- or bilateral; routine referral appropriate if slow progressive loss over mo–y

- **DDx: Refractive error (improves w/ pinhole or glasses):** Myopia, hyperopia, astigmatism; presbyopia (farsightedness 2/2 ↓lens flexibility) if >40 y
- **Cataract:** Age-related (most common), metabolic, traumatic, congenital; *Sx:* ↑ glare, halos, difficulty w/ night driving, difficulty reading in low light, frequent change in glasses
- **Open-angle glaucoma:** Asx peripheral vision loss often w/ ↑ IOP & ↑ cup:disc ratio; *RF include:* ↑ Age, African or Hispanic ethnicity, ⊕ FHx; *Screening:* Refer if age >40 & 1st-degree relative w/ glaucoma; progression can be slowed/halted w/ proper tx (incl. laser trabeculoplasty, topical gtts, surgery if severe); Compliance w/ gtt important
- **Diabetic retinopathy:** Initially asx → **leading cause of legal blindness** among working-age Americans; Nonproliferative (NPDR, early stage) vs. Proliferative (PDR, late stage, neovascular); Common reasons for ↓ VA in DM: Diabetic macular edema (DME), vitreous hemorrhage, macular ischemia, tractional RD; *RF:* ↑ HbA1C, ↑ disease duration, HTN, ↑ lipids; *Tx:* Strict BP/glucose control; peripheral retinal laser (PRP) & intravitreal anti-VEGF if high risk for PDR; anti-VEGF (e.g., ranibizumab, aflibercept, off-label bevacizumab), intravitreal steroids, or macular laser for DME
- **Age-related macular degeneration (AMD):** ↓ central vision; most common cause of blindness in US; "dry" = slowly progressive disease, "wet" = neovascular w/ risk for sudden ↓ central vision due to hemorrhage; *RF:* **tobacco, poor diet/nutrition**,↑ age, ⊕ FHx, genetic polymorphisms; *Tx:* Monitor w Amsler grid (new metamorphopsia suggests progression), AREDS2 vitamins if moderate stage "dry," & intravitreal anti-VEGF as often as q1–2mo if "wet," sustained release drugs in pipeline
- **Medications:** See Table "Ocular Side Effects of Systemic Medications" in "*Ophtho Eval*"
- **Idiopathic intracranial hypertension (pseudotumor cerebri):** *RF:* ♀ gender, obesity, steroid use & cessation, high-dose vit A, tetracyclines, OCPs; *Sx:* Transient visual obscuration, diplopia, positional HA worse when supine, pulsatile tinnitus "whooshing sound," N/V; *Findings:* Variably ↓ VA, ± CN VI palsy, b/l optic nerve edema, MRI w/o mass/thrombi, ↑ICP; *Tx:* **Referral w/in 24 h;** see

Neurology section, *"HA"* for more details

- **Amblyopia:** Unilateral chronic ↓ VA due to asymmetric childhood cortical visual input; normal ocular findings, if mild, may not be detected until adulthood; *Tx:* Routine referral

Patient Information

- **Driving guidelines:** www.mdsupport.org/library/drivingrequirements.html
- **Patient education:** www.aao.org/eyesmart, for diabetic retinopathy: aao.org/eye-health/diseases/what-is-diabetic-retinopathy

EYE COMPLAINTS

General Approach

- Initial management by PCP often appropriate; routine referral → ophtho if sx >3–4 wk
- **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
- **Urgent referral for red flags & vision-threatening etiologies** (below); also 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
- Symptom-based approach to differential helpful (below):

Differential of Eye Complaints, by Presentation	
Painless red eye	Subconjunctival hemorrhage, episcleritis, dry eye syndrome (DES), blepharitis/meibomian gland dysfunction (MGD); *see below*
Painful red eye	Inflamed pingueculum or pterygium, acute conjunctivitis, keratitis, tear deficiency, iritis/uveitis, scleritis, endophthalmitis, acute angle closure glaucoma; *see below*
Photophobia	Iritis/uveitis, corneal abrasion, keratitis, DES, postconjunctivitis,

	retinal macular diseases (chronic), physiologic
Eye itching/burning	Infectious or allergic conjunctivitis, blepharitis, DES, pterygium
Foreign-body sensation	Corneal or upper lid foreign body, DES, trichiasis (misdirected eyelashes), conjunctivitis
Swollen eyelid	Hordeolum/"stye" (chronic → chalazion), atopic dermatitis, contact dermatitis, preseptal cellulitis, orbital cellulitis
Drooping eyelid	Ptosis, dermatochalasis (excess upper eyelid skin)
Other	"Bubble on the white part": conjunctivochalasis (redundant conjunctiva), conjunctival cyst, pingueculum → all nonurgent referral "Dot on the clear part": corneal foreign body, corneal ulcer

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Painless Red Eye

Painless Red Eye

- **Subconjunctival hemorrhage:** *Etiologies:* Valsalva, eye rubbing, HTN, bleeding dyscrasia, anticoagulant use, idiopathic; *Findings:* Unilateral, no vision change; well-demarcated plane of heme obscuring sclera; *Rx:* **urgent referral if bullous or follows significant trauma,** otherwise benign—artificial tears PRN discomfort, check BP, check PLT, & coags if recurrent
- **Episcleritis:** Idiopathic, self-limited unilateral, painless focal erythema w/out d/c or vision change; *Findings:* Mild hyperemia of superficial vessels, possibly sectoral; *Rx:* Artificial tears, referral if persistent or recurrent
- **Dry eye syndrome:** *S/sx:* Bilateral burning, FB sensation, ↑ by wind/cold & prolonged eye use (e.g., computer, tablet, reading), ± reflex tearing; mild diffuse hyperemia, sx severity disproportionate to exam findings, often coexistent with blepharitis; may have diffuse punctate staining on fluorescein exam (see *"Findings in Common Eye Disorders"*). *Etiologies:* ↓ tear production or ↑ evaporation from altered composition; idiopathic, autoimmune, rosacea, or 2/2 meds. *Rx:* Artificial tears QID, artificial tear gel QHS, omega-3 supplementation (e.g., Fish Oil 1000 mg PO BID), cyclosporine (Restasis) or lifitegrast (Xiidra) by ophthalmologist

- **Blepharitis/Meibomian gland dysfunction:** Chronic b/l lid margin inflammation → burning, itching, mild AM lid crusting, minimal d/c, sx worse in AM, dandruff-like flakes on lashes, mild diffuse hyperemia *Rx:* Warm compresses BID, gentle lid scrubs (commercially available), artificial tears PRN, erythromycin or bacitracin ophthalmic ointment BID if severe

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Painful Red Eye

- **Inflamed pingueculum or pterygium:** ± hx UV/sun exposure; irritation, foreign body sensation; *Findings:* Wing of hyperemic thickened tissue from conjunctiva (often nasal) → cornea; *Rx: UV protection,* artificial tears PRN, referral if persistent
- **Keratitis (corneal inflammation)** *S/sx:* pain & photophobia, tearing, ± ↓ vision, diffuse hyperemia ± mild lid edema; pain relieved w/ proparacaine gtts
  - *Corneal ulcer (usually bacterial):* White **corneal opacity often visible w/ penlight**, ± mucopurulent d/c, ± hypopyon, often hx contact lens use; **same-day referral**
  - *Herpetic:* **Vesicles in V1 dermatome on affected side** (VZV), ± lid vesicles or hx oral lesions (HSV), corneal dendrites w/ fluorescein & Wood lamp (see *"Findings in Common Eye Disorders"*) → start systemic tx (e.g., valacyclovir 1 g PO TID), see "*HSV*"; **same-day referral**
  - For management of UV or chemical-associated keratitis, as well as corneal abrasion, see *"Eye Injury"*
- **Severe tear deficiency** (e.g., Sjogren's, ocular GVHD): **Diffuse punctate staining may be visualized on fluorescein exam** (see "*Findings in Common Eye Disorders*"); Preservative-free artificial tears q1h while awake, gel lubricants qhs, refer w/in 1 wk, sooner if severe pain or ↓ VA
- **Iritis/Uveitis:** Autoimmune disease (assoc w/ HLA-B27), post-trauma, idiopathic; *S/sx:* Often unilateral, severe photophobia, tearing, ↓ vision, conjunctival & limbal hyperemia, sluggish pupillary rxn → **Refer w/in 24 h**, defer steroids until after ophtho exam

- **Scleritis:** vasculitis, 50% assoc w/ autoimmune dz (e.g., RA). *S/sx:* **"Boring" HA-like pain**, sectoral or diffuse boggy red/pink sclera, exquisitely tender globe, pain w/ EOM, wakes pt from sleep, vision change rare. *Rx:* Oral NSAIDs (e.g., naproxen 250–500 mg BID), **refer w/in 24 h**
- **Endophthalmitis:** Assoc w/ hx recent eye surgery or intravitreal injection, IDU, trauma, immunosuppression, systemic bacteremia or **fungemia**; *S/sx:* Severe pain, floaters, ↓ vision, variable degrees of conjunctival injection, + hypopyon → **same-day referral**
- **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 gentle palpation through lids → **same-day referral**

Acute Conjunctivitis (*JAMA* 2013;310:1721)

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; POC adenoviral swab commercially available may help with diagnosis/risk stratification
- **Viral:** *Microbiology:* Frequently adenovirus, highly contagious; *Hx:* ± sick contact, URI sx, watery discharge, gritty sensation, mild photophobia, itching, crusty eyelids, unilateral can → bilateral; *Exam:* Diffuse hyperemia, ± periocular swelling, seromucoid discharge, preauricular LAD common, epidemic keratoconjunctivitis (EKC) may → sequelae, refer if ↓ vision, severe photophobia
- **Bacterial:** *Microbiology:* Typically *S. pneumoniae, S. aureus,* or *H. influenzae,* contagious; may also be chlamydia (1–5% of all cases) or gonorrheal, often if concurrent genital infection; *Exam:* Thick/purulent d/c; copious crusting, 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 weeks-months, usually *C. trachomatis,*

suspect if no improvement w/ ocular abx

- **Allergic:** Commonly occurs w/ allergic rhinitis; *Precipitants:* Ragweed, grass pollen common; *hx:* chronic or seasonal pattern, hx atopy, "watery" discharge, severe ocular pruritus; *Exam:* b/l, mild hyperemia, serous/stringly discharge

Treatment

- **Counseling:** No contact lens wear while sx present; 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 ointment 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, health care worker, or tx prerequisite to return to work/school; also tx if chlamydial or gonorrheal
- **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)
- **Recurrent or chronic:** refer to r/o insidious or chronic infectious/inflamm etiology

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Eyelid Complaints (*AFP* 2015;92:106)

Swollen Lid

- **Hordeolum ("stye"):** Acute lid inflammation due to occluded meibomian gland; *S/sx:* Lid erythema, typically focal palpable and/or visible tender nodule; ± conjunctival hyperemia, drainage, cellulitis; *Rx:* Warm compresses QID, erythromycin oint BID, oral abx if cellulitis present (see *"Skin and Soft Tissue Infections"*)

- **Chalazion:** Chronic granulomatous lesion resulting from obstructed gland; *S/sx:* typically painless, rubbery nodule; *Rx:* warm compresses; referral to ophthalmology if persistent
- **Contact dermatitis (see *"Dermatitis"*):** Use caution with steroid ointments around eyes; recommend low-potency (e.g., loteprednol, fluorometholone if possible, otherwise Dex/Neo/Poly ophthalmic ointment); need Ophthalmology f/u if long-term use of periocular steroid
- **Preseptal cellulitis:** Superficial periocular skin infection, may be assoc w/ hordeolum, hx eyebrow tweezing, no visual s/sx, eyes white and quiet; tx with antibiotics (e.g., amox/clav, cefpodoxime); see *"Skin and Soft Tissue Infections"*
- **Orbital cellulitis:** *RF:* Hx sinusitis, orbital trauma, facial surgery, diabetes/DKA; *S/sx:* Severe lid edema & erythema, chemosis, ↓ VA, proptosis, ↓ EOM ± diplopia, pain w/ EOM, HA, ± nasal congestion, ± fever; *Rx:* orbital or maxillofacial CT w/ contrast, CBC, **same-day referral w/ hospital admission for IV abx, close monitoring**
- **Idiopathic orbital inflammation/orbital pseudotumor:** *S/sx:* Can mimic orbital cellulitis (must r/o infectious etiology first); **same-day referral as above**

Droopy Lid

- **Ptosis:** congenital, age-related (levator muscle dehiscence), postsurgical (eyelid speculum can hasten dehiscence)
- **Dermatochalasis; redundant upper eyelid skin, benign**

Lid Skin Lesion or Rash

- Differential includes SCC or BCC; see *"Skin Cancer";* consider atopic dermatitis, contact dermatitis, HSV, or rosacea (see respective chapters)

EYE INJURY

General Approach (*AFP* 2015;92:106)

- Detailed hx re: mechanism & general ophthalmic screening exam critical

- **Urgent referral** if ↓ vision, or ambiguity re: mechanism of trauma or full extent of injuries
- 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., polycarbonate safety goggles/glasses w/ yard & household chores; appropriate occupational eyewear)

Cornea and Conjunctiva

- **Chemical (acid/alkali) 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, litmus paper placed under lower lid (nl 6.8–7.2); followed by proparacaine drop & irrigation w/ Ringer's or saline for 30 min; recheck after 10 min & continue cycle until pH neutralized; ensure fornices adequately flushed as retained particulates may prevent neutralization. *Tx:* Refer w/in 24 h in all cases w/ erythromycin or bacitracin ophth 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 exposure:** Follows unprotected exposure to welder's arc, tanning bed, high-altitude "snow blindness," electric sparks; sx often begin hrs post-exposure; *Findings:* punctate or confluent fluorescein staining on cornea; *Rx:* Artificial tears q1h PRN, erythromycin oint QID × 5 d; **refer if severe or not improved w/in 24 h**
- **Corneal abrasion:** (*AFP* 2013;87:114) Often hx *mild* identifiable trauma; *Sx:* Pain, FB sensation, photophobia, tearing; *Findings:* ± ↓ VA if within visual axis, pain relieved w/ topical proparacaine, focal fluorescein staining w/ Wood lamp (see *"Findings in Common Eye Disorder"*), possible FB w/ eversion of upper lid; *Tx:* No contact lenses until healed; patching not routinely done; **do not send home w/ topical anesthetics;** artificial tears & cool compresses PRN; *Peripheral abrasion:* 0.5% erythromycin oint QID × 5 d for small

(e.g., 1–2 mm diameter); if larger or from contaminated object (e.g., fingernail, organic material) add FQ (e.g., 0.3% ofloxacin 1gtt QID × 5 d); **Refer w/in 24 h** if *central (involving visual axis, or concern for corneal laceration);* **Refer if not improved w/in 48 h**

- **Cyanoacrylate adhesive ("Super glue"):** *Tx:* Warm compress to separate lids/lashes; glue usually flakes off over days; do not cut lashes w/o ophtho involvement; tx as corneal abrasion
- **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; fluorescein staining (see *"Findings in Common Eye Disorder"*); *Tx:* Conjunctival: *If provider comfortable,* may remove conjunctival FB w/ cotton swab & tx w/ 0.5% erythromycin or bacitracin ophthalmic ointment QID × 5 d; corneal: **Refer w/in 24 h**

Anterior Chamber

- **Hyphema:** Typically follows blunt orbital trauma (e.g., soccer ball or fist) but maintain suspicion for penetrating injury; *Sx:* Dull pain, ± ↓ vision; *Findings:* ± ↓ VA, clot or layered blood in the anterior chamber visible w/ penlight; may have ↑ IOP; *Tx:* **Same-day referral:** 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**

Orbit, Adnexa, and Globe

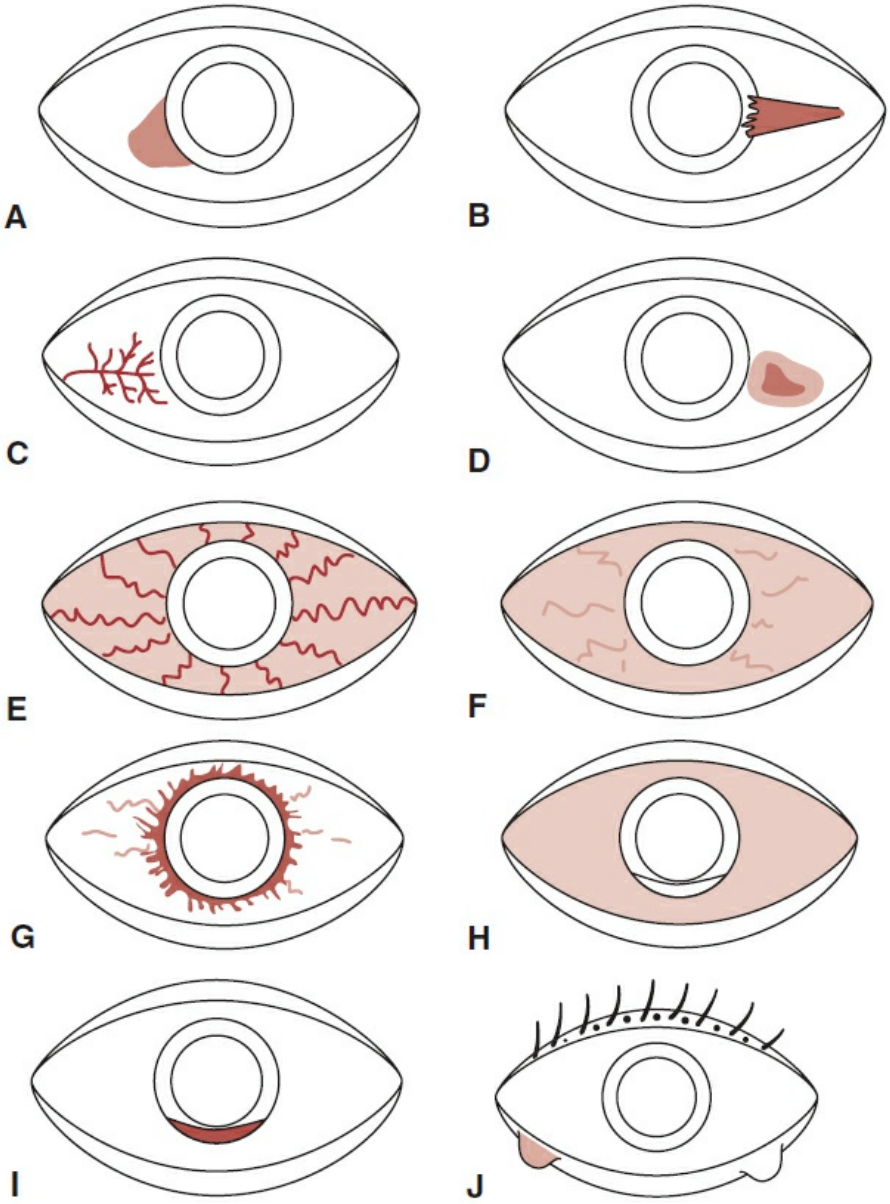
- **Orbital fracture:** Follows blunt trauma (e.g., MVC, fist, fall); *Findings:* Periorbital ecchymosis, point tenderness ± palpable orbital rim deformities, V1/V2 hypesthesia, painful or ↓ EOMs; *Tx:* **ED/Same-day referral** for imaging & DFE
- **Lid lacerations:** Superficial-appearing injuries may mask more

significant injury to surrounding tissues and globe; *Tx:* Tetanus update, cool gauze to injury, **same-day referral** for repair

- **Ruptured globe:** Full-thickness disruption of eye wall; can follow penetrating **or** blunt injury; have ↑ suspicion in elderly w/ facial trauma after fall (esp. w/ hx prior eye surgery); *Findings:* ↓ VA (mild to NLP), subconjunctival hemorrhage (↑ suspicion if circumferential & bullous), irregular or peaked pupil, shallow anterior chamber w/ penlight, leaking intraocular fluid visualized w/ fluorescein & Wood lamp; *Tx:* **Emergent referral for suspected rupture as repair w/in 24 h å risk of endophthalmitis**, NPO, update tetanus, place hard protective shield over the eye

FINDINGS IN COMMON EYE DISORDERS

External Ocular Exam Patterns



A. Subconjunctival hemorrhage: Well-demarcated erythema that obscures sclera; rest of eye uninvolved

B. Inflamed pterygium: Wing of inflamed tissue.

C. Episcleritis: Focal hyperemia of superficial vessels

D. Nodular scleritis: Localized, deep red boggy sclera, may be raised; very tender

E. Diffuse scleritis: Engorged, tortuous scleral vessels w/overlying redness; excessive tearing/ discharge absent

F. Viral conjunctivitis: Diffuse pink "glassy" appearance 2/2 tearing ± conjunctival edema; elevated "tear lake"

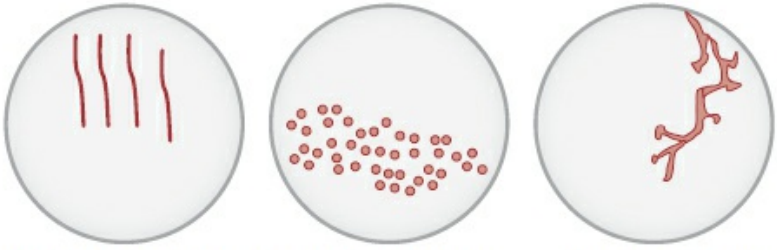
G. Anterior uveitis: Ciliary flush (may also be seen with mod-severe keratitis)

H. Endophthalmitis: Diffuse injection with hypopyon (layering of pus in anterior chamber)

I. Hyphema: layering of blood in anterior chamber (usually traumatic)

J. Meibomian Gland Dysfunction: prominent inspissation of Meibomian glands (white dots along lid margin); gland obstruction can → indurated nodule (acute/inflamed = hordeolum; chronic = chalazion)

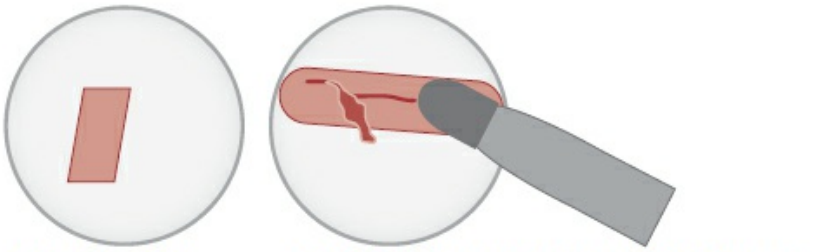
Fluoroscein Staining Patterns



Vertical striations: Evert upper lid to check for a foreign body

Punctate staining: Ocular surface dryness, contact lens overuse, "superficial punctate keratopathy" (SPK)

Dendritic: branching w/ or w/o terminal bulbs → HSV or VZV keratitis

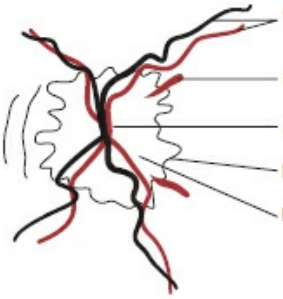


Confluent staining: Corneal abrasion. Edges may be rolled or irregular-appearing

Seidel-positive full-thickness laceration: Aqueous leakage visible after fluorescein strip painted on eye. Appears green if viewed under blue light. Beware: some full thickness lacerations are self-sealing and may be Seidel-negative

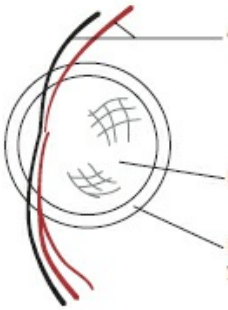
Fundoscopic Exam Patterns (L eye)

Acute ONH Edema



- Tortuous/congested vessels
- Flame hemorrhages
- Almost obliterated cup
- Feathery margins
- Nerve tissue may appear whitish

Advanced Glaucoma



- "Nasalization" of vessels
- Large central cup: cup:disc ratio ≈ 0.95
- Extremely thin rim of yellowish/pink tissue

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 increasing; highest in children and teens; currently affects >8% of US adults; accounts for >13 million US health care visits annually (cdc.gov/nchs)
- **Risk factors:** Include ⊕ FHx of allergic disease (possibly mediated by genetics [multiple loci]), ↑ exposure to pollutants, dust mites, and early exposure to cigarette smoke (*JACI* 2011;128:816)
- **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 (*JACI* 2002;109:57); ocular sx occur in 50–70% of pts w/ AR (see *"Eye Complaints"*); 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 sx, 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	Tree **pollen** (spring), grasses (summer), weeds (fall)
Perennial	Animal hair (cat, dog, etc.), **dust mites**, **cockroaches** (urban areas), mold
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, or GPA) 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, HCTZ, β-blockers; and OCPs (*JACI* 2006;16:148) rhinitis medicamentosa ("rebound" 2/2 chronic use of topical nasal decongestants, e.g., oxymetazoline; also seen w/ cocaine)
  - *Autoimmune:* Churg–Strauss, GPA, 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 wk) vs. persistent (>4 d/wk or >4 wk)
  - *Severity:* Mod–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, risk of *N. fowleri*); 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 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 Can ↓ to 1 spray/nostril QD for maintenance; onset ~12 h, should be used consistently for ↑ efficacy Also effective in mixed rhinitis (e.g., irritant) *S/e:* Nasal irritation, epistaxis, bitter taste; systemic s/e rare 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 Cetirizine 10 mg QD **2nd-generation preferred** (↓ sedation, ↓ anticholinergic effects, although may be ↓ effective rhinorrhea tx) Faster onset, less effective than ICS for severe disease or nasal congestion; can be used PRN but more effective if used regularly Fexofenadine/loratadine/desloratadine less sedating, cetirizine more sedating

	Cetirizine and loratadine are category B for pregnancy
Nasal antihistamines	**Azelastine 1–2 sprays/nostril BID or olopatadine 2 sprays/nostril BID** Equal or superior efficacy to oral Rx for nasal sx; less effective than intranasal corticosteroids *S/e:* Bitter taste, somnolence May be given in combination with glucocorticoid sprays and oral antihistamines
Intranasal anticholinergics	Ipratropium (0.03%): 2 sprays/nostril BID–TID Good for ↓ rhinorrhea; not effective at ↓ congestion
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

- **Other:**
  - **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
  - **Acupuncture:** Nonpharmacologic therapy; may ↑ QoL and ↓ symptoms (*Ann Allergy Asthma Immunol* 2015:115:4)
  - **Oral decongestants**: Pseudoephedrine: IR: 60 mg q4–6h; Extended release: 120 mg q12h or 240 mg QD (max 240 mg/24 h); **unclear efficacy**—may be no better than placebo; use only short term (5–7 d) (*JACI In Practice* 2015;3:5); *S/e:* HTN, insomnia, palpitations, urinary retention

When to Refer

- **Allergy/immunology:** For severe/refractory/recurrent sx; for allergen-specific IgE skin/serum testing; if dx uncertain; for treatment with sublingual immunotherapy (ragweed or grass pollen) or subQ **immunotherapy** (*desensitization, "allergy shots,"* often requires 3–5 y of tx) to alter immune response
- **Otolaryngology:** If suspect structural etiology (e.g., deviated septum, nasal obstruction)

UPPER RESPIRATORY INFECTION

Background (*Ann Intern Med* 2009;151:ITC-5-1; *NEJM* 2003;348:1256; 2009;360:2245)

- "The Common Cold"; adults have 2–3 viral upper respiratory infections each y → 25 mil 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 *"Pharyngitis," "Allergic Rhinitis," "Rhinosinusitis," "Otitis," "Pneumonia," and "Influenza"*)
- Sinus inflammation occurs in majority of cases, but only ~2% of cases complicated by bacterial rhinosinusitis (see *"Rhinosinusitis"*)

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 weeks**; 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** (see *"Influenza"*)
- **Exam:** *HEENT:* Nasal discharge, middle ear effusion, sinus tenderness, tonsillar exudates; *Lymph nodes:* Cervical, periauricular; *Pulmonary:* Consolidation, wheezing
- **Diagnostics:** None needed in simple URI, if influenza suspected, see below

Treatment

- **Supportive care** (*AFP* 2012;86:153; 2016;94:1016)
  - **Decongestants:** Intranasal oxymetazoline (limit to 3 d to avoid rebound congestion), phenylephrine, pseudoephedrine; caution in pts w/ arrhythmias, HTN
  - **Antihistamines:** Diphenhydramine, chlorpheniramine effective if combined w/ 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 Rx of sx relief agent above); (4) Advise f/u if sx do not improve

Abx misuse: Risks include disruption of nl flora, *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 home

RHINOSINUSITIS

Background (*Otolaryngol Head Neck Surg* 2015;152:S1)

- **Rhinosinusitis (term preferred to "sinusitis," as nasal cavity inflammation almost always accompanies sinusitis)** 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
- **Etiology: Viral rhinosinusitis (VRS) accounts for >98% of acute rhinosinusitis;** only 1–2% go on to develop secondary acute bacterial infection **(acute bacterial rhinosinusitis, or ABRS)**
- **Pathogens:** *Viral:* Rhinovirus, parainfluenza, influenza; *Acute bacterial: H. flu* (75%), *S. pneumoniae*, *M. catarrhalis*; *Chronic:* Bacterial often involved (although may not be primary cause): *S. aureus*, anaerobes; *Fungal:* Mucor, rhizopus, aspergillus

- **Epidemiology**: >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)
- **Prescription antibiotic overuse: More than half of US pts presenting to PCP w/ uncomplicated acute rhinosinusitis receive antibiotic Rx; acute rhinosinusitis is associated w/more outpt abx Rx than any other diagnosis;** abx overuse → abx resistance (*Laryngoscope* 2016;126:2439, *Otolaryngol Head Neck Surg* 2015;137:152)
- Complications of ABRS are rare (1/10,000 cases); most common are orbital (orbital cellulitis or abscess) & CNS (meningitis or epidural abscess)
- **Risk factors:** *VRS*: Upper respiratory infection (87% assoc w/sinus inflammation)

  ABRS: Allergies, mechanical obstruction of the nose, swimming, odontogenic infection, intranasal cocaine, impaired mucociliary clearance (CF, cilial dysfunction, **smoking**)

  Chronic: Allergy, immunosuppression or immunodeficiency (CVID, IgA deficiency), ciliary dyskinesia (incl CF), Aspirin-Exacerbated Respiratory Disease (AERD, formerly Samter's Triad), nasal polyps

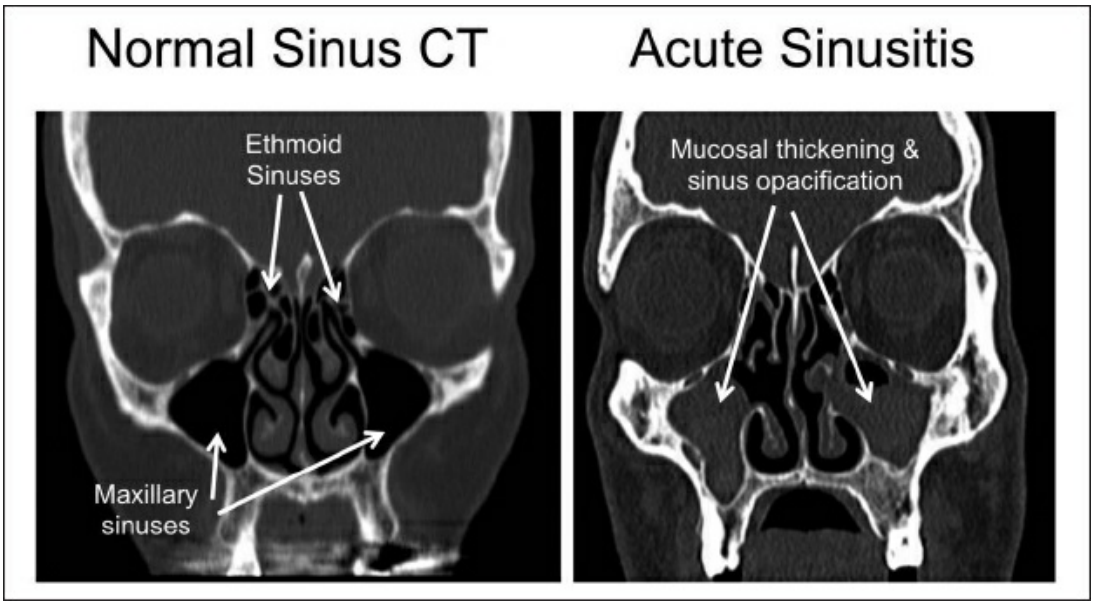
  Invasive fungal: Immunosuppression, DM

Evaluation (*Ann Allergy Asthma Immunol* 2014;113:347; *NEJM* 2004;351:902)

- **General approach:** Dx of CRS and distinction between VRS & ABRS are **clinical**; consider fungal on DDx for all pts w/chronic sinusitis or those w/ DM or immunocompromise; ask about red flags (below) and obtain further imaging/eval if ⊕
- **History:** Nasal congestion, purulent nasal discharge, facial pain/pressure, hyposmia/anosmia, tooth discomfort (ABRS Se/Sp 66%/49%), cough, HA, fever, malaise, halitosis, ear pressure/fullness
- **Exam:** Purulence of nasal cavity/posterior pharynx (ABRS Se/Sp 35%/78%), nasal turbinate edema, ↑ pain w/ leaning forward (ABRS Se/Sp 75%/77%)
- **Red flags**: Dark, necrotic turbinates (suspect fungal = **surgical emergency**), *Systemically ill:* High fevers (>102°F), *Orbital*

complaints: Eyelid edema/erythema, proptosis, visual Δ, diplopia, ophthalmoplegia, *CNS complaints:* Severe HA, ΔMS, stiff neck → ED; **persistent unilateral sx should ↑ concern for neoplasm**

- Labs: None typically needed (may be helpful in the acutely ill); pts with CRS or recurrent acute rhinosinusitis (RARS) should be tested for specific IgE antibodies to airborne allergens (by allergist/immunologist)
- **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



Sinusitis Diagnostic Criteria	
Acute bacterial rhinosinusitis (ABRS)	≤4 wk of s/sx that are: **Persistent:** >10 d w/o improvement *and* **Severe:** Temp >102°F, severe facial pain/purulent discharge *and* **Worsening:** "Double-sickening": 5–6 d of typical URI, initially improving → new onset of fever, HA, ↑ nasal d/c
Recurrent acute rhinosinusitis (RARS)	ABRS occurring ≥3–4 (guidelines vary) times/y **w/o** s/sx of rhinosinusitis btw episodes; each episode must meet ABRS diagnostic criteria
Chronic rhinosinusitis	≥12 wk 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) **Hyposmia** (↓ sense of smell [hyposmia])

- **DDx:** *Acute:* URI, noninfectious rhinitis (see *"Allergic Rhinitis"*), HA (migraine, tension, cluster), odontogenic pain (see *"Dentofacial Pain"*)

  Chronic: AR, nonallergic rhinitis, septal deviation, nonrhinogenic facial pain; neoplasm

Treatment (*Otolaryngol Head and Neck Surg* 2015;152:S1)

- **General approach:** All pts should be offered sx treatment; those w/coexisting asthma or other comorbidities should have lower threshold for abx tx, but for most patients antibiotics not indicated
- **Symptomatic:** Recommended in all acute rhinosinusitis

  Oral analgesics/antipyretic: APAP, NSAIDs
  Oral decongestants: Pseudoephedrine, 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 ↓ rhinorrhea & nasal obstruction (*Allergy* 1997;52:650), no efficacy studies 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 & risk for harm if pts w/ VRS; for ABRS, data mixed re: effectiveness (likely in part 2/2 inclusion of VRS in trials → ↓ est of tx effect); however, can ↓ risk of serious complications, particularly in immunocompromised (cdc/gov/getsmart)

  Mild illness or dx uncertain: Reasonable to prescribe watchful waiting; initiate abx if no improvement after 3–7 d and can ensure f/u (consider "Wait and see" Rx – see *"Otitis"*)
  Mod illness or mild illness in immunocompromised/ill: Empiric tx

(table)

Severe illness: Referral (below), esp in immunocompromised

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 true 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 in true 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*)

- **Chronic sinusitis treatment:** (Once confirmed) intranasal corticosteroids, nasal irrigations, allergen control & reduction (antihistamines, allergen immunotherapy, avoidance measures), consider surgical tx in refractory disease

When to Refer (*Clin Infect Dis* 2012;54: e72)

- **Emergency department:** If red flags (above) → ED for urgent CT w/contrast, initiation of abx, & ENT eval, ophthalmology, possible neurosurgery consultation
- **Infectious disease (ID):** Immunocompromised, multiple limited tx options or h/o unusual organisms
- **Otolaryngology or allergy/immunology:** Referral indicated if
  - **CRS:** All pts with w/ confirmed/suspected CRS (ideally w/ CT prior to visit)
  - **RARS:** Concern for immunodeficiency or anatomic abnormality; pts w/allergic component 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 desired), allergy (if allergy suspected), or ID (if resistance suspected, immunocompromised host)

PHARYNGITIS

Background (*AFP* 2011;83:26; *Infect Dis Clin North Am* 2007;21:449; *NEJM* 2001;344:205)

- **Epidemiology:** Pharyngitis (sore throat, hoarse voice) results in ~2M outpatient visits in US annually (*Vital Health Stat* 2011;13:169). Commonly results in inappropriate antibiotic rx; 50–70% tx w/antibiotics despite GAS prevalence of 20–30%; significant contributor to population-level abx resistance
- **Etiology:** 25–45% viral, 20% bacterial, (co-infection w/ group A *Streptococcus* [GAS] + viral may occur), 30% no pathogen isolated (*Mandell,* 2011;815:821); STIs, GAS, EBV, *Arcanobacterium haemolyticum*, *Fusobacterium necrophorum* more likely in younger pts
- **Complications:** Rare, but can include peritonsillar or retropharyngeal abscess, suppurative jugular thrombophlebitis (Lemierre syndrome 2/2 *F. necrophorum*); spread to parapharyngeal space (carotid sheath) or sublingual space (Ludwig angina)

Evaluation (*Ann Intern Med* 2009;151:812; *NEJM* 1999;340:969; 2011;364:648)

- **History:** Inquire about coryza-like sx (URI, influenza), profound fatigue, wt loss (EBV), fever (GAS, EBV, influenza), new sexual partners and oral sex (gonorrhea, HIV, HSV), rash (GAS, *A. haemolyticum*)
- **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), scarlatiniform rash (GAS, *A. haemolyticum*),
- **Other etiologies:** HSV (5–10% pharyngitis in college students;

minority assoc w/ anterior mouth or lip lesion see *"HSV"*); *Mycoplasma* & *Chlamydophila* pneumoniae (assoc w/ acute bronchitis); influenza (assoc w/ cough, coryza see *"Influenza"*); gonorrhea (assoc w/ urethritis see *"STI"*); thrush (DM, recent steroids, immunosuppressed)

- **Red flags:** Systemic toxicity/respiratory sx; severe unilateral pain, inability to swallow, drooling, hoarse voice, trismus, worsening sx after several days (peritonsillar or retropharyngeal abscess), pseudomembrane, ↑↑ tonsillar swelling (diphtheria)
- **General approach:** No need for testing if suspect viral etiology; consider throat culture if suspect *F. necrophorum* or *A. haemolyticum*; GAS testing as below
- **If EBV is suspected: 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 (*Ann Intern Med* 2001;134:506; *CID* 2002;2:113)

- **Sx management:** Antipyretics, NSAIDs, warm salt water gargles, lozenges, humidifier
- **Non–GAS infection:** Group G or C β-hemolytic strep: not assoc w/ rheumatic fever, but abx *may* result in earlier sx relief (*BMJ* 2000;320:150); in young adults **w/o** associated viral sx, *F. necrophorum* causes similar proportion of pharyngitis to GAS; consider empiric tx (B-lactam, clindamycin, or flagyl, **not** macrolide)
- ***N. gonorrhoeae:*** Treat as per genital infection (see *"Sexually Transmitted Infections"*); more difficult to clear from oropharynx than from GU tract
- **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, stiff neck

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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 **reduce symptoms:** Sore throat & fever ↓ by 0.5–3 d, **prevent suppurative complications:** sinusitis, parapharyngeal abscess; **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 pretest probability, treat if rapid test ⊕ otherwise wait for culture; if high pretest probability: Treat empirically w/o testing; empiric tx can lead to unnecessary abx use (59% appropriate, 32% unnecessary, 9% underuse)
- **Testing:** *Rapid* Ag-*detection test:* (Se 86%; Sp 95%) (*Cochrane Database Syst Rev* 2016;7:CD010502); 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; not needed in adults due to very low incidence of GAS pharyngitis and rheumatic fever*; 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 ë 10 d** or benzathine PCN G 1.2 million units IM × 1; alternatively amoxicillin 500 mg BID × 10 d; if pen-allergic (not anaphylaxis), cephalexin 500 mg BID × 10 d or clindamycin 300 mg TID × 10 d; often macrolide resistant; avoid unless confirmed sensitivity; NSAIDs helpful but adjunctive tx with steroids not recommended
- **Follow-up:** Advise pts to seek care if no sx improvement 3–4 d after abx; failure to improve → reconsider dx or 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%	
2	11–17%	Test, treat pts w/ a ⊕ rapid test or cx
3	28–35%	Option 1: Test, treat pts w/ a ⊕ rapid test or cx Option 2: Treat empirically
4	51–53%	Treat empirically

HOARSENESS

Background (*JAMA* 2009;302:1954; *Otolaryngol Head Neck Surg* 2009;141:S1)

- **Definition:** Hoarseness (dysphonia) is a change in voice quality, pitch, amplitude, or vocal effort that impairs communication or reduces voice-related QoL
- **Physiology:** Phonation requires harmonic function of the cartilaginous skeleton, mucosa (incl vocal folds), muscles (intrinsic & extrinsic), & nerves (vagus, recurrent, & superior laryngeal); airway obstruction → hoarseness can occur at any level and in multiple anatomic structures (oral cavity, pharynx, larynx, or trachea)
- **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)

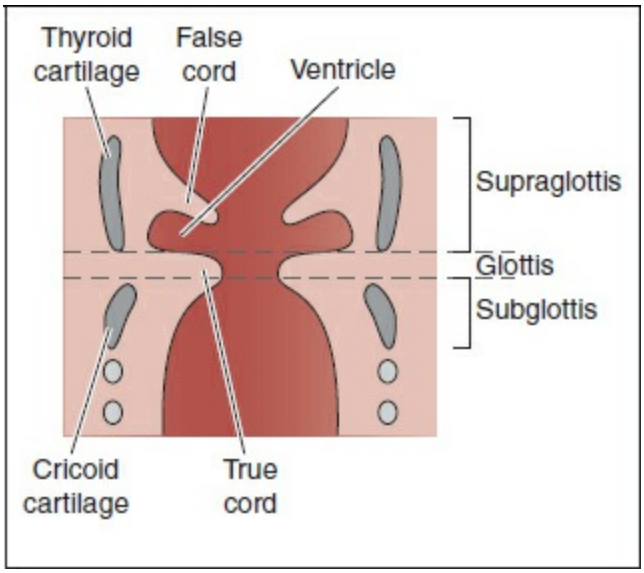

Figure 10-1. Larynx (Coronal View)

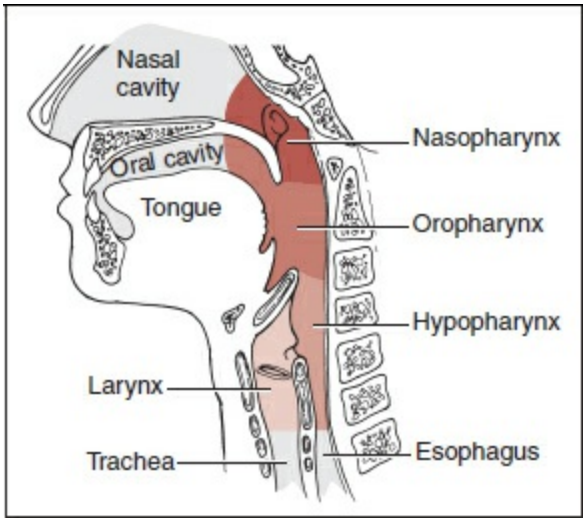

Figure 10-2. The Upper Aerodigestive Tract (Sagittal View)

Modified from Oatis CA. Kinesiology: The Mechanics and Pathomechanics of Human Movement. 3rd ed. Philadelphia, PA: Wolters Kluwer, 2016.

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, 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 (*Rubin et al. Diagnosis and Treatment of Voice Disorders, 2006*)

- **General approach:** Specific etiologies below; most cases self-limited/benign; refer for full ENT exam and laryngoscopy if dysphonia persists >2 wk 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
- **Acute infectious laryngitis:** Acute inflammation/edema of entire larynx; may be 2/2 phonotrauma (voice misuse, protracted coughing → hemorrhage of true vocal cord); viral (rhinovirus > VZV, coronavirus), or rarely bacterial (dramatic, more commonly epiglottis) or fungal; *S/sx:* loss of voice +/– fever, cough, throat pain, difficulty swallowing; may occur w/hemorrhage—abrupt onset during ↑ vocal cord effort (see *"Hemoptysis"*); *Tx:* Phonotrauma or viral; supportive/rest; **no role for abx or steroids**
- **Chronic infectious laryngitis:** Similar process to acute but longer time course; more likely to be 2/2 bacterial (incl TB) or fungal infection; refer and tx underlying process
- **Laryngeal irritation:** Multiple etiologies: Smoking, EtOH, GERD, inhaled fumes/smoke, vocal strain, post-nasal drip; *Tx:*

Withdraw/treat irritants or treat underlying d/o, refer if refractory/persistent; more details on specific etiologies below

- **Laryngopharyngeal reflux:** Damage to supraglottic and glottic mucosa by reflux contents (controversy re: role of acid in damage); presents w/ throat clearing, persistent cough, dyspepsia, & globus present in >95% (*Curr Opin Otolaryngol Head Neck Surg* 2006;14:143); *Tx:* Consider trial of acid suppression/PPI; no evidence to initiate w/o other GERD sx
- **Neurologic:** Incomplete closure of vocal cords; presents w/ breathy voice
  - Unilateral true cord paralysis: 2/2 nerve injury, compression, neuropathy; *Tx:* laryngoscopic tx/VF injections or surgery
  - *Bilateral paresis:* Consider MG, ALS (25% p/w dysphonia); *Tx:* Refer for swallow eval
  - *Parkinsonism:* Hypophonia, tremor, breathiness, monotone: *Tx:* See *"Parkinson's"*
  - *Essential tremor:* (25% have laryngeal tremor); *Tx:* see *"Tremor"*
- **Functional:** Dx of exclusion, cannot be made w/o laryngoscopy; often occupational; paradoxical true vocal cord motion (dysphonia w/ stridor), conversion d/o (see *"Somatic Symptoms"*); *Tx:* Voice therapy (*Otolaryngol Head Neck Surg* 2008;138:557)
- **Other:**
  - *Benign vocal fold lesions:* Polyps, nodules, or polypoid corditis affecting true vocal cords; presents w/coarse, irregular voice, chronic hoarseness: generally 2/2 chronic irritation
  - *Systemic inflammation:* Deposition of inflammatory cells in larynx (sarcoidosis → supraglottic, amyloidosis → glottis)
  - *Autoimmune disease:* Epithelial loss & inflammation triggered by auto-antibodies; can affect entire larynx

DENTOFACIAL PAIN

Background

- Pain may be 2/2 pathology of nerves (CN V), joints (temporomandibular joint, or TMJ), bones (maxilla/mandible), teeth,

salivary glands, soft tissue (gums, oral mucosa)

Evaluation (*NEJM* 2008;359:2693)

- **History:** Onset & duration of sx; assess for facial/alveolar erythema/swelling (dental or salivary infection), cold/hot sensitivity (pulpitis), pain/swelling w/ food (sialadenitis), dysphagia/dyspnea (deep neck space infection), trismus (TMJ d/o or muscular inflammation); shooting facial pain or numbness (neuralgia); h/o XRT or bisphosphonate exposure (osteonecrosis), tobacco & EtOH use d/o (↑ risk of oral cavity malignancy)
- **Physical exam:** Full head and neck exam
  - *Dental exam:* Inspect teeth & palpate → tenderness (caries/periapical infection)
  - *TMJ exam:* Nl jaw opening is 35–55 mm; eval for 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 of CN V branches (neuralgia)
- **Diagnostic studies:** Dental pathology → panoramic radiograph of jaw; TMJ dysfunction → MRI of joint (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

Epidemiology and Management (*Oral Maxillofac Surg Clin North Am* 2009;21:293)

- **TMJ d/o:** Most common among 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 → ears, posterior neck; sx ↑ in AM esp in pts who clench/grind teeth at night; +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 therapy, 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); rarely: Sarcoid, Sjögren, HIV, malignancy

  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 evidence of 2° infection (purulence from duct, erythema, fever) (*Otolaryngol Head Neck Surg* 2011;145:935)

- **Odontogenic disorders** (cdc.gov/oralhealth/): Advanced periodontal disease affects 4–12% of US adults; ↑ prevalence of poor oral health in racial/ethnic minorities, poor; ↑ risk in smokers, sicca/Sjögren, eating d/o, meth use, chemo, antipsychotic meds

  Etiology: Gingivitis (inflammation of the gums), periodontitis (inflammation → loose teeth), pulpitis/pulp necrosis (dental caries), dental abscess

  Sx: Tooth/jaw pain, heat/cold sensitivity

  Tx: Analgesics; abx if e/o acute infection (purulence, erythema, fevers/chills)

- **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), CN VII involvement (w/ parotitis) → ED

- **Neuralgia/paresthesia:** If severe, not responsive to initial tx → Neuro or NSG
- **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* 2014;150:S1)

- **Definition:** Inflammation of the external ear canal, often w/ infection, that may be acute (AOE <6 wk), subacute (6–12 wk), or chronic (>3 mo)
- **Microbiology:** Primarily bacterial (98% in North America) in origin (*P. aeruginosa, S. aureus*), fungal "otomycosis" (aspergillus, candida); viral (VZV, HSV)
- **Epidemiology**: Lifetime incidence 10%; often after local trauma or swimming; ↑ in summer
- **Risk factors:** Eczema of auditory canal, swimmers, humidity, poor production or removal of ear wax, narrow auditory canals, hearing-aids, mechanical trauma (including scratching/instrumentation of ear canal w/ cotton swab)

  Risk factors for complicated otitis externa: DM, cranial radiation, immunocompromise (incl HIV), hx cranial XRT
- **Complications** (rare): Osteitis, abscess, middle ear disease, or recurrent infection

Evaluation (*AFP* 2012;86:1055; *Otolaryngol Head Neck Surg* 2014;134:S4)

- **History:** Otalgia (70%), itching (60%), fullness (20%), ± hearing loss, ± jaw pain, ± vertigo; assess for risk factors (above); acute

otitis externa typically rapid onset (<48 h)

- **Exam:** Tenderness of tragus/pinna, ear canal edema or erythema, ± otorrhea, ± regional LAD, ± TM erythema or cellulitis of the pinna; **verify TM intact** if possible
- **Red flags:** Pain/HA out of proportion to exam, fever, granulation tissue at bony-cartilaginous junction (floor of EAC) all concerning for necrotizing infection
- **DDx:** Otitis media w/ perforation (see below); otomycosis, varicella zoster oticus, atopic or contact dermatitis, psoriasis, seborrheic dermatitis, acne, SLE (rare); assess for other skin conditions

Treatment (*Cochrane Database Syst Rev* 2010:CD004740)

- **General approach:** Pts w/uncomplicated OE should have gentle cleaning and otic gtt; avoid cleaning in pts w/ DM or immunocompromise, use FQ gtt in pts w/known or suspected TM perforation; **no role** for oral abx unless extension beyond ear canal or specific host consideration, as no e/o benefit over topical and ⊕ evidence of harm, incl ↑ s/e and ↑ disease persistence/recurrence (*Int J Antimicrob Agents* 2005;25:282; *J Infect* 1991;22:233)
- **Ear canal cleaning:** For healthy patients w/intact TM, in-office gentle cleaning w/warmed 3% H_2O_2
- **Symptom management:** PO analgesia as needed; **avoid topical anesthetic** as can mask sx of progression
- **Topical otic agents:** Steroids, antiseptic, antibacterial, antifungal, & combination available; no difference shown between agents for empiric Rx;
  - *Pts w/intact TM:* 2% acetic acid typically effective; apply TID–QID × 7–14 d
  - *Pts w/known or suspected TM perforation:* Rx may pass through middle ear → inner ear; avoid aminoglycosides, neomycin, or EtOH-containing drops; FQ safe (ofloxacin 0.3% 10 gtt QD x 7d)
  - *Gtt admin instructions:* Lie down w/affected ear toward ceiling; instill 3–4 drops (have someone else administer drops if possible), light tragal massage w/ 3–5 min of head tilt (set a timer)
- **Pt 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 canal dry; avoid cleaning ear canal at home (to avoid injury); may take 1–2 wk to resolve; f/u (call vs. visit) if not improving w/in 3 d → ENT referral; avoid ear candling (proven harm, no proven benefit)

- **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 abx ± surgical debridement (*Lancet Infect Dis* 2004;4:34)
- **When to refer:** For known or suspected complicated OE, failure to improve w/in 48–72 h or failure to resolve w/in 2 wk, suspected malignant otitis externa

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Otitis Media

Background (*Nat Rev Dis Primers* 2016;2:16063, *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; *Chronic Suppurative Otitis Media (CSOM):* Infection & inflammation of middle ear >3 wk; can be assoc w/ TM perforation or cholesteatoma; often multiple bacteria w/ combo aerobes/anaerobes
- **Microbiology:** Viral > bacteria, in AOM (*S. pneumo* > *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 ↓↓ ↓ w/ age, ↑ risk if: H/o previous AOM, 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 AOM, 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); for OME: fluid (usually serous) without inflammation
- **Red flags:** Pain/swelling over mastoid, bloody otorrhea, facial weakness, vertigo, nystagmus, HA, neck pain, photophobia

Treatment (*Cochrane Database Syst Rev* 2013:CD000219)

- **General approach:** No large RCTs/guidelines for AOM in adults; abx can → significant clinical improvement by 3 d in children; APAP, NSAIDs 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 wk; if persistent >3 mo → ENT referral (*Cochrane Database Syst Rev* 2012;9:CD009163)

When to Refer

- Recurrent AOM (>2 episodes/6 mo), OME lasting >3 mo, unilateral persistent OME or otalgia (ENT exam to r/o nasopharyngeal tumor), CSOM, or AOM complications (TM perforation, mastoiditis, labyrinthitis, facial palsy, meningitis)

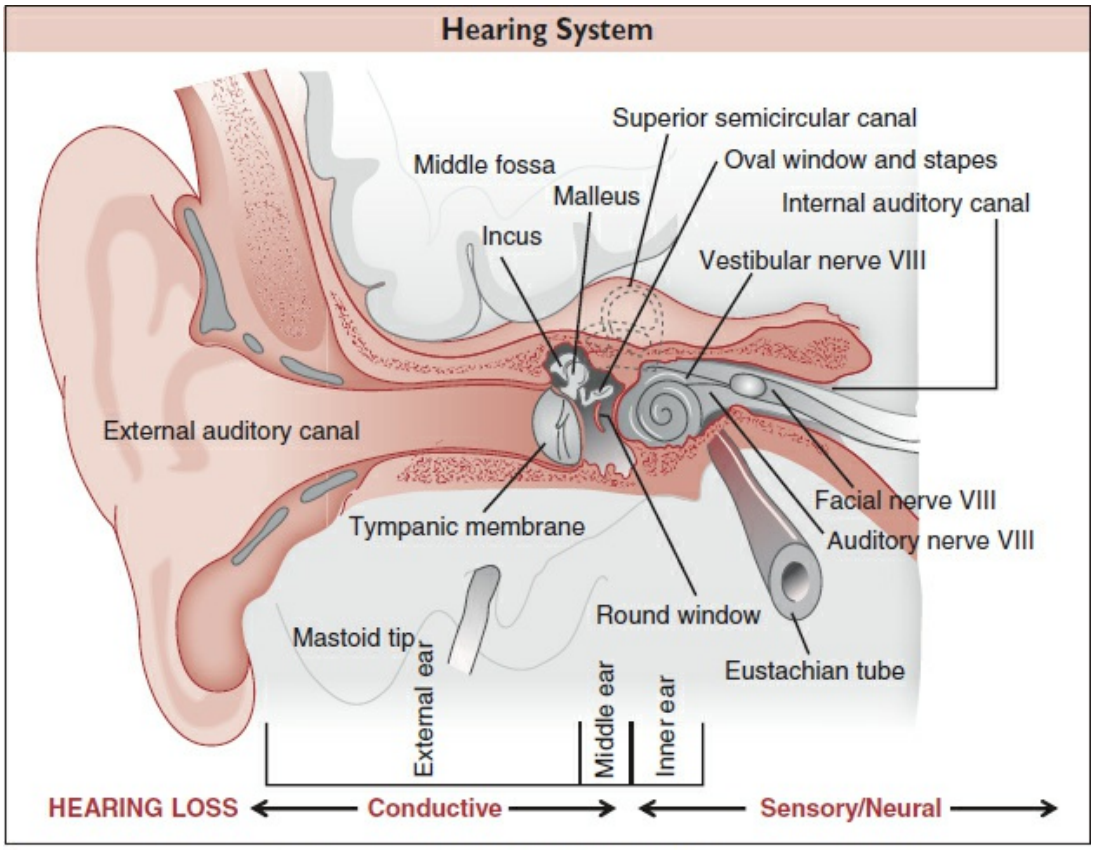
Patient Information

- **Otitis externa:** www.nlm.nih.gov/medlineplus/ency/article/000622.htm; www.aafp.org/afp/2001/0301/p941.html

HEARING LOSS

Background (*NEJM* 2008;359:833; *Otolaryngol Head Neck Surg* 2012;146:S1)

- 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 Factors:** ↑ Age; ♂ > ♀, Caucasian, HTN, DM, CKD, immunosuppressed
- **Screening:** Required in Medicare annual wellness visit; ask “Would you say you have any difficulty hearing?”; ask family members when feasible
- **Conductive hearing loss (CHL):** A *mechanical* problem; hearing loss 2/2 abnormalities in the structures that “conduct” sound waves to the cochlea: Auricle, external auditory canal, tympanic membranes, middle ear airspace or ossicles
- **Sensorineural hearing loss (SNHL):** A *neurologic* problem; hearing loss 2/2 abnormalities in the structures that transmit neural impulses to the auditory cortex: cochlea, auditory nerve
- **Mixed hearing loss:** Hearing loss w/ conductive & sensorineural components
- **Severity/Classification:** *Mild*: 20–40 dB loss, *Mod:* 40–70 dB, *Severe:* 70–90 dB, *Profound:* >90 dB
- **Hearing physiology:** Sound waves enter the ear canal → vibrate TM and ossicular chain → stimulus to cochlea, where sensory cells convert sound energy to electrical stimuli → brain via the auditory nerve



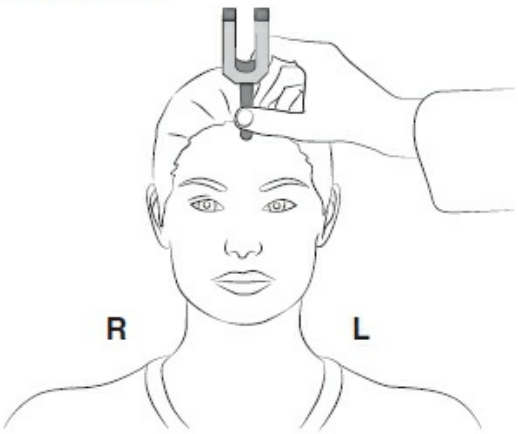
From Nadol JB. Hearing loss. *N Engl J Med* 1993;329(15):1092–1102. Copyright © 1993 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Evaluation (*AFP* 2012;85:1150; *JAMA* 2012;307:1185)

- **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, aminoglycosides, 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)

Testing for Hearing Loss

Weber test

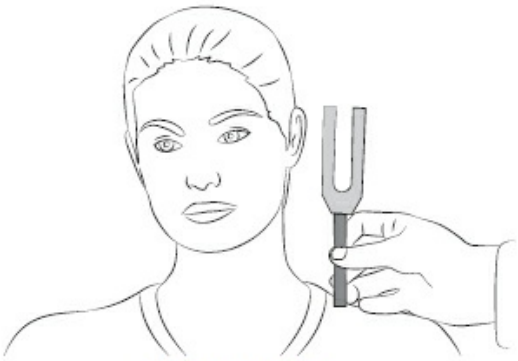


Weber: Distinguish SNHL from CHL; place vibrating 512-Hz tuning fork to midline forehead and ask pt, "Where do you hear the sound best; L, R, or equal on both sides?"

CHL will make sound louder on the "bad side" (think of humming with finger in your ear); SNHL will make sound louder on the "good side"

Pt with L-sided hearing loss; if SNHL, Weber will lateralize to R ear, if CHL, Weber will lateralize to L ear

Rinne test



Air conduction

vs.

Bone conduction

Rinne: Compares bone & air conduction: place vibrating tuning fork firmly on mastoid (bone conduction) and then in front of auricle (air) and ask pt, "Which is louder?"; then may repeat test on other ear; a ⊕ test is air > bone (suggests normal *or* SNHL), a ⊖ test is bone > air (consistent w/ CHL ≥25 dB)

When to Refer

- Sudden hearing loss → emergent ENT referral (*NEJM 2008;359:833)*; gradual SNHL → ENT, audiologist; gradual CHL—depends on etiology; see CHL, below

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Conductive Hearing Loss

General Approach (*Cummings Otolaryngology* 2015;143)

- **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 (e.g., 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	
Otitis externa or eczema	Pain, itchiness, edema	See *"Otitis"*
Exostosis (external canal osteoma)	Otoscopy ± temporal bone CT	Observe if nonobstructing + asx, otherwise 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, 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)

Sensorineural Hearing Loss

General Approach (*Cummings Otolaryngology* 2015;150:2319–2335.e6)

- 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
- Assess degree of loss, laterality, chronicity

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 2/2 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 d—tx 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 present w/ progressive or sudden onset unilateral 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 (high frequency); *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 and clearly
- **Amplification:** Improve outcomes of speech perception, understanding & hearing-related QoL, but are **expensive** & infrequently covered by insurance; Personal Sound Amplification Products (PSAPs or "pocket talkers") are less costly alternative to hearing aids, but less-targeted sound amplification (e.g., all noises louder) & not regulated by FDA

  Pt education: Key for managing expectations; hearing aids help but cannot erase deficit, take multiple adjustments to be set properly & can take a few months to be helpful
- **Cochlear implantation** (*NEJM* 2010;363:1438): Considered in setting of severe/profound SNHL in adults or congenital deafness→ significant gain in hearing clarity and sensitivity

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Tinnitus

Background (*Otolaryngol Head Neck* Surg 2014;151:S1; *JAMA* 2016;315:2221)

- **Definition:** The false perception of sound in the absence of an acoustic stimulus; it is a symptom rather than single disease process, and etiology not well understood; thought to be often due to abnormal neural activity in response to hearing loss
- Many people experience occasional or nonbothersome tinnitus; others have significantly ↓ QoL (affects hearing, sleep, concentration)
- **Epidemiology and risk factors:** prevalence ↑ w/age, affecting 9% of 60–69 y in US, assoc w/hearing loss, noise exposure; more common in ♂, whites, pts w/ HTN, DM, HLD, obesity, depression, and/or anxiety
- **Natural hx:** Persistent bothersome tinnitus may resolve

spontaneously, 20–50% over several years

- **Classification:** Management determined by bothersome or not bothersome, persistent (≥6 mo) or not persistent (<6 mo); can be primary (idiopathic, often assoc w/SNHL) or secondary to other process (**cerumen impaction**, Eustachian tube dysfunction, Ménière's, vascular anomalies, vestibular schwannoma, intracranial HTN)

Evaluation

- **General approach:** Targeted Hx/PE to identify conditions that may be causing/contributing to tinnitus, presence of red flags
- **History:** *Quality of sound:* may be buzzing, rushing, whooshing, or clicking, usually worse in quiet room, may seem to derive from internal/external source; onset, unilateral (focal anatomic lesion), pulsatile (vascular lesion)

  Hearing: Sudden hearing loss, unilateral or bilateral
  Medications: Salicylates, ototoxic meds, NSAIDs, loop diuretics, quinine
  Comorbid d/o: SNHL, anxiety, depression, dementia
  Bothersome vs. not: affecting QoL? Bothersome enough to desire tx?
- **Red flags:** persistent pulsatile tinnitus (vascular lesion), unilateral tinnitus w/hearing loss (anatomic/focal lesion—r/o cerumen impaction), sudden onset hearing loss, vertigo/balance problem, objective tinnitus, head/neck mass, focal neurologic signs
- **Exam:** *VS:* BP; *Head/Neck:* Auscultate over the ear/mastoid to differentiate subjective (no noise, usually benign) from objective tinnitus (rare, heard by clinician, can suggest ICA/vertebral artery aneurysm), LN exam, *Otoscopy:* Evidence of otitis externa/AOM, cerumen impaction, other EAC pathology); *CV:* If concern for vascular d/o; *Neuro:* Attention to CN and vestibular exam
- **Audiology referral:** For all pts w/ unilateral, persistent, or assoc w/hearing loss; consider for others w/persistent, bothersome tinnitus
- **Imaging:** Generally *not* indicated; however, for pts w/pulsatile tinnitus that corresponds to cardiac cycle, focal neurologic abnormalities, concomitant asymmetric hearing loss or concern for vascular cause, obtain CTA or MRA/MRV of neck/skull base to r/o

vascular abnormality

Treatment

- **General approach:** For those in whom evaluation has not determined reversible cause, pt education on prognosis and tx options key; no need to tx if not bothersome
- **Pt education:** Tinnitus is a symptom, not dangerous in and of itself; may remit or persist; no obvious cure but mgmt strategies exist; counsel pts on hearing protection, self-help (CBT) books may ↓ depression and ↑QoL by managing pt response to sx; sound therapy
- **Other therapies:** Some evidence for CBT, sound therapy (use of "white noise") to cancel out tinnitus, **tinnitus retraining therapy (by specialist) may ↑ QoL** (*Cochrane Database Syst Rev* 2010;CD007330); acupuncture of unclear benefit
- Anxiolytics, antidepressants, anticonvulsants, ginkgo biloba, melatonin, zinc, other supplements not shown to have benefit and not recommended

Patient Information

- **Hearing loss:** asha.org/public/hearing/Hearing-Loss
- **Tinnitus:** asha.org/public/hearing/Tinnitus, ata.org/resources, entnet.org/content/tinnitus

ANXIETY DISORDERS

Background (*AFP* 2015;91:617; *Ann Int Med* 2013;159:ITC6-1; *NEJM* 2015;373:2059)

- **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)
- **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; screen for depression (see *"Depression"*), mania (see *"Bipolar Disorder"*), suicidal ideation (see *"Suicide Risk Assessment"*); prior psych hx; FHx

Evaluation and Management (*AFP* 2005;71:733; 2009;79:785; *JAMA* 2014;312:78; *NEJM* 2004;351:675)

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 mo period from excessive, uncontrollable worry about a number of concerns (e.g., finances, health, safety); anxiety is assoc w/ ≥3 of: **(1)** Restlessness/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

Screening: 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)

Therapy: CBT as effective as medication; exercise also helps (*JAMA* 2009;301:1460),

relaxation training; **Rx:** 1st-line → SSRIs (generally, all SSRIs equally effective) or SNRIs; consider benzodiazepine bridge; *Sample Rx:* Citalopram 10 mg/d, titrate to 40 mg over 2–6 wk as needed, (± clonazepam 0.25–0.5 mg BID during acute phase/SSRI titration). Buspirone is an effective 2nd-line agent. Hydroxyzine is useful in treating insomnia assoc w/ GAD. Drug efficacy may be monitored with GAD-7 scale. Therapy continued for 6–12 mo after sx resolution; 20–40% of pts will relapse within 1 y.

Panic disorder: Recurrent, out-of-the-blue panic attacks w/ concern about the attacks or their implications, & assoc behavior D; **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

Panic attack: Discrete, sudden, intense apprehension, impending doom, & discomfort, usually peaking in ≤10 min; often assoc w/ palpitations, chest/abd discomfort, sweats, shakes, hot flushes, chills, SOB/choking feelings, nausea, dizziness, paresthesias, derealization, depersonalization, fear of losing control/dying

Screening: Panic disorder severity scale: 7 items assessing attacks, anticipatory anxiety avoidance; can be clinician or self-rated (*Depress Anxiety* 2002;15:183)

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 wk; 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; 2017)

Screening: Mini-SPIN (social phobia inventory) → 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 center of attention; (3) Worst fears include embarrassment, humiliation (*Prim Care Comp J Clin Psychiatr* 2009;11:231)

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

Therapy: CBT incl exposure therapies (imagined or live exposures); systematic desensitization; **Rx:** Rare PRN benzodiazepine use

- **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; 2011;305:1256; 2012;308:729

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 Y 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; *NEJM* 2013;369:1935)

- **History:** Adult ADHD Self Report Scale (psychology-tools.com/adult-adhd-self-report-scale/) is a useful screening tool for adults (available online); interview pt & collateral sources about sx in past 6 mo & 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; 2013;369:1935)

- **General principles:** Comanagement with 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)

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

Interactions: avoid w/ MAOI antidepressants; serum levels of some agents may be ↑ by treatments that lower acidity (e.g., PPI)

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
Dextroamphetamine ER (Dexedrine spansules)	8
Mixed amphetamine salts (Adderall)	5
Mixed amphetamine salts ER (Adderall XR)	12
Lisdexamfetamine (Vyvanse)	12
Stimulants: Methylphenidates	
Methylphenidate IR (Ritalin)	4
Methylphenidate SR/ER (Metadate CD, ER, Ritalin SR, LA)	8
OROS methylphenidate (Concerta)	12
Dexmethylphenidate ER (Focalin XR)	12
Nonstimulants: Atomoxetine (Strattera); not a controlled substance	24

(Adapted from *AFP* 2012;85:890)

- **Nonpharmacologic treatment:** Cognitive behavioral & group tx (*Am*

J Psychiatry 2010;167:958; *JAMA* 2010;304:875), ADHD coaching, disability accommodations

- **Patient information:** *JAMA* 2013;309:1843; chadd.org

BIPOLAR DISORDER

Background (*Acta Psychiatr Scand Suppl* 2009;439:27; *AFP* 2012;85:483; *Lancet* 2016;387:1561)

- **Bipolar type I:** ≥1 manic episode, usually alternating w/ depressive episodes; prevalence: 1–2%
- **Bipolar type II**: Major depressive episode w/ hypomanic episodes; prevalence: >2%
- **Manic episode:** Abnormal & persistently elevated, expansive or irritable mood, lasting >1 wk (less if hospitalized), and ≥3 of following sx (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 with ↑ potential for painful consequences; 2/3rds of manic episodes have psychotic sx (hallucinations, delusions); manic episodes often accompanied by psychotic features (delusions, hallucinations)
- **Hypomanic episode:** Abnormal & persistently elevated, irritable, or expansive mood that lasts ≥4 d w/ 3 or more sx of mania, but w/o significant change in social/occupational functioning, and w/o psychotic symptoms
- **Depressive episode:** "Atypical" sx (hypersomnia, hyperphagia) common; psychotic sx can be present
- **Mixed features:** 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

history for past manic sx important (*PsychiatrServ* 2001;52:51); screening ? s: “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 and still felt rested?” Assess risk of suicide and violence at each visit→ >50% of pts w/ BPAD attempt suicide during their lifetime (*J Clin Psychiatry* 2005;66:1456)

- **Workup:** TSH, RPR, UTox, B12; Medication monitoring: CBC, ECG, Chem-12, BMI, waist circumference, lipids, fasting glucose

Treatment (*Acta Psychiatr Scand Suppl* 2009;439:27; *BMJ* 2012;345:e8508)

- **General principles:** Avoid SSRIs b/c their efficacy is unclear; if used, should be used only in adjunct with mood stabilizer; sleep hygiene important; disrupted sleep is a major trigger for mania; individual or group psychotherapy improves outcomes (*Arch Gen Psychiatry* 2007;64:419); patients may need combination therapy to achieve remission; maintenance therapy is typically continuation of initial regimen used to achieve mood control, and may need to be continued indefinitely
- **If not on a mood stabilizer:** Trial lithium or valproic acid
  - **Lithium:** Levels of ~0.8 mEq/L (range: 0.5–1.2); kidney function should be assessed prior to initiation and then 1–2 times a year thereafter; check lithium levels every 6 mo once stabilized; monitor TSH yearly; monitor for weight and BMI
  - **Valproic acid:** Levels > 45 mcg/mL (range: 50–125); monitor CBC and LFTs at least yearly; valproic acid level at least yearly and when doses change
- **If psychotic features present:** Start antipsychotic; for 2nd-generation antipsychotics, frequent monitoring of BMI, waist circumference, lipids, fasting glucose (see section on *Psychosis*)
  - **Olanzapine:** Start 10 mg, titrate up to 30 mg/d
  - **Quetiapine:** Start at 100 mg daily
  - **Risperidone:** Start at 1–2 mg daily

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 wk
  - **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; depression is the leading cause of disability worldwide (*JAMA* 2017;317:1517)
- **Differential diagnosis:** Ψ: dysthymia, cyclothymia, adjustment d/o w/ depressed mood, seasonal affective d/o; *organic:* Meds (antiarrhythmics, steroids, BZD, βB, others), SUD, thyroid (hypo/hyper), Cushing's, hypercalcemia, DM, dementia, neuro d/o, infection (mono/flu/HIV/syphilis/Lyme), B_{12}/zinc deficiency, cancer (classically pancreatic), postsurgical, stroke

Evaluation (*Ann Int Med* 2016;165:ITC49)

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 wk how often have you been bothered by: (1) little interest/pleasure in doing things; (2) feeling down, depressed, or hopeless?
Any + response → 96% Se/57% Sp for depression → screen with PHQ-9 for severity (below)

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 wk 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, coherence, spontaneity); **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)

PHQ-9 Assessment of Depression Severity

Over the last 2 wk how often have you:

- Felt little interest/pleasure in doing things
- Felt badly about yourself, felt you are a failure or let your family down
- Had trouble falling or staying asleep, or slept too much
- Moved so slowly or were so fidgety that others noticed
- Thought you would be better off dead or wanted to hurt yourself
- Felt down/depressed/hopeless
- Had trouble concentrating
- Felt tired or had little energy
- Had a poor appetite or overate

Scoring: 0 = not at all, **1** = several days, **2** = more than half the days, **3** = nearly every day
0–4: Nondepressed, **5–9:** Minor depression, **10–14:** Mild depression, **15–19:** Moderately severe depression, **20–27:** Severe depression

- **Ongoing assessment:** Important to review at each visit: sx (SIGECAPS, above), severity (PHQ-9), suicide (see "*Suicide Assessment*"); MDD is a chronic illness, defined by episodes of variable length & frequency; patients w/ a major depressive episode may expect resolution with time, as well as likely recurrence in the future; treatment is therefore dynamic
- **Workup:** Consider TSH, CBC (anemia), vitamin D level

Treatment (*AFP* 2006;73:83; 2008;77:785; 2009;80:167; *JAMA* 2006;295:318; *NEJM* 2005;353:1819)

Evidence-Based Treatments for Depression

Psychotherapy: Equivalent efficacy to pharmacotherapy & effects of the 2 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. Improves response and remission in depression (*Lancet* 2013;381:375).

Pharmacotherapy: Counsel pts it may take 1–6 wk 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, appetite Δ, sleep disturbance, psychomotor Δ); 2nd-gen meds (e.g., SSRIs, SNRIs) more tolerable than TCAs & less dangerous in O/D; pts should be followed closely after initiation

Duration of therapy: Typically at least 6–9 mo 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

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 (*JAMA Psychiatry* 2016;73:56)

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)

Depression Pharmacotherapy by Class/Agent

	Class Characteristics	Drug (dose, mg)	Notes
SSRI	Better tolerated, little risk in O/D 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** SD: 10–20 TD: 20–40	More stimulating; long-acting metabolite; Least amount of wt gain or withdrawal among SSRIs; ↑ drug interactions; helpful for anxiety;
		Paroxetine SD: 10–20 TD: 20–40	Helpful for anxiety/OCD. More withdrawal sx[a], sedation, sexual dysfunction, wt gain, orthostatic HoTN vs. other SSRIs
		Citalopram, SD: 10–20, TD: 20–40	Helpful for anxiety; ↓ Na; risk of ↑ QTc;
		Escitalopram SD: 10, TD: 10–20	↓ drug–drug interactions
		Sertraline, SD: 50 TD: 50–100 mg	More diarrhea[a]; helpful in anxiety/OCD; stimulating
		Vilazodone, 10–40	↓ sexual side-effects
		Vortioxetine, 5–20	May improve cognition
TCA	Similar efficacy to SSRIs but more S/E; anticholinergic,	**Amitriptyline** SD: 25–50,	Most sedating/anticholinergic;

arrhythmogenic & possibly **lethal** in O/D; Wt gain	TD: 100–300	helpful in chronic pain/migraines; SD: 25–50 mg; TD: 100–300 mg
	Imipramine, SD: 25–50; TD: 100-300	Oldest TCA;
	Desipramine, SD: 25–50; TD: 100-300	Least sedating/anticholinergic
	Doxepin, SD: 25–50, TD: 100-300	Mod sedating/anticholinergic
	Nortriptyline, SD: 25; TD: 50–150	Less sedating/anticholinergic; lower orthostatic HoTN compared to other TCAs; helpful in chronic pain/IBS

Other Pharmacologic Agents	
Drug (dose, mg)	**Notes**
Bupropion SD: 50–75 BID TD: 300–450 TID	Dopamine & noradrenergic reuptake inhibitor; fewer sexual s/e, not assoc w/ wt gain; stimulating; used as adjunct or for smoking cessation; ? helpful in ADHD; ↓ seizure threshold (little risk at low dose); may be fatal in O/D. May enhance response when given with SSRI.
Venlafaxine SD: 37.5 BID; TD: 75–300 BID/TID	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
Duloxetine, SD: 30 QHS; TD: 60–120[b]	SNRI; s/e similar to venlafaxine w/ less e/o CV effects; contraindicated in liver disease; may worsen DM2; helpful in chronic pain
Mirtazapine, SD: 15 QHS; TD: 15–45 QHS	Acts on norepinephrine, serotonin; ↓ drug–drug interactions; wt gain, sedation (useful in insomnia)
Trazodone, SD: 50; TD: 75–500[b]	Serotonin antagonist & partial agonist; sedation, postural HoTN, priapism
MAOIs (tranylcypromine,	May be fatal in O/D, in drug combinations, or w/ tyrosine-rich food or drink; also cause HoTN, insomnia; rarely initiated by PCPs

phenelzine, selegiline)	

PCPs; demonstrated efficacy in atypical depression & elderly.

SD, starting dose; TD, therapeutic dose.

[a]S/E differences supported in meta-analysis (*Annals Intern Med* 2011;155:772)

[b]At lower doses, may be given as a single-dose QHS; otherwise should be divided BID or TID

- **Refractory depression:** If no response in 4–10 wk, 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; bupropion, mirtazapine, or 2nd-generation antipsychotics (quetiapine, aripiprazole, brexpiprazole) may augment the effectiveness of SSRIs
- **Relapse:** Consider rechallenge of antidepressant that led to remission
- **Indications for psych referral:** Multidrug Rx, suicidality/thought d/o, depression refractory to 1st-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."
- **Exercise:** In some trials results in ↓ in depressive sx (*JAMA* 2014;311:2432)

Special Populations (*AFP* 2010;82:926; 2011;84:1149; 2015;92:94; *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 Rx (SSRIs) at very low doses & avoid TCAs if possible; ECT is an option for refractory sx (*AFP* 2004;69:2375; *JAMA* 2017;317:2114; *NEJM* 2014;371:1228); preferred medications include citalopram, escitalopram, mirtazapine, sertraline, and venlafaxine

  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 wk; 5–15% of ♀ develop postpartum depression, likely due to lifestyle changes w/ childbirth (loss of sleep) (*AFP* 2016;93:852; *JAMA* 2006;296:2616); most SSRIs pass into milk and are thought to be safe in breastfeeding, although long-term studies lacking; sertraline is the most well-studied antidepressant in breast feeding (*NEJM* 2016;375:2177)
- **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

EATING DISORDERS

Background (*AFP* 2015;91:46; *Arch Gen Psych* 2000;57:659; *Int J Eat Dis* 2002;31:151; *JAMA* 1998;279:1992)

Classification of Eating Disorders (*Mayo Clin Proc* 2010;85:746; *Curr Opin Psych* 2013;26:532)
Anorexia nervosa (AN): ↓ food intake → significant ↓ wt w/severity mild (BMI ≥17), moderate (BMI ≥16), severe (BMI ≥15), extreme (BMI <5); Intense fear of gaining wt; body image disturbance; *Restrictive type:* No binging/purging in past 3 mo; *Binge eating/purging type:* ⊕ binge eating or purging in past 3 mo; Lifetime prevalence: 0.9% in ♀; 0.3% in ♂; fatal in 8–16% of pts
Bulimia nervosa (BN): Recurrent binging (consuming large amounts of food in a discrete time period w/sense of lack of control) followed by inappropriate compensatory behavior to prevent wt gain (e.g., purging, exercise, fasting, laxatives, diuretics) which occurs, on avg, ≥1×/wk for 3 mo; *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 mo; assoc w/ lack of control & distress over eating; lifetime prevalence: 3.5% in ♀; 2% in ♂
Avoidant/restrictive food intake disorder: Avoiding or restricting food intake, not related

to distorted body image or general medical condition, leading to persistent failure to meet nutritional energy needs demonstrated by at least 1 of the following: (1) Clinically significant wt loss; (2) Nutritional deficiency; (3) Supplementary enteral feeding or oral supplements required; (4) Impaired psychosocial functioning
Pica: The following criteria must be met: (1) Repeated eating of nonfood, nonnutritional substances (e.g., chalk, clay, dirt) for at least 1 mo; (2) Eating behaviors are inappropriate to developmental level & outside of cultural/societal norms; (3) If it occurs in context of other mental disorder or general medical condition, it must have a severity warranting clinical attention; may be a manifestation of iron deficiency anemia
Rumination disorder: The following criteria must be met: (1) Repeated regurgitation of food, which may be rechewed/reswallowed/spit out for at least 1 mo; (2) Behavior not due to general medical condition (e.g., GERD); (3) Does not occur solely during course of other eating disorder; (4) If it occurs in context of other mental disorder or general medical condition, it must have a severity warranting clinical attention
Other specified feeding or eating disorder: Aberrant eating patterns & wt mgmt that cause significant distress/impairment but do not meeting above criteria

- **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/ 1st-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 lb) in a 3 mo 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 for anorexia nervosa:** *Gen:* Emaciated, lack of ♀ fat distribution; *VS:* BMI, ↓ HR, hypothermia, HoTN; *CV:* MVP murmur; *Ext:* Ankle or pretibial edema; *Derm:* xerosis, hypercarotenemia, lanugo, thinning scalp hair
- **Exam for bulimia:** *HEENT:* dental enamel erosion, enlarged parotid glands; *Ext:* Russell sign (callous over knuckles from purging)
- **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 suggest 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 evidence-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 therapy 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; 2008;78:223; anad.org nationaleatingdisorders.org

INSOMNIA AND SLEEP DISORDERS

Background (*AFP* 2013;88:231; *BMJ* 2004;329:724; *JAMA* 2013;309:706; *NEJM* 2015;373:1437)

- **Insomnia:** Difficulty initiating/maintaining sleep or early awakening

→ fatigue, daytime sleepiness, mood disturbance, impaired attention/concentration/memory, functional (occupational, academic, social) impairment. Occurs ≥ 3×/wk, is present for ≥3 mo, and occurs despite adequate opportunity for sleep

Epidemiology: Most common sleep disorder; ~30% of adults have sx, prevalence 10–15%; incidence ↑ w/ age, 2:1 ♀:♂

Ddx: Psych (anxiety, depression, mania/hypomania, adjustment disorders, PTSD), SUD, chronic pain, CHF, OSA (see *"Obstructive Sleep Apnea"*), COPD, asthma, hyperthyroidism, menopause, BPH, restless leg syndrome, meds (steroids, stimulants, levothyroxine, albuterol, BZD/EtOH withdrawal, caffeine, tobacco), high altitude

Forms of Insomnia (*DSM-V*)	
Type	**Clinical Features**
Short-term	<3 mo 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
Chronic	≥3 mo duration with sx of sleep initiation or maintenance occurring ≥3x/wk. Sx occur despite adequate opportunities and circumstances for sleep and lead to daytime consequences
Other	Difficulty w/sleep initiation or maintenance, do not meet above criteria

- **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 Y disorders

Evaluation (*AFP* 2007;76:517; 2015;92:1058; *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* 2017;96:29; *Am J Med* 2010;123:1087; *Ann Int Med* 2016;165:103;113; *JAMA* 2017;317:762)

- **Insomnia: Sleep hygiene counseling:** 1st-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); treat comorbid conditions like polyuria/BPH and restless legs

  Psychotherapy: CBT, relaxation techniques, sleep restriction Rx (limiting total time in bed to improve sleep efficiency) (*AFP* 2009;79:125; *JAMA* 2009;301:2005); Mindfulness also shown to be effective (*JAMA Int Med* 2015;175:494)

  Pharmacotherapy: Pts w/ difficulty in sleep onset may receive short-acting Rx (zolpidem, zaleplon, lorazepam, triazolam, ramelteon); pts w/ difficulty staying asleep should receive longer-acting Rx (zolpidem ER, eszopiclone, temazepam, estazolam, doxepin, suvorexant); 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; *Ann Int Medicine* 2016;165:103)

Type	Features
Benzodiazepines Risk of **tolerance, dependence, impairment** in attention, concentration, memory	*Long-acting:* **Flurazepam, quazepam** (↑ likelihood of daytime impairment); avoid diazepam 2/2 metabolite accumulation *Intermediate-acting:* **Lorazepam, temazepam, estazolam** *Short-acting:* **Triazolam**
Non-BZ Receptor Agonists Similar adverse effects as BZs. Sleep may be worse the 1st night after discontinuation. Eszopiclone & zolpidem ER eval in trials for up to 6 mo use; zaleplon for up to 12 mo (*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). SL form useful for middle of the night awakenings. **Eszopiclone:** Effective for sleep-onset & maintenance (*AFP* 2005;71:2359); **Zaleplon:** Effective for sleep initiation & nocturnal awakenings; ultra-short half-life
Melatonin agonists Ramelteon eval in clinical trials for up to 6 mo use (*Sleep* 2009;32:351)	**Melatonin** (1–10 mg), several hours before bedtime; effective in circadian rhythm disorders (jet lag, shift work) **Ramelteon** (8 mg) ↓ sleep onset latency, ↑ sleep time. Approved in US but not Europe due to lack of efficacy; not DEA-controlled; fewest s/e among sedative-hypnotics, not habit forming
Orexin receptor antagonists Suvorexant evaluated in clinical trial for 12 mo (*Lancet Neurol* 2014; 13:461)	**Suvorexant** (5–20 mg) 12-h half-life; most common s/e is sedation, may have rebound insomnia
Antidepressants 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 1st-line **Doxepin:** 3–6 mg QHS; FDA approved for insomnia (*AFP* 2011;84:453); **Mirtazapine:** 7.5–15 mg QHS (*AFP* 1999;59:159)
Antipsychotics Consider where indicated for 1° mood or psychotic disorder	*Often used off-label despite lack of RCT data* **Quetiapine:** 12.5–100 mg QHS **Olanzapine:** 2.5–10 mg QHS
Antihistamines (Risk of oversedation the next day, anticholinergic s/e)	**Diphenhydramine** (25–50 mg), **doxylamine** (25 mg), **hydroxyzine** (25–50 mg)

- **Narcolepsy:** Strategic daytime naps; modafinil (1° pharmacotherapy); methylphenidate or dextroamphetamine 2nd-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

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
- **Hoarding:** Now defined in DSM-5 as difficulty/distress in parting w/ possessions → distress, impairment, severely cluttered living spaces; typically treated w/ CBT (*NEJM* 2014;370:2023)
- **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)

Psychiatric Conditions Mistaken for OCD		

Condition	Similar Sx	How to Distinguish
Anxiety	Worry	No rituals; OCD usually irrational
Bipolar	Manic delusions	Usually grandiose (ego-syntonic)
Body dysmorphic disorder	Preoccupation with bodily defect	Related to body alone
Depression	Ruminations	No rituals. Depressive ruminations often negative (guilt, regret)
Hypochondriasis	Fear of illness	Doesn't arise from external stimuli (i.e., contamination), instead misinterpret regular body sx
OCPD	Hoarding, perfectionism, preoccupation w/ rules	Ego-syntonic, global traits not specific
Paraphilia	Intrusive sexual thoughts and urges	OCD obsessions are ego-dystonic
PTSD	Intrusive thoughts/images	Result of actual events (OCD anticipates future consequences)
Psychosis	Delusional beliefs	OCD pts realize delusions irrational

Evaluation and Prognosis (*JAMA* 2001;285:2121; *NEJM* 2004;350:259; 2014;371:646)

- **History:** *Screening questions:* Do you have unwanted ideas, images, or impulses that seem silly, nasty, or horrible? Do you worry you might impulsively harm someone? Do you have to count things, wash your hands, or check things over and over? Do you worry a lot about whether you have been immoral? Are there certain behaviors that you feel compelled to repeat? Evaluate for safety of pt and others around (does it affect home life and lead to danger, i.e., chemicals/physical illness/children at risk). Assess insight (i.e., does pt realize intrusive thoughts are not true)?
- **Natural history:** 2/3rds 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 (*AFP* 2015;92:896; *Cochrane Database Syst Rev* 2008:CD001765; *JAMA* 2017;317:1358; *J Clin Psych* 1999;60:101; *J Clin Psychopharm* 2002;22:309;

2014;28:403)

- **General principles:** Treatment should be initiated by providers confident of dx and comfortable with Rx options; comanagement w/ psychiatry is typical; CBT is typically 1st-line for mild/moderate OCD in pts w/ good insight; Yale-Brown OCD Scale (Y-BOCS) can be useful in tracking sx; making goal quantifiable can be useful (i.e., < h/d spent performing behaviors)

Management of OCD (*NEJM* 2014;371:646)
Pharmacotherapy: Options include SSRI, SSRI + antipsychotic, clomipramine, SSRI + clomipramine. **Efficacy:** For SSRIs no difference in efficacy w/in class. Pts typically take longer to respond than for depression (i.e., 4–6 wk for initial response, 10–12 wk for max benefit). 25–40% of pts relapse if meds discontinued by taper after 1–2 y compared to 80% relapse rate for shorter Tx durations **Dosing:** Tx doses often 150% or more of typical max dose in depression, maximum tolerated dose usually most effective: Sertraline (50–300 mg), paroxetine (10–60 mg), fluoxetine (20–80 mg), fluvoxamine (50–300 mg); see *"Psychotropic Medications"* for specific properties & s/e. 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. **Antipsychotics:** Consider if partial response w/ SSRI (risperidone has the most data)
Cognitive behavioral therapy: Exposure & response prevention (most effective behavioral intervention); graded exposure to anxiety-provoking stimuli; cognitive restructuring; pt & family psychoeducation; 13–20 weekly sessions = adequate trial. Used alone if milder sx or pt resistant to meds. 83% of pts responded to exposure-based CBT (>30% sx reduced); 76% show improved sx long-term. (*J Consult Clin Psychol* 1997;65:44) **Internet-based CBT:** ocdchallenge.com; managingyouranxiety.com; liveocdfree.com. **App-based CBT (iTunes):** Anxiety coach, icounselorOCD, OCD manager,
Surgery: Anterior cingulotomy, deep brain stimulation can be effective in refractory cases (*Am J Psych* 2002;159:269)
Relapse prevention: May be on meds indefinitely. If CBT completed, periodic sessions can be helpful to reinforce skills.

- **Patient information:** *JAMA* 2011;305:1926; iocdf.org

PSYCHOTROPIC MEDICATIONS

Antidepressants (*Ann Int Med* 2016;165:ITC49)		
	Class Characteristics	**Drug and Notes (Doses in mg)**

SSRI	Better tolerated, little risk in O/D 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 mitigates w/d, missed doses; least amount of wt gain among SSRIs; ↑ drug–drug interactions (2D6 & 3A4 inhibitor); helpful for anxiety; SD: 10–20; TD: 20–40
		Paroxetine: Helpful for anxiety/OCD; withdrawal sx; more sedation, sexual dysfunction; ↑ orthostatic HoTN vs. other SSRIs; SD: 10–20; TD 20–40
		Citalopram: Helpful for anxiety; ↓ Na; risk of ↑ QTc; SD: 10–20; TD: 20–40
		Escitalopram: ↓ drug interactions; SD: 10; TD: 10–20
		Sertraline: More diarrhea; helpful in anxiety/OCD; stimulating; SD: 50; TD: 100–200
SNRI	Well tolerated, helpful in chronic pain S/e: GI upset, withdrawal sx; stimulating; ? ↑ CV events; lethal in OD; ↑ drug interactions	**Venlafaxine:** ↑ doses may cause HTN; SD: 37.5 BID; TD: 75–300 BID or TID
		Duloxetine: S/e similar to venlafaxine w/ less e/o CV effects; contraindicated in liver disease; may worsen DM2; SD: 30 QHS; TD: 60–120
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; TD: 100–300
		Imipramine: Oldest TCA; SD: 25–50; TD: 100–300
		Desipramine: Least sedating/anticholinergic SD: 25–50; TD: 100–300
		Doxepin: Mod sedating/anticholinergic SD: 25–50; TD: 100–300
		Nortriptyline: Less sedating/anticholinergic; lower orthostatic HoTN compared to other TCAs; helpful in chronic pain/IBS; therapeutic at 50–150 ng/mL. Monitor BMP. SD: 25; TD: 50–150
MAOI	Can be effective in treatment resistant/atypical depression S/e: May be fatal in O/D, in drug combinations, or w/ tyrosine-rich food or drink; risk of hypertensive crisis and serotonin syndrome	**Tranylcypromine:** More stimulating than phenelzine, but less likely to ↑ wt; SD: 10 daily; TD 30-60 daily
		Phenelzine: Can rarely cause hepatotoxicity; SD: 15 daily; TD 60–90 daily

	Selegiline: Selective MAO-B inhibition at low doses; available as transdermal patch that does not require dietary restrictions at 6 dose; SD: 6 daily; TD 6–12 daily
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); contraindicated in eating disorders; may be fatal in O/D; SD: 50–75 mg BID; TD: 300–450 mg TID	
Mirtazapine: Acts on norepinephrine, serotonin; ↓ drug–drug interactions; wt gain, sedation (useful in insomnia); less sedation, possible energy boost at doses 30 mg and above. Avoid EtOH, benzodiazepines. SD: 15 mg QHS; TD: 15–60 mg QHS	
Trazodone: Serotonin antagonist & partial agonist; sedation, postural HoTN & priapism; SD: 25 mg; TD: 75–500 mg	
Reactions Requiring Immediate Medical Attention (i.e., ED Referral)	
Serotonin syndrome: From serotonergic agents alone or in combination: Fever, diarrhea, myoclonus, hyperreflexia, altered mental status, agitation (*AFP* 2010;81:1139)	
Hypertensive crisis: From MAOIs combined with tyrosine-rich food or drink	
Common Adverse Effects Requiring Outpatient Medical Attention	
Antidepressant discontinuation syndrome: Dizziness, lightheadedness, 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 wk; **Management:** Pt education re: avoiding abrupt d/c of med; gradual taper (*AFP* 2007;74:449)	

(Stahl's Essential Psychopharmacology. 2014*)*

Antipsychotics (Drug & Notes, Doses in mg)			
	Class Characteristics	**Drug**	**Notes**
First Generation	**High potency:** ↑ risk of EPS; less association with sedation, weight gain, anticholinergic activity	**Haloperidol:** Available in oral, IM, long-acting injectable formulations. Oral SD: 1–15 QD; TD: 1–40 QD	
		Fluphenazine: Available in PO, IM, long-acting inj formulations. Oral SD: 12.5–25 QD; TD: 1-20 QD	
		Pimozide: Oral formulation only. SD: 1–2 mg/d in divided doses; TD: less than 10 mg/d	
		Loxapine: Oral formulation only. SD:	

	Mid potency: Side effect profile more similar to high than low potency	20 mg/d in 2 doses; TD: 60–100 mg daily in 2–4 divided doses
		Perphenazine: Available in oral, IM formulations. Oral SD: 4–8 BID or TID; TD: 12–64 QD in divided doses
	Low potency: More sedating and anticholinergic effects; ↓ risk of EPS	**Chlorpromazine:** Available in oral, rectal, IM formulation. Oral TD: 50–800 mg daily
		Thioridazine: Available in oral formulation only. SD: 50–100 mg TID; TD: 200-800 mg/day in divided doses
Second Generation	**Aripiprazole:** Available in oral, IM, long-acting injectable formulations. Can be used as augmentation to antidepressants. Oral SD: 2.5–5 QD; TD: 2.5–30 QD	
	Risperidone: Available in oral, long-acting injectable formulations. Oral SD: 0.5–1 mg QD; TD: 0.5–8 mg QD	
	Quetiapine: Oral formulation only. Oral SD: 25–50 mg daily; TD: 400–800 mg daily in 1–2 doses for psychosis, 300 mg daily for bipolar depression	
	Ziprasidone: Available in oral, IM formulations. Oral SD: 20 mg BID; TD: 40–200 mg QD in divided doses (with food) for psychosis, 80–160 mg QD for bipolar disorder	
	Lurasidone: Available in oral formulation only. SD: 20–40 mg daily with food; TD: 40–80 mg/day for psychosis, 20–60 mg/day for bipolar depression	
	Olanzapine: Available in oral, IM, long-acting injectable formulations (risk of delirium, requires 3-h monitoring postinjection). Oral SD: 5–10 mg QD; TD: 10–30 mg QD	
	Clozapine: PO only. Indicated for treatment-resistant schizophrenia. May ↓ suicide. Therapeutic concentration 300–500 ng/mL. S/e include risk of agranulocytosis, seizure, myocarditis. Pts must be enrolled in clozapine registry w/ monitoring of CBC w/diff. Oral SD: 25 mg QD, increase by 25 mg QD. TD: 300–900 mg QD	
Reactions Requiring Immediate Medical Attention (i.e., ED Referral)		
Acute dystonic reaction: From antipsychotics; painful muscle spasms, posturing		
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		
Clozapine agranulocytosis or myocarditis: Incidence 0.05–2% (*Schizophr Bull* 1995;21:579)		
Common Adverse Effects Requiring Outpatient Medical Attention		

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 wk, then annual), fasting lipids (at 4–6 wk 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, & q6mo (*Curr Drug Safety* 2010;5:97)

(Stahl's Essential Psychopharmacology. 2014*)*

Mood Stabilizers (*Acta Psychiatr Scand Suppl* 2009;439:27)		
	Drug (labs)	**Notes**
Acute Mania	**Lithium** BMP, TSH, Ca (& PTH if abnl)	Therapeutic 0.6–1.2 mEq/L (12 h trough), 0.8–1.2 for mania. Takes 1–3 wk to work. May decrease suicide. S/e incl tremor, polyuria/dipsia, GI, wt. gain, acne. SD: 300 mg 1-2x daily, titrate to therapeutic range.
	Valproic acid CBC, LFT_s, NH_3	Therapeutic 50–125 µg/mL (12 h trough). May see effects within a few days. S/es sedation, GI, alopecia, wt gain PCOS. Rare hepatotoxicity, liver failure. SD: 15–20 mg/kg in 2 divided doses, titrate to therapeutic range.
	Carbamazepine BMP, LFTs q6–12mo	Therapeutic 4–12 µg/mL. Takes a few weeks to work. S/e incl sedation, GI, blurred vision, benign leukopenia, rash. Rare aplastic anemia, agranulocytosis, SJS, SIADH, cardiac problems. SD: 200 mg BID, titrate to therapeutic range.
	2nd-generation antipsychotics	Risperidone and olanzapine most common agents used.
Bipolar Depression	**Lamotrigine**	S/e incl rash, sedation, blurred vision, insomnia, tremor, GI. Rare SJS, blood dyscrasias, aseptic meningitis. SD: 25 mg daily x 2 wk, increase to 50 mg/d wk 3, 100 mg/d wk 5, 200 mg/d wk 6; TD: 100–200 mg/d.
	Olanzapine + fluoxetine	SD: olanzapine 6 mg/fluoxetine 25 mg daily; TD: 6–12 mg olanzapine/25–50 mg fluoxetine.
Reactions Requiring Immediate Medical Attention (i.e., ED Referral)		
Lithium toxicity: Level >1.2 mM → tremor, vomiting, diarrhea, confusion		
Stevens–Johnson syndrome: 2/2 rapid dose ↑ of lamotrigine (incidence 0.1–0.8%) (*Clin Neuropharmacol* 2011;34:39)		
Common Adverse Effects Requiring Outpatient Medical Attention		

Hyponatremia: Any SSRI, AP, mood stabilizer may cause SIADH; ↑ risk w/ carbamazepine, oxcarbazepine, citalopram; **Management:** Baseline Na before starting med, q1–6 mo thereafter, r/o psychogenic polydipsia; see "*Sodium Disorders*"
Lithium-induced hypercalcemia: 4–6 fold ↑ incidence of hyperparathyroidism, up to 80% pts w/ some rise in Ca; **Management:** Stop lithium ± cinacalcet; see *"Calcium 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"*

(Stahl's Essential Psychopharmacology. 2014*)*

Special Populations (*AFP* 2012;85:483)

- **Cardiovascular disease:** Many meds interact w/ warfarin; significant cardiotoxicity w/ thioridazine, disulfiram; SSRIs are 1st-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/ HLD
- **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); paliperidone is not hepatically metabolized
- **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 (*Curr Psychiatry Rep* 2012;14:376)		

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, dose ↓
Carbamazepine/Valproic acid	Warfarin ↓ INR (CYP2C9)	Monitor INR, dosing
Lamotrigine/Valproic acid	VPA inhibits lamotrigine metabolism → ↑ plasma concentration → ↑ risk SJS	Dose and titration adjustment

POSTTRAUMATIC STRESS DISORDER

Background (*Am J Med* 2006;119:383; *Occ Med (Lond)* 2007;57:399; *World Psychiatry* 2014;13:265)

- **Definition:** >1 mo of disturbances due to a traumatic event with sx of (1) Re-experiencing event, (2) Avoidance of situations that recall the trauma, (3) Negative mood/thoughts due to the trauma, (4) Chronic hyperarousal
  - **Traumatic event:** Includes threat of death, serious injury, sexual violence; Experience may be direct, witnessed, or may have occurred for a close family member/friend
  - **Acute stress disorder (ASD):** Same criteria as PTSD, though sx last only 3 d–1 m; ~50% develop PTSD, worsening thought due to stressors/additional traumatic events
- **Pathophysiology:** Driven by changes in the amygdala and hippocampus
- **Epidemiology:** 10% ♀ and 5% ♂ exposed to trauma develop

PTSD; lifetime prevalence is 6.8%; assoc w/ anxiety, mood, SUD, personality disorders, aggression, & overall disability

- **Risk factors:** ↑ risk: ♀, young age, low socioeconomic status, low education, minority, interpersonal violence (kidnapping, physical/sexual assault), ↑ #/duration of trauma, ↑ perceived threat, ↑ peritraumatic emotion/dissociation, poor social support, ↑ life stress

Evaluation and Prognosis (*JAMA* 2015;314:501; *NEJM* 2017;376:2459)

- **History:** Triggers to relive event (i.e., flashbacks), times of day, nightmares, response to triggers, avoidant behaviors; screen for depression and anxiety; impact of symptoms on functioning; sx of ↑ arousal (difficulty sleeping/concentrating, anger, arguments, violence, easy startling); physical sx (palpitations, nausea, etc.)
  - **Evaluate for safety:** Pts w/ PTSD 6× more likely to commit suicide

Primary Care PTSD Screen (Adapted from *J Gen Int Med* 2016;31:1206)

In your life have you had an experience that was so frightening/horrible/upsetting that in the past month you:

- Had nightmares/thought about the event even though you didn't want to?
- Tried not to think about the event or went out of your way to avoid situations that reminded you of the event?
- Been consistently on guard, watchful, easily startled?
- Felt numb or detached from people, activities, or your surroundings?
- Felt guilty/unable to stop blaming yourself/others for the event/resulting problems?

Scoring: Yes: 1 pt, No: 0 pt. In veterans, score ≥ 3 95% sens, 85% specific.

Treatment (*AFP* 2013;88:827; *Am J Psychiatry* 2004;161:3; *J Psychopharmacol* 2014;28:403)

- **General principles:** 3 approaches may be used alone or in combination, include psychotherapy, medications, education/support; Goals include (1) ↓ severity of sx, (2) better tolerate/manage distress, (3) ↓ intrusive re-experiencing, (4) ↓ trauma-related avoidant behaviors, nightmares, sleep problems, (5) develop problem solving/emotional regulation skills, (6) educate about natural course of sx (worsen w/ re-exposure, perceptions of being unsafe, life stress, medication discontinuation)
- **Education and support:** Helpful as early interventions ↓ sx after

trauma; encouraging acutely traumatized persons to first rely on their inherent strengths, their existing support networks, and their own judgment may ↓ the need for further intervention

- **Psychotherapy:** Speeds recovery and prevents PTSD when given 2–3 wk after trauma exposure
  - **CBT:** Desensitize to trauma-related triggers (e.g., exposure tx)
  - **Eye movement desensitization & reprocessing (EMDR):** Exposure-based therapy (brief, interrupted exposure to traumatic material) w/ eye movement, recall, tackling about memories; efficacy similar to CBT
  - **Psychodynamic psychotherapy:** Focuses on meaning of the trauma in developmental experience and relationships
- **Psychopharmacology:**
  - **SSRIs:** Only sertraline (50–200 mg QD) and paroxetine (20–60 mg QD) FDA approved, all have empirical support; treats all PTSD symptom clusters (i.e., re-experiencing, avoidance/numbing), common comorbid disorders (depression, panic, OCD), and ↓ sx (SI, impulsive/aggressive behaviors); treatment of responders generally continues for at least 12 mo
  - **Other antidepressants:** TCAs & MAOIs may ↓ sx; little evidence available for other antidepressant categories (e.g., venlafaxine, mirtazapine, bupropion)
  - **Benzodiazepines:** May Tx anxiety and ↑ sleep, but do not address core symptoms of PTSD; worsening of sx with benzodiazepine discontinuation possible; may interfere with the cognitive processing needed for psychotherapeutic interventions to work

Medical Management of PTSD		
Sx Cluster	**1st-Line Treatment**	**2nd-Line Treatment**
Re-experiencing	Prazosin: nightmares; start 1 mg QHS, ↑ as tolerated up to 10 mg QHS; some data for higher doses	Anticonvulsants: May improve sx related to re-experiencing; topiramate (most data) carbamazepine, divalproex, lamotrigine
Increased arousal	Propranolol 10 mg TID	2nd-generation antipsychotics may help if 1st-line ineffective, olanzapine and risperidone most

		studied

- **Treatment of nonresponders:** Combine treatment modalities, augment antidepressant with olanzapine, risperidone or prazosin, refer to specialist.
- **Patient information:** *JAMA* 2015;314:532

PSYCHOTIC DISORDERS

Background (*AFP* 2007;75:1821; 2014;90:775; 2015;91:856; *NEJM* 2003;349:1738)

- **Definition:** Disturbance in perception of reality (hallucinations, delusions, thought disorganization)
  - **Schizophrenia:** Chronic/recurrent psychosis w/ impaired social/occupational functioning
  - **Schizoaffective disorder:** Psychosis + mood disorder
  - **Brief psychotic d/o:** Psychosis in stressful situation; resolves w/ removal of stressor
  - **Postpartum psychosis:** Typically presents 2 wk after childbirth in 0.1–0.2% postpartum ♀; assoc w/ ↑ risk of suicide, infanticide
- **DDx: 1° 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, hallucinogenics, bath salts, analgesics; **Psychosis 2° to a medical condition:** Delirium, dementia, CVA, CA, heavy metals, demyelinating dz, seizures, neuropsychiatric d/o (Wilson's, Huntington's, etc.), autoimmune, infections, endocrinopathies, nutritional deficiencies, metabolic d/o

Evaluation (*Arch Gen Psychiatry* 2005;62:247; *Early Interv Psychiatry* 2009;3:10; *JAMA* 2002;287:3249)

- **History:** Mental status exam, MOCA, FHx of psychiatric problems, head trauma, screen for suicidality (lifetime risk of 4.8%) & homicidality
  - **Positive symptoms:** Hallucinations (auditory, visual, tactile,

olfactory, gustatory); delusions, especially paranoid; disorganized speech and thought pattern

Negative symptoms: Blunted or flattened affect; anhedonia; alogia (poverty of speech); avolition; asociality or isolation; impaired self-care

Cognitive symptoms: Impaired executive function, 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 1st episode of psychosis:** CBC, Chem-12, ESR, ANA, serum & urine tox, TSH, HIV, ceruloplasmin, folate, B_{12}, VDRL; brain MRI & EEG if clinically indicated

Treatment (*Harv Rev Psychiatry* 2007;15:189; *Lancet* 2013;382:951)

Comparative Risk of Side Effects of Antipsychotics (*CNS Drugs* 2007;21:911)

Drug	↑ QTc	Orthostasis	DM2	HLD/↑ wt	AC	EPS	Sedation
Aripiprazole	Low	Low	Low	Rare	Rare	Low	Low
Clozapine	Low	High	Med	High	High	Rare	High
Olanzapine	Low	Low	Med	High	Low	Low	Med
Quetiapine	Low	Low	Low	Medium	Low	Rare	Medium
Risperidone	Low	Med	Low	Medium	Rare	High	Low
Ziprasidone	Med	Low	Low	Rare	Rare	Low	Low

Medication	Considerations
Aripiprazole	Long half-life; ↑ risk of akathisia
Clozapine	Agranulocytosis, requires weekly ANC; used in refractory cases, not 1st-line
Olanzapine	↓ rate of discontinuation in chronic schizophrenia compared to other 2nd-generation antipsychotics
Quetiapine	Wide dosing range (≥200 mg likely for maintenance)
Risperidone	Hyperprolactinemia; ↑ risk of EPS at higher doses compared to other

	atypicals
Chlorpromazine, haloperidol, perphenazine: Risk of tardive dyskinesia; EPS common; hyperprolactinemia	

AC, anticholinergic side effects; EPS, extrapyramidal side effects.

- **Medication selection:** Choice guided by patient preference, tolerability, and clinical situation (e.g., medical comorbidities, FHx, or psychopathological sx profile); no antipsychotic (1st or 2nd generation, including clozapine) clearly outperforms other antipsychotics in 1st-episode patients; American Psychiatric Association recommends 2nd-generation antipsychotics given potentially more tolerable side-effect profile
  - **Initial antipsychotic:** Choices could include risperidone, aripiprazole, quetiapine, or ziprasidone
- **General principles for antipsychotic prescribing:** Start low, ↑ slowly until effective
  - **Monitoring:** Baseline & follow-up weight, BMI, waist circumference, lipids, and glucose
  - **Adverse effects:** Extrapyramidal symptoms (dystonia, parkinsonism, akathisia); neuroleptic malignant syndrome; tardive dyskinesia; ↑ weight, HLD, DM2, ↑ QTc/TdP
  - **Anticholinergic co-prescribing:** Benztropine frequently given with 1st-generation antipsychotics to prevent dystonic reactions/EPS (but ↑ cognitive side effects)
- **Tardive dyskinesia:** A potentially permanent & debilitating side effect; track involuntary movements using Abnormal Involuntary Movement Scores (AIMS) scale w/ all pts; can be reduced with slow dose decreases or using clozapine (*Am J Psychiatry* 1980;137:900)

Somatic Symptoms and Related 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 women, 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. Up to 1/3rd of common symptoms seen in primary care do not have a disease-based explanation.

DSM-5 Diagnostic Criteria for Specific Disorders
Somatic symptom disorder: 1+ sx causing distress or psychosocial impairment; excessive thoughts, feelings or behaviors about sx as demonstrated by 1+ of the following: persistent thoughts about seriousness of sx, severe anxiety about sx or health, excessive time and energy devoted to sx; duration of 6+ mo.
Illness anxiety disorder: Mild or **nonexistent** somatic sx paired w/ preoccupation of having a serious, undiagnosed illness; anxiety about health & low threshold for alarm about health; excessive health behaviors or avoidance of activities thought to threaten health; not better explained by other mental disorders; duration of 6+ mo.
Conversion disorder: Sx/deficit affecting voluntary motor/sensory function (seizure, sensory loss, weakness/paralysis); often 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:* Multiple sclerosis, myasthenia gravis, movement disorders, stroke, epilepsy, nerve entrapment
Psychological factors affecting other medical conditions: A general medical d/o must be present paired w/1+ of the following: behaviors/factors that increase health risks, exacerbate underlying pathophysiology, or affect course or treatment of medical condition
Factitious disorder: Intentionally feigning sx to assume the sick role, without obvious external benefits (e.g., financial gain or avoiding responsibilities)

Evaluation (*AFP* 2007;76:1333; 2015;93:49; *Ann Int Med* 2014;161:579)

- **History and exam:** Diagnostic yield typically 70–80%; thorough evaluation of the following: relation of sx to pt emotions & social situation; hx physical/sexual abuse, domestic violence; substance use; past medical & psychiatric hx; hx of pattern of similar presentations; complete physical exam
- **Workup:** Rating tools: Patient Health Questionnaire 15, Somatic Symptom Index, somatization subset of Symptom Checklist-90, Somatic Symptom Scale-8, Somatic Symptom Disorder-B Criteria Scale, Somatic Symptoms Experiences Questionnaire

Treatment (*JAMA* 2004;291:1464)

- **Share the dx:** Explain which medical conditions are ruled out and reassure no evidence of life-threatening conditions
- **Validate patient complaints:** Empathically acknowledge the patient's experience; "It must be difficult to have recurrent pain," or "Tell me more about how this is affecting you."
- **Follow-up:** Regular appts; avoid urgent appts, diagnostic tests, surgery unless indicated; communicate w/ involved specialists
- **Medications:** Antidepressants are the mainstay of tx; TCAs for pain, SSRIs for other somatic symptom disorders (*J Psychosom Res* 2004;56:455)
- **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 and correct distortions, misperceptions, and misattributions of symptoms

SUICIDE RISK ASSESSMENT

Background (*Mayo Clin Proc* 2011;86:792; *JAMA* 2005;294:2064; 2013;309:2432; *Am J Psych* 2003;160:3)

- **Epidemiology:** 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
Modifiable Risk Factors	• Psychiatric symptoms: Depression, psychosis (esp. command auditory hallucinations/paranoia), impulsivity, agitation, severe anxiety • Substance use: Suicide mortality ↑6× in EtOH use d/o • Living situation (living alone, homelessness, living in rural setting ↑ risk) • Current stressful life events • Medical problems + demoralization • Posthospitalization transition
Nonmodifiable Risk Factors	• Past/aborted suicide attempts — (↑ risk if recent) most consistent predictor of future and completed suicide attempts • Past self-injurious behavior (include risk taking, unsafe sex, and reckless driving) • Family history of suicide • Multiple psychiatric diagnoses or history of abuse (esp depression, BPAD, EtOH/substance use, schizophrenia, personality disorders, anxiety disorders) • Demographics: ♂ complete suicide >3× more often, ♀ attempt suicide >2× more often; White; older age (♂ >50, ♀ >60); single status (never married > widowed > separated > divorced > married)

Evaluation (*AFP* 2003;68:1814; 2006;74:1159; 2012;865:602)

- **History: Inquiring about suicide does not ↑ likelihood a pt will make an attempt;** depression, EtOH, & SUD screening; suicidal thoughts/behaviors should be assessed in all pts w/ depression/hx depression, using a step-wise approach (*J Clin Psychiatry* 1998;59:58)

Step-Wise Evaluation of Suicide Risk
Thoughts of death or suicide: Passive vs. active, timing, frequency, precipitants, whether thoughts can be controlled/ignored, what will be accomplished with suicide (e.g., reunification w/ deceased loved one, ending pain, escaping shame, peace) **Plan: Access to firearms,** other means, specificity (place/time, plan details) **Suicidal intent:** Preparation or rehearsal, why not acted on thus far **Past attempts:** Timing, precipitants, intent, risk/rescue ratio, consequences, intoxication prior to attempt (20–25% who complete suicide are intoxicated) **Other:** Self-injurious behavior (frequency, severity, reason), presence of homicidality **Sample questions:** "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**
Symptom	No specific plan or intent to commit suicide; no H/o suicide attempts.	Suicidal ideation + plan, but no intent or behavior	Serious thoughts of suicide; plan and/or intent; prominent agitation, impulsivity, psychosis; recent attempt
Rx	Outpatient f/u, remove obvious means of self-harm (i.e., firearms, large quantities of meds). Consider safety contract. Provide suicide hotline (1-800-273-TALK).	Urgent referral to a psychiatrist vs. emergency department	Constant observation and monitoring until transfer for psych eval/hospitalization

Patient information: *AFP* 2006;74:1165; 2012;85:610; *JAMA* 2004;291:1158; 2005;293:2558

DIAGNOSIS AND TREATMENT OF SUBSTANCE USE DISORDERS

Background (*AFP* 2013;88:113; *Ann Int Med* 2016;164:ITC49)

- **Goals:** (1) Identify SUD for treatment (2) ↑ trust in primary care, (3) prevent overdose and medical complications, (4) ↓ drug–drug interactions, (5) identify comorbid conditions, (6) ↓ stigma
- **Standard of care:** Expert consensus to screen for substance use disorders in primary care clinic based on high prevalence, high morbidity/mortality, and availability of effective interventions; SUDs are underdiagnosed and undertreated chronic illnesses

Diagnostic Criteria for Substance Use Disorders (DSM-5)	
A problematic pattern of substance use leading to clinically significant impairment/distress, as evidenced by ≥2 of the following over a 12-mo period:	
• Failure to fulfill roles • Use in risky situations • Persistent desire or unsuccessful efforts to cut down • Use despite known ⊖ impact on med/psych dx • Tolerance	• Cravings • ↑ doses or longer period of use than intended • ↑ time finding, using, recovering • Evidence of withdrawal • Abandonment of other pleasurable activities • Use despite adverse effects on relationships
Severity grading: Mild 2–3, Mod 4–5, Sev ≥6	

Evaluation

- **Screening questionnaires:** Many options → consider feasibility

based on length, complexity of administration, appropriateness based on substances (EtOH vs. all substances); most do not include tobacco (https://www.drugabuse.gov/sites/default/files/resource_guide.pdf)

- **Introduction to screening:** Normalize with "I'm going to ask you a few questions that I ask all my patients" and explain purpose, "this will help me give you better medical care; the questions relate to your experience with alcohol, drugs, and nicotine."
  - **Quick screen** (from National Institute on Drug Abuse): 1st pass, designed to precede in-depth screen, e.g., NIDA-modified ASSIST: How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons or had ≥5 (♂) or ≥4 (♀) drinks/day? Score ≥ 1 ⊕ 100% sensitive, 73.5% specific (*Arch Intern Med* 2010;170:1155). If pts screen positive, use a more in-depth screen (box).
- **Screen for other comorbidities:** Intimate partner violence (IPV) → 50% of pts w/ SUD are victims of IPV (*Subst Use Misuse* 2009;44:1298); screen for concomitant mental health disorders: anxiety, depression, bipolar, PTSD, personality disorders
- **Workup:** *With pt permission:* Urine or serum toxicology; screen for hepatitis A/B/C, HIV, STDs, TB

Management

- **Harm reduction:** Goal is to ↓ ⊖ consequences of drug use using a patient-centered, nonjudgmental approach.
  - **Vaccinations:** Hepatitis A, B; Meningococcus, tetanus; *see "Vaccines"*
  - **Infection prevention:** *Counsel* on safe injection techniques: Clean needles/hands/injection site, no needle sharing, use a different site each time, safe needle disposal; *Provide* information on needle exchange programs
  - **Accident reduction:** Counsel on driving, firearms
  - **Overdose prevention:** *Counsel* to use small amount of new batch as "test shot" before shooting full amount; Avoid injecting alone; Highest risk of O/D is after a period of no use; *Provide* naloxone (see "*Opioid Use Disorder*"); Review prescribed medications for possible interactions; judiciously prescribe opioids/benzodiazepines

Ensure access to contraception
Recovery coaches

- **Detoxification Programs:** Manage acute withdrawal, appropriate for pts w/ risk severe withdrawal; wide variability in completion of programs (*J Subst Abuse Treat* 2015;52:31); LOS: D–wk, typically 4–6 d
- **Adjunctive treatment:** Counseling should be an adjunct to pharmacotherapy of SUD; Levels of care include inpatient, residential, intensive outpatient, and outpatient counseling. Insufficient evidence to recommend for or against specific psychosocial intervention; Setting should be determined based on patient preference, provider competence, risk of relapse, need for supervision, anticipation of detoxification; Referrals at: findtreatment.samhsa.gov/
  - **Brief Intervention:** High efficacy for EtOH abuse, unclear efficacy in other SUD (*JAMA* 2014;312:502) (sbirttraining.com/about)
  - **Motivational Interviewing**: Patient-centered, empathetic and nonjudgmental approach; Aims to enhance intrinsic motivation by eliciting discrepancies btw future goals & current behavior and pros & cons of substance use
    - **Elicit-provide-elicit method:** Elicit knowledge and opinions regarding aspect of SUD, “What do you know about how alcohol affects your health?” Provide salient information and advice. Elicit response to your comments and pt opinion, “How does this information strike you?”
  - **Cognitive behavioral therapy:** Development of coping skills; May have efficacy in cannabis use disorder; may be effective as adjunct to nicotine replacement therapy (*Cognit Ther Res* 2012;36:427)
  - **Contingency management (CM):** Incentives for target behaviors, often monetary for participation in therapy sessions or abstinence; Vouchers w/ monetary value provided for ⊖ tox screens most effective w/ opioids & cocaine (*Addiction* 2006;101:1546); Risk of relapse after CM ends may be high; environmental and neurocognitive factors that make CM more successful yet to be identified (*J Subst Abuse Treat* 2017;72:10)
  - **Intensive outpatient program (IOP):** Counseling-based outpatient program, typically group setting; May offer adjunctive pharmacotherapy, individual counseling, and/or psychiatry;

LOS: Typically 3 half days/wk; Less disruption of work/family/social life

Clinical stabilization service (CSS) and transitional support service (TSS): Inpatient programs serve as transition from detox → long-term residential treatment; include education and counseling but services vary; LOS: (CSS) 10–14 d; (TSS) 30 d

Residential treatment: Highly structured, sober, and stable living environment; May be private (typically $$$, insurance not accepted) or publicly funded (may accept insurance); Halfway houses/recovery homes offer stable, sober, supportive place to live with group meetings; typically require mutual help meetings; LOS: Wk–mo, up to 6–12 mo

Mutual help meetings: Peer support groups; adjunct to treatment. ↓ risk of relapse largely through facilitating sober contacts and sponsorship; increased engagement with mutual help is associated with increased treatment success

Narcotics Anonymous (NA, na.org), **Alcoholics Anonymous** (AA, aa.org): voluntary attendance, usually 12-step meetings, optional mentor known as sponsor, abstinence not required, free, widely available at different times and locations; closed meetings for those with addiction only vs. open meetings

Self-Management and Recovery Training (SMART, smartrecovery.org): Nonreligious, designed for all types of addiction; offers "4-Point Program" (1) building and maintaining motivation, (2) coping w/ urges, (3) managing thoughts, feelings & behaviors, (4) living balanced life; daily online meetings, online message board, chat room, face-to-face meetings

12-Step Facilitation Therapy (National Institute on Alcoholism and Alcohol Abuse 1995 Twelve-Step Facilitation Therapy Manual): Individual, adapted to group format, outpt; typically 12–15 sessions

Technologic innovations: Interactive websites, mobile apps, videoconferencing

National Institute on Drug Abuse Modified ASSIST
In your lifetime, which of the following substances have you ever used? (i.e., cannabis,

cocaine, prescription stimulants, inhalants, sedatives, sleeping pills, hallucinogens, street/prescription opioids, other)

For each drug ask: In the past 3 mo how often have you because of substance use (points):
Used the substances mentioned? Never (0), 1–2× (2), Monthly (3), Weekly (4), Daily/Almost daily (6)
Had a strong desire/urge to use? Never (0), 1–2× (3), Monthly (4), Weekly (5), Daily/Almost daily (6)
Had health, social, legal or financial problems? Never (0), 1–2× (4), Monthly (5), Weekly (6), Daily/Almost daily (7)
Failed to do what was normal expected of you? Never (0), 1–2× (5), Monthly (6), Weekly (7), Daily/Almost daily (8)
Had a friend, relative, or anyone else express concern about your use? Never (0), Yes, but not in past 3 mo (3), Yes, in past 3 mo (6)

Tried & failed to control, ↓, or stop using? Never (0), Yes, but not in past 3 mo (3), Yes, in past 3 mo (6)
Final question: Have you ever used any drug by injection? If answer is "Yes" consider screening for blood-borne disease. If "Yes in the past 3 mo" also counsel harm reduction of IVDU (below)

Severity grading: For each substance, calculate Substance Involvement Score: 0–3 lower risk, 4–26 mod, ≥27 high. ASSIST sensitivity 90%, specificity 78% (*Drug Alcohol Rev* 2005;24:217)

Other screening tools:
Drug abuse screening test (DAST-10): Considered as reliable as original DAST-28 or modified DAST-20 *(J Subst Abuse Treat* 2007; 32:189*)*
Tobacco, EtOH, Prescription Drugs & other Substance Use (TAPS) Tool (*Ann Intern Med* 2016;165:690)
CAGE-AID: Adapts CAGE to include drug use (i.e., cut down on drinking or drug use). "Yes" 1 pt, "No" 0 pt. Score 0–1 ⊖ screen; 2–4 ⊕; 12–78% PPV, 78–99% NPV; sensitivity 79–91%, specificity 48–77% *(Wis Med J* 1995;94:135*)*.
CRAFFT: Only screen validated for adolescents (*Arch Pediatr Adolesc Med* 2002;156:607)

TOXICOLOGY TESTING (*AFP* 2010;81:635; *Mayo Clin Proc* 2008;83:851)

- **Background:** <50% of pts abusing drugs present with aberrant behavior (*Anesth Analg* 2003;97:1097)
- **Sample sources:** Testing typically done using immunoassays with gas chromatography/mass spec confirmation. 2nd-hand marijuana exposure unlikely to give a positive result

  Urine: Most common modality; Assesses 24–72 h use; only

modality approved for federally mandated testing. Standard 9-panel test includes amphetamines, cocaine, marijuana, opiates (codeine, morphine), PCP, barbiturates, benzodiazepines, methadone, propoxyphene; Specific pain panel may be needed to detect oxycodone and other narcotics

Subversion: False-negative results may be caused by excess water ingestion, masking agents (niacin), adulterants (ammonia, bleach, eye drops, hydrogen peroxide, nitrates, papain, soap, zinc sulfate), substitution of drug-free urine

Serum: May be limited by half-life of illicit substances (i.e., heroin has a serum half-life of 6–15 min); typically performed by liquid chromatography/mass spec

Hair: Provides 90-d history of drug use; detects amphetamines, cocaine, marijuana, PCP, opiates

Saliva: Allows direct observation of sample collection; common tests include amphetamines, cocaine, marijuana, methamphetamines, opiates, and PCP

Timeframe When an Ingestion is Likely to Produce a Positive Screen Result	
Amphetamines: 1–3 d **Benzodiazepines:** 1–7 d (except for diazepam, which may be weeks) **Cocaine:** 1–3 d	**Ketamine:** 3–7 d **Marijuana:** Months **Opiates:** 1–3 d (except methadone which is 3–10 d) **PCP:** 1–7 d
Substances That May Cause False Positives	
Amphetamines: Amantadine, atenolol, bupropion, carbidopa, ephedrine, labetalol, levodopa, phenylephrine, promethazine, pseudoephedrine, trazodone **Benzodiazepines:** Oxaprozin, sertraline **Marijuana:** Hemp food products, marinol, NSAIDs, pantoprazole **Opioids:** Dextromethorphan, diphenhydramine, fluoroquinolones, poppy seeds, quinine, rifampin, verapamil **PCP:** Dextromethorphan, diphenhydramine, doxylamine, ibuprofen, imipramine, tramadol, venlafaxine	

ALCOHOL USE DISORDER

Background (*JAMA* 2015;314:2123*; NEJM* 2013;368:365; *Niaa*, nih.gov)

- **Epidemiology:** 70% of US adults consumed EtOH in last year; 7% of all adults annually have AUD; 88,000 deaths (1 in 10 working age adults) and $250 billion cost in US, 6% of all deaths globally; 15% of pts w/ AUD have another substance use disorder
- **Special populations:** *Adolescents:* Consume 90% of EtOH by binge drinking; *College:* ↑ risk of sexual assault; ↓ availability ↓ consumption; *Seniors:* Medication interactions; ♀: ↑ risk of side effects given lower weight and body water content; *Minorities:* Variation in cultural norms around abstinence and openness to treatment; 12% of Native American deaths involve EtOH; *HIV:* ↑ risky behaviors, ↓ adherence to ART

1 Drink is 12–14 g EtOH (i.e., 12-oz beer, 5-oz wine, 1.5-oz spirits)
"Low-Risk" Drinking: ♂/♀: ≤4/3 drinks/d and ≤14/7 drinks/wk. For pts >65 criteria are the same as for ♀; **Light Drinking and the "J-Curve"**; some observational studies have shown a "J-curve" suggesting light drinking associated with ↓ risk of CAD but these data are controversial and given risks, encouraging light drinking is not recommended (*Arch Int Med* 2006;166:2437; *BMJ* 2014;349:4164*; JAMA* 2010;303:2065)
Binge Drinking: ≥5 drinks/occasion in the last mo
Heavy Drinking: ≥5 drinks/occasion on ≥5 days in the last mo
Alcohol use disorder (DSM-5): A maladaptive pattern of EtOH use leading to clinically significant impairment or distress as manifested by **2 (or more) of the following,** occurring w/in a 12-mo period (≥6 considered severe AUD): **(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 and Social Consequences
Cardiac: HTN, nonischemic dilated cardiomyopathy, afib. EtOH ↑ HDL short-term; ~1 to 2 drink/d associated with ~30% ↓ risk of CAD and ~18% ↓ mortality in observational studies (*Arch Int Med* 2006;166:2437). Moderate drinking not recommended as a CAD preventative strategy given risks/harm of EtOH and absence of randomized trials (*JAMA* 2010;303:2065).
Hematology/oncology: ↓ HCT, ↓ PLT due to B12/folate deficiency, marrow suppression. Macrocytosis. ↑ breast CA risk even at levels as low as 3 drinks/week (*JAMA* 2011;306:1884). ↑ risk of oral, GI, & liver CA (*Lancet Oncol* 2009;10:1033). No safe threshold for EtOH and cancer risk (*Am J Public Health* 2013;103:641).
Neurologic: Korsakoff syndrome (memory deficits), Wernicke's encephalopathy

(encephalopathy, gait ataxia, oculomotor dysfunction), peripheral neuropathy, seizures.

Pregnancy: Abstinence recommended. ↑ risk of stillbirth, low birth weight, fetal alcohol syndrome (growth problems, facial dysmorphia, CNS/cognitive problems). Naltrexone and acamprosate are both Category C

GI: Cirrhosis, gastritis, hepatitis, pancreatitis. 2× ↑ progression to cirrhosis in pts w/ Hep C (*Am J Gastroenterol* 2002;97:1807).

Social: ↑ domestic violence, sexual assault, use of firearms (in particular suicide), drunk driving (1 US death every 53 minutes), legal consequences (custody of children, employment termination, loss of housing, and incarceration), and ↓ work productivity.

Evaluation

- **Screening: Single Item Screening Question:** "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)
  - **AUDIT-C:** (1) How often drink containing alcohol? (2) How many drinks on a typical day? (3) How often >6 drinks at once?
- **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 alcohol use disorder thought to be genetic, prevalence higher w/ affected 1st-degree relative (*Curr Psych Rep* 2009;11:364)
  - **AUD history:** Prior tx, other substance use, attempts to quit, duration of episodes of sobriety, environment where drinking occurs, relapse triggers, consequences
  - **Evaluation of other substance use and comorbid psych disease**
- **Physical:** Hepatomegaly, neuropathy, asterixis, stigmata of chronic liver disease (spider angiomas, caput medusa, splenomegaly, palmar erythema, ascites, jaundice)
  - **Withdrawal Sx's:** 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

Management (*Ann Int Med* 2016;164;*NEJM* 2005;352:596)

Psychosocial Interventions

Brief interventions: Counseling (~10–15 min) w/ motivational interview (see *"Patient Counseling"*) ↓ risky drinking; consider involving family members; arrange f/u; if pt unwilling to stop, consider harm reduction (e.g., to cut back or not to drink & drive)
- **Show concern, give specific 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 tx are available including medications and 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"

Counselling: (findtreatment.samhsa.gov)
- **Cognitive behavioral tx:** Skills to avoid situations that cause heavy drinking
- **Motivational enhancement tx:** Resolve ambivalence, elicit pt goals
- **Peer support/mutual help:** Not formal treatment but can be very effective. Correlation btwn participation and abstinence; No evidence for mandating. Alcoholics Anonymous (12-step). SMART Recovery (nonreligious alt to AA)

Pharmacotherapy (*AFP* 2016;93:457;2016; 94:155; *JAMA* 2014;311:1889; *NEJM* 2005;352:596)

General principles: Safe, easy to prescribe & underutilized; naltrexone and acamprosate equal in efficacy with different side-effect profile; typical course 3–12 mo; medication combinations do not ↑ efficacy (*JAMA* 2006;295:2003); medication + brief counseling by PCP 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); recommended for maintenance of abstinence, ideally abstinent at tx initiation; halve dosage in renal insufficiency (CrCl 30–50 mL/min)
- **Naltrexone:** May ↓ craving for EtOH, ↓ frequency & intensity of drinking; useful for controlled consumption; ? effect on abstinence. Daily PO or monthly naltrexone IM. IM (380 mg) ↓ event rate of heavy drinking in pts w/ AUD by 25% compared to placebo (*JAMA* 2005;293:1617); contraindicated in pts using or who may take opioids. Use w/ caution if LFTs >5× normal; pts should 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)
- **Disulfiram:** (RCTs do not support efficacy unless dosing is observed, 3rd-line AHRQ);

aldehyde dehydrogenase inhibitor leads to ↑ acetaldehyde → vomiting w/ EtOH consumption; efficacious/best suited for supervised administration; s/e include risk of fulminant hepatitis, neuropathy, psychosis; contraindicated in CAD, metronidazole use, or rubber allergy

Topiramate: Gradually uptitrated over several weeks from 25 mg BID up to max dose 150 mg BID; should be tapered off to avoid rebound during discontinuation

Supportive treatment: Thiamine 100 mg PO QD, folic acid 1 mg PO QD, MVI

- **Outpatient detoxification:** Requires close supervision by provider, may be safe & effective even in heavy drinkers (*AFP* 2013;88:589; *Alcohol* 2000;35:66)
- **Inpatient detoxification:** H/o seizure, detoxes, psych disease, BAL >150 mg/dL, acute illness, unstable Y 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
- **Harm reduction:** Counseling about driving, firearms, mixing meds w/ EtOH
- **Treat comorbid psychiatric conditions:** Many affective sx abate w/ abstinence; however, may use SSRI to treat associated depression (*JAMA* 2004;291:1887)
- **Referral:** Consider addiction medicine physician/psychiatrist, esp if complex hx
- **Patient information:** Rethinking Drinking: rethinkingdrinking.niaaa.nih.gov; NIAAA AUD Treatment: pubs.niaaa.nih.gov/publications/Treatment/treatment.htm

OPIOID USE DISORDER

Background (samhsa.gov/atod/opioids; *NEJM* 2015;372:241; 2016;374:154; 1253)

- **Epidemiology:** Approximately 4 mil people in US use prescription (Rx) opioids for non–medical use each month; >80% new heroin users start w/ Rx opioids (*Drug Alcohol Deped* 2013;132:95); overdose deaths are the #1 cause of accidental death in US (3× ↑ since 1999) (*MMWR Morb Mortal Weekl Rep* 2016;65:1445)
- **Opioid use disorder (DSM-5):** Primary, chronic, treatable, brain disease arising from genetic risk + environmental exposures; defined by DSM-5 as pattern of opioid use leading to

impairment/distress manifested by ≥2 in 12-mo period: **(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

Chronic disease model: Tx adherence & relapse rates similar to other chronic dz (*JAMA* 2000;284:1689); Stigma significant barrier to tx. Language counts: In RCT, "abuse" vs "SUD" assoc w/ judgments of culpability & that pts deserve punishment (*Int J Drug Policy* 2010;21:202)

- **Consequences:** *Medical:* Respiratory depression, rhabdomyolysis, compartment syndrome, ↑ risk of HIV, hepatitis, osteomyelitis, endocarditis, septic arthritis, skin/soft tissue infections; *Social:* Incarceration, economic insecurity, homelessness, high-risk sexual behavior, trauma, family instability; loss of child custody (*J Food Drug Anal* 2013;21:S73)

Evaluation (*J Addict Med* 2015;9:358; *NEJM* 2016;375:357)

- **Screening:** No USPSTF-recommended screen. Quick Screen: "How many times in the past year have you used an illegal drug or prescription medication for nonmedical reasons?" ≥1 100% sens, 73.5% spec (*Arch Intern Med* 2010;170:1155)
- **History:** Concurrent SUDs, esp other CNS depressants inc EtOH, benzos, sedatives; Amount used daily/weekly, route of use, last use, h/o medical complications, OD hx, tx hx (specific medications, dosages, setting of care), prior periods of sobriety, consequences of use, patient's perception of +/− aspects of use
- **Exam**: S/Sx of intoxication (slurred speech, sedation, miosis, injection sites, recent trauma) withdrawal (rhinorrhea, lacrimation, yawning, muscle twitching, hyperactive BS, piloerection, myadriasis), e/o IDU (track marks at peripheral venous and subQ sites inc. b/t fingers, legs, neck, under nails, axillae, breast, penis)
- **Labs:** CBC, BMP, LFTs, HIV, syphilis, HepA/B/C serologies, TB skin test, pregnancy if appropriate, UTox (absence of opioid metabolites NOT contraindication to tx)

- **Meds:** Review Prescription Monitoring Program

Management (*J Addict Med* 2015;9:358; *JAMA* 2016;316:338; 2017;317:967; *NEJM* 2005;352:596; 2016;375:357; pcssmat.org)

- **Counseling:** (findtreatment.samhsa.gov)
  - **Cognitive behavioral tx:** Skills to avoid situations that cause use
  - **Motivational enhancement:** Resolve ambivalence, elicit pt goals
  - **Peer support/mutual help:** Not formal treatment but can be very effective; Correlation btwn participation and abstinence; Alcoholics Anonymous (12-step). SMART Recovery (nonreligious alt to AA)
- **Withdrawal management:** "Detoxification" alone is not treatment (relapse risk >80% with high mortality due to loss of tolerance) (*Arch Gen Psych* 2011;68:1238; *BMJ* 2003;326:959); If pt insists on detoxification alone, (1) Counsel re: risk of death, (2) Rx naloxone, and (3) Est firm f/u plan; Methadone, buprenorphine superior to symptomatic treatment with a2-adrenergic agonists (*Cochrane Database Syst Rev* 2016;3:CD002024)
- **Opioid agonists:** Buprenorphine & methadone ↓ mortality ~50%, ↑ treatment retention, ↓ HIV, HCV, and criminality (*Am J Public Health* 2013;103:917); buprenorphine and methadone similar in efficacy when adequately dosed; methadone may ↑ pt retention (*Cochrane Database Syst Rev* 2014;6: CD002207; 2016;9:CD011117); **Treatment goals:** ↓ withdrawal sx, ↓ cravings, ↓ illicit opioid effects, and ↑ QOL; maintenance tx, not taper is goal; longer duration of tx assoc w/ better outcomes
  - **General principles:** Primary care med mgmt noninferior to med mgmt + counseling; frequent visits early on to maintain relationship, facilitate psychosocial support, monitor for relapse, ensure adherence, detect potential diversion; if pt struggling w/ cravings, illicit use, intensify treatment (NOT discontinuation) w/ ↑ visit frequency, medication titration, consider referrals; toxicology offers objective data on treatment response, false positive and false negative can occur; requires pt consent
  - **Methadone:** Full opioid agonist; only available at Opioid Treatment Programs (OTPs), highly structured programs w/ daily dosing; initial dose 30 mg/d, uptitration takes wk–mo w/ ↑

risk of OD in first 2 wk; more effective at high doses (60–100 mg) (*Cochrane Database Syst Rev* 2003;3:CD002208); ↑ QTc, esp at high doses → baseline ECG before initiation, repeat w/ dose ↑ or additional QT prolonging meds; d/c or ↓ dose at >500 ms, consider change to buprenorphine at 450–500 ms (*J Pain* 2014;15:321); multiple CYP450 interactions, especially ARVs

Buprenorphine: Partial opioid agonist ∴ ceiling effect on respiratory depression ↓ OD risk; strong receptor affinity ∴ displaces most full opioid agonists, can precipitate withdrawal; *Eligible prescribers*: Licensed MD w/ 8 h "waiver training" or PA/NP w/ 24-h training (www.samhsa.gov) and DEA registration; office-based treatment = more patient flexibility vs. methadone; initiation in acute setting leads to successful remission (*JAMA* 2015;313:1636); buprenorphine + naloxone formulation prevents IV abuse because naloxone is poorly absorbed orally with proper use

Induction: 4-mg initial dose → wait 1–4 h → eval for withdrawal s/s, if + addn'l 4 mg → wait 3–6 h → addn'l 4 mg PRN; daily dose generally 8–24 mg, recent studies show continued benefit at doses up to 32 mg (*Addiction* 2014;109:79); must induce while pt in moderate withdrawal to avoid precipitating withdrawal; no short-acting opioids ×12 h prior. If on methadone, taper to 20–30 mg daily ×1 wk → initial buprenorphine dose 36–72 h after last dose (*J Gen Intern Med* 2009;24:226)

Antagonist therapy w/ extended-release naltrexone: No head-to-head trials vs. agonist treatment; oral naltrexone not effective for OUD (*Cochrane Database Syst Rev* 2011;16:CD001333); consider in pts w/ occupational restrictions against agonist therapy, pending incarceration, younger w/ new dx, or in remission on agonist therapy desiring antagonist therapy; improves treatment retention, opioid abstinence vs. placebo (*Arch Gen Psychiatry* 2012;69:973; *Lancet* 2011;377:1506); ↓ relapse in recently incarcerated patients (*NEJM* 2016;374:1232); ↑ risk of death at treatment cessation (*Drug Alcohol Rev* 2007;26:405); before initiation, pt must be 7–10 d opioid-free w/o s/sx withdrawal.

- **OD death prevention: Naloxone:** Potent, short-acting (duration 30–

90 min) antagonist. Lay/community administration assoc w/ ↑ chances of revival (*Inj Epidemiol* 2015;2:10); available in 4-mg intranasal, 0.4-mg IM, and 0.4-mg Evzio IM/SubQ auto-injector formulations; not a controlled substance; can be Rx'd by any prescriber, and in many states obtained w/o Rx; should be Rx to all pts w/ OUD; counsel patients & family to: (1) Assess for OD: respiratory depression, cyanosis, unresponsiveness; (2) Call 911; (3) Give rescue breaths; (4) Administer naloxone; (5) Repeat; may need >1 dose; give q2–3 min and stay w/ patient until care escalation; discourage other revival efforts, i.e., salt water injections, milk, cold water baths

- **Psychosocial support:** Individual or group counseling emphasizing relapse prevention, recovery support, self-care, and coping skills required for most OTP programs and encouraged w/ buprenorphine, however no e/o better outcomes than tx alone (*J Addict Med* 2016;10:283) (see *"Psychosocial Support"*)
- **Patient information:** samhsa.gov/medication-assisted-treatment/physician-program-data/treatment-physician-locator; *JAMA* 2013;309:2055

OTHER DRUG USE DISORDERS

Cannabis

- **Epidemiology:** 13.5% past-year use in US; ↑ prevalence in young adults; ♂ > ♀ (2:1)
- **Cannabis use disorder:** 1.5% US prev; ~9% of users (*NEJM* 2014;370:2219); defined as persistent use leading to clinically significant impairment or distress as manifest by 2 (or more) of the following w/in a 12-mo period (DSM-5): **(1)** ↑ doses or ↑ period than intended, **(2)** persistent desire/unsuccessful efforts to cut down, **(3)** ↑ time finding, using, recovering, **(4)** Cravings, **(5)** Failure to fulfill work/school/home roles, **(6)** Cravings, **(7)** ↓ social/work/recreational activities d/t cannabis use, **(8)** recurrent use when physically

hazardous, **(9)** Use despite known ⊖ impact on physical/psych problems, **(10)** Tolerance (↑ cannabis for desired effect; ↓ effect w/ same amt of cannabis), **(11)** Withdrawal

- **Routes of use & pharmacology**: Inhalation most common route; hashish is a resin cake that can be ingested/smoked; tinctures and oils widely used; 50% of THC in cannabis is inhaled, THC absorbed thru lungs & reaches brain through bloodstream in min; rapid onset (s–min) & ↓ duration (2–4 h); bioavailability = 25–30% of smoked amt due to 1st-pass metabolism in liver; onset delayed (0.5–2 h) & ↑ duration (4–12 h) w/ ingestion (*Brit J Clin Psychol* 2001;178:101)
- **Intoxication**: Impaired motor coordination, time perception, judgement; anxiety, conjunctival injection, ↑ appetite, dry mouth, ↑ HR, ↑ RR, HTN, orthostatic HoTN, nystagmus, ataxia, slurred speech (*Addiction* 1996;91:1585; *Brit J Clin Psychol* 2001;178:101)
- **Withdrawal syndrome**: ≥ daily dose of 180 mg of THC (1–2 joints) × 11–21 d to produce W/D sx restlessness, insomnia, anxiety, increased aggression, anorexia, muscle tremor, and autonomic effects
- **Complications**: Include periodontal disease, memory impairment, ↑ psychosis risk

  Hyperemesis syndrome: Severe emesis in chronic cannabis users 2/2 downregulation of CNS cannabinoid receptors & upregulation of gut cannabinoid receptors; typically relieved by hot showers; supportive mgmt w/ IVF, antiemetics (ondansetron, metoclopramide), benzos, & cannabis cessation (*Hosp Pharm* 2013;48:650)
- **Management**: No effective pharmacotherapy; CBT and motivational enhancement therapy effective (*Drug Alcohol Depend* 2014;132:185; *Cochrane Database Syst Rev* 2016;5:CD005336*)*
- **Toxicology**: THC detected in urine × h–12 d (occasional user) & up to 1 mo (chronic user) (*J Anal Toxicol* 1999;23:323)

Patient Evaluation for Medical Marijuana (Adapted from *JAMA* 2015;313:2474)
General principles: Laws vary by state. Physicians should counsel patients on risks & benefits and document patient was advised not to drive/engage in dangerous activities.
(1) Medical condition: Patient should have Dx that RCT suggest may respond to marijuana

Moderate quality evidence in support of marijuana use: Chronic pain, spasticity. *Low-quality evidence:* N/V from chemotherapy, cachexia from cancer/AIDS, sleep disorders, Tourette syndrome *(JAMA* 2015;313:2456; *NEJM* 2013;368:866*)*.
(2) Symptoms refractory to pharmacotherapy: Patients sx unrelieved by conventional treatments or a trial of FDA-approved cannabinoid (dronabinol or nabilone)
(3) No SUD or psychiatric comorbidity

Synthetic Cannabinoids (K2, Spice, Kronic, etc.)

- **Epidemiology**: ↑ avail in US/Europe since 2000s, rising popularity as not detected in standard tox screens; ↑ toxicity cases reported annually to US poison control centers (thousands), mainly ♂ 20–30s y/o (*J Pediatr* 2013;163:213)
- **Routes of use & pharmacology:** Hundreds of different compounds; mainly inhaled, but can be ingested or insufflated (i.e., snorted). Binds CB_1/CB_2 cannabinoid receptors similar to but more tightly than THC; onset of effect usually within minutes, lasts hours, length depending on compound (*NEJM* 2015;373:103; *Toxicology* 2013; 44:360)
- **Intoxication:** Tachycardia, conjunctival injection, N/V, HTN, ↑ appetite, nystagmus, ataxia, slurred speech, hallucinations, delirium, psychosis, agitation, seizure (*Am J Med* 2016;129:240; *Curr Psychiatry Rep* 2016;18:52)
- **Withdrawal**: Can occur as soon as 15 min after smoking in daily users; presents as headache, anxiety, insomnia, N/V, ↓ appetite, diaphoresis; severe w/d present with seizures, CV/respiratory risks (tachycardia, CP, palp, SOB) (*Curr Psychiatry Rep* 2016;18:52)
- **Complications:** *Cardiac:* STEMI w/ clean coronary arteries, mechanism unclear, ? ↑ O_2 supply-demand mismatch, vasoconstrictive effect (*Pediatrics* 2011;128:e1622). *Renal:* AKI, ATN, rhabdo (*Am J Emerg Med* 2016;34:121.e1; *Clin J Am Soc Nephrol* 2013; 8:523)
- **Management**: Supportive w/ benzos & neuroleptics (esp quetiapine) for agitation/anxiety/psychosis from intox or w/d (*Curr Psychiatry Rep* 2016;18:52)
- **Toxicology:** Liquid chromatography & mass spec available for some compounds in reference laboratories, but not routinely used

given time required for test & constant changes in chemical structures (*Am J Med* 2016;129:240)

HALLUCINOGENS

- **Epidemiology:** ~4 mil people/y in US use hallucinogens; most common in adolescents/young adults; LSD most common w/ 23 mil US lifetime users
- **Complications:** Agitation can cause trauma, rhabdo → AKI
- **Management:** Mostly supportive, place in calm & quiet environment while intoxicated. Benzos = 1st-line for agitation, antipsychotics as adjunct (e.g., IV haloperidol), may need restraints if violent
- **Toxicology:** PCP detected in urine × 2–4 d, up to 1 wk in chronic users; LSD detected in urine × 2–5 d; otherwise, most standard tox screens do not detect hallucinogens

Common Hallucinogens (*Biol Psychiatry* 2012; 72:871; *Psychopharmacology* 2012;223:1)

Drug (route)	Pharmacology	Intoxication
Dextromethorphan Capsule, pill, liquid	NMDA antagonist. Onset ~0.5–1 h, lasts up to 6 h	Out-of-body sensation, ↑ HR, HTN, lethargy, mydriasis, agitation, vomiting.
LSD Capsule, pill, liquid (added to blotter paper)	Binds 5-HT_{2A} receptors. Effect lasts 6–12 h.	Distortion of time, visual illusions, euphoria, depersonalization, synesthesia, tachycardia, HTN, mydriasis, piloerection, diaphoresis.
Mescaline Prepared as tea	Binds 5-HT_{2A} & 5-HT_{2C} receptors. Onset ~ 45–60 min, lasts 4–8 h.	Similar to LSD. Visual distortion, N/V, sympathomimetic sx. Legal use allowed by Native American Church members
PCP Snorted, smoked, ingested, or injected. *Most deaths due to trauma.*	NMDA antagonist. Effect lasts 4–6 h, or longer at higher doses.	Bizarre/violent behavior, nystagmus, amnesia, analgesia. *Lower doses:* Dissociation, sound/vision distortion. *High doses:* Severe agitation, violence,

		auditory hallucinations, catatonic stupor.
Psilocybin Ingested fresh/dried	Binds 5-HT_{2A}. Effects last up to 6 h.	Similar to LSD. Nausea, vomiting, diarrhea. Serotonin syndrome.
Salvia Leaves chewed (fresh)/smoked (dry)	κ opioid agonist. Effect lasts 1–2 h if ingested, less when smoked.	Sensory distortion, synesthesia, sedation, euphoria, mild sympathomimetic sx. No deaths/severe toxicity reported

Cocaine

- **Epidemiology:** Used by 1.4% of US population aged 18–25; 6% of users meet criteria for cocaine use disorder; most common illicit drug assoc w/ ER visits
- **Pharmacology:** 2 forms of same compound–base (smoked/injected) and salt (inhaled/injected); blocks reuptake of dopamine, norepinephrine, and serotonin in the central and peripheral nervous system; onset of effect usually in seconds if smoked, 30 min if delivered via mucous membrane (*Biochem Pharmacol* 2008;75:196)
- **Intoxication:** Tachycardia, diaphoresis, nausea, mydriasis; alertness, euphoria → dysphoria, paranoia, psychotic syndromes with increasing doses or duration of use
- **Withdrawal:** Depression, anxiety, fatigue, anhedonia; often initially intense "crash" with improvement in 1–2 wk
- **Complications:**
  - **CNS:** ↑ risk hemorrhagic and ischemic stroke. No good evidence that cocaine causes seizures. (*Drug Alcohol Depend* 2013;133:795; *Stroke* 2016;47:918)
  - **HEENT:** Snorting → nasal septum perforation, ulcers, chronic rhinitis (*NEJM* 2016;374:969)
  - **Cardiac:** ↑ HR, BP, SVR via adrenergic activation, vasospasm → MI, ventricular arrhythmia. Chronic use → LVH, cardiomyopathy/fibrosis (*NEJM* 2001;345:351)

Pulmonary: Sx in up to 50% of users, e.g., cough, SOB, hemoptysis, asthma exacerbation; Direct lung injury (e.g., PTX, hemorrhage) often 2/2 additives such as levamisole; "Crack lung" is poorly understood acute pulmonary syndrome with fever, hypoxemia, respiratory failure, and diffuse, eosinophil-rich infiltrates (*Clin Rev Allergy Immunol* 2014;46:82)

GI: Gastric ulcers, ischemic colitis

Renal: Rhabdomyolysis, renal infarction

- **Management, acute intoxication:** Supportive care; benzodiazepines; Phentolamine for refractory HTN; Avoid β blockers acutely; nitroglycerin, ASA if c/f ACS; Na bicarb if QRS widened (rare) (*NEJM* 2001;345:351)
- **Treatment:** Individual/group counseling, intensive outpatient/inpt setting; best evidence for topiramate (✓ LFTs, Cr; hold in hepatic injury, dose reduce for poor renal fxn); start 25 mg QD, uptitrate weekly, max dose 150 mg BID for remission maintenance; disulfiram 250 mg daily + CBT shown to reduce use; some evidence for stimulant treatment, e.g., dextroamphetamine 30 mg QD (*Arch Gen Psychiatry* 2004;61:272; *J Clin Psychopharmacol* 2001;21:522; *JAMA Psychiatry* 2013;70:1338)
- **Toxicology:** Detected in urine 2–15 d after use

Benzodiazepines

- **Epidemiology:** Commonly abused with EtOH, narcotics (*AFP* 2000;61:2121)
- **Pharmacology:** ↑ binding of GABA to receptors, making GABA signaling more efficacious
- **Intoxication sx:** Memory impairment, disinhibition, psychomotor retardation, depression; effect may be amplified with other sedatives/EtOH and may be more pronounced in elderly
- **Withdrawal sx:** Anxiety, autonomic instability, insomnia, hypersensitivity; timeline to development of withdrawal symptoms related to half-life of benzodiazepine being abused
- **Management:** To prevent withdrawal, taper daily dose by 10–25% every 2 wk; severe withdrawal should be managed as an inpatient;

unclear whether switching short-acting to long-acting benzodiazepines improves success of treating withdrawal; no medication approved for treating benzodiazepine use disorders; psychotherapy and motivational interviewing may help (*NEJM* 2017;376:1147)

- **Toxicology:** Not detected in standard drugs of abuse screen; benzodiazepine-specific urine screen may not detect clonazepam, lorazepam, midazolam, or alprazolam

TOBACCO USE

Background

- **Consequences:** Tobacco use **is the leading preventable cause of death in 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 accounts for 49% of cancer-related deaths in US (*JAMA Int Med* 2014;175:1574); smoking is considered a chronic disease requiring longitudinal, coordinated care w/ behavioral & medical tx
- **Epidemiology:** 15% 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 min 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 (*Ann Int Med* 2016;164:ITC33)

- 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 min, based on 5As model

5As Model for Treating Tobacco Use and Dependence	
Ask	Identify & document use of tobacco *(e.g., cigarettes, cigarillos, chewing tobacco, loose tobacco, pipe tobacco, hookah)* routinely for every pt
Advise	Strongly advise every user to quit; individualize using pt's current health concerns, costs, or impact on their household & children "As your provider, I strongly recommend that you quit smoking" "Quitting smoking is the most important thing you can do to protect your health now & in the future"
Assess	"Are you ready to quit smoking in the next 30 d? I can help with this"
Assist	For those ready to quit, offer medication & counseling For those not ready to quit, provide a motivational intervention
Arrange	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; 2014;311:193)

- **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); success rate for unassisted attempts is ~5%; abrupt smoking cessation more likely to result in long-term abstinence compared to taper (*Ann Int Med* 2016;165:742)
- **Counseling:** Range of options; generally ↑ intensity, time, or number of sessions → ↑ likelihood of quitting; odds of quitting 2.3 × ↑ if counseling >10 min (*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 wk), pts w/ serious arrhythmia or UA; however, NRT is safe in pts w/ stable CAD; unclear whether combination of short-acting (i.e., gum) with long-acting (i.e., patch) ↑ success rates; efficacy of nicotine patch beyond 6 m unclear (*JAMA Int Med* 2015;175:504)

Nicotine Replacement Therapy (*JAMA* 2012;308:1573)		
Form	**Sample Rx**	**Notes**
Patch	*Dosing:* 21 mg/24 h × 4 wk, then 14 mg/24 h × 2 wk, then 7 mg/24 h × 2–6 wk *Duration:* 8–12 wk	Slow onset, steady levels for 16 or 24 h Available OTC. *S/e:* Skin irritation, insomnia, vivid dreams *Efficacy:* RR vs. placebo: 1.66
Gum	*Dosing:* ≥25 cig/d → 4 mg/piece; >25 cig/d = 2 mg/piece, use q1–2	Rapid onset: 20–30 min Available OTC

	h × 6 wk, max 24 pieces/d *Duration:* 12 wk	*S/e:* Mouth soreness, dyspepsia, hiccups, jaw ache *Efficacy:* RR vs. placebo: 1.43
Inhaler	*Dosing:* 6–16 cartridges (4 mg ea)/d *Duration:* Up to 6 mo	Rapid onset: 20–30 min *S/e:* Local irritation in mouth, throat *Efficacy:* RR vs. placebo: 1.90
Lozenge	*Dosing:* 1st cig after waking: >30 min → 4 mg/piece <30 min → 2 mg/piece 9–20 pieces/d *Duration:* 12 wk	Rapid onset: 20–30 min Available OTC *S/e:* Nausea, hiccups, heartburn, HA, coughing *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 *Duration:* 3–6 mo	Most rapid onset: 5–10 min *S/e:* Nasal irritation, congestion, highest dependence potential of NRT *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 wk before quit date; 150 mg Q_{AM} × 3 d, then 150 mg BID
  - *Duration:* 7 wk–6 mo; safely used for years to treat depression
  - *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 wk) MAOI use; monitor pts w/ psych hx for exacerbations or ↑ SI
- **Varenicline:** Selective partial α4β2 nicotinic receptor agonist, relieves withdrawal & blocks smoking reinforcement; varenicline + NRT ↑ abstinence at 24 wk compared to varenicline alone (49% vs. 33%) (*JAMA* 2014;312:155); varenicline monotherapy as effective as nicotine patch (*JAMA* 2016;315:371); combination of varenicline and bupropion did not increase cessation rates (*JAMA* 2014;311:155)
  - *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 mo; safety established for up to 1 y
  - *S/e:* Nausea (take w/ food), insomnia/vivid dreams; use cautiously in pts w/ > stage 3 CKD; varenicline did not ↑ risk of depression, suicidal ideation, or suicide compared to placebo

(*BMJ* 2015;350:h1109)

- **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)
- **2nd-line agents:** (not FDA-approved for smoking cessation); *Nortriptyline:* 75–100 mg QD, start 10–28 d before quit, 6 wk–6 mo, 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/on quit date; s/e: Dry mouth, sedation, ↓ BP
- **Electronic cigarettes:** Aerosolize a solvent containing nicotine + flavoring; few randomized trials to assess efficacy in smoking cessation; contain carcinogens such as formaldehyde; meta-analysis shows use of e-cigarettes as a smoking cessation was less successful compared to other forms of nicotine replacement or no cessation aid (*NEJM* 2016;374:2172; 2016;375:1372)
- **Complications of quitting**

  Wt gain: Most smokers experience modest (≤10 lb) wt ↑ after quitting; bupropion & NRT may delay wt gain; counsel re: diet/exercise (*Am J Prev Med* 2008;35:158)

  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

PULMONARY FUNCTION TESTS

Background (*Eur Respir J* 2005;26:720)

- Pulmonary function testing refers to a suite of measurements which are used to assess air movement, volume, and diffusion capacity of the lungs; these tests are used to diagnose, assess severity of, and follow course of major pulmonary diseases
- **Spirometry: "fundamental" PFT—measures volume and flow of air with inspiration & expiration**; pt takes deep breath and exhales as forcefully as possible into the spirometry tube; this test provides:
  - *Forced vital capacity (FVC)*: Volume of air a person can exhale for the duration of the test during max effort: Pt inhales as deeply as possible, then exhales as long and forcefully as possible, should last ≥6 s; ↓ in restrictive disease
  - *Forced expiratory volume (FEV*1): volume of air expelled in the 1st s at max effort
  - *FEV_1/FVC:* % of FVC expired in 1st second; ↓ in obstructive disease
  - *Bronchodilator response:* Test may be repeated after administration of SABA; allows to assess for reversibility of obstructive component (e.g., distinguishes asthma from COPD); **fully reversible defined as FEV_1 ↑ by 200 mL & 12%**
- **Plethysmography:** Used to measure **lung volumes**; pt placed in large airtight box (w/ clear walls) w/ breathing tube and asked to inspire with mouth on a shutter valve; subsequent change in box pressure + Boyle's law ($P1V1 = P_2V_2$) used to calculate lung volumes (alt: nitrogen or helium gas washout); key measurements include: provides →
  - *Total lung capacity (TLC):* Total amt of air lungs can hold, ↓ in

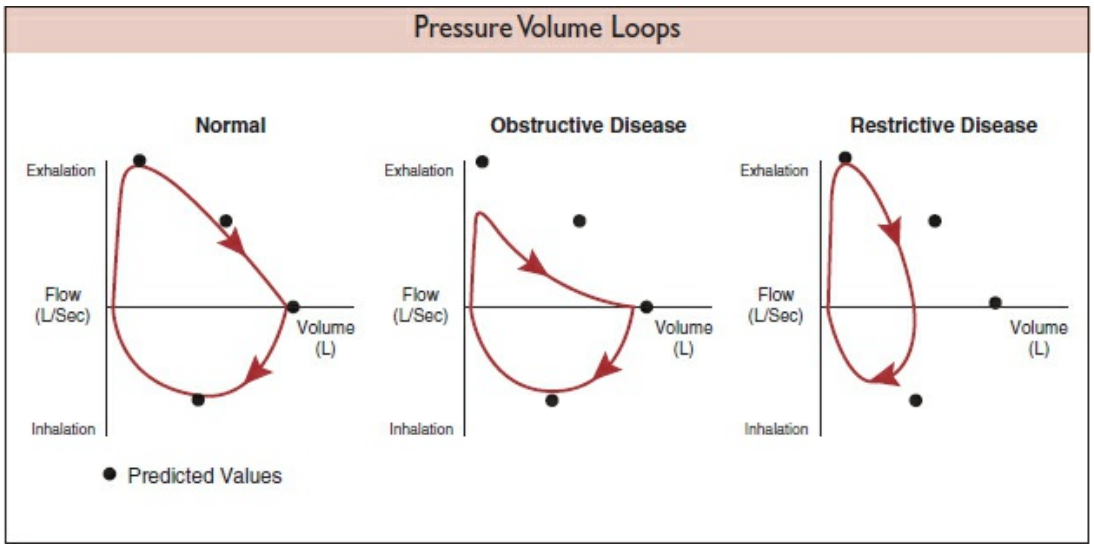
restrictive disease

Residual volume (RV): Amt of air left in lungs after complete exhalation

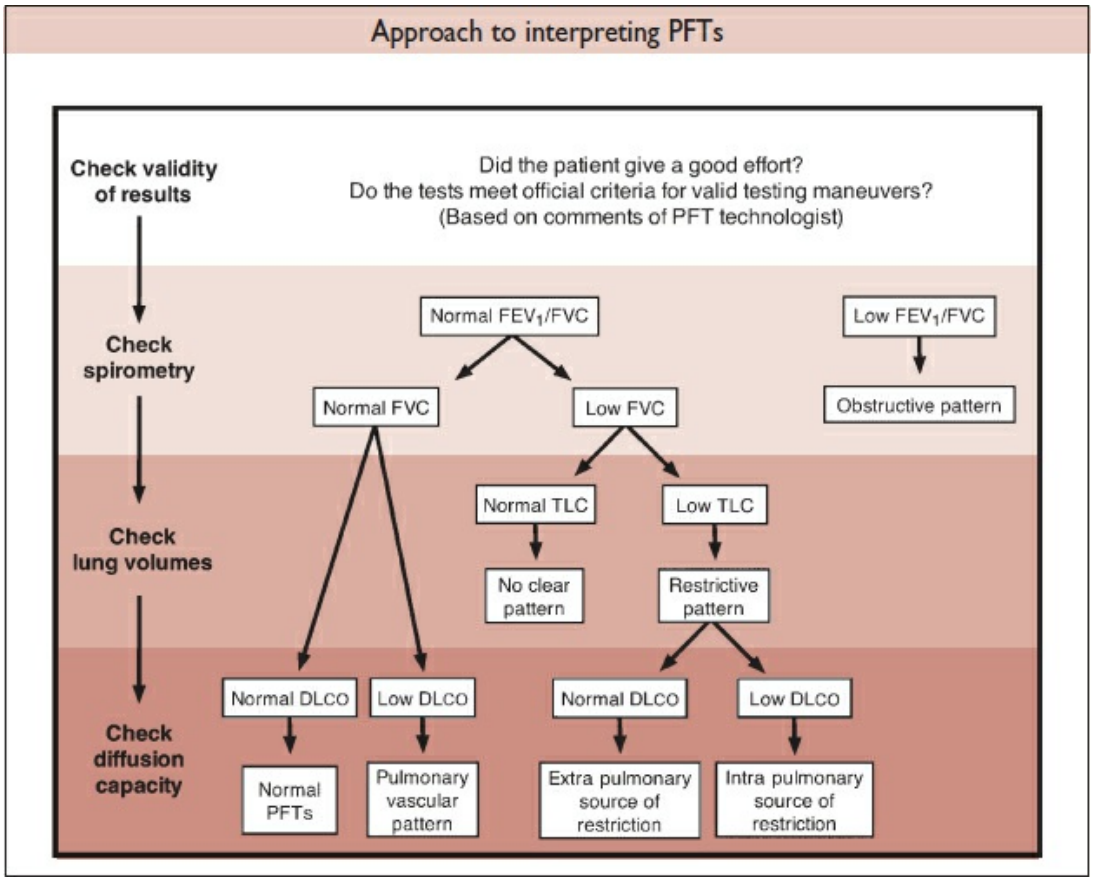
- **DLCO:** Diffusing capacity of lung (ability for gas exchange), measured using carbon monoxide (counsel pts to avoid cigarettes, SABA on day of test as possible; if on supplemental O_2, avoid 15 min prior to test if possible)
- Spirometry may be done in office setting, whereas lung volumes and DLCO are typically measured in dedicated laboratory
- **If performing spirometry in primary care office:** Examine pt effort and flow loops for validity and reversibility; poor validity if: Forced expiration ≤6 s (will mimic restriction), distortion of flow loops due to cough on expiration (will mimic obstruction), delay of peak flow maneuver or poor peak flow effort (will mimic obstruction), FVC maneuver does not end in a plateau

Interpretation (*AFP* 2014;89:259)

- Obstructive pattern characterized by low FEV_1/FVC; restrictive pattern characterized by ↓TLC; mixed/overlap syndromes may exist (e.g., obesity + COPD); consider referral if restrictive lung disease or interpretation unclear



Courtesy of A. Luks



Courtesy of A. Luks

Typical PFT Results, by Disease				
Disease	FEV_1	FVC	FEV_1/FVC	Notes
Asthma	Nl/↓	Nl	Nl/↓	May be nl in mild–mod disease; obstructive deficit reversible w/bronchodilator
COPD	↓	Nl	↓	See *COPD*; deficit not reversible w/ bronchodilator
Restrictive lung disease (due to lungs, e.g., ILD)	nl	↓	nl	DLCO decreased; order lung volumes to confirm
Restrictive	↓	↓	nl	DLCO normal;

lung disease (external source, e.g., obesity)				order lung volumes

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 Aspergillosis* (*ABPA*) (asthma + bronchiectasis+ 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, bronchoconstriction, ↑ edema/mucus → airflow 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)

Diagnosis

- Hx/PE and spirometry used to diagnose and assess comorbidities, triggers and severity
- **History:** *Classic sx:* Intermittent episodes of dyspnea, chest tightness, wheezing, cough, frequently w/ identifiable triggers (below), often early-AM or **nighttime coughing**

PMHx: Atopy (atopic dermatitis, allergic rhinitis), seasonal allergies, rhinitis/sinusitis, GERD, CHF, OSA, obesity, depression/anxiety, vocal cord dysfunction
Meds: ASA/NSAIDs (use or hx sensitivity), βB, ACEI
FHx: Asthma, atopy, other pulm diseases
Social hx: Tobacco exposure, occupational & home exposures, incl pets

- **Exam:** Often unremarkable exam if not in acute exacerbation; HEENT (nasal polyps, allergic "shiners" or rhinitis), skin (atopic dermatitis), full chest & pulm exam
- **Spirometry: Recommended in all pts** in whom asthma is considered; documents *obstruction* (FEV_1/FVC <70%) & its potential *reversibility* (FEV_1 ↑ 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; see "*Pulmonary Function Tests"*
- **Labs:** Not routinely indicated; if severe asthma, consider serum IgE, CBC w/ diff (↑eos), 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/advanced imaging* if indicated by Ddx
- **Differential diagnosis:** COPD, PE, CHF, bronchiectasis, hypersensitivity pneumonitis, eosinophilic lung disease, tracheobronchomalacia, mechanical airway obstruction, (tumor), ABPA, med-induced cough (ACEI), vocal cord dysfunction (see "*Hoarseness*")

Evaluation (*NEJM* 2001;344:350)

- **General approach:** Patients w/ asthma should be assessed for symptom control, medication/tx adherence, and trigger exposure to determine management plan
- **Asthma history:** age of onset, exacerbations (PO steroids, ED,

inpatient, **intubation**); recent poor control/hx intubation assoc w/ ↑ asthma mortality (*Chest* 2003;124:1880), peak flow

Potential Asthma Triggers (cdc.gov/asthma/healthcare)	
Allergens	*Persistent:* Dust mites, cockroaches, pets, *Seasonal (some regional variability):* trees (spring), grass (summer), weed pollen (fall)
Occupational	Smoke, irritants, mold
Meds/toxins	Tobacco smoke exposure, outdoor air pollution, perfumes, ASA, NSAIDs, nonselective βB (though some controversy)
Infections	Viral upper respiratory infections
Other	Stress, cold air, strenuous physical activity, food additives (sulfites), hard laughing/crying

- **Current control**: For pts already on treatment, review current inhaler adherence and technique, as well as current symptoms, can use Asthma Control Test (qualitymetric.com/act; score >20 indicates control)
- **Exam**: often unremarkable; wheezing on routine exam suggests poor control/exacerbation
- **Peak flow:** Used to assess control (comparing current test against personal best), but improvement by 20% w/ bronchodilator can be used to support dx; n.b. reduced peak flow ≠ airway obstruction

Treatment (*NEJM* 2009;360:1002)

- **Nonpharmacologic treatment:** Indicated for all pts, 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); consultation with allergy specialist may be helpful
  - **Irritant avoidance:** Avoid outdoor exercise during periods of ↓ air quality (airnow.gov/ offers US air quality forecasts), avoid exposure to wood stoves, tobacco smoke

Smoking: Smoking & 2nd-hand smoke may ↓ response to asthma medication, ↓ lung function, & trigger exacerbations; counsel all pts & family members to quit (see *"Tobacco Use"*) & ask housemates to smoke outside (*AJRCCM* 2007;175:783)

Immunizations: Influenza & pneumococcal vaccines 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.

Asthma action plan: Pts & providers should establish an asthma action plan, using sx or peak flow: sample at www.nhlbi.nih.gov/health/public/lung/asthma/asthma_actplan.pd

Pharmacologic Treatment

General Approach: Initial tx dictated by severity; **subsequent tx dictated by degree of control; all pts should have "rescue" inhaler Rx; All other Rx's are "controller":** effective in preventing/reducing sx over long-term, **not useful in acute management of sx**

- **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
- **Continuing treatment:** For pts currently treated, assess control (see above) and then 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

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% pred; *FEV_1/FVC:* ↓	*FEV_1:* <60% pred; *FEV_1/FVC:* ↓
Exacerbations	<1/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 *Alt:* Antileukotriene, theophylline, cromolyn			
Step 3	**Low-dose ICS** & **LABA** *Alt:* Medium-dose ICS, low-dose ICS + (LTRA, theophylline, or zileuton); consider adjunct tiotropium, allergen immunotherapy			
Step 4	**Med-dose ICS** & **LABA,** specialist referral *Alt:* Med-dose ICS & (LTRA, theophylline, or zileuton); consider adjunct tiotropium, allergen immunotherapy			
Steps 5, 6	High-dose ICS + LABA ± oral corticosteroids, **specialist referral**, consider anti-IgE therapy or anti-IL5 therapy if appropriate phenotype			
Features of Well-Controlled Asthma				
No limitation of activities No nocturnal sx/awakenings Validated survey indicating control (see above)			PEF or FEV_1 nl **Reliever/rescue tx ≤2 d/wk** **Daytime sx ≤2 d/wk**	
Treatment Plan by Level of Control				
Well-controlled: All control criteria met or n/a	*<3 mo:* maintain regimen; *≥3 mo:* consider step-down reassess in 1-6 mo			
Partially controlled: 1–2 of the listed criteria not met	Step-up 1 step Reassess in 2–6 wk			
Poorly controlled: ≥3 of the listed criteria not met	Step-up 1–2 steps: Consider short course PO corticosteroids (40–60 mg QD × 3–10 d) Reassess in 2 wk			

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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Asthma Medications

Inhalers: Multiple devices (below); pt education key, as many use inhalers incorrectly (*AJRCCM 1994;150:1256*); inhaler how-to videos at cdc.gov/asthma/inhaler_video/default.htm

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 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
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

- **"Quick-relief" or "rescue" inhaler:** Should be prescribed **for all** pts; to be used PRN or as ppx prior to anticipated exposure (e.g., exercise)
  - **Short-acting beta agonists (SABA, e.g., albuterol):** 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
  - Short-acting anticholinergics (e.g., ipratropium): less-effective *alternative* in pts w/ mild sx who do not tolerate SABA or as *adjunct* in pts w/ severe sx; not FDA-approved
- **Inhaled corticosteroids (ICS):** controller Rx

Mechanism: ↓ airway inflammation & bronchial hyperresponsiveness → fewer asthma sx, ↑ lung function, ↑ QoL, ↓ exacerbations & ↓ mortality (*JAMA* 1997;277:887*; NEJM* 2000;343:332)

S/e: Hoarseness, sore throat, oral candidiasis; can → systemic s/e in ↑ doses (e.g., >1000 µg beclomethasone/d)

Dosing: Delivered by DPI or HFA (see above) and **divided into low, medium, or high dose:** determined by individual steroid's potency, concentration ("dose/puff"), and number of inhalations ("puffs")

Example Rx: fluticasone offered at 3 strengths (44 mcg/inh, 110 mcg/inh, and 220 mcg/inh); low dose = 88–264 mcg/d, med dose = 264–440 mcg/d, high dose >440 mcg/d

Best to pick one agent and step up/down; use conversion chart to switch agents

Pt education: rinse mouth after use, if delivery vehicle is MDI, use w/ spacer or VHC

- **Combination ICS + long-acting beta agonist (LABA): In asthma, LABA always used in combination w/ ICS** 2/2 risk of ↑ asthma-related deaths (*Chest* 2006;129:15), though some believe risk may be overstated (*NEJM* 2016;375:850)

  Benefits: Combination tx → sustained improvement in lung function, ↓ in sx, exacerbations, ICS dose (*Cochrane Database Syst Rev* 2010;4*:CD*005533)

  Dosing: In combination inhalers, LABA dose constant but ICS may come in different strengths; most inhalers are BID, although some newer agents (e.g., Breo, fluticasone-vilanterol) are QD; may have to Rx LABA and ICS as separate inhalers (to be used together) depending on insurance formulary

  Example Rx: Fluticasone/salmeterol 100 mcg/50 mcg inh BID, 200/50 mcg inh BID, or 500 mcg/50mcg inh BID

  S/e: Usually mild; muscle cramps, ↑ HR

- **Leukotriene modifiers:** Used as adjunct/alternative to ICS; also effective for AR, may be preferable to ICS in pts w/ mild sx and allergic component; also consider in obese, smokers, ASA hypersensitivity; additive benefit to ICS in exercise-induced bronchospasm (*AJRCCM* 2007;175:783; *AJRCCM* 2006;173:379; *JACI* 2012;130:535)

Dosing: PM dosing preferred for montelukast; onset is hours, peak few days

Example Rx: Montelukast 10 mg PO QPM (leukotriene receptor antagonist); Zileuton XR 1200 mg BID (leukotriene formation inhibitor)

S/e: Hepatitis (zileuton 2–4%, requires LFT monitoring), possible mood/behavior sx

- **Long-acting muscarinic antagonists (LAMA):** Adjunct to ICS ± LABA; Not FDA-approved for asthma; adding tiotropium superior to doubling ICS dose re: ↑ asthma control days, PEF, & ↓ daily sx (*NEJM* 2010;363:1715); Can ↓ exacerbation freq when added to pts w/ sx despite LABA/ICS (*NEJM* 2012;367:1257) *example Rx:* tiotropium 18 mcg inh QD
- **Other:** Typically Rx'ed by specialist for pts w/ severe or refractory disease

  Omalizumab: Anti-IgE; SC q2–4wk; >$10K/y; must have ↑ IgE & sensitization to perennial aeroallergen (e.g., dust mite, pet) *S/e:* Local reaction, anaphylaxis (rare)

  Mepolizumab: Anti-IL5; pts w/ poorly controlled asthma on high-dose ICS with ↑eos; found to ↓exacerbation rate, ED visits/hospitalizations *(NEJM 2014; 371:1198)*

  Theophylline: Can be useful in refractory disease; narrow therapeutic window (can → arrhythmia, N/V, HA, sz)

  Mast-cell stabilizer: Cromolyn sodium, Nedocromil: Specific benefit for ASA-sensitive pts or exercise-induced asthma; few s/e (*AJRCCM* 2002;165:9*; Ann Intern Med* 2000;132:97)

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% (<40% 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 → ED**

- **Management of mild–mod exacerbation:** (Some limitation of activity, peak flow 50–80% personal best): SABA 2–6 puff (or neb) now then Q2–4h 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

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Background (*NEJM* 2010;362:1407; *GOLD 2016* Report, goldcopd.org; NHAMCS 2010, cdc.gov)

- **Definition:** COPD is a chronic, often progressive pulmonary disease characterized by airflow limitation and assoc w/ exposure to noxious particles, most commonly tobacco
- **Pathophysiology:** Genetic predisposition + toxic inhalants → airway inflammation, mucus hypersecretion, parenchymal destruction (with emphysema) → persistent, sometimes progressive airflow limitation in small airways (*Lancet* 2012;379:1341)
- **Etiology:** Most cases assoc w/ smoking (cigarette, cigar, pipe); 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, whites, ♀, hx asthma, ⊕ FHx; accounts for >5% of US outpt visits

Evaluation (*NEJM* 2010;362:1407, *GOLD* 2011)

- **General approach:** Clinical diagnosis, confirmed w/ spirometry (**need postbrochodilator testing**); distinguished from asthma by smoking/exposure hx & incomplete bronchodilator reversibility (see "PFTs") (though recent interest in asthma/COPD overlap syndrome, *NEJM* 2015; 373:1241)
- **History: Cough, DOE or ↓ exercise tolerance, ↑ sputum**

production; ± wheezing, frequent chest infections; wt loss/anorexia in advanced disease; ↑ suspicion in current/former smokers

Meds/Toxins: Smoking hx: Calculate cumulative pack-years (packs/d × number of years smoked); occupational exposure to biomass fuel (esp if foreign-born)/dusts/chemicals

PMHx: Comorbidities—CAD, CHF, anxiety, depression, osteoporosis FHx; hx asthma or atopy, hx emphysema (especially in nonsmokers)

- **For patients with known COPD:**

  COPD hx: Exacerbation freq, prior hospitalizations, results of sputum cx

  Sx assessment: CAT (COPD Assessment Test) (catestonline.org); Clinical COPD questionnaire (http://ccq.nl/); mMRC (modified Medical Research Council) dyspnea scale. (*Chest* 2009;*136*:*1473–1479*)

  Staging: GOLD advocates for combined assessment using severity of obstruction or h/o disease activity (exacerbations/hospitalizations) and symptoms to determine staging (A–D); A = low risk, less sx, B = low risk, more sx, C = high risk, less sx, D = high risk, more sx; goldcopd.org

- **Exam:** Can be nl in mild disease; varied presentation can include pursed-lip breathing,↑ AP diameter, hyperresonance, distant breath sounds, prolonged expiration, wheezing, cachexia (late stage); clubbing *not* sign of COPD (think: liver disease, ILD, cancer)

- **Spirometry:** Obtained at dx, may be used to track disease progression; COPD dx requires obstruction (**FEV_1/FVC <0.7**) not fully reversible after bronchodilator

  FEV1 used to classify **severity**: *mild* >80% predicted; *mod* 50–80%; *severe:* <50%

  Bronchodilator response: Often minimal; marked response → FEV_1/FVC >0.7 suggests asthma (see *"Asthma," "PFTs"*)

  Other studies, if obtained (not needed for all pts): Lung volumes can assess for hyperinflation, airtrapping, or restrictive deficit (see "PFTs"); DLCO measurement can assess degree/impact of emphysema (and can be disproportionately low in PH); Note: peak flow may underestimate obstruction in COPD

- **Chest imaging:** Consider baseline CXR; CT chest not indicated unless particular symptoms indicate complication, new pulmonary process, or if characterization of emphysema required
- α1-antitrypsin testing (serum): Consider in pts <45 y, non/minimal smokers, or ⊕ FHx
- **Other:** Baseline ECG; ABG in severe disease/hypoxemia (to assess alveolar ventilation)
- **Differential diagnosis (and comorbidities):** Asthma, bronchiectasis, bronchiolitis, ILD, CHF, lung CA

Nonpharmacologic Therapy (*NEJM* 2010;362:1407; *GOLD 2016*; *Eur Respir J* 2004;23:932)

- **Smoking cessation:** ↓ FEV_1 decline & ↓ **all-cause mortality** (*JAMA* 1994;272:1497; *Ann Intern Med* 2005;142:233); *see "Tobacco Use"*
- **Supplemental oxygen:** *Long term:* If PaO_2 <55 mmHg or SpO_2 ≤88%; or If PaO_2 <59 mmHg or SpO_2 ≤89% and cor pulmonale, RV failure, or HCT >55; for goal SpO_2 90–92%; ↓ **all-cause mortality** by 20% (*Ann Intern Med* 1980;93:391; *Lancet* 1981;1:681); counsel re: home O_2 safety (smoking is absolutely contraindicated, tubing can be fall risk); *Nocturnal/exercise*: If PaO_2 <55 mmHg or SpO_2 ≤88%; *Air travel or altitude:* If resting SpO_2 <92%, eligible for in-flight O_2 (see *"Travel Medicine"*)
- **Vaccines:** Influenza, pneumococcal (see *"Immunizations"*)
- **Pulmonary rehabilitation** (inpatient and outpatient): ↑ functional capacity & QoL (*Cochrane Database Syst Rev 2015;*2:CD003793); includes conditioning, breathing retraining, education, and psychological support
- **Goals of care:** Discussion indicated for all pts w/ mod–severe disease; explore/document preferences including intubation, tracheostomy; see *"Advance Care Planning"*

Pharmacotherapy (*NEJM* 2010;362:1407; *GOLD* 2016; *Eur Respir J* 2008;31:416–468)

- 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 (SABA) (i.e., albuterol) & anticholinergic (SAMA); (i.e., ipratropium) improve symptoms, health

status

Nebs vs. MDI: Generally equivalent; see "Inhaled medications" in *"Asthma"*

- **LABA:** ↑ FEV_1, ↓ sx, 25% ↓ in exacerbations, ↓ hospitalizations (*Eur Respir J* 1997;10:1696; *Cochrane* 2013;10:CD01017)
- **LAMA:** ↑ FEV_1, ↓ exacerbations, compared w/ LABA, 11% ↓ freq & severity of exacerbations (*NEJM* 2011;364:1093); preferred to LABA monotherapy; now many LAMAs, some QD, some BID; equivalent to tiotropium; choice often dictated by insurance
- **LAMA/LABA**: Improve sx and FEV_1 compared with monotx *(AJRCCM* 2015;192(9): 1068–1079*)*; may ↓ exacerbation frequency when compared w/LABA + ICS (*NEJM* 2016;374:2222)

  ICS: Only in addition to LABA or tiotropium (↓ exacerbations, improve health status); *not* recommended as monotherapy (*NEJM* 2007;356:775); s/e include thrush, dysphonia (rinse mouth after use, use spacer w/ MDI—requires Rx)
- **LABA + ICS + LAMA ("triple therapy"):** When compared w/ LABA + ICS alone, may ↓ mortality, PO glucocorticoid use, & hospitalizations, but prospective RCT lacking (*Chest* 2012;141:81; *Cochrane* 2011;3:*CD008532*); note: withdrawal of ICS from triple therapy does not increased risk of exacerbation) *NEJM* 2014; 371:1285–1294
- **Other:** Typically Rx'ed by specialists for pts w/severe disease

  Roflumilast (PDE5 inhibitor): used as adjunct, ↓ exacerbation frequency *(AJRCCM* 2016;194(5):559–567)

  Theophylline: May have bronchodilator effect in some patients (*Lancet* 2009;374:695–703) but requires monitoring for toxicity; typically slow release formulations used
- **Azithromycin ppx:** 250 mg QD → ↓ exacerbation frequency by 27%, unknown long-term effects; concern for abx resistance, ↑ QTc, ototoxicity (*NEJM* 2011;365:689; 2012;367:340)

Initial Approach to Therapy of Stable Disease (*GOLD* 2016)

Recommended escalation & de-escalation strategy depending on clinical course; start with preferred regimen, then "step-up/down" to alternative

GOLD Category	Regimen

A (FEV 50–80% predicted or <1 exacerbation/y; mild sx [e.g., CAT score <10])	PRN SABA or SAMA *Alt:* LABA, LAMA, SABA & SAMA
B (FEV 50–80% pred or <1 exacerbations/y; sx not well-controlled [e.g., CAT ≥10])	LABA or LAMA Alt: LAMA/LABA
C (FEV_1 < 50% pred or ≥2 exacerbations/y or ≥1 hosp; mild sx)	LAMA or ICS/LABA Alt: LAMA/LABA
D (FEV_1 <50% pred or ≥2 exacerbations/y or ≥1 hosp; sx not well-controlled)	LAMA/LABA Alt: ICS & LABA & LAMA, then consider PDE5 inhibitor, macrolide

- **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)

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 exacerbation 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 2016*; *Eur Respir J* 2004;23:932)

Pharmacologic Management	

Medication	Comment
Oxygen	Target SpO_2 ≥88–92%; concern about ↑ $PaCO_2$ risk often overstated
Bronchodilators	SABA + SAMA; nebs vs. MDI equivalent *(Arch Intern Med* 1997;157:1736.*)* Consider "stepping up" baseline regimen.
Glucocorticoids	↓ recovery time, ↓ risk of early relapse, ↑ FEV_1 & PaO_2 Recommend prednisone 40 mg PO QD x 5 d; no difference in time to next exacerbation between 5-d vs. 2-wk course (*JAMA* 2013;309:2223) However, some pts may have h/o requiring higher doses or taper Consider PCP ppx if prolonged steroid course (see *"PCP"*)
Antibiotics	Outpt data lacking but likely ↓ tx failure, possibly ↓ mortality; consider if ↑ sputum production/purulence (*Chest* 2000;117:1638; *Thorax* 2007;62:29) Consider resistance patterns, ± pseudomonal coverage in adv disease In general, if used, *low risk:* macrolide, doxycycline, cefpodoxime; *high risk* (older, lower FEV_1, high exacerbation freq, comorbidities): augmentin or FQ; *h/o pseudomonal PNA*: FQ

INTERSTITIAL LUNG DISEASE

Background (*AJRCCM* 2013;188:733)

- **Definition:** Heterogeneous group of diseases, all characterized by replacement of normal lung parenchyma w/ varying degrees of inflammation and fibrosis; described by both clinical and pathologic diagnoses
- Idiopathic pulmonary fibrosis (IPF): Most common form of ILD, usually presents in 6th–7th decades, ♂ > ♀; risk factors include smoking, ⊕ FHx, GERD *(AJRCCM* 2011; 183:788*)*; pathologic correlate is usual interstitial pneumonitis (UIP)
- Incidental lung abnormalities (ILA): Findings of fibrosis on imaging (CXR, CT chest, lung cuts of CT abdomen; clinical significance of findings w/o symptoms not yet clear) (*AJRCCM* 2012;185:1147)
- **Epidemiology & risk factors:** All very rare; most data for IPF, w/reported prevalence 7–16 cases/100,000 in US (*AJRCCM* 2006;174:810); risk factors vary by ILD
- **Clinical classification:** *Idiopathic* (idiopathic interstitial pneumonias) or *secondary* (related to systemic disease): rheumatologic/connective tissue disorders (RA, SSc, MCTD,

dermatomyositis), vasculitis, sarcoid, amyloid, IBD, malignancy, meds (chemotherapy, antirheumatologic agents, amiodarone), exposures (asbestos, silicosis, coal)

- **Pathologic classification:** Many histopathologic patterns (UIP, NSIP, BOOP/OP, RBILD, DIP, LIP, DAD, EP, PAP, DAH)
- **Pathologic dx does not always = clinical dx** (IPF = clinical dx, UIP = Pathologic dx; NSIP = Pathologic and clinical dx); some clinical ILD dx assoc w/ multiple histopathologic patterns (e.g., hypersensitivity pneumonia can be assoc w/ UIP, BOOP, or NSIP patterns on pathology) (*AJRCCM* 2013;188:733)
- **Presentation:** Typically presents w/ DOE & dry cough; may also be incidental finding on imaging (see ILA, above)
- **Prognosis:** Varies by form of ILD; IPF has worst prognosis, medial survival 2–3 y (*AJRCCM* 2011;183(4):431*; Ann Intern Med* 2012;156:684)

Evaluation (*AJRCCM* 2012;185:1147)

- **General approach:** Early referral to pulmonary specialist recommended if suspect ILD
- **History:** Detailed exposure hx (hobbies, occupations), medication hx, past medical history, s/sx of connective tissue disease, smoking hx, GERD
- **Exam:** *Vitals:* SpO_2 rest **& exertion**; *Pulmonary*: Bilateral fine inspiratory crackles (often referred to as "velcro" crackles; *CV*: Look for signs of PH, cor pulmonale; *Ext:* Look for clubbing (if longstanding); *Skin/joint exam:* Look for rashes, joint findings c/w CTD
- **Diagnosis:** Based on clinical s/sx and imaging; pathology often but not always required; PFTs may also support diagnosis
- **Imaging***:* **High-resolution chest CT** permits better visualization of pulm anatomy (secondary pulmonary lobule); expiratory phase assesses for "air trapping" present only in some ILDs (e.g., hypersensitivity pneumonia, bronchiolitis obliterans) and better characterizes airways disease
- Imaging pattern may help support specific ILD diagnoses:
  - **UIP (IPF)**: Peripheral reticular changes, honeycombing, traction bronchiectasis, +/– peripheral, subpleural, basilar-predominant GGO

NSIP: Characterized by GGO, though fibrotic NSIP can be difficult to distinguish from UIP

- **PFTs**: Demonstrate restriction and impairment in gas exchange (nl FEV_1/FVC ratio, ↓ FEV_1, FVC, TLC, DLCO)
- **Labs***:* **No routine labs;** consider ANA, Anti-Ro, La, Jo-1, Scl70, ANCA, HSP, CPK, aldolase; Note: Sometimes ILD can precede systemic sx of CTD
- **Bx:** Often, tissue dx required (with exception of UIP/IPF)
- **Management:** Treatment depends on ILD; newer options for IPF that prevent ↓ in FVC include pirfenidone (antifibrotic) and nintenanib (TKI) *(NEJM* 2014;370:2083*; NEJM* 2014;370:2071); for ILD secondary to rheumatologic/connective tissue disorders, typically comanaged by pulmonary & rheumatology; PCPs should ensure pts current on immunizations, have oxygen Rx if appropriate, & support transplant candidacy if appropriate

OBSTRUCTIVE SLEEP APNEA

Background (*Lancet* 2002;360:237)

- **Definitions:** *Sleep apnea:* Disorder in which pts experience *apneas* (cessation of breathing) or *hypopneas* (shallow breathing) often → daytime hypersomnolence

  Obstructive: Due to upper airway collapse/closure; *Central:* Due to ↓ respiratory drive; *Mixed:* Central pause → resumption of resp effort against relaxed/closed upper airway
- **Epidemiology:** 2–14% of the general population, ♂ > ♀ (*JAMA* 2013;310:731)
- **Risk factors:** *Obstructive:* Obesity, ♂ sex, age >50, postmenopausal, African-American descent, ⊕ FHx, EtOH use (*Arch Intern Med* 2002;162:893); *Central*: Assoc w/ Cheyne–Stokes breathing (assoc w/ **CHF**, prior stroke), opioid use
- **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 (*JAMA* 2013;310:731)

- **General approach:** Suspicion based on hx/exam, confirmed w/ sleep study
- **History:** Witnessed apneas/gasping (LR 3.3); snoring common but presence not useful for making diagnosis (LR 1.1); Absence of snoring makes OSA less likely (LR 0.12–0.45)
  - *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, CVA, DM, unexplained pHTN, polycythemia, ↑ $PaCO_2$, history of multiple motor vehicle crash
  - *Meds/Toxins:* Respiratory depressants (opiates, sleep aids, EtOH)
- **Exam:** *Vitals:* BP, **BMI**, SaO_2; *HEENT;* septal deviation, turbinate hypertrophy, nasal polyps or nasal valve collapse, enlarged tonsils or uvula, macroglossia,↑ Mallampati score (obscured view of soft palate/uvula), ↑ neck circumference, micro/retrognathia; *CV* (cor pulmonale, LVH)
- **Screening**: Consider **STOP-Bang score**; 8 yes/no questions with high Se & high NPV for OSA; (loud Snoring, Tired/sleepy during the day, Observed apneas, high blood Pressure or HTN tx; BMI >35, Age >40, Neck circumference >40 cm/16 in, ♂ gender);
  - *Scoring:* 1 point for each criteria met; *High risk*: total score ≥5 or STOP score ≥2 *and* any of the following: BMI >35, male gender, or large neck (*Chest* 2016;149:631)
- **Sleep study:** Either lab-based polysomnography (PSG) or in select pts w/ high pretest probability, a home-based study; can be used in diagnosis and/or for titration of optimal CPAP Rx; records sleep stages using EEG, EMG, & eye movements; evaluates for respiratory events (≥10 s)
  - *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, hypothyroidism, med effects/sedatives

Management (*J Clin Sleep Med* 2009;5:263)

- **Behavioral:** ↓ Wt; avoid EtOH/sedatives, positional Rx to avoid supine sleep, external nasal dilators (e.g., nasal adhesive strips), dental/oral appliance for patients with mild to moderate OSA who are intolerant of CPAP
- **Positive pressure ventilation:** CPAP or BiPAP
  - *CPAP:* Generally 1st-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 try in pt intolerant of continuous ⊕ pressure, although more expensive & not shown to ↑ adherence; used in patients who require high pressure; 1st-line for **central** sleep apnea, may be helpful if concomitant hypoventilation (e.g., COPD or obesity hypoventilation)
  - *APAP:* Varies pressure based on flow, can try in pt intolerant of continuous ⊕ pressure
- **Surgery:** Consider referral in refractory disease or severe disease w/CPAP intolerance; nasal surgery can improve nasal CPAP adherence (*Otolaryngol Clin North Am* 2016;49:1373); propharyngeal surgery can improve OSA of palate/tonsils are obstructive source (*Pediatrics* 2017;139:e20163314)
- **Referral:** If intolerant of CPAP/BiPAP or sx do not improve → ENT

Common Forms of CPAP Intolerance and Solutions	
Dry mouth	Rx: Nasal mask
Dry eyes	Rx: Check for mask fit/leaks
Soreness or skin irritation	Rx: Check mask fit, mask cleanliness
Claustrophobia	Rx: Check mask fit, use nasal mask, have get used to mask with

	machine off
Sensation of suffocation or intolerance of pressure	May be caused by poor mask fit, leaks Rx: Check for mask fit/leaks consider BiPAP or APAP, pressure relief
Nasal problems (dry nose, congestion, postnasal drip)	Rx: Heated humidification, nasal corticosteroid or saline, if no improvement ENT referral to eval for polyps, deviated septum
Abdominal bloating	More common with full face mask Rx: Nasal mask, BiPAP

Obesity Hypoventilation Syndrome (OHS)

- **Diagnostic Criteria:** Obesity (BMI >30 kg/m^2) + awake alveolar hypoventilation ($PaCO_2$ >45 mmHg) + sleep-disordered breathing + exclusion of other causes of hypercapnea
- **Epidemiology:** 85–90% have coexisting OSA, ↑ prevalence w/↑ BMI (*Chest* 2007;131:1678); assoc w/ ↑ CV mortality when compared to similarly obese w/o OHS (*Chest* 2016;149:756)
- **Typical presentation:** S/sx: Similar to OSA + **dyspnea on exertion**; may have s/sx of pHTN and R-sided HF, hypoxia when awake, ± plethoric complexion from polycythemia; labs may include ↑ serum bicarb (compensatory metabolic alkalosis), ↑ HCT
- Differential diagnosis includes severe COPD, ILD, chest wall disorders such as kyphoscoliosis, neuromuscular disorders
- **Evaluation:** if suspicion for OHS (obese, OSA, any sx), screen with serum bicarbonate; if elevated → ✓ ABG, PFTs (may be restrictive pattern 2/2 obesity), sleep PSG, CXR (r/o diaphragmatic paralysis), ECG (eval for RAA, RVH), TTE (eval for RVH) ± RHC (eval for pHTN) (*Am J Med* 2004;116:1; *Chest* 2007;131:1678)
- **Treatment:** OSA **behavioral tx** (wt loss, avoiding sedatives, treating comorbid conditions); CPAP or **BiPAP** (CPAP okay if maintains adequate ventilation); may also require supplemental oxygen, surgical intervention (incl bariatric surgery; see *"Obesity"*)

CHRONIC COUGH

Background (*NEJM* 2000;343:1715)

- **Definitions:** *Subacute cough:* 3–8 wk; *Chronic cough:* >8 wk
- **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 initiated or suppressed voluntarily); cough mechanism involves diaphragm, glottis, & muscles of expiration
- **Etiology:** Varies by duration, can include airway (upper airway cough syndrome [UACS]), HEENT, GI, and CV causes

Evaluation (*Chest* 2006;129:S1; *AFP* 2011;84:887)

- **General approach:** Hx/exam to screen potential etiologies; if none discovered → trial of empiric tx for either UACS (upper airway cough syndrome), asthma, or GERD
- **History:** Often nonspecific; ask about onset (post-URI), duration, triggers (after meals—GERD, allergens—asthma); **Red flags:** Wt loss, hemoptysis, systemic sx

  Assoc sx: Postnasal drip, sinusitis, hoarseness, reflux sx, edema
  PMHx: Atopy, GERD, CHF, immunocompromise, CA, TB exposure/RF
  Meds/toxins: ACEI, βB, smoking status/exposure, occupational/environmental 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 (*Lancet* 2008;371:1364; *NEJM* 2000;343:1715)

- **Subacute cough:** Postinfectious cough *(48%)*, infectious sinusitis (33%), asthma (16%) (*Chest* 2006;129:1142; *NEJM* 2006;355:2125)

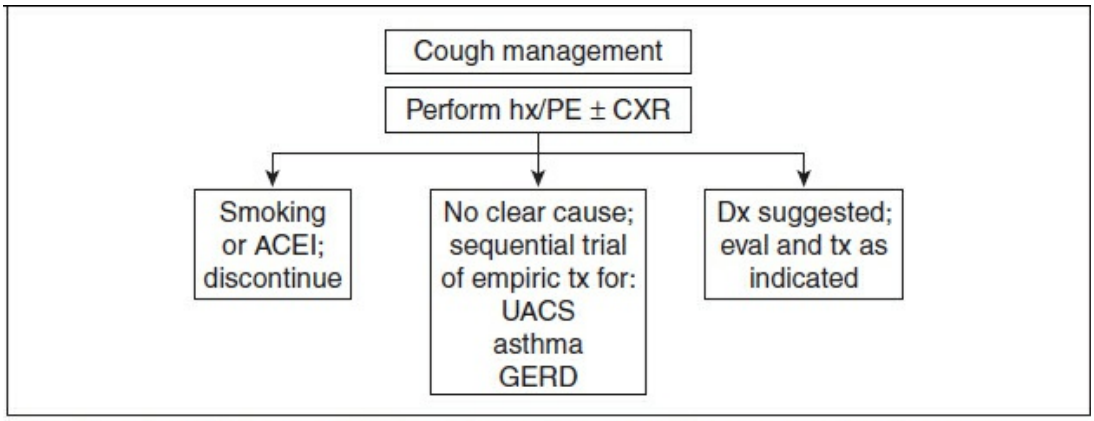
  Postinfectious cough: Respiratory tract infection → postnasal drip, tracheobronchitis; resolves w/o tx; **average duration of bronchitis-associated cough is 24 d**

  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 mo after starting Rx; cough resolves w/in 2–4 wk of discontinuation of Rx
UACS (34%)	Allergic or nonallergic rhinitis, sinusitis Tx: See *"Allergic Rhinitis"*
Cough-variant asthma (28%)	Dx: PFTs (for cough, may start w/ trial of empiric SABA tx) Tx: See *"Asthma"*
GERD	Dx/Tx: Empiric trial of PPI; see *"Gastroesophageal Reflux Disease"*

- **Other:** COPD, bronchiectasis, eosinophilic bronchitis (dx'ed w/ induced sputum, rx w/ ICS), *B. pertussis* (see *"URI and Influenza"*), CHF, ILD, bronchogenic CA, metastatic CA, mediastinal or hilar tumors, allergic alveolitis, lung abscess, EGPA, sarcoidosis, TB, fungal pneumonia (e.g., Cryptococcus), hypersensitivity pneumonitis, allergic bronchopulmonary aspergillosis, habitual cough, foreign body, irritation of external auditory meatus, recurrent aspiration

Management



Adapted from Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:S1–S23. Copyright © 2006 The American College of Chest Physicians. With permission.

Figure 13-1. Chronic cough management

When to Refer

- If red flags present or sx persist despite empiric tx for common problems, referral to pulmonology for consideration of bronchoscopy/further studies

HEMOPTYSIS

Background & Evaluation (*AFP* 2015;91:243; *Chest* 1997;112:440)

- **Definition:** Blood (mixed w/ sputum or pure blood) expectorated from airway; "massive hemoptysis" defined variably but generally >400 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

  Ddx: pseudohemoptysis may be due to ENT (**epistaxis**), oropharynx (gingivitis, dental disease), or GI (hematemesis) causes

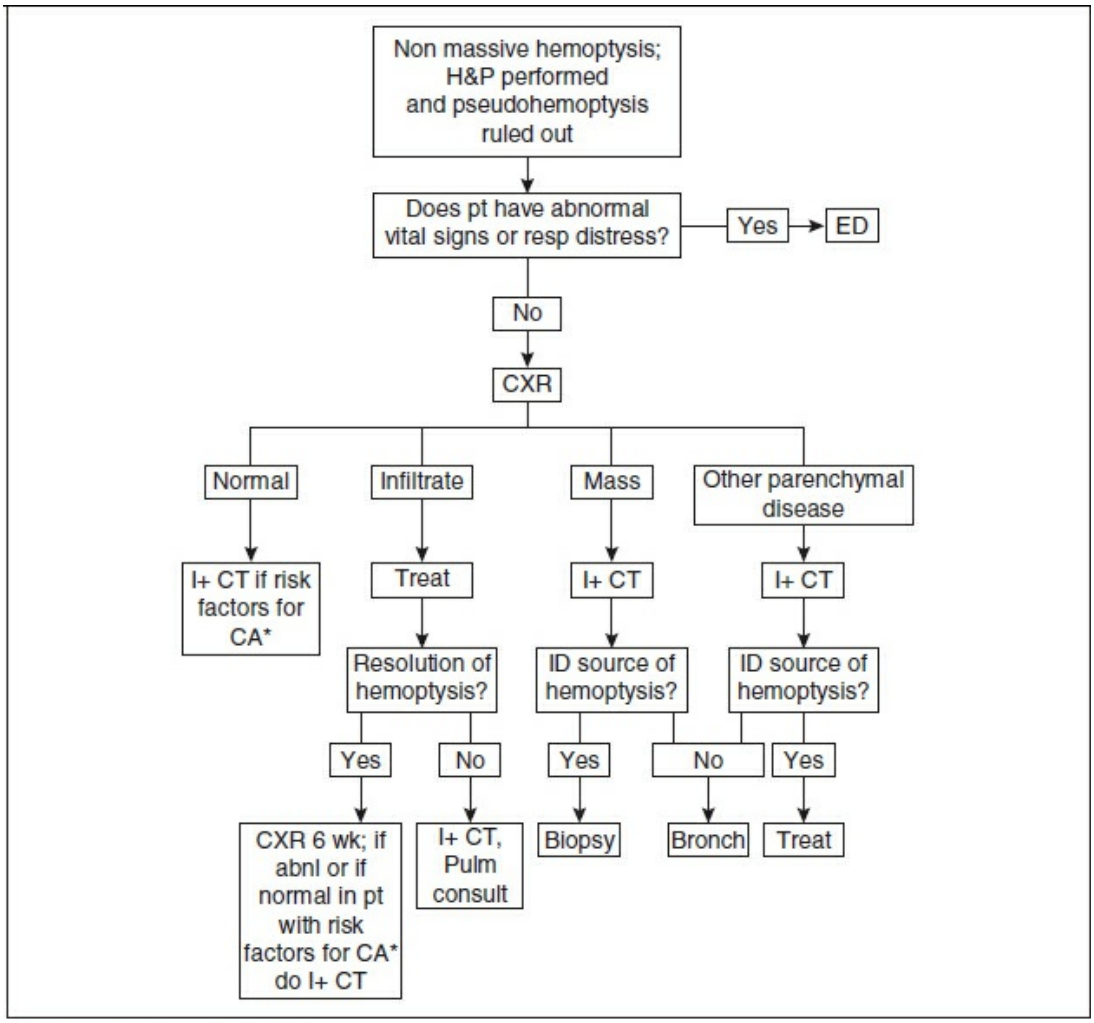
PMHx: COPD or other lung disease, immunocompromise, autoimmune disease, CHF, coagulopathy (anticoagulants, liver disease), TB exposure/risk factors, smoking hx, malignancy (lung or other primary), travel hx

- **Labs:** Consider CBC, coags, further labs as dictated by eval
- **Imaging:** Chest CT w/ contrast; further studies as dictated by eval
- **Bronchoscopy:** Low threshold to refer

Selected Differential Diagnosis of Hemoptysis (*AFP* 2005;72:1253)
Airway disease: Bronchitis (most common, 26%), bronchiectasis (i.e., CF); *S/sx:* Chronic/subacute cough & sputum which turned bloody/blood-streaked *Dx:* Consider resp viral panel, bronchiectasis w/u, sputum gram stain/culture if suspect bronchiectasis flare
Neoplasm: Primary lung cancer (23%), metastasis to lung (melanoma, breast, colon, RCC), bronchial carcinoid, Kaposi sarcoma *S/sx:* Smoking hx, elderly, wt loss, dry cough, known nonlung malignancy, HIV⊕ *Dx:* Consider sputum cytology, referral for bx
Infection: PNA (10%, often staph, pseudomonas, aspergillus), lung abscess, **TB** (8%) *S/sx:* Cough w/ purulent sputum, fevers, chills, wt loss, HIV⊕, immunosuppression *Dx:* Sputum gs/culture (± AFB), fungal markers, likely referral for bronchoscopy; suspicion of TB requires resp isolation during w/u (see *"Tuberculosis"*)
Increased pulmonary venous pressure: PE, CHF, mitral stenosis *S/sx:* Dyspnea, hypoxemia, cardiac hx, high risk for DVTs *Dx:* TTE, consider RHC, 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) *S/sx:* As per syndrome: Systemic sx, renal failure/CKD, sinus sx, autoimmune hx *Dx:* ANCA, anti-GBM, *UA/urine sediment,* BUN/Cr, ANA, anti-dsDNA, anti-Smith, tox screen; referral for bronchoscopy w/ BAL vs. → likely ED/inpt
Other: Vascular (AVM, bronchovascular fistula; usually p/w massive hemoptysis); trauma, foreign body, 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



*Include age >40 y, smoking history

Adapted from Ketai L, Mohammed T-L, Kirsch J. ACR Appropriateness Criteria® Hemoptysis. *J Thor Imag* 2014;29(3): W19-W22. With permission.

Figure 13-2. Management of nonmassive hemoptysis

PULMONARY NODULES

Background (*Chest* 2013;143:*s*93)

- Frequently encountered incidentally during chest CT for other causes; recommendations range from no f/u, to interval f/u w/ repeat chest CT, to biopsy; management strategy and communication of risks to pts key role of PCPs
- **Definitions:** Via radiographic characteristics

Solitary pulmonary nodule (SPN): Intraparenchymal lung lesion <3 cm in diameter, not assoc w/ atelectasis or adenopathy
Ground glass nodule (GGN): Area of ↑ parenchymal attenuation but with preservation of underlying lung structures, such as airways and vasculature
Subsolid nodule: Mixed GGN and solid nodule
Indeterminate: Nodules do not have a clearly benign appearance

- **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)
- **Etiology:** *Benign:* Nonspecific granuloma > hamartoma, infectious granuloma (Aspergillosis, Cocci, Cryptococcus, Histo, TB); *Malignant:* Adenocarcinoma, squamous cell, undifferentiated NSCLC, small cell, bronchioloalveolar cell, metastases
- **Malignancy risk factors:** *Nodule:* Diameter, **spiculation** (2–2.5x ↑ risk), 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

Evaluation (*NEJM* 2003;348:2535)

- **General approach:** Determine if pt high- or low-risk for malignancy based on validated tool (below); use surgical candidacy & pt preference to dictate surveillance strategy; always review prior imaging
- **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 reference.medscape.com/calculator/solitary-pulmonary-nodule-risk; consider Brock Calculator for pts w/ nodule detected on lung CA screening (validated in this population) (*NEJM* 2013;369:910)
- **Surgical risk:** See *"Preoperative Evaluation"*

Management

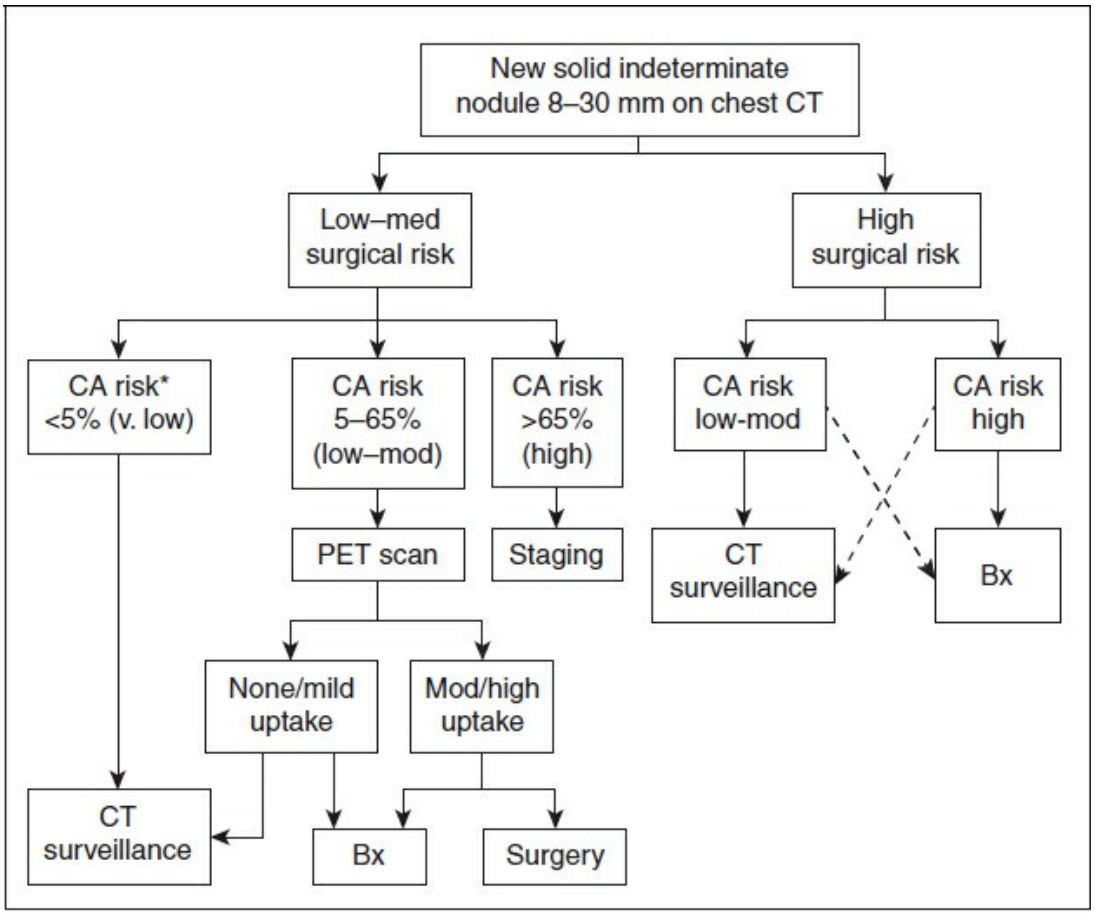
- Management options include careful observation, further diagnostic testing, or surgery

- **Shared decision-making:** Discussion of risk/benefits of different strategies appropriate, esp for pts of intermed probability where advantages of any particular approach less certain; in general, if f/u recommended (incl CT) below, >1% risk of malignancy
- Fleischner surveillance criteria (below) are for incidental nodules, *not* those detected via lung cancer screening or those found in immunosuppressed or pts w/hx of malignancy
- **Surveillance:** Done w/ repeat chest CT; generally indicated if **low** pretest probability

Fleischner Criteria for Solid Nodule Surveillance (*Rad* 2017;284:228)		
Nodule Size	**Low Risk**	**High Risk**
<6 mm	Not indicated	Consider at 12 mo (optional)
6–8 mm	6–12 mo, then consider at 18–24 mo	6–12 mo, then at 18–24 mo
>8 mm	3 mo or tissue sampling	3 mo, PET/CT, or bx
Multiple nodules		
<6 mm	Not indicated	Consider at 12 mo (optional)
6–30 mm	3–6 mo, then consider at 18–24 mo	3–6 mo, then at 18–24 mo

Fleischner Criteria for Subsolid Nodule Surveillance (*Rad* 2017;284:228)		
Nodule Type	**Management**	**Remarks**
Solitary pure GGN ≥6 mm	6–12 mo, then q2y until 5 y	No f/u if <6 mm unless ↑susp, then at 2,4 y; if ↑ in size or develops solid component, consider resection
Solitary, part-solid nodule ≥ 6 mm	3–6 mo, if unchanged & solid component <6 mm, q1y for 5 y	No f/u if <6 mm, part-solid nodules w/solid component >6 mm are highly suspicious
Multiple subsolid nodules <6 mm	CT 3–6 mo; if stable, consider repeat at 2, 4 y	Usually benign; consider 2, 4 y if pt at ↑ risk
Multiple subsolid nodules ≥6 mm	CT 3–6 mo; then manage based on most suspicious nodule(s)	

- **Further diagnostics:** Generally indicated if **intermediate** pretest probability for CA
  - *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) (*AJRCCM* 2012;185:363–372)
- **Surgical diagnosis/treatment:** Generally indicated if **high** pretest probability for CA VATS, traditional thoracotomy, lobectomy



*CA risk based on validated model (i.e., Mayo Clinic Model)

(Adapted from Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:S93–S120. Copyright © 2013 The American College of Chest Physicians. With permission.)

Figure 13-3. American College of Chest Physicians (ACCP) Guidelines for Management of Solid Pulmonary Nodules

- **Multiple nodules:** Higher number of nodules (>4) may be assoc w/↓ risk of lung CA (more likely to be benign etiology); surveillance guidelines as above; use most suspicious nodule as guide to management (*Rad* 2017;284:228)

CHRONIC KIDNEY DISEASE

Background (*Ann Int Med* 2015;162:ITC-1; *JAMA* 2015;313:837; *Lancet* 2012;379:165; *NEJM* 2014;371:58)

- **Definition:** ≥3 mo w/ GFR <60 mL/min/1.73 m^2 **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; Preferred formula: CKD-EPI, but MDRD equation also commonly used; (*JAMA* 2012;307:1941); online calculator: kidney.org/professionals/kdoqi/gfr_calculator.cfm
  - **Proteinuria:** See *"Proteinuria"* section
  - **Nephrotic syndrome:** Proteinuria >3.5 g/d, serum albumin <3.5 g/dL, edema, HLD, HTN
  - **Glomerulonephritis:** Hematuria (dysmorphic RBCs or RBC casts), subnephrotic proteinuria, often AKI, HTN, edema
  - **Medications that interfere w/ serum Cr assay:** TMP-SMX, cimetidine, cefoxitin
- **Pathophysiology:** Diabetes mellitus (45%), HTN (27%), glomerulonephritis (10%), interstitial/obstruction (4%), polycystic kidney disease (PKD) (2%) (*NEJM* 2010;362:56)
  - **Reversible causes:** Hypovolemia, hypotension, nephrotoxic agents, urinary obstruction
- **Epidemiology:** Prevalence ~16.8% in US, by stage: 1: 1.8%, 2: 3.2%, 3: 7.7%, 4: 0.35%, ESRD: 2.4% (*JAMA* 2007;298:2038)
- **Risk factors:** More likely to suffer CV events/mortality with each stage of CKD than progress to ESRD (*NEJM* 2004;351:1296); severity of proteinuria assoc w/ worse outcomes independent of eGFR

CKD Staging (*Kid Int* 2013;3:19)			
Stage	**Description**	**GFR (mL/min/1.73 m^2)**	**Actions**

1	Nl or GFR	≥90	Dx/Rx underlying condition/ comorbidities, CVD risk reduction
2	Mild ↓ GFR	60–89	Est progression, CVD risk reduction
3a	Mod ↓ GFR	45–59	Eval & Rx complications
3b	Mod/sev ↓ GFR	30–44	Nephrology referral (if not yet done)
4	Sev ↓ GFR	15–29	Prepare for RRT, transplant referral
5	Kidney failure	<15 or dialysis	Dialysis if uremic
Albuminuria stage based on albuminuria (mg/d) or spot urine alb (mg) to Cr (mg) ratio (ACR): **A1:** nl or mildly ↑ (ACR <30); **A2:** mod ↑ [formerly microalbuminuria] (ACR 30–299); **A3:** or severely ↑ [formerly macroalbinuria] (ACR ≥300)			

Evaluation (*AFP* 2011;84:1138)

- **History:** Variety of presentations, from asx to edema, HTN, uremia (nausea, pericarditis, anorexia, neuropathy, altered MS), hematuria, flank pain, neuropathy; urine output
- **Exam:** Regular exam, emphasis on volume status and vascular system
- **Workup:** Urine microscopy/sediment, Chem-7, Ca, PO_4, PTH, lipids, serum albumin, CBC, urine protein:creatinine ratio (UPCR), SPEP; urine albumin:creatinine ratio (UACR); renal ultrasound; *Consider:* HbA1c, hepatitis serologies, HIV, RPR, based on clinical suspicion; *Can usually defer to specialist:* 24-h urine protein, ESR, CRP, C3, C4, ANA, anti-dsDNA, ANCA, anti-GBM, $APLA_2R$ Ab, cryoglobulins, serum/urine immunofixation for amyloid, light chains, renal biopsy
  - **Screening for CKD:** Indicated in pts w/ CKD risk factors (HTN, DM, FHx CKD); ✓ serum Cr, UA, UACR; USPSTF found insufficient evidence to recommend screening asx adults (excluding those w/ HTN, DM2) (*Ann Intern Med* 2012;157:567)
  - **Monitoring:** Chem-7, CBC, Ca, PO_4, PTH, vit D, UACR, iron studies (q3–12mo based on CKD stage)

Management (*AFP* 2012;86:749; *Ann Int Med* 2013;158:825; *Kidney Int Sup* 2013;3:5; *NEJM* 2010;362:56)

- **Correct reversible causes:** Dehydration, meds (diuretics, NSAIDs,

ACEI/ARB), infection, urinary obstruction

- **Lifestyle modification:** Smoking cessation (see "*Tobacco Use*"), weight loss; mod exercise 30–60 min 4–7 d/wk, nutrition referral
- **Nephrology referral:** Early referral assoc w/ ↓ mortality (*Am J Med* 2007;120:1063). Refer if: eGFR <30, stage 4/5 CKD; DM w/ mod albuminuria (30–299 mg/d); any UACR ≥300 mg/g, ? etiology, rapidly ↓ GFR, complications of CKD requiring Rx (i.e., Epo, PO_4 binders, vit D), hyperkalemia, resistant HTN, recurrent nephrolithiasis, suspicion of hereditary CKD
- **Slowing CKD progression:**
  - **BP control:** Goal <130/80, <120/80 if tolerated (*NEJM* 2015;373:2103); start w/ ACEI (or ARB), then add diuretic, then CCB
  - **ACEI or ARB:** 1st-line/renoprotective in all CKD (*NEJM* 2004;351:1952); tolerate 25% ↑ in Cr and K <5.5; no benefit of ACEI + ARB combined and assoc w/ adverse outcomes (*NEJM* 2013;369:1892); 2nd-line agents include loop diuretics (if edema present) or diltiazem/verapamil (↓ proteinuria; antiproteinuric effect not seen w/ amlodipine)

Renal Nutrition Suggestions	
Factor	**Goal/Rational**
Sodium	<2 g/d. For BP and volume control
Potassium	<2 g/d if hyperK, to tolerate ACEI/ARB
Glucose	Low carb/sugar, if diabetic. See "*Diabetes"*
Phosphorus	Low PO_4, ↑ PO_4 assoc w/ increased mortality, vasc. calcification
Protein	0.6–0.8 g/kg/d. ↓↓ protein diet assoc w/ ↑ mortality (*Cochrane* 2009;8:CD001892)
Herbal Suppl.	Avoid and/or review with nephrologist before taking

- **Vaccines:** PSV23, PCV13, Influenza, HBV (see "*Immunizations*")
- **CV risk reduction:** BP control, lipids at goal (*Ann Int Med* 2012;157:251)
- **Renal replacement therapy:** Includes hemodialysis (HD), peritoneal dialysis (PD), transplant

Renal Replacement Therapy Options		

Modality	Pros	Cons
Transplant	Outcomes approach general population 1 y after transplant	Wait list, risks of surgery. Refer when eGFR <20
Hemodialysis	Common	Vascular complications; requires being at an HD center
Peritoneal dialysis	Preserves residual renal function; independence	Sterile technique; requires compliant, knowledgeable patient

Indications: Clinical decision; consider when eGFR 5–10 & sx of uremia/fluid overload (*CJASN* 2011;6:1222). No mortality benefit to early initiation of dialysis & no difference in CV events, infection, HD complications (IDEAL, *NEJM* 2010;363:609)

Preparation for HD: For stage 4 CKD, avoid subclavian or PICC lines; AV fistulas take mo to mature; synthetic grafts mature in wks, but have thrombosis/infections

- **Care after transplant checklist for PCPs:** ✓ all medications for interaction w/ immunosuppressants; all fevers need broad w/u; avoid live vaccines; annual derm exam for ↑ risk of skin cancers; prompt w/u for change in SCr (*Med Clin N Am* 2016;100:435)
- **Patient information:** *JAMA* 2007;298:1244

Complications of CKD (*NEJM* 2010;362:56;1312)

- **Anemia:** ↓ renal Epo production, ↓ iron absorption in CKD; goal Hgb 10–11 g/dL; correct iron deficiency before starting epoetin/ darbepoetin (*NEJM* 2009;361:2019)
- **Bone disease:** ↓ GFR → ↑ PO_4, ↓ Ca, ↓ calcitriol, ↑ FGF-23 → ↑ PTH → renal osteodys

1. PO_4 binder (calcium acetate, sevelamer, lanthanum) if ↑ PO_4

å Ca (<8.4 mg/dL): Use calcium acetate (Phos Lo) or carbonate (Tums)

Intermediate Ca (8.4–9.5): Calcium 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 wk)

2. **1,25-(OH) vit D** (calcitriol, paricalcitol) if ↑ PTH (*AJKD* 2009;53:408)
3. **Cinacalcet** (parathyroid Ca-sensing receptor agonist) or parathyroidectomy if ↑↑ PTH despite above measures (*CJASN* 2016;11:161)

- **Volume overload/edema:** <2 g/d Na restriction + diuretics
- **Metabolic acidosis:** ↓ GFR → ↓ acid excretion → ↓ HCO_3 → osteopenia, ↑ PTH, ↑ inflammation, muscle wasting, progressive CKD; treat w/ sodium bicarbonate or citrate to HCO_3 goal of 23–29 mEq/L (*J Am Soc Nephrol* 2015;26:515; *Kidney Int* 2010;78:303); 1 tsp baking soda ≈ 6 tabs of Na-HCO_3 ≈ 50 mEq HCO_3; citrate contraindicated in pts on aluminum-containing medications, i.e., antacids, buffered aspirin, sucralfate, or some phosphate binders due to ↑ aluminum absorption → intoxication and osteomalacia
- **Diabetic nephropathy:** Occurs in both type 1 and 2 DM, most common cause of CKD worldwide (*AJKD* 2014;63:S3; *JASN* 2007;18:1353); tracks with other microvascular changes (retinopathy), occurs 10–15 y after Dx

  Pathogenesis: Hyperfiltration, advanced glycation due to hyperglycemia, hypoxia/inflammation; degree of proteinuria predicts progression to ESRD

  Treatment: Prevention of progression with ACEI/ARB and tight glycemic control

  Diabetic medications in CKD: Metformin can be safely used until eGFR <30 (risk of lactic acidosis); reduced dose sulfonyl urea are alternative (e.g., glipizide); SGTL2-I may have additional renal protective effects (*NEJM* 2016;375:323)

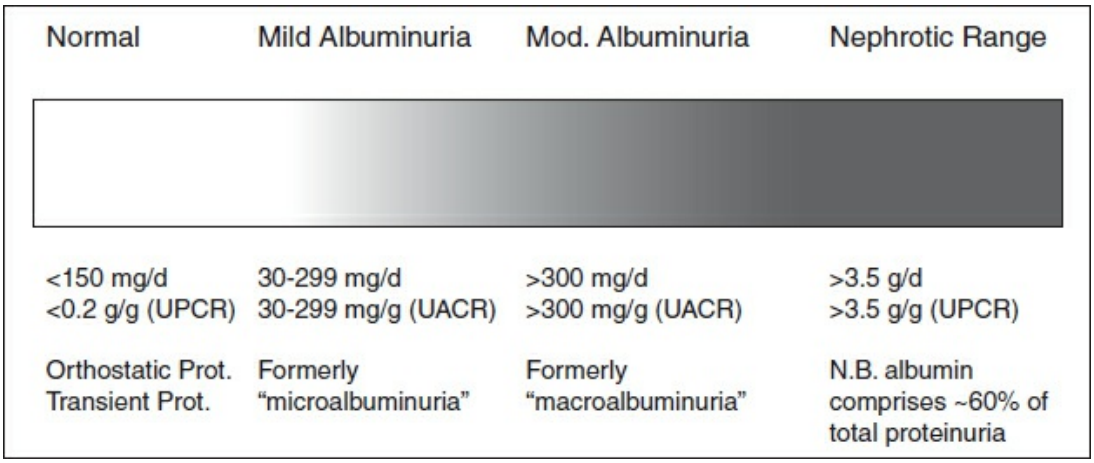
PROTEINURIA

Background (*AFP* 2000;62:1333; 2009;80:1129; *JABFM* 2008;21:569)

- **Normal physiology:** Kidney filters 180 L ultrafiltrate/d with approx; 1 mg/dL albumin in Bowman space; majority of protein (albumin, low–molecular-weight protein) reabsorbed in the proximal convoluted tubule (PCT); healthy individuals secrete <150 mg/d of protein
- **Nephrotic syndrome:** >3.5 g/24 h proteinuria, hypoalbuminemia

(<3 g/dL), and peripheral edema; may be accompanied by protein malnutrition, renal failure, hyperlipidemia, arterial/venous thromboses, atherosclerosis, urinary hormone loss

Etiologies of Proteinuria		
Category	**Description**	**Etiologies**
Glomerular (can be >3 g/d)	Disruption of filtration barrier → lose albumin	Glomerulonephritis Nephrotic syndrome
Tubulointerstitial (usually <1–2 g/d)	↓ reabsorption of freely filtered proteins → lose globulins	ATN; AIN Fanconi syndrome
Overflow	↑ production of freely filtered proteins	Multiple myeloma Myoglobinuria
Isolated	By def'n: asx, normal renal fxn, sed, & imaging, no h/o renal disease	Functional (fever, exercise, CHF) Orthostatic (only when upright) Idiopathic (transient or persistent)



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 (AL from light chains or AA 2/2 inflammation),

cryoglobulinemia, infection (HIV, HBV, HCV, poststreptococcal, syphilis, malaria, endocarditis), GI/lung cancer, lymphoma, small vessel vasculitis (ANCA) or anti-GBM dz

Medications associated w/ proteinuria: NSAIDs, heroin, lithium

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, recent infxn; *Meds:* (NSAIDs); *FHx:* Alport syndrome
- **Exam:** BP, wt, periorbital or dependent edema, ascites
- **Workup:** See Evaluation section of "*Chronic Kidney Disease*"
  - **Urinalysis ("Dipstick"):** Measures albumin concentration via colorimetric reaction; false ⊖ if nonalbumin proteinuria, false ⊕ if urine pH >7.5, SG >1.015, hematuria, mucus, semen, leukocytes, recent IV contrast. 1+ → ~30 mg; 2+ → 100 mg; 3+ → 300 mg; 4+ → >1–2 g
  - **Urine microscopy ("sediment"):** May help to distinguish glomerular vs. other proteinuria (i.e., presence of RBCs, WBCs, eosinophils, casts)
  - **Spot UPCR or UACR:** Acceptable for screening (vs. 24-h collection; proteinuria underestimated in muscular pts & overestimated in cachectic pts); 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 & ✓ UPCR in sample after awakening (<0.2 g/g suggests orthostasis); uncommon in pts >30 y

Management (*AFP* 2009;80:1129; *Kid Int Sup* 2012;2:143; *NEJM* 2013;368:10)

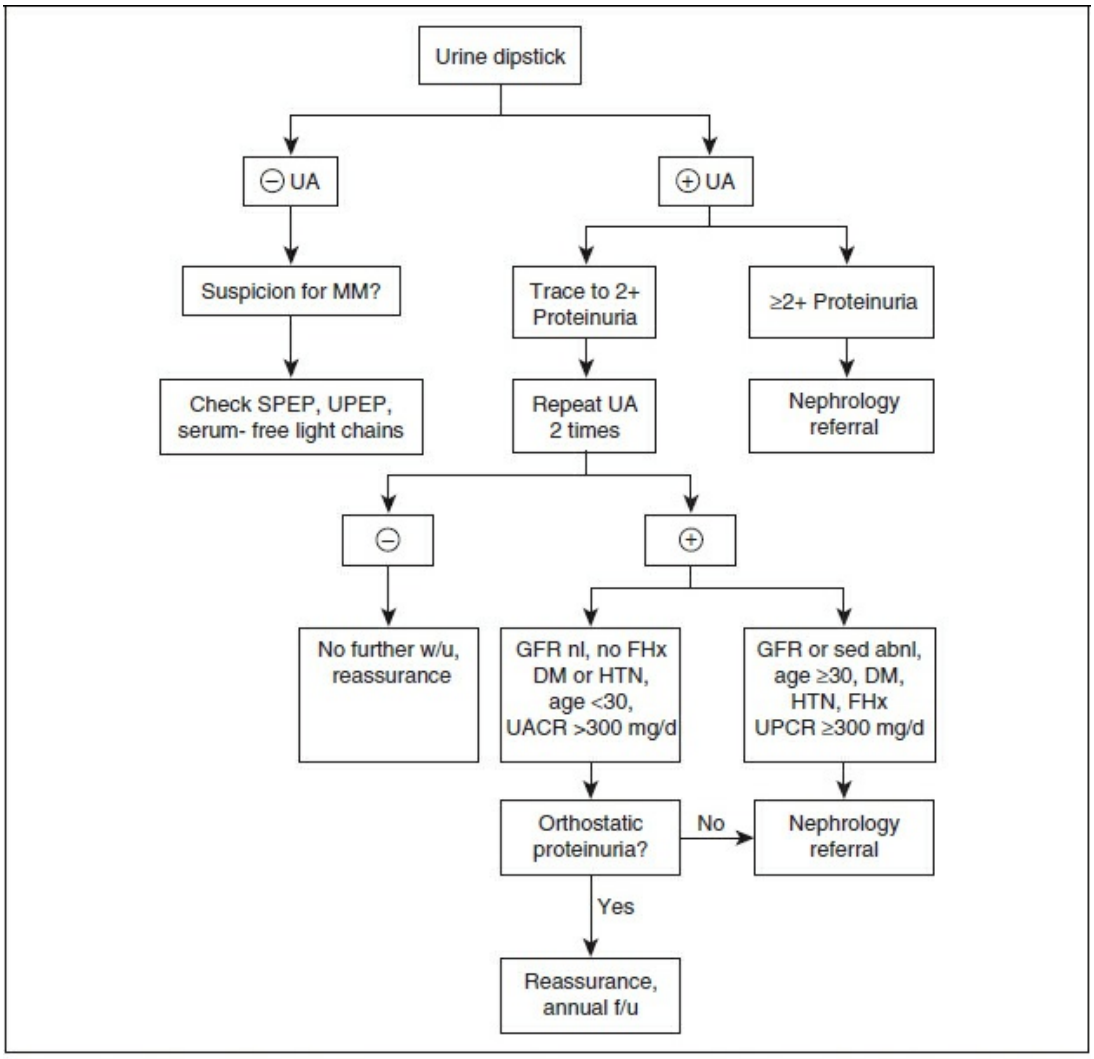
- **General principles:** Varies by etiology; treat underlying disease & factors that predict CKD progression (see Management section of "Chronic Kidney Disease")
- **ACEI** or **ARB**: ↓ proteinuria → slow nonimmunologic progression of renal disease
- **1° glomerular dis:** Steroids ± cytotoxic therapy; cancer screening if membranous neph
- **Secondary causes:** Treat underlying disease
- Watch for malnutrition (protein loss), thrombosis (in ~25%, esp. renal vein, no consensus re: ppx anticoagulation), infxn (esp. encaps.

organisms b/c loss of Ig)

- **Edema:** Dietary Na restriction (2 g/d) & diuretics
- **When to refer to nephrology:** see Management section of "*Chronic Kidney Disease*"
- **Information for patients:** *JAMA* 2010;303:470

Proteinuria in Pregnancy (*Int J Gynaecol Obstet* 2002;77:67)

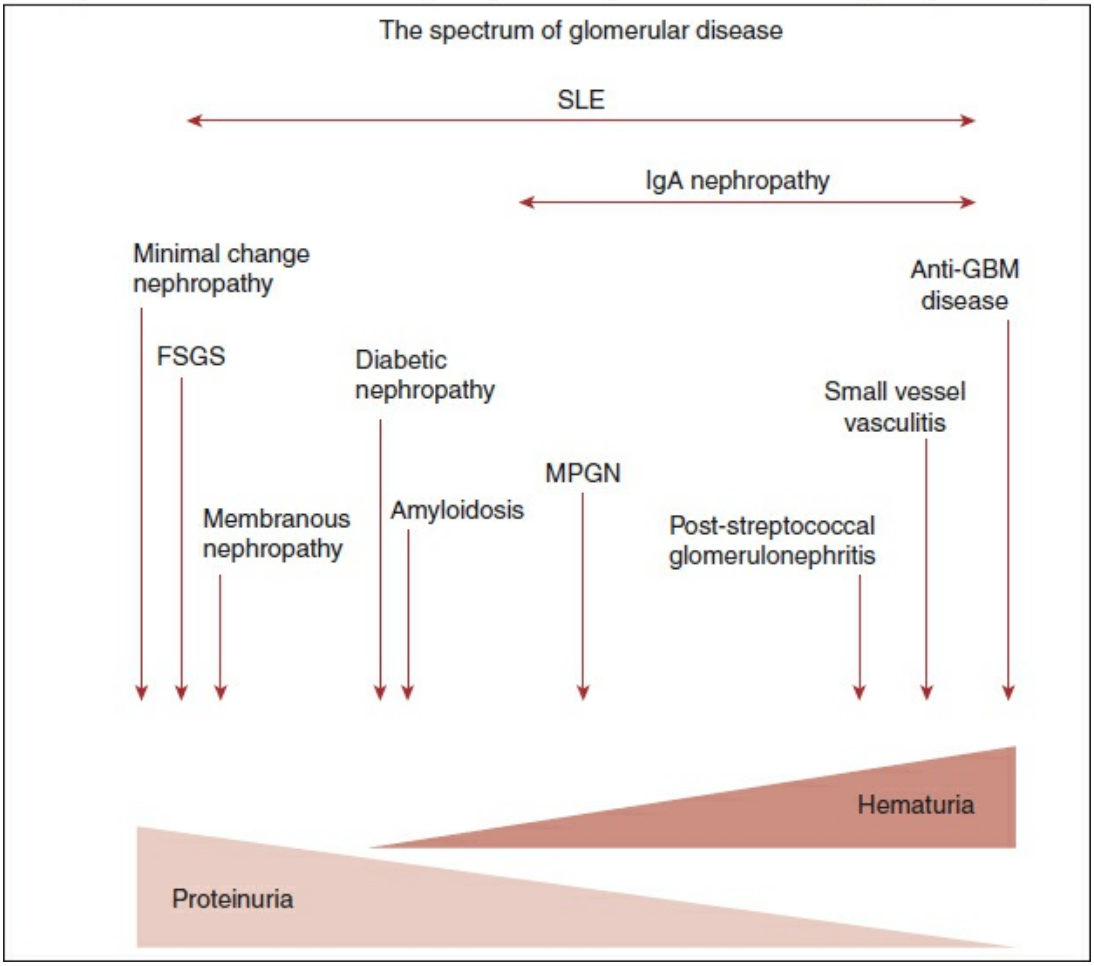
- **Pathophysiology:** In normal pregnancy, urinary protein excretion increases due to ↑ GFR and ↑ permeability of the GBM; normal up to 250 mg/d in third trimester
  - **Abnormal level of proteinuria:** >300 mg/d anytime during gestation based on 24-h urine collection (correlates with 1+ on urine dipstick)
  - **Onset *prior to 20-wk* gestation:** Suggestive of pre-existing renal disease
  - **Onset *after 20-wk* gestation:** Must exclude preeclampsia



(Adapted from Naderi ASA, Reilly RF. Primary care approach to proteinuria. *J Am Board Fam Med* 2008;21(6):569–574. Copyright © 2008 American Board of Family Medicine. Reprinted with permission.)

Figure 14-1. Proteinuria evaluation

Spectrum of Proteinuria ("Nephrotic") and Hematuria ("Nephritic")



HEMATURIA

Background (*AFP* 2006;73:1748; *BMJ* 2009;338:a3021; *JAMA* 2015;314:1865; *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 to rule out 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)

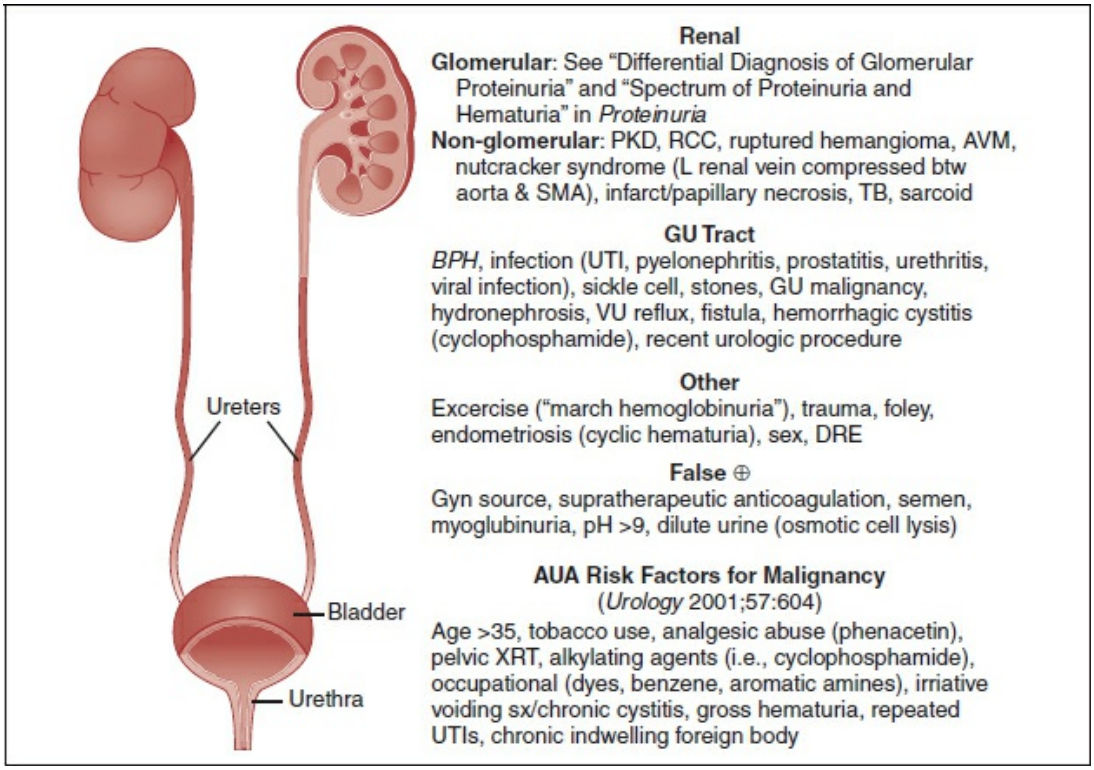


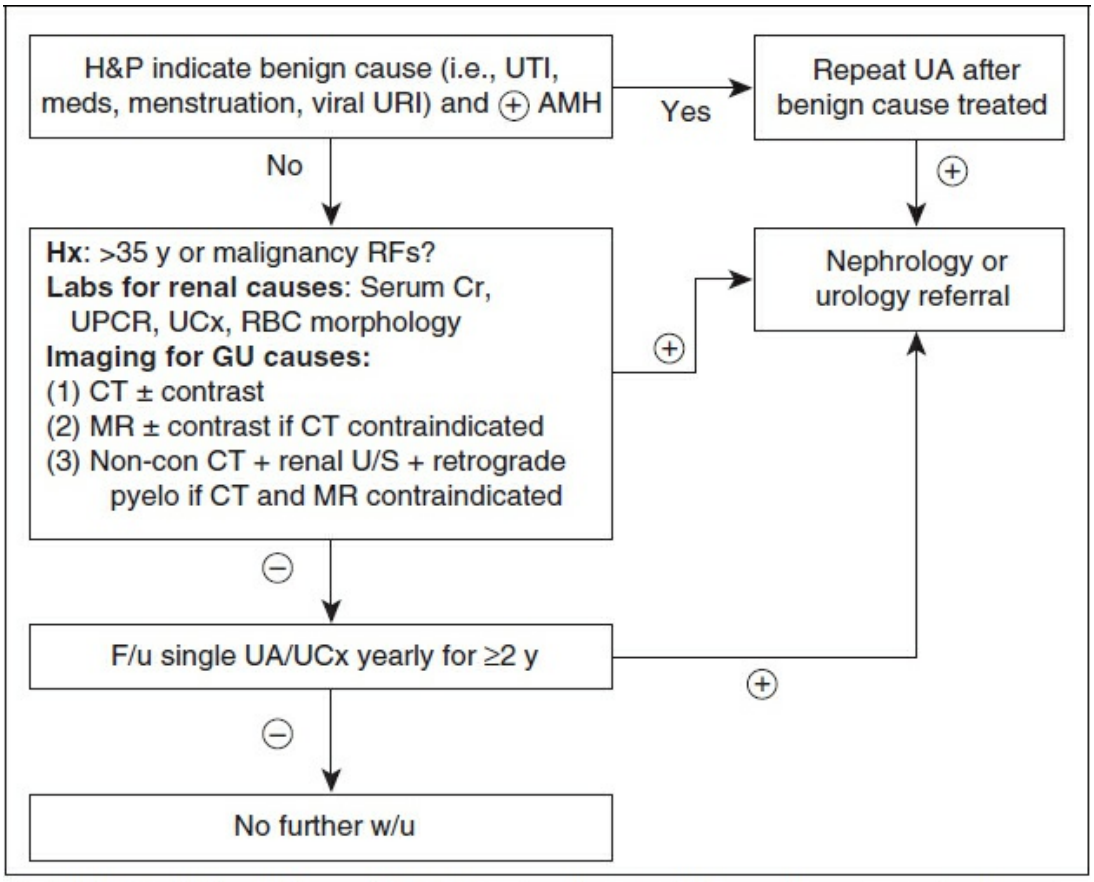
Figure 14-2. Differential diagnosis of hematuria

Evaluation (*AFP* 2008;78:347; 2013;88:747; *Ann Int Med* 2016;164:488; *JAMA* 2016;315:2726; *NEJM* 2003;348:2330; *Urology* 2001;57:604)

- **History:** Transient vs. persistent hematuria, fevers, pain, medications, trauma, pyuria, dysuria; blood clots; *lower urinary tract symptoms* (Chap X); recent URI (postinfectious glomerulonephritis/IgA nephropathy) or sexual activity; personal/family history of renal disease, malignancy, bleeding disorders; occupational exposures, travel Hx
  - **Medications & food associated w/ red urine:** Rifampin, phenazopyridine, iron sorbitol, nitrofurantoin, chloroquine; rarely beets, blackberry, rhubarb, food coloring
  - **Medications → hematuria:** Aminoglycosides, amitriptyline, analgesics, anticonvulsants, ASA, diuretics, OCPs, penicillins

(extended spectrum), warfarin OD (*AFP* 2006;73:1748)

- **Workup:** UA, UCx, microscopic urine evaluation (to confirm positive 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 & evidence of a UTI should have a repeat UA 6 wk later to confirm resolution of hematuria
  - **Urine cytology:** *Cannot* r/o bladder Ca (Se 40–76%), but ⊕ cytology diagnostic of urothelial Ca; NOT recommended as part of routine eval of AMH, but may be useful if workup otherwise ⊖ (*Cancer* 1987;60:1423)
  - **CT "hematuria protocol":** initial test of choice for gross hematuria or AMH w/o infection or glomerular bleeding; MRI urography or U/S are alternative in pregnant pts
  - **Cystoscopy:** Gold standard for gross hematuria w/o glomerular disease or infection; indicated in **all pts who pass urine blood clots**, AMH w/o glomerular disease, infection, or other known cause of hematuria, & pts w/ malignancy risk factor (above)
- **Exam:** Urethral exam, pelvic exam in ♀, DRE to assess for *BPH* in men; ✓ BP



(Derived from Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. *J Urol* 2012;188(6 Suppl):2473–2481. Copyright © 2012 American Urological Association Education and Research, Inc. With permission.)

Figure 14-3. Hematuria workup algorithm

- **Nephrology referral if:** Suspect glomerular hematuria (RBC casts, dysmorphic urine RBC, *absence* of clots), ↑ Cr, eGFR <60, new HTN, >300 mg/g UPCR (see "*Proteinuria*")
- **Urology referral if:** Urinary blood clots, unexplained AMH, malignancy risk factor
- **Pts on anticoagulation:** Same eval as if not anticoagulated (*Arch Intern Med* 1994;154:649)
- Insufficient evidence for bladder CA screening per USPSTF (*Ann Intern Med* 2011;155:246)
- **Follow-up for AMH:** In pts with negative workup but malignancy risk factors, check annual UA; If ⊖ for 2 consecutive y, then annual UAs may be discontinued

- **Patient information:** *AFP* 2005;71:135; 2006;73:1759

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:** Supersat; urine w/ stone-forming salts + predisposing metabolic factors
  - **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 Findings
Ca Oxalate > phosphate (80%)	Dehydration, diet (↑ animal protein & salt), IBD, CKD, RTA, hyperparathyroidism, sarcoidosis, obesity, gastric bypass	↑ Ca, ↑ oxalate (Ca-Ox), ↓ pH (Ca-PO_4), ↓ citrate
Uric acid (5–10%) (Pure uric acid stones are radiolucent on x-ray)	Dehydration, diet (high animal protein), gout, neoplastic disease w/ chemo, TLS, obesity, myeloproliferative d/o	↓ pH, ↑ uric acid
Struvite (Mg-ammonium phosphate)	Urease-splitting UTIs (*Proteus, Klebsiella*) → staghorn stones; indwelling catheters	↑ pH, ↑ NH_3, bacteria
Cystine	Autosomal recessive d/o → cystinuria	↓ pH

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 (frequency, urgency, dysuria) occur with distal ureteral stones or UTI; fluid intake, diet (salt, animal protein, spinach/nuts [↑ oxalate]); pts may be asymptomatic and the stone may be an incidental finding

on CT done for other reasons

Medications: Vitamin C (metabolized to oxalate), triamterene, protease inhibitors (Indinavir), furosemide (↑ calcium excretion), sulfadiazine, acyclovir

- **Exam:** Flank tenderness, fever, hemodynamic instability (S/Sx of pyelonephritis/urosepsis)

  Clinical pearl: Pts w/acute abdomen lie still, pts w/renal colic writhe in pain

- **Workup:** UA (⊕RBCs, ⊕WBCs), UCx, CBC, Chem-7; **Noncontrast low dose CT scan** (gold standard; 97% sens, 96% spec; *AJR* 2008;191:396) or KUB + U/S (~60% sens, ~90% spec) to identify stone (*Eur Urol* 2002;41:351)

  Urine strainer: Strain all urine & save passed stone for analysis

  24-h urine (×2): >6 wk after acute setting, measure Ca, PO_4, oxalate, citrate, Na, Cr, pH, K, volume; monitor response to lifestyle mod/meds to prevent recurrence

- **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)

General Treatment Measures (*Ann Int Med* 2014;161:659)	
Hydration	Increase fluid intake (>2.5 L/d) for goal UOP >2 L/d
Pain control	NSAIDs 1st line (unless preg, CKD, GI bleed, age >65 or otherwise contradind), then narcotics, APAP
Ureteral relaxation	α-Blocker (tamsulosin) > CCB
Indications for urgent urology/ED referral	AKI, >10 mm size (unlikely to pass on own); refractory pain, N/V; concurrent UTI; obstruction (esp. single or kidney transplant); staghorn; occupation (pilot, truck driver)
Surgical options	Extracorporeal shockwave lithotripsy (noninvasive), percutaneous nephrolithotomy (for large/cystine stones, staghorn), ureteroscopy (best for mid-distal ureteral stones)

Stone Specific Management	
Calcium	↓ Na diet, ↓ animal protein, ↑ dietary calcium (will ↓ oxalate absorption) though unclear role of Ca supplements. HCTZ or chlorthalidone to ↓ urinary Ca excretion
Uric acid	Urine alkalinization (K-citrate or K-bicarbonate), allopurinol
Struvite	Antibiotics to treat UTI
Cystine	Urine alkalinization, penicillamine, tiopronin

- **Medications for prevention (prescribed based on 24-h urine studies):**
  - **Potassium citrate:** Alkalinizes urine as citrate is metabolized to bicarbonate; useful for calcium or uric acid stone formers, staghorn calculi prevention, cystine stones, urine pH <6, RTA, or if urine citrate is low; 10 mEq PO TID and titrate to urine pH 6.1–7.0; 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 patients w/ cystine stones; penicillamine also may be helpful; measurement of urine cystine assists in titration of dose
  - **Calcium supplements:** If urine oxalate is high
- **Patient information:** *AFP* 2006;74:99; 2011;84:1243; *JAMA* 2012;307:2557

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)
  - **Continuous urinary incontinence:** Continuous loss of urine

usually d/t fistula

Overactive bladder (OAB): Sx of urgency, frequency, nocturia ± urge incontinence

Overflow incontinence: Incomplete bladder emptying or overdistension → dribbling

Stress urinary incontinence (SUI): Incontinence due to ↑ abdominal pressure (i.e., cough, exertion) with decreased outlet resistance

Urge urinary incontinence (UUI): Urgency + involuntary urination due to bladder overactivity/irritation

Mixed urinary incontinence (MUI): UUI + SUI; common in ♀; tx of SUI alone may not help UUI and can make worse

- **Epidemiology:** 15–30% of pts >65 y
- **Risk factors:** Age, female gender, 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, severity (# pads per day), urgency, dysuria, interference w/ daily activities/sleep, degree of bother; bowel & sexual function, hematuria, meds, fluid & caffeine consumption, voiding diary, access to bathrooms; Obstetric/Urologic/Neurologic hx or hx of pelvic surgeries
- **Exam:** Mobility; pelvic/genital exam (assess for pain, prolapse, voluntary control of pelvic floor muscles, S/Sx inflammation/infection); consider DRE for masses/prostate size/fecal impaction; check for pressure ulcers; volume status

- **Workup:** UA, consider Chem-7, UCx, UCytology, HbA1c, & B_{12} based on clinical suspicion; bladder U/S for sudden-onset UUI w/ neg UA to r/o bladder pathology (diverticulum, mass, etc.)
  - **Cough stress test (SUI):** Pt coughs w/ full bladder checked for urine leakage
  - **Postvoid residual (PVR):** Remaining urine in bladder measured by catheter or U/S after pt attempts to urinate; **PVR >200 mL** suggests obstruction or bladder weakness

Treatment (*AFP* 2005;71:315; 2006;74:2061; 2013;87:634; *JAMA* 2004;291:986; *NEJM* 2004;350:786) *See also "BPH and Lower Urinary Tract Symptoms"*

- **Pt education:** Nl urinary tract fxn, benefits/risks tx, discuss goals of tx
- **Behavior modification: 1st-line tx for all forms of incontinence;** frequent voiding while awake (q2h), prompted voiding in pts w/ dementia; bladder training (relaxation & deep breathing w/ sense of urgency to delay need to void), Kegels, pelvic floor physical therapy; wt loss (*NEJM* 2009;360:481), ↓ caffeine/EtOH, ↓ fluid intake (esp at night), smoking cessation; pads & protective garments; treat constipation & coughing; pessaries of prolapse
- **Medications** (if behavioral tx ineffective/partially effective)
  - **OAB/UUI/MUI:**
    - **Antimuscarinics:** Effects seen at 1 wk, max at 3 mo; pts should try medication for 4–8 wk before switching (can adjust dose), but most stop due to side effects (dry mouth, constipation, blurry vision, HA, dizziness, confusion); caution in elderly due to confusion, esp if dementia on cholinesterase inhibitors; **Contraindications:** urinary/gastric retention, intestinal obstruction, uncontrolled narrow-angle glaucoma, myasthenius gravis β_3 agonists: may be better tolerated/can be combined with antimuscarinics; caution if HTN
  - **SUI:** Usually d/t intrinsic sphincter deficiency (♂/♀) or urethral hypermobility (♀) ∴ unlikely to respond to antimuscarinics/β_3 agonists; tx primarily surgical
- **If behavioral tx/medications insufficient:** Re-assess (UA/UCx, post void residual, bladder diary, other diagnostic tests)

Referral to specialist (urogynecology/urology): Painful sx, fistulas, hematuria w/o UTI, neuro conditions/sx, persistent sx despite behavioral tx/medication, h/o pelvic surgery/XRT, pelvic organ prolapse, recurrent infections

Further testing: Cystoscopy, urodynamic testing,

OAB/UUI surgical tx: Intradetrusor onabotulinumtoxinA injection, peripheral tibial nerve stimulation (PTNS), sacral neuromodulation

SUI surgical tx: Periurethral bulking agents, perineal/bladder/urethral slings, artificial urinary sphincter; will not improve/may worsen urge incontinence if mixed; surgery contraindicated in ♀ who wish to have future children

Medical Therapy for Incontinence	
Antimuscarinics (Starting dose → Maximum dose)	
Solifenacin 5 mg→10 mg QD	More effective than tolterodine in urge incontinence (*Eur Urol* 2005;48:464)
Oxybutynin IR: 2.5 mg BID/TID→20 mg/d ER: 5 mg QD→30 mg QD TD: 1 patch q3d Gel: 1 mL QD	Less anticholinergic sx w/ ER & TD compared to IR; IR & ER are generic
Tolterodine IR: 1–2 mg BI 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 4 mg QD→8 mg QD	Useful in overactive bladder (*Urology* 2010;75:62) & more effective than tolterodine; nonhepatically metabolized, s/e constipation
Trospium IR: 20 mg BID ER: 60 mg QD	Renally cleared; ∴ fewer medication interactions & avoid in CKD; take on empty stomach; does not enter CNS (∴ may be better in elderly)
Darifenacin 7.5→15 mg QD	Useful in overactive bladder (*Int J Clin Pract* 2006;60:119); provides more "warning time" for urination
β3 Agonists	
Mirabegron 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
Other	
Topical estrogen 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

- **Patient information:** NAFC.org; simonfoundation.org; *JAMA* 2003;290:426; 2010;303:2208; www.urologyhealth.org/urologic-conditions/urinary-incontinence

SODIUM DISORDERS

Background (*AFP* 2015;91:299; *Am J Med* 2013;126:256; *NEJM* 2015;372:55)

- **Definition:** Na = 1° extracellular osm; disorders of serum Na are generally due to d/o of total body H_2O (regulated by thirst response & ADH), not total body Na content
  - **Urine osm:** 50 mOsm/L (no ADH) to 1200 mOsm/L (max ADH) (*NEJM* 1960;262:1306)
- **Key principle**: Hyper- or hypo-osmolality → rapid water shifts → Ds in brain cell volume → DMS, seizures
- **Epidemiology:** In pts >55 y, hyponatremia found in 7.7%, hypernatremia in 3.4%
- **General approach:** (1) acute vs. chronic (>48 h); (2) sx severity; (3) risk for neuro complications (alcoholism, malnourished, cirrhosis, older females on thiazides, hypoK); if chronic or asx, correct ≤6–8 mEq/d

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HYPONATREMIA (*Ann Int Med* 2015;163:ITC1-19; *JASN* 2012;23:1140; *NEJM* 2015;372:55)

Evaluation (*NEJM* 2000;342:158; *JAMA* 2015;313:1260; *Nephrol Dial Transplant* 2014;29S2:11)

- **History:** Fluid intake (including alcohol), diet, fluid losses (GI,

diuretics/urine output), PMHx (cirrhosis, CKD, CHF), changes in cognition

- **Exam:** Volume status, orthostatic BP, axillary sweat
- **Workup:** Chem-7 & other tests (below)
  - **Plasma osmolality:** Confirms hypotonic "true" hyponatremia; excludes rare cases of pseudohyponatremia (↑↑ TGs, paraproteinemia) & hypertonic (↑↑ glucose) hypoNa
  - **Urine osmolality:** Surrogate for ADH; U_{osm} >100 mOsm/L in an euvolemic pt w/o other pathologies is suggestive of SIADH
  - **Urine Na:** Surrogate for volume status; U_{Na} <20 → volume depletion; U_{Na} >40 → suggests euvolemia; U_{Na} unreliable if diuretic use, aldo def, metabolic alkalosis, polydipsia
  - **TSH & ACTH stimulation:** To exclude endocrinopathy

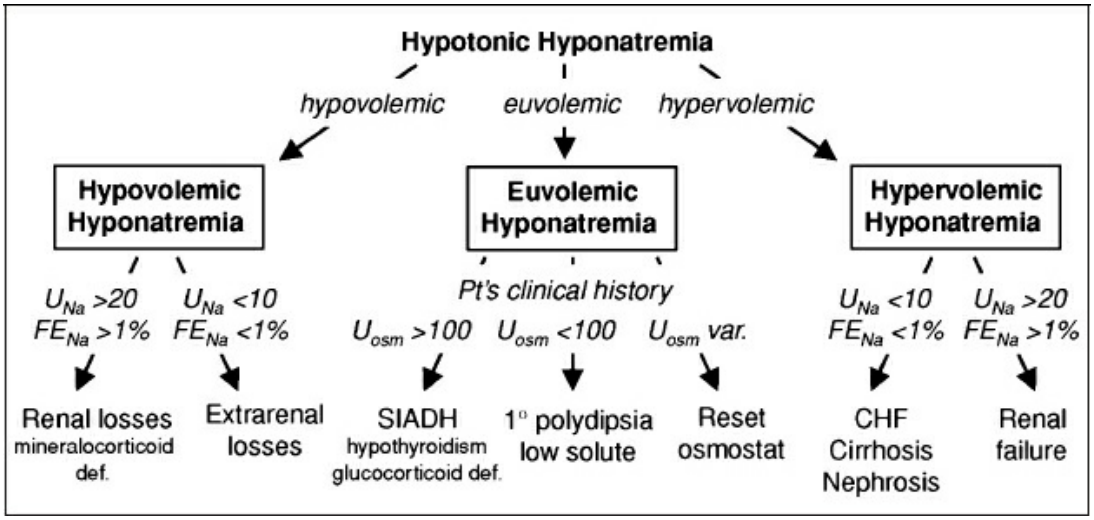

Figure 14-4. Approach to Hyponatremia

Common Outpatient Causes and Management of Euvolemic Hyponatremia	
Cause	**Management**
Medications (SIADH)	Discontinue offending agent. Includes thiazide diuretics (see below), SSRIs, opiates, NSAIDs, MDMA ("ecstasy," causes free water cravings)
Poor solute intake	"Tea & toast" diet or "beer potomania"; insufficient Na/osm intake relative to fluid intake. Rx: dietary consult, alcohol counseling,

	"beer nuts"
1° polydipsia	Associated with thought disorders like schizophrenia. Rx: ψ referral, aggressive water restriction
CNS insult	Includes tumor, ICH, pain. Requires specialist/neurology input
Malignancy	Small cell lung, pancreas, lymphoma, leukemia. Rx: oncology referral

Thiazide-Induced Hyponatremia (*Am J Med* 2011;124:1064; *Chest* 1993;103:601)

- **Epidemiology:** Affects up to 30% of pts on long-term thiazide Rx
- **Pathophysiology:** Manifests within first 1–2 wk of Rx w/ acute illness, & w/Δ in dose → ✓ Na 1 wk after starting & w/Δ in clinical status; can be euvolemic to mildly hypovolemic
- **Risk factors:** Elderly & low BMI (*QJM* 2003;96:911); alcoholics; avoid in pts w/ hx ↓ Na

Hypovolemic Hyponatremia

- **Extrarenal loss (U_{Na} <20):** Diarrhea, vomiting, poor solute intake
- **Renal losses (U_{Na} >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 if $Osm_{IVF} < Osm_{urine}$ due to free water retention
- **Adrenal insufficiency:** ↓ cortisol → hyperkalemia (due to ↓ aldosterone) + hyponatremia due to co-secretion of ADH with 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 psychiatric dz (schizophrenia) and hypothalamic dz
- **Poor solute intake (U_{osm} <100):** Solute intake insufficient to excrete daily water load; seen w/ "tea and toast" diet or "beer potomania"

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)

- **ED referral if:** Sx (AMS, seizure, coma), Na <120, hypovolemia suspected and severe vomiting/diarrhea, concern that correction will be >6–8 mEq/d (risk of osmotic demyelination/central pontine myelinolysis)
- **Hypovolemic:** Give fluids, stop diuretics & treat underlying cause
- **SIADH:** Treat underlying cause & stop offending medications
  - **Fluid restriction:** Goal of <800 mL/d (adherence difficult)
  - **Defer to specialist:** Salt tabs, demeclocycline, V2 antagonists (tolvaptan)
- **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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HYPERNATREMIA (*Crit Care* 2013;17:206; *NEJM* 2015;372:55)

Evaluation (*NEJM* 2000;342:1493)

- **History:** Must have both lack of access to free H_2O AND loss of hypotonic fluid
- **Exam:** Volume status, orthostatic BP, axillary sweat
- **Workup:** Generally can be diagnosed from Chem-7 and history
  - **Urine osmolarity:** Should be >700 due to max ADH effect
  - **U_{osm} >700** → extrarenal H_2O loss; **U_{osm} <700** → renal H_2O loss

Common Outpatient Causes and Management of Hypernatremia	
Cause	**Management**
Insensible loss in nurs home resident	Often due to fever/infection. May warrant evaluation for elder abuse/neglect
GI loss (vomiting, diarrhea)	Requires lack of access to free H_2O. May warrant evaluation for elder abuse/neglect
Medications (causing nephrogenic DI)	Includes lithium, demeclocycline, cidofovir, foscarnet, didanosine. Discontinue offending agent, refer to specialist. Li-related DI occurs in 40% long-term users, can be

	irreversible (*Nat Rev Nephro* 2009;5:27)
HyperCa, HypoK	Correct metabolic abnormalities.

Treatment (*J Clin Endocrinol Metab* 2012;97:3426)

- **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; evaluate for elder abuse/neglect if appropriate
- **Central DI:** Refer to endocrine for eval (H_2O deprivation test) & possible Rx: desmopressin
- **Nephrogenic DI:** Refer to nephrology; consider d/c Li or amiloride if related to Li (*CJASN* 2008;3:1324)

POTASSIUM DISORDERS

Potassium Content in Foods Recommended RDA for K is 4700 mg/d (~120 mEq). Low K diet is 2500 mg/d (~60 mEq)	
High (>400 mg/serving)	Tomato, tomato sauce, potato, sweet potato, French fries, banana, broccoli, cantaloupe, orange juice, apricot, beets
Mod. (200–400 mg/serving)	Strawberries, almond, chocolate, milk, canned soup, prunes, figs, whole grains
Low (<200 mg/serving)	Turkey, tuna, raisins, apple, rice, white grains (including pasta), cucumber, coffee, onion, cranberry juice, grapes, most berries

- **Patient information:** https://www.kidney.org/atoz/content/potassium
  Web search for "potassium" and food item yields K content in mg or mEq (39 mg = 1 mEq)

HYPOKALEMIA (*AFP* 2015;92:487; *NEJM* 2015;373:60)

Causes of Hypokalemia (*Ann Int Med* 2009;150:619)	
General Mechanism	**Specific Etiologies**
Pseudohypokalemia	CML, CLL (WBC >10^5/μL → leukocyte uptake → falsely ↓ K)

Intracellular shift (most common)	↑ Insulin (including hyperalimentation), β_2-agonists, caffeine, thyrotoxicosis, familial periodic paralysis, increased hematopoiesis (esp AML, megaloblastic anemia), alkalemia
GI loss	(↓ U_K): Diarrhea, laxative abuse. Vomiting manifests as renal loss due to 2° hyperaldosteronism
Renal loss	(↑ U_K): Divided into normo/hypotensive (diuretic, ↓ Mg, Bartter's or Gitelman's [rare]) and hypertensive (1° or 2° hyperaldosteronism). ↑ Aldosterone activity (primary hyperaldosteronism, renovascular disease, Cushing's, licorice, chewing tobacco) Metabolic acidosis (proximal and some distal RTAs) Hypomagnesemia (alcoholism, prolonged PPI)
Medications and substances	Diuretics (thiazides (10–40% of treated pts)), laxatives, penicillins (especially in high doses), β_2-agonists, insulin, theophylline, chemotherapy, alcohol, caffeine, cola (>3 L/d)

UK	Metabolic Acidosis	Metabolic Alkalosis
↑	DKA, type 1 (distal) or type 2 (proximal) renal tubular acidosis	Mineralocorticoid excess, renovascular dz, diuretic use (after diuretic has worn off)
↓	Lower GI loss	Vomiting, diuretic use, laxative abuse

Evaluation (*AJKD* 2005;45:233)

- **History:** Medication and diet review (including OTCs & wt loss agents), PMHx (esp eating d/o, alcohol intake), FHx, GI fluid loss; sx rare unless K <3 mEq/L, include muscle weakness, cramping, constipation, fasciculations, tetany
- **Workup:** Repeat K if reported as hemolyzed or suspect lab artifact; ✓ Mg, CK, plasma renin:aldosterone (if HTN present), U_K, U_{Cr}. 24 h U_K > 30 mEq or U_K:U_{Cr} >13 mEq/g (1.5 mEq/mmol) creatinine suggests renal loss.

  ECG changes: May be normal; ↑QT, T wave flattening, U waves, ectopy, AVB, VF

Management

- **Remove offending agents**
- **K supplementation:** May also need to replete Mg, ↓↓ Mg (<1.2 mEq) hard to replete orally

  K-rich foods: See above

  Liquid/powder potassium: Inexpensive, rapid, many pts dislike

taste

Slow-release K: Wax/microencapsulated formulation; more expensive

K-sparing diuretics: Spironolactone, eplerenone

- **When to refer:** To ED if K <2.5 mEq/L, esp if pre-existing CV disease or ECG changes; To nephrology if persistent low K despite repletion; concurrent hypertension (suggests hyperaldosteronism state, see *"Hypertension"*)

HYPERKALEMIA (*JAMA* 2015;314:2405; *NEJM* 2015;373:60)

Evaluation (*Am J Med* 2009;122:215)

- **History:** Medication and diet review, PMHx (esp DM, CKD, cirrhosis, CHF), FHx; sx rare unless K >6.5–7 mEq/L, include muscle weakness, nausea, paresthesias
- **Workup:** Repeat K, especially if reported as hemolyzed or suspect lab artifact, Chem-7. Hyponatremia and hyperkalemia are suggestive of adrenal insufficiency

ECG: Can be normal; If K >6 mEq/L, can have peaked T waves, ↑ PR, ↑ QRS, loss of P wave, sine wave, VF, cardiac arrest

Causes of Hyperkalemia	
General Mechanism	**Specific Etiologies**
Pseudohyperkalemia	Gross hemolysis of sample, massive ↑ WBC or PLT, exercise (i.e., 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
Decreased renal secretion	Advanced CKD (GFR <15), CHF/cirrhosis, tubulointerstitial dz (DM, sickle cell, SLE, amyloid), hypoaldosteronism, Addison disease, congenital adrenal hyperplasia, type IV renal tubular acidosis, adrenal insufficiency (in association w/ ↓ Na.
Medications and substances	NSAIDs, ACEIs/ARBs (occurs in ~10% of pts), K-sparing diuretics, β-blockers, TMP-SMX, digoxin, heparin, pentamidine, calcineurin inhibitors, transfusions, CsA.

- **Most common outpatient causes:** CKD with dietary indiscretion (esp in DM), meds including ACEI/ARB, K-sparing diuretics, NSAIDs, TMP-SMX

Management

- **Dietary counseling:** Nutrition referral, see “Potassium Content in Foods” above
- **Medication review:** In advanced CHF, survival benefit of ACEI/ARB & aldosterone antagonists → K ≤5.5 acceptable (*Expert Opin Pharmacother* 2011;12:2329); if K ↑ >5.5 on ACEI/ARB/aldosterone antagonist, ↓ dose or implement measures below; If on combination, d/c 1 & recheck K; Avoid NSAIDs, COX-2 inhibitors, other meds which ↑ K
- **Diuretics:** Thiazides (GFR >30) or loop (GFR <30)
- **Correct metabolic acidosis: Na** bicarbonate in pts w/ CKD
- **K-binding resins** (Kayexalate, Patiromer, Na zirconium)**:** Binds K in GI tract (*NEJM* 2015;372:211; 222); s/e include N/V, constipation, diarrhea, ? rare bowel necrosis w/ Kayexalate (*AJKD* 2012;60:409)
- **When to refer to ED:** Any K >6.5; acute K >6; K >5.5 w/ sx; unable to make safe outpt plan

BREAST HEALTH

Breast Pain (Mastalgia)

Background (*JGIM* 2012;27:817; *Mayo Clin Proc* 2004;79:353; *Clin Evid* 2011;01:812)

- Most common breast sx prompting consultation to PCP (up to 70% ♀ pts), premenopausal > postmenopausal, highest in pts 30–50 y; most commonly due to benign etiology: 0–3% pts w/ isolated pain found to have CA; localized pain = only presenting sx in <15% breast CA pts (*AFP* 2000;61:2371); no histologic correlations; 50–90% asx women have fibrocystic changes
- **Classification:** Helpful to organize differential (*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; resolves spontaneously in 20–30% pts, but high recurrence risk (60% pts) (*Clin Evid* 2011;01:812)
  - **Noncyclic mastalgia:** *Unrelated* to menstrual cycle or in postmenopausal pts; typically unilateral, sharp/burning, localized, most common in pts 40–50 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; often responds poorly to Rx but spontaneously resolves in ~50% pts (*NEJM* 2005;353:275; *Clin Evid* 2011;01:812)
- **Differential diagnosis:** Extramammary causes of chest pain include costochondritis, Tietze syndrome, MI, PNA, pleural pain, rib fx, zoster

Evaluation (*AFP* 2000;61:2371; *Obstet Gynecol Clin N Am* 2013;40:459)

- **History:** *Pain:* Type, location, relationship to menses, bi- vs. unilateral, radiation, duration, resolution, erythema; *Exacerbating factors:* Irregular menses, stress; *Medications:* esp OCPs, HRT, spironolactone, SSRIs; infectious s/sx, prior breast infection/abscess, recent surgery or piercing, lactation, h/o chest wall trauma (including remote); smoking (strongly assoc w/ periductal mastitis)
- **Exam:** Thorough breast exam to exclude mass vs. possible infection; costochondral/chest wall palpation (including w/ pt lying on side vs. leaning forward); palpable cord-like SC induration suggests Mondor disease
- **Red flags:** H/o rapid onset breast erythema, edema, nipple crusting/retraction/inversion ± palpable mass or regional LAD strongly suggestive of inflammatory breast CA → prompt diagnostic U/S + mammography, bx if indicated (*Ann Oncol* 2011;22:515)
- **Imaging** (*AFP* 2012;86:343)
  - **Diffuse pain:** Pts >40 y → mammogram if none in past 12 mo, consider for pts >30 y if ⊕ RFs for breast CA (limited data to support)
  - **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)
  - **Palpable mass:** Mammogram + targeted U/S, consider referral to breast surgeon (see *"Breast Mass"*)
  - **Mastitis (lactational or periductal):** U/S for possible abscess if no resolution w/ po abx

Treatment (*AFP* 2000;61:2371; *Obstet Gynecol Clin N Am* 2013;40:459)

- **General approach: Reassurance** for the majority of pts w/ no abnormality on exam ± imaging, recommend regular exercise; review nl breast physiology; Rx indicated only if pain interferes w/ activity or lasts several d/mo (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 (*NEJM* 2005;353:275)

- **Initial treatment: NSAIDs** (topical diclofenac > po), 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 (menorrhagia, acne, weight gain, voice deepening, hirsutism, muscle cramps); tamoxifen, bromocriptine have shown efficacy, former preferred due to more favorable s/e profile despite ↑ risk DVT, endometrial CA, consider use in consultation w/ specialist (*J Reprod Med* 2005;50:933; *Clin Evid* 2011;01:812)

Nipple Discharge

Background (*AFP* 2012;86:343; *NEJM* 2005;353:275; *Obstet Gynecol Clin N Am* 2013;40:459)

- Second most common breast complaint after breast pain; benign in 97% cases, but pathologic discharge 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 pregnancy vs. weaning
  - *Galactorrhea:* Milk production unrelated to pregnancy/nursing, occurs in response to inappropriate stimulus, e.g., prolactinoma (*see "Hyperprolactinemia"*)
  - *Physiologic:* Nl variant, originates from multiple ducts; up to 80% of reproductive age ♀ able to express small amount of d/c w/ compression
  - *Pathologic:* D/c that is spontaneous, unilateral, bloody, serosanguineous, watery, or assoc w/ mass; most common etiologies = intraductal papilloma > duct ectasia > breast CA (5–15% pts) > infection

Evaluation (*AFP* 2012;85:1073; *AFP* 2012;86:343)

- **General approach:** Exclude lactation, differentiate between physiologic vs. pathologic d/c, based on hx/PE
- **History:** *Discharge:* Unilateral vs. bilateral, spontaneous vs. only w/ compression, color, sanguinous or not, associated mass

  Gyn hx: Menstrual hx, pregnancy, recent childbirth, fibrocystic / other prior breast disease

  Medical hx: Chest wall trauma, h/o breast surgery, hypothyroidism, pituitary disease

  Meds: OCPs, estrogen; verapamil, methyldopa, spironolactone; cimetidine, metoclopramide; SSRIs, MAOIs, TCAs, antipsychotics; opioids

  ROS: Endocrine ROS for thyroid disease, pituitary tumor (visual field defect, HA, amenorrhea, s/sx acromegaly)

  Social hx: Cocaine, heroin, methadone (assoc w/ galactorrhea); smoking (assoc w/ duct ectasia)

  Family hx: Breast, ovarian CA
- **Exam:** Thorough breast exam: inspect discharge, differentiate single vs. multiple duct involvement; inspect/**palpate for associated mass** or chest wall lesions (prior breast surgery, burns, zoster); also HEENT: Visual field testing, thyroid exam
- **Red flags:** Pathologic discharge, breast mass; erythema/dermatitis of nipple suggest Paget disease of the breast → refer for bx and mammogram
- **Initial studies:**

  Physiologic: Repeat PE in 3–4 mo; consider mammogram in pts >35 y

  Pathologic: Examine d/c for occult blood, obtain **dx mammogram** (retroareolar magnification views may be helpful) +/– subareolar U/S followed by image-guided bx if abnl; refer for bx if BI-RADS 4–5, consider ductography if BI-RADS 1–3; cytology not recommended (poor Se/Sp, ↓ cost-effectiveness)

  Galactorrhea: Check β-hCG, TSH, PRL; consider Cr (see *"Hyperprolactinemia"*)

Treatment (*AFP* 2000;61:2371)

- **Physiologic:** If exam ± mammogram nl → reassure, counsel to avoid nipple stimulation and to report any spontaneous d/c; if sx

persistent/bothersome, refer for duct excision

- **Pathologic: Refer all pts** w/ spontaneous or unilateral d/c to surgery for terminal duct excision
- **Galactorrhea: Stop potentially offending medications**; if TSH or PRL abnl, Rx as indicated (see *Endocrine section*); 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** (especially in upper outer quadrant) very common, as nl glandular breast tissue is nodular; **fibroadenomas** very common, including in younger pts
- **Cysts:** Common masses in premenopausal women >40 y; infrequent in younger pts or postmenopausal pts not on HRT; *Risk factors:* Late menopause, HRT, low BMI (*NEJM* 2005;353:275)
- **Dominant mass:** Single mass differing from surrounding tissue and from corresponding area in contralateral breast, persisting throughout menstrual cycle; may be discrete or poorly defined
- **Differential diagnosis:** Fibroadenoma, phyllodes tumor, hamartoma, fibromatosis, lactating adenoma, 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, duration, changes in size/character, associated pain, fluctuations w/ menstrual cycle (suggests cyst); h/o prior cyst at site; review RFs for breast CA (see "Breast Cancer Screening" subsection below)
- **Exam:** Thorough breast exam, including visual inspection (asymmetry, d/c, masses, skin changes, nipple retraction) and palpation of entire breast, axillae, supraclavicular areas b/l; document mass location (clockface & distance to nipple), size, texture, mobility

- **Red flags:** Associated skin changes; hard, fixed/immobile, or poorly defined mass
- **Initial studies:** Diagnostic mammogram + U/S

Management (*AFP* 2000;61:2371; *NEJM* 2005;353:275; *AFP* 2005;71:1731; *AFP* 2012;86:343)

- **Communication:** Breast masses are source of anxiety for clinicians and pts; be open about potential for false ⊕ / ⊖ results; encourage pts to f/u promptly w/ persistent concerns; establish a plan for f/u and discussion of test results; document discussion/plan
- Nl mammogram misses 10–15% palpable malignant breast masses, thus ⊖ test does not exclude CA
- MRI not usually recommended, given poor Sp compared w/ 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%
- **No mass palpable:** Reassure, recommend awareness of changes in breasts w/ prompt reporting (SBE controversial), confirm screening up-to-date, repeat exam in 2–3 mo
- **Irregularity** (i.e., vague nodularity/asymmetry) noted but *no clear dominant mass*

  Women <30 y of average risk: Directed U/S

  Women >30 y or high risk: Diagnostic mammogram w/ f/u midcycle exam in 1–2 mo, consider directed U/S (preferred in pt w/ dense breasts); refer for bx if persistent (even if imaging ⊖)
- **Palpable mass w/ benign features:** Diagnostic mammogram + directed U/S; consider FNA for pts with low pretest probability of CA (PE + imaging + FNA = "triple test," >99% likelihood of benign mass if all 3 ⊖)
- **Palpable mass w/ suspicious features:** Diagnostic mammogram + directed U/S, followed by image-guided bx (core needle biopsy vs. excisional) (see Figure 15-1)

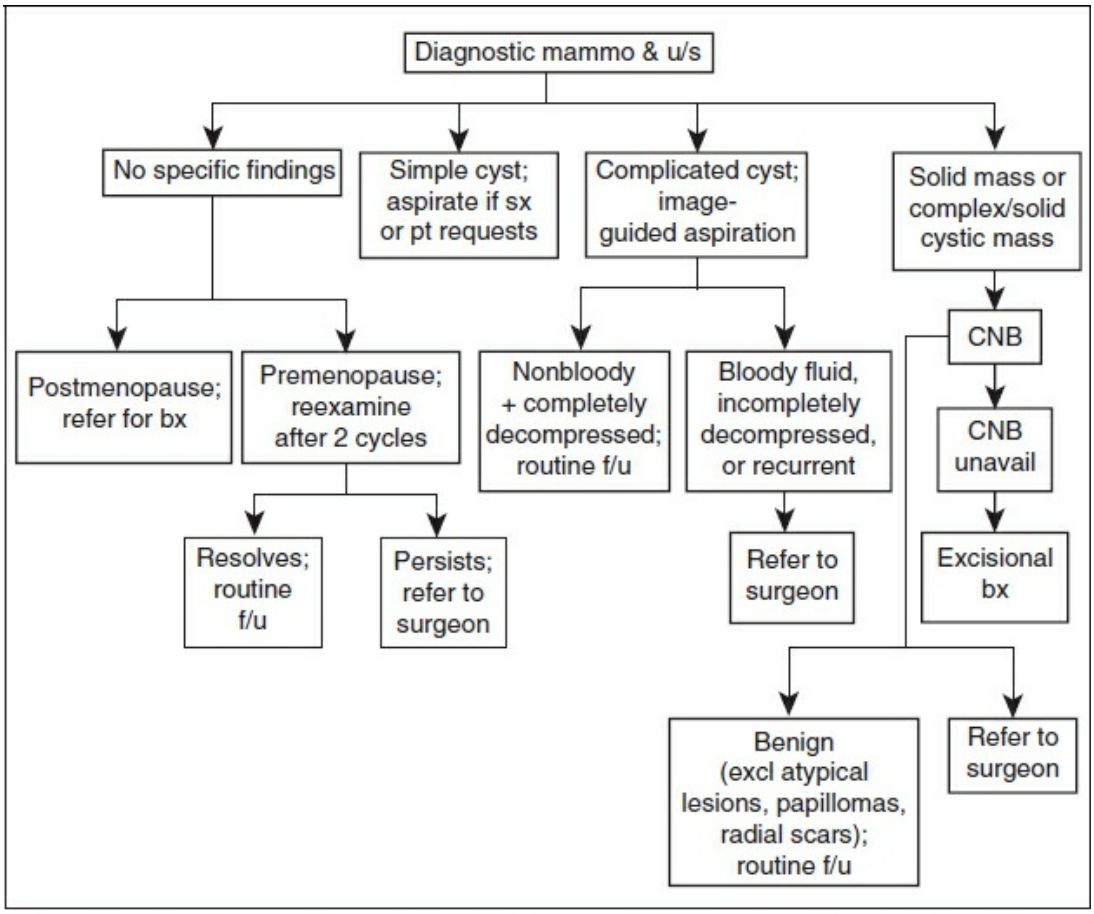
Interpretation (*AFP* 2012;86:343)

Imaging Results and Management	
BI-RADS* Classification	**Management**
0 = Incomplete assessment	Order additional imaging (more views vs. U/S)
1 = Negative findings	Consider further imaging +/– specialist referral for persistent palpable mass at rpt PE in 1–2 mo
2 = No e/o malignancy	Routine f/u if imaging result c/w clinical findings
3 = <2% risk of malignancy	CNB if clinical concern for CA Rpt mammogram +/– U/S q6mo × 2 y to ensure stability
4 = Suspicious abnormality	CNB; refer to specialist
5 = >95% risk of malignancy	CNB; urgently refer to specialist
6 = Bx-proven malignancy	Ensure completion of Rx and appropriate f/u

**BI-RADS* = *Breast Imaging Reporting and Data System*

Further Evaluation (*Obstet Gynecol Clin N Am* 2013;40:459)

- **Cysts:** Common incidental finding on mammography, no further w/u required
- **Proliferative lesions w/o atypia:** Fibroadenomas, intraductal papilloma do not require further w/u, refer for excision only if bothersome; refer pts w/ radial scar for excisional bx; consider excisional bx for pseudoangiomatous stromal hyperplasia (PASH) if imaging suspicious for secondary process
- **Proliferative lesions w/ atypia:** Atypia is assoc w/ ↑ risk of breast CA; includes atypical lobular hyperplasia (ALH), atypical ductal hyperplasia (ADH), flat epithelial hyperplasia → excisional bx given ↑ risk carcinoma in situ, consider ↑ risk in screening decisions



(Adapted from https://www.rmf.harvard.edu/Clinician-Resources/Guidelines-Algorithms/2014/Breast-Care-Management-Algorithm. Copyright © The Risk Management Foundation of the Harvard Medical Institutions Incorporated. With permission.)

Figure 15-1. Breast care management algorithm

BREAST CANCER SCREENING

Background (*AFP* 2008;78:1361; *AFP* 2012;86:343; *AFP* 2013;87:274; *JAMA* 2014;311:1327)

- Breast cancer is the 2nd leading cause of CA-related deaths among US ♀; cumulative lifetime risk ~1:8; mortality ↓ over past 30 y, although how much to attribute to screening vs. improved tx remains uncertain (*NEJM* 2016;375:1438)
- **Risk factors:** ↑ age, female sex, overweight/obesity, white race, Ashkenazi Jewish heritage, dense breast tissue, h/o prior breast bx,

h/o breast or ovarian CA, h/o XRT, 1st-degree relative w/breast or ovarian CA, BRCA1/BRCA 2, menarche <12 y, menopause >55 y, first delivery >35 y, nulliparity, EtOH >1 drink/d, current/prior use of HRT or OCPs

Evaluation

- **Risk assessment:** Assess 5 y and lifetime risk for all pts, e.g., Breast Cancer Risk Assessment Tool; avg risk ≤15%, mod risk = 15–20%, high risk ≥20%: high-risk patients include those w/ strong FHx, including BRCA mutations, h/o chest XRT age <30 y, h/o lobular carcinoma in situ (LCIS) or atypical hyperplasia (ADH, ALH)

Screening Modalities (*AFP* 2013;87:274; *Ann Int Med* 2016;164:268)

- **Screening mammography:** Primary screening modality; assoc w/ ↓ breast CA mortality and also ↑ overdiagnosis: risk–benefit profile varies by age, screening interval, individual risk and preferences (see table)

Estimate of Benefits & Harms of Annual Mammography		
If 1000 women at this age underwent *annual* mammography for 10 years…		
Age	**Benefits**	**Harms**
40	0.1–0.6 women will avoid dying from breast cancer	510–690 will have a "false alarm" requiring further tests (for 60–80, this will include biopsy) 0–11 will be overdiagnosed and treated for breast CA
50	0.3–3.2 women will avoid dying from breast cancer	490–670 will have a "false alarm" (for 70–100 this will include biopsy) 3–14 will be overdiagnosed and treated for breast CA
60	0.5–4.9 women will avoid dying from breast cancer	390–540 will have a "false alarm" (for 50–70 this will include biopsy) 6–20 will be overdiagnosed and treated for breast CA

Adapted from *JAMA Intern Med* 2014;174:448

- **Ultrasound:** No data to support U/S screening alone; mammogram + U/S in high-risk ♀ w/ dense breast tissue → ↑ Se but also ↑ false ⊕; no clear benefit from automated breast U/S vs. hand-held U/S in pts w/ dense breasts
- **Breast self-awareness:** Counsel pts to recognize nl appearance/feel of their breasts and promptly report any changes;

formal/regular breast self-exams no longer recommended in avg-risk pts, given ↑ false ⊕ and no ↓ in breast CA dx mortality rates (*JNCI* 2002;2:1445)

- **Clinical breast examination (CBE):** Variable evidence on Se/Sp of CBE in conjunction with screening mammography but no clear ↓ in mortality; USPSTF reports insufficient evidence, ACS no longer recommend screening breast exam, ACOG recommends as part of annual exam
- **MRI:** Controversial, generally not recommended in avg-risk pts; ↑ Se but also ↑ false ⊕; consider as adjunct to mammogram in pts w/ high lifetime risk of breast CA ⊕/⊖ dense breast tissue
- **Digital breast tomosynthesis (DBT):** Controversial, generally not recommended; in conjunction w/ mammogram, may ↑ Sp and ↓ false ⊕/recall rates for pts w/ dense breasts but ↑↑ radiation exposure

Management (*AFP* 2013;87:274; *Med Clin North Am* 2015;99:451; *JAMA* 2015;314:1615)

- **Shared decision-making:** *All* decisions assoc w/ screening (to screen or not, and if so at what age and what interval) present risks and benefits; incorporate individual risk of breast cancer as well as individual values into screening plan and then document plan; see "Disease Screening"
- Individual guidelines are somewhat controversial (see *NEJM* 2012;367:e31 "Clinical Decisions" for divergent expert opinion); generally, consensus that for women of average risk, screening mammogram be offered to those 50–74 y; screening mammogram q2y in women 50–74 y is cost-effective; consider local practice patterns in light of medicolegal risk (*JAMA* 2013;309:2555)

Selected Breast Cancer Screening Guidelines for Average-Risk Patients

	USPSTF	ACOG	ACS
Avg risk, 40–49y	Consider mammogram q2y per individual values, RFs, esp if ⊕ FHx (Grade C)	Discuss benefits/harms of screening; mammogram q1y in pts who desire screening	Consider mammogram q1y for pts 40–44 y; start mammogram q1y at 45 y
Avg risk, 50–	Mammogram q2y (Grade B)	Mammogram q1y	Mammogram q1y for pts 50–54 y; consider transition to q2y at 55

74 y			y
Avg risk, ≥75y	Insufficient evidence to continue screening (Grade I)	Discuss benefits/harms of screening, in conjunction w/ LE, comorbidities	Continue mammogram q1–2 y for pts in good health with LE ≥10 y

- **High-risk patients:** Offered enhanced screening, ACOG recommends SBE, CBE q6m, annual mammogram + MRI, and risk reduction tx starting at age 40; ACS recommends annual mammogram + MRI starting age 20–40 per pt risk factors (insufficient evidence for pts w/LCIS, ALH, ADH, or personal hx breast CA) (ACS, *JAMA* 2015;314:1599; ACOG, *Obstet Gynecol* 2011;118:372)
- **When to refer:** High-risk patients often **start screening <40 y**; refer to specialist for determining optimal screening plan/modality and for consideration of risk reduction methods (SERMs/aromatase inhibitors, prophylactic b/l mastectomy, BSO) (*Curr Opin Obstet Gyn* 2015;27:6); those w/ suspected or confirmed genetic BRCA mutations should also be referred to genetics counselor

CERVICAL CANCER SCREENING

Background

- **Cervical cancer:** Malignancy of squamous (most common) or glandular cervical cells; progressive, disease w/ predictable course involving clearly defined precursor lesions → well suited for screening; incidence in US ↓ >50% since screening began (www.seer.gov)
- **Epidemiology:** ~12,200 new diagnoses of invasive cervical CA & >4,200 cervical CA deaths annually in US; incidence/mortality rates ↑ in ethnic minorities (Hispanics/Latinos > African-Americans > Native Americans > whites), women living in rural areas or poverty, HIV⊕; 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) (*Ann Int Med* 2012;156:880)

- **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 (all types) in US women 20–34 y ranges 40–58%, ↓ w/ age; since introduction of vaccine, ↓ in 4vHPV type prevalence in women <24 y but no change in older pts (*Pediatrics* 2016;137:e20151968)
- **Risk factors for 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:** in ↑ order of severity
  - *ASC-US:* Atypical squamous cells of undetermined significance
  - *ASC-H*: Atypical squamous cells of high grade
  - *LSIL:* Low-grade squamous intraepithelial lesion; usually assoc w/ active HPV, mild dysplasia; typically corresponds to cervical intraepithelial neoplasia (CIN)-1 on histology
  - *HSIL:* High-grade squamous intraepithelial lesion; moderate/severe dysplasia; CIN2–3 or carcinoma in situ on histology
  - *Squamous cell carcinoma*
- **Glandular cell:** in ↑ order of severity; (1) Atypical glandular cells (AGC): Endocervical, endometrial, NOS or "favor neoplastic"; (2) Endocervical adenocarcinoma in situ; (3) Adenocarcinoma

Screening Modalities

- **Cytology** (Papanicolaou smear): Sampling of endocervical/ectocervical cells; 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 frequency to prevent overdiagnosis & overtreatment of HPV-related abnormalities that would clear spontaneously
- **Co-testing:** HPV & cytology for 1° screening; preferred screening strategy of ASCCP & ACOG **for women >30 y** (not appropriate strategy for women <30 y)
- **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

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 (preferred) **or** Pap q3y (cytology alone)
Over 65 y	Stop screening **if** pt has had adequate screening & ≥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, h/o cervical CA, h/o in utero DES exposure	Annual screening Pap indefinitely for HIV, some ↓ frequency w/co-testing or nl prior exams (see "HIV Primary Care" in "HIV/AIDS")

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
- If screening using Pap alone ⊕/⊖ reflex HPV, see "Selected Cytology Results and Follow-Up"; if screening using co-testing (pts >30 y only), see "Selected Cotesting Results and Follow-Up"

Selected Cytology Results and Follow-Up	
Result	**Management**
Unsatisfactory (inadequate sample)	Repeat Pap
Negative but lacking endocervical cells	Routine screening; no early repeat
Negative for intraepithelial malignancy (“normal”)	Routine screening, as above
ASC-US in women 21–24 y	Repeat cytology at 12 mo **(preferred)** or reflex HPV **Reflex HPV Testing:** If HPV ⊖ → routine screening If HPV ⊕ → repeat cytology at 12 mo **12-mo cytology:** Negative, ASC-US, or LSIL → repeat in 12 mo ASC-H, AGC, HSIL → colposcopy **24-mo cytology:** Negative × 2 → routine screening ≥ASC-US → colposcopy
ASC-US in women >24 y	Reflex HPV **(preferred)** or repeat cytology at 12 mo **Reflex HPV testing:** If HPV ⊖ → cotest at 3 y If HPV ⊕ → refer for colposcopy If reflex HPV unavailable → repeat cytology at 12 mo **12-mo cytology:** Negative → resume routine screening ≥ASC-US → colposcopy
ASC-H, any age	Refer for colposcopy
LSIL in women 21–24 y	Repeat cytology at 12 mo **12-mo cytology:** Negative, ASC-US, LSIL → repeat in12 mo ASC-H, AGC, HSIL → colposcopy **24-mo cytology:** Negative × 2 → routine screening ≥ASC-US → colposcopy
LSIL in premenopausal women >24 y	If no HPV test or HPV ⊕ → colposcopy If HPV ⊖, repeat cotesting at 12 mo preferred, but colposcopy acceptable **12-mo cytology:** Negative **&** HPV ⊖ → resume routine screening, HPV ⊕ and/or ≥ASC-US → colposcopy
LSIL in postmenopausal women	Refer for colposcopy **or** Repeat cytology at 6 mo & 12 mo **or** HPV test: If ⊕, refer to colposcopy; if ⊖, repeat cytology in 12 mo

LSIL in pregnant women	Refer for colposcopy
HSIL	Refer for colposcopy
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)

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: If ⊕ → colposcopy If ⊖ → repeat cotesting at 12 mo **Or:** Repeat cotesting at 12 mo: If both ⊖ → repeat cotesting at 3 y 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 mo (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

When to Refer

- **Colposcopy:** Identifies macroscopic changes in cervical epithelium contour, color, & vasculature assoc w/ malignancy/premalignancy; accuracy varies w/ experience of colposcopist
- **Dysplasia:** PCP can provide general education re: "what to expect": *CIN1:* Managed expectantly **if** preceded by low-grade lesion **or** if present for <24 mo; *CIN2–3:* Managed w/ ablative (e.g., cryotherapy/laser) or excisional (e.g., loop electrosurgical excision) tx
- **Cervical CA:** Management depends on staging, comorbidities,

desire to preserve fertility

MENOPAUSE

Background (*Obstet Gynecol Clin North Am* 2011;38:425)

- **Menopause:** Permanent cessation of menstruation 2/2 loss of ovarian follicular activity, defined retrospectively after 12 consecutive months of amenorrhea w/o other cause
- **Perimenopause:** Defined by the 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 on average 2 y earlier, typical US range 40–60 y
- **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

Manifestations

- **General:** In longitudinal studies adjusted for confounders, only vasomotor sx, vaginal sx, and sleep disturbances consistently assoc w/ menopausal transition (*NEJM* 2006;355:2338)
- **Vasomotor instability (hot flashes/flushes):** 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 spontaneously improve w/in 2–3 mo** (30–50% pts) vs. w/in 4–5 y (85–90% pts); sx continue for years in only 10–15% pts (*Ann NY Acad Sci* 1990;592:52)
- **Genitourinary syndrome of menopause:** Formerly known as atrophic vaginitis; constellation of vaginal, urinary, and sexual sx assoc w/ menopause

  Vaginal sx: ↓ estrogen → vaginal atrophy, ↓ secretions; incidence

from 30% (early postmenopausal) to 47% (late), as sx tend to ↑ w/ aging (*Obstet Gynecol* 2000;96:351)

Urinary sx: Vaginal fluid pH ↑ after menopause → ↑ UTI-related enteric organisms, ↓ estrogen → vaginal shortening; no clear correlation w/ menopausal transition (*Obstet Gynecol* 2000;96:351)

Sexual sx: Very common but underreported; multiple manifestations, including dyspareunia, ↓ desire, ↓ arousal, and/or difficulty w/ orgasm; assoc w/ ↓ satisfaction w/ relationships and sexual function; emphasize ↓ desire is expected and that contributing factors can be individually addressed (see "Treatment," below)

- **Psychological sx:** Menopause well characterized as being a high-risk period for development or worsening of depression (*Women's Health* 2015;11:397)

Evaluation

- **General approach:** Dx is primarily clinical, based on hx and PE
- **History:** Assess for menopause vs. features suggestive of alternate cause for AUB / amenorrhea (e.g., pregnancy, ↑ PRL, PCOS, meds; see *"Menstrual Disorders"*)

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: Systemic disease that might impact Rx choice (CAD, breast/uterine cancer, DVT, acute liver disease)

FHx: Any h/o early menopause; age of menopause in mother/sisters closely correlated (*Menopause* 2008;15:940)

Other causes of vasomotor instability: EtOH consumption; panic attacks; carcinoid; dumping syndrome; thyroid dysfunction; pheo; opioid w/d; use of nitrates, niacin, CCBs, GnRH agonists, antiestrogens

- **Exam:** Pelvic exam (vaginal pallor, dryness, ↓ mucosal rugosity = atrophy; r/o trauma, infxn); consider HEENT, neck, abdominal, skin exams if hx suggests alternate etiology of vasomotor instability

- **Labs: In ♀ 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); ✓FSH in younger ♀ w/ vasomotor sx s/p hysterectomy; ✓β-hCG if younger pts: >1% annual unintended pregnancy rate in women 40–44 y (*Contraception* 2011;84:478)

Menopausal Transition Stages (*NEJM* 2006;355:2338)			
	Premenopause	**Menopausal Transition**	**Postmenopause**
Menstrual cycle	Regular →	Variable (↑ missed cycles/y) →	absent
Hot flashes (%)	10 → 40 →	65 → 50 → 10–15	
Estradiol (pg/mL)	50–200 →	40 → 0–15	
FSH (mU/mL)	10[a] →	≥10[a] → >100	
LH (mU/mL)	10[a] →	≥10[a] → >100	

[a]On d 2–4 of menstrual cycle.

Treatment (*NEJM* 2006;355:2338; *AFP* 2016;94:884)

- **General approach:** Intent of treatment is to manage bothersome sx; not all women desire treatment for menopausal symptoms; those who do often seek Rx for vasomotor/vaginal sx; counseling/education important part of Rx; sx-based approach below

Symptom-Based Approach to Menopausal Symptoms	
Symptom	**Treatment**
Vasomotor	**Notes:** Subjective improvement w/ placebo alone; counsel pts that for most pts, duration of sx is limited to a few months **Behavioral modifications:** Dress in layers, ↓ ambient temp, ↓ EtOH, healthy diet/exercise **Hormone replacement therapy:** for mod–severe disease, can ↓ freq of flashes by 80–95%, regardless of type/route, w/ dose-related response (see *"Estrogen Therapy,"* below) **Alternate tx:** SSRI/SNRIs (esp. paroxetine); gabapentin/pregabalin (sedating s/e), no clear benefit from clonidine **CAM:** *Best evidence*: Soy, sage, black cohosh, yoga *Mixed evidence*: acupuncture *Poor evidence:* DHEA, dong quai, evening primrose, ginseng, kava, St. John's wort, valerian, wild yam, or vit E
Sexual	**Notes:** Pts w/ more frequent sexual activity ↓ likely to develop

	vaginal atrophy; may refer for vaginal dilators if medical Rx contraindicated **Vaginal estrogen:** Sx improve in 80–100% pts, minimally ↑ serum levels; no need to add progestin w/ std dosing; PO generally **not** indicated for isolated vaginal sx **Vaginal lubricants/moisturizers: Replens** (moisturizer) shown to have similar sx relief as vaginal estrogens **Alternate Tx:** Ospemifene: SERM approved for dyspareunia 2/2 vulvovaginal atrophy; *Contraindications:* estrogen-dependent neoplasia, h/o VTE, stroke, MI, or breast CA; *s/e:* hot flashes, vaginal d/c, muscle spasms Bupropion**:** ↑ Libido in premenopausal pts (no studies in perimenopausal pts)
Urinary	**PV estrogen:** May ↓UTI recurrence **Estrogen (PO or PV):** may ↓ subjective urinary incontinence sx, no clear impact on urodynamic testing
Psych	**Notes:** Fatigue, ↓ concentration/memory likely 2/2 poor sleep, may ↓ w/ Rx for vasomotor sx **Estrogen:** May ↓ dysphoria, ineffective for 1° depression **SSRI/SNRIs:** May be helpful, caution re: ↓ libido

(naturaldatabase.therapeuticresearch.com; *Am J Ob Gyn* 2016;215:704; *AFP* 2014;90:338; *BJU Int* 2010;106:832; *Obstet Gynecol* 1996;87:20S; 1996;88:745)

Estrogen Therapy

- **Indications:** Those w/ mod–severe vasomotor or vaginal sx (very effective); ± for urinary, psychological sx
- **Contraindications:** hx or high risk for CVD, breast/uterine cancer, DVT, active liver disease, inability to obtain routine mammogram
- **Progestin: Unopposed estrogen may → endometrial hyperplasia/CA ∴ all pts w/ intact uterus receiving PO/transdermal estrogen should receive combination Rx** (not necessary for PV estrogen)
- **Side effects:** Estrogen tx (w or w/o progestin) assoc w/ ↑ stroke risk; risk may be less w/low-dose (<50 mcg) *transdermal* estrogen (*BMJ* 2010;340:c2519); combination Rx assoc w/ ↑ relative risk MI, DVT/PE, breast CA (*AFP* 2016;94:884; *JAMA* 2004;291:1701); common s/e include uterine bleeding, breast tenderness; use may also ↓ hip fractures
- **Dosing:** *Prescribe lowest effective dose for shortest possible time;* peak effect reached w/in 4 wk (standard dosing) vs. 8–12 wk (lower dose); attempt d/c q6–12 mo w/ gradual taper

Estrogen + Progestin Preparations for Vasomotor Sx (*AFP* 2016;94:884)			
Combination Estrogen/Progestogen			
Preparation	**Generic Name**	**Brand Name**	**Dosing** (mg)
Oral	Estradiol/norethindrone acetate	Activella, Femhrt	Activella: 0.5/0.1, 1.0/0.5 (daily); Femhrt: 0.25/0.5 (daily)
Oral	Estradiol/ drospirenone	Angeliq	0.5/0.25, 1.0/0.5 (daily)
Oral	Conjugated equine estrogen/bazedoxifene	Duavee	0.45/20.0 (daily)
Oral	Estradiol/norgestimate	Prefest	1.0/0.09 (daily—see package insert for dosing details)
Oral	Conjugated estrogen/ medroxyprogesterone	Premphase, Prempro	Premphase: 0.625/5.0 (daily—see package insert for dosing details); Prempro: 0.3/1.5, 0.45/1.5, 0.625/2.5, 0.625/5.0 (daily)
Transdermal patch	Estradiol/levonorgestrel	Climara Pro	0.45/0.015 (weekly)
Transdermal patch	Estradiol/norethindrone acetate	CombiPatch	0.05/0.14, 0.05/0.25 (twice weekly)
Vaginal Estrogen for Vaginal Sx			
Cream	Estradiol	Estrace	0.5g PV daily × 1–2 wk, then 2× weekly
Cream	Conjugated estrogen	Premarin	0.5g PV 2× weekly
Insert	Estradiol	Vagifem	10 mcg PV daily × 2 wk, then 2× weekly
Ring	Estradiol	Estring	Replaced by provider or pt q90d
Estrogen-Only Preparations for Vasomotor Sx (for women w/o uterus)			
Oral	Conjugated estrogens	Enjuvia, Premarin	0.3, 0.45, 0.625, 0.9, 1.25 (daily)
Oral	Estradiol	Estrace	0.5, 1.0, 2.0 (daily)
Oral	Esterified estrogen	Menest	0.3, 0.625, 1.25, 2.5 (daily)
Transdermal patch	Estradiol	Alora, Climara, Minivelle	Climara: 0.025, 0.0375, 0.05, 0.06, 0.075, 0.1

patch		Minivelle, Vivelle Dot	0.05, 0.06, 0.075, 0.1 (weekly); All others: 0.025, 0.0375, 0.05, 0.075, 0.1 (twice weekly)
Transdermal gel	Estradiol	Divigel, Elestrin, Estrogel	Use daily, doses vary based on product
Transdermal spray	Estradiol	Evamist	1.53 per spray, use 1–3 sprays (daily)
Vaginal insert	Estradiol acetate	Femring	0.05, 0.1 (every 90 d)

MENSTRUAL DISORDERS

Background

- **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
- **Normal menstrual cycle:** 21–35 d w/ avg duration of menses = 5 d, blood loss <80 mL
- **Definitions & classification of menstrual disorders:**

  Abnormal uterine bleeding (AUB): Abnormal menstrual cycle pattern (subtypes below)

  Heavy menstrual bleeding (HMB): Heavy/prolonged menses; previously "menorrhagia"

  Polymenorrhea: Cycle length <21 d (↑ freq); previously "metrorrhagia"

  Irregular bleeding: Cycle length >35 d (↓ freq), <9 cycles/ y; previously "oligomenorrhea"

  Intermenstrual bleeding: Bleeding at any time other than nl menses

  Amenorrhea: Absence of menses (subtypes below)

  Primary amenorrhea: Absence of menarche in ♀ >15 y w/ 2° sex characteristics or ♀ >13 y w/o 2° sex characteristics

  Secondary amenorrhea: Absence of menses × 3 mo in ♀ w/ previously nl menstruation or 6 mo in ♀ w/ previous irregular

menstrual bleeding

- **Dysmenorrhea:** Painful menses

  Primary dysmenorrhea: Painful menses w/ nl pelvic anatomy
  Secondary dysmenorrhea: Painful menses 2/2 pelvic d/o (e.g., endometriosis, fibroids)

Abnormal Uterine Bleeding

Background (*AFP* 1999;60:1371; *Obstet Gynecol* 2012;120:197)

- Abnormal uterine bleeding (AUB) accounts for 1/3 outpt gynecology visits overall & >70% gynecologic consults for peri- & postmenopausal pts
- **Dysfunctional uterine bleeding (DUB):** Dx of exclusion in pts w/ AUB not due to pregnancy, pelvic pathology, medications, or systemic disease

Differential Diagnosis of Causes of Abnormal Uterine 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; if present → determine subtype/bleeding pattern (HMB, polymenorrhea, irregular bleeding, or intermenstrual bleeding)

Anovulatory (more common: **Irregular** flow/duration of menses, premenstrual sx often absent)

- **Menopausal status:** *Perimenopausal:* ⊕ onset of clinical/endocrinologic changes (hot flashes, vaginal dryness, irregular menses) but menses persistent; *Menopausal:* >12 mo amenorrhea (see *"Menopause"*)
- **Medical history:** *PMH:* 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 if due, ± STI testing
- **Initial labs:** 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, h/o unopposed estrogen, or no response to Rx, & postmenopausal women who do not undergo TVUS or w/ abnl TVUS

Management

- **Postmenopausal:** Bleeding usually 2/2 vaginal/endometrial atrophy, but CA must be excluded → transvaginal ultrasound **(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)

Premenopausal AUB Management by Subtype	
Anovulatory pattern	(1) Assess for thyroid dysfunction, hyperprolactinemia: TSH, PRL (2) Assess for hypothalamic dysfunction (e.g., stress, eating d/o, chronic

	disease); if ⊕, see "Amenorrhea" subsection below (3) Consider systemic disease (see Ddx above) (4) Eval for PCOS and its Ddx (see "PCOS), chronic anovulation (FSH nl/↓); for either dx, consider OCPs, levonorgestrel IUD, or q3mo PG
Polymenorrhea	Trial OCPs; consider evaluation for luteal phase defect
Irregular bleeding	Seen w/ prolonged follicular phase; trial OCPs
Intermenstrual bleeding	(1) R/o cervical pathology (pelvic exam + Pap) (2) Remove IUD if present (3) Trial OCPs
Heavy menstrual bleeding	(1) R/o bleeding disorder (2) TVUS for fibroids/uterine pathology (3) If above nl, trial OCPs, NSAIDs, or levonorgestrel IUD
Perimenopausal AUB Management	
(1) R/o genital tract lesion (pelvic exam) (2) Evaluate for endometrial hyperplasia with TVUS and/or bx: If normal or atrophic → observe vs. trial of OCP or levo-IUD if abnormal (atypical, hyperplasia, carcinoma) → gyn referral; hyperplasia often tx w/progesterone, D&C if persistent (*Obstet Gynecol* 2012;120:197)	
Postmenopausal AUB Management	
Bleeding usually 2/2 vaginal/endometrial atrophy (95%), but CA (5%) must be excluded (1) **TVUS** *(may also go directly to endometrial bx)* If endometrial stripe <4 mm (i.e., atrophic) → observe If endometrial stripe ≥4 mm or irregular → endometrial bx (2) Endometrial biopsy: If normal & bleeding resolves → observe If nl but bleeding persists **or** atypia/hypertrophy on bx → TVUS (if not yet done) **and** gyn referral for hysteroscopy or sonohysterography (*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 mo, **(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

- **For endometrial bx**: Premenopausal pts <45 y w/ persistent abnl bleeding, h/o unopposed estrogen exposure, or no response to Rx; postmenopausal pts w/ abnl TVUS

- **Severe/heavy bleeding** which does not respond to initial tx, consideration of surgical tx
- **Persistent AUB** after initial Rx should undergo TVUS → if abnl, refer for hysteroscopy ± bx or sonohysterography
- **If uterine enlargement/irregularities on exam**→ consider TVUS, referral for f/u sonohysterography/hysteroscopy/ablation

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Amenorrhea

Background (*AFP* 2006;73:1374)

- **Epidemiology:** Incidence of primary amenorrhea = 0.3% general population, secondary amenorrhea = 1–3% general population; can be assoc w/ infertility, osteopenia, ↑ CV risk

Etiologies

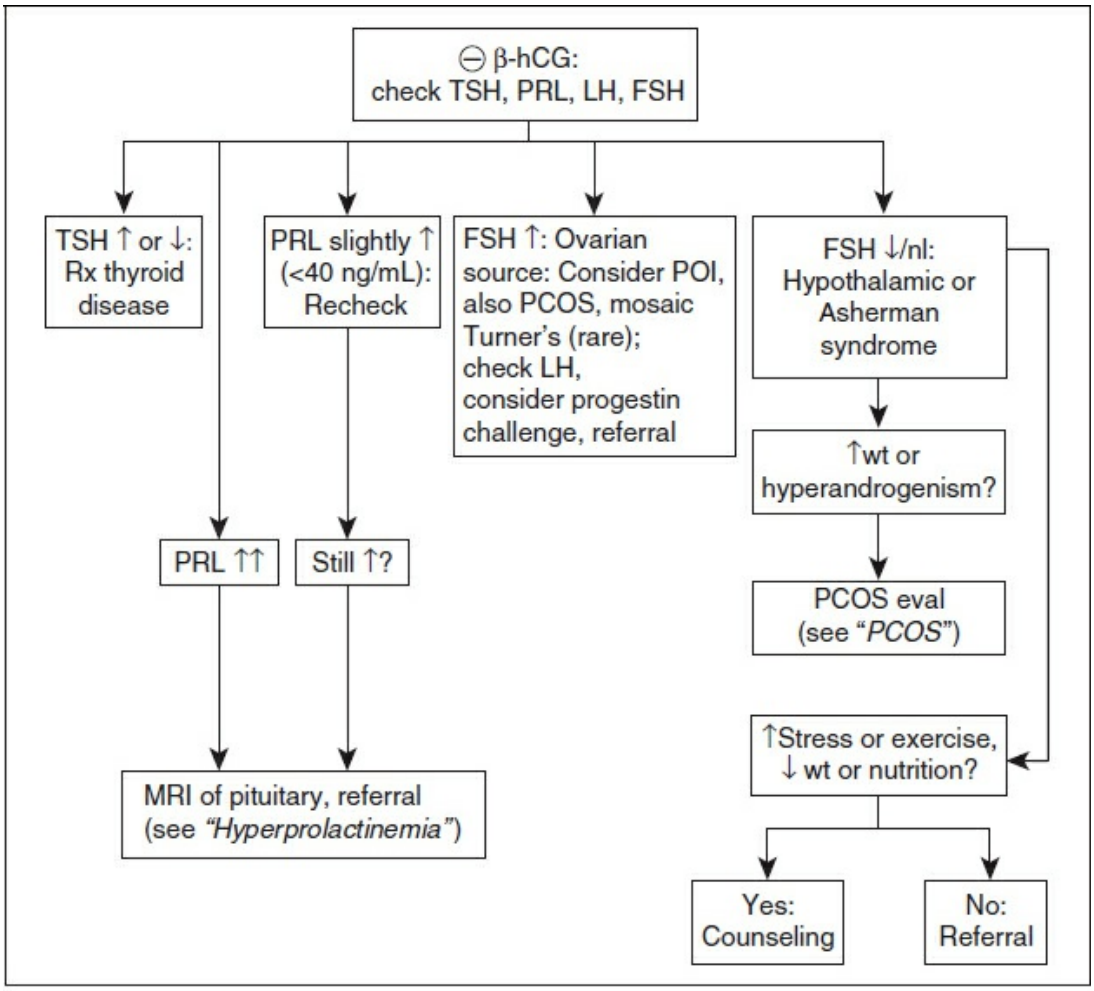
- **Primary amenorrhea:** Rare, initial w/u usually w/ pediatrician; etiologies include causes of 2° amenorrhea, anatomic & genetic defects (incl craniopharyngioma, primary ovarian insufficiency, Turner syndrome, Kallmann syndrome, androgen insensitivity); eval for 2° sex characteristics, presence of uterus/vagina; refer to 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:** Often 2/2 eating d/o (esp anorexia nervosa), excess exercise/wt loss, ↑ stress; **female athlete triad** (restrictive eating + amenorrhea + osteoporosis) Also: Hypothalamic destruction, CNS tumor, cranial XRT
Pituitary	**Hyperprolactinemia:** 2/2 pituitary adenoma, medications, breastfeeding, idiopathic (see *"Hyperprolactinemia"*) Hypopituitarism (↓ LH, FSH): Infiltrative, Sheehan's
Ovarian	**PCOS:** Anovulation w/ hyperandrogenism (see *"PCOS"*) **Ovarian insufficiency** or failure: "Premature" = age <40 y; can be primary (POI) or 2/2 autoimmune disease, iatrogenic/chemo/XRT, genetic d/o, mumps, or

	pelvic XRT
Uterine	Asherman syndrome (uterine scarring 2/2 D&C, infxn) Cervical stenosis (seen more w/ 1° amenorrhea)
Other	**Pregnancy, hypo/hyperthyroidism,** celiac disease, ↑ androgens (Cushing's, nonclassical CAH, steroids)

Evaluation

- **General approach:** Majority of diagnoses can be made w/ careful hx & 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 XRT
  - *Medications:* OCPs, antipsychotics, H_2-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:** Height, weight, 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: β-hCG, TSH, PRL, LH, & FSH**



(Adapted from Fertil Steril 2008;90:S219; AFP 2013;87:781)

Figure 15-2. Diagnostic w/u of amenorrhea (in absence of structural abnormality)

- **Additional testing:** May be useful in specific circumstances

Progesterone Challenge ("Withdrawal") Test	
Purpose/Physiology	Progesterone should → mature uterine lining, and w/d should → menses, lack of response **suggests low-estrogen state**
Test characteristics	Poor Se/Sp (e.g., 50% of POI pts have some w/d bleeding) thus unreliable (*Fertil Steril* 2008;90:S219)
Sample dosing	Medroxyprogesterone acetate (Provera) 10 mg PO QD × 7–10 d
Pt instructions	Can start anytime; expect bleeding 3–7 d after last dose

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 or disease states; may help interpret FSH levels

Pelvic U/S: Consider if uterine pathology suspected (e.g., Asherman syndrome)

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 mo 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 and/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 → Endocrinology
- Consideration of estrogen tx (outside of menopause) → Gynecology or Endocrinology
- Uterine pathology or outflow obstruction → Gynecology

Dysmenorrhea

Background

- **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 (*AFP* 2005;71:285)
- **Secondary causes of dysmenorrhea:** Endometriosis, PID, adenomyosis, leiomyomata, ectopic pregnancy, interstitial cystitis, chronic pelvic pain

Evaluation

- **General approach:** Primary dysmenorrhea is a clinical dx

  (1) Exclude 2° causes (endometriosis, PID, adenomyosis, leiomyomata, ectopic pregnancy, interstitial cystitis, chronic pelvic pain–see "Pelvic Pain"), (2) Assess severity, (3) Assess prior tx attempted (*AFP* 2014;89:341)
- **History:** (1) Confirm history typical: **recurrent, midline pelvic pain at/near onset of menses × 1–3 d** w/o other explanation; onset usually in adolescence (atypical should prompt additional consideration for Ddx, above); (2) assess severity of sx/desire for tx; (3) assess prior tx attempted
- **Red flags:** Onset > age 25 y, pain not related to menses, AUB, nonmidline pelvic pain, ⊕ dyspareunia, ↑ sx severity → refer to OB/GYN
- **Exam:** Should be nl in primary dysmenorrhea; 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/ β-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

Management

- Management below is for 1° dysmenorrhea; refer for severe sx or suspected 2° causes
- **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, but may not be effective in severe pain (*JAMA* 2001;285:2347); no RCT directly comparing NSAIDs & hormonal contraception, can initiate either (*Cochrane Database Syst Rev* 2009;4:CD002120)
  - **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
- If no response after 3 mo, change to or add additional class of Rx
- If refractory to combination NSAID + hormonal contraception × 3 mo, consider 2° cause & gynecology referral for laparoscopy
- **Complementary/alternative medicine:** No high-quality data on effectiveness of CAM (e.g., herbs, acupuncture), though some herbal preparations merit further review (*Cochrane Database Syst Rev* 2008;2:CD005288*;* 2016;3:CD002124; 2016;4:CD007854)

First-Line Pharmacologic Therapy		
Class	**Sample Rx w/ Usual Dosing**	**Notes**
NSAID	Ibuprofen 800 mg q8h × 3 d Mefenamic acid 500 mg × 1, then 250 mg q6h × 3 d 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	Efficacy > placebo; no evidence 1 preparation better than another (*Cochrane Database Syst Rev*

	tablet QD Extended or continuous cycle > relief than cyclic (*Contraception* 2010;81:215)	2009:CD002120)
Other Hormone	Vaginal ring Depot medroxyprogesterone acetate	Efficacy: Ring = OCP 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	N.b. nulliparity not contraindication

- **Patient information:** acog.org/Resources_And_Publications/Patient_Education_FAQs_Lis (see *"Dysmenorrhea (FAQ046)"* under Gynecological Problems)

POLYCYSTIC OVARIAN SYNDROME

Definition (*JCEM* 2013;98:4565; *Endocr Pract* 2015;21:1291; *NEJM* 2016;375:54)

- Polycystic ovarian syndrome (PCOS) is a common, heterogeneous endocrine disorder affecting 6–10% of reproductive-aged women
- **Pathophysiology:** Underlying causes still unknown; some genetic predisposition; role/prominence of obesity in causing PCOS undefined, although it may worsen syndrome; 2 pathways below play role
  - (1) Rapid GnRH cycling → ↑↑LH and ↓↓FSH → ↑ androgen production and impaired ovarian follicular development;
  - (2) Insulin resistance → hyperinsulinemia → ↑ androgen production by ovaries and adrenal glands *and* ↓SHBG production which ↑ free T levels

PCOS Diagnostic Criteria (must meet 2 of 3)	
Criteria	**Notes**
Androgen excess	Evidence may be clinical or biochemical
Ovulatory dysfunction	Anovulatory bleeding pattern or amenorrhea
Polycystic ovaries	Exclusion of other disorders

- **Comorbidities:** PCOS assoc w/ obesity, depression, OSA, NAFLD,

DM, CVD, dyslipidemia, infertility, pregnancy complications (related to obesity and/or glucose intolerance), endometrial CA

Evaluation (*JCEM* 2013;98:4565)

- **General approach:** (1) Assess for above criteria (2) Rule out PCOS mimics
- **History:** Assess OB/GYN hx including menses frequency and onset, infertility, hirsutism (interpret in context of familial patterns, ask about use of hair removal methods), acne, alopecia, CV disease risk (smoking hx, family hx), alternative diagnoses (see below)
- **Exam:** Assess body habitus, terminal hair growth (Ferriman Gallwey score), acne, androgenic alopecia, acanthosis nigricans, skin tags
- **Laboratory:** Standard testing and values below; additional tests guided by clinical suspicion

Standard Laboratory Testing and Expected Values in PCOS		
Laboratory Test	**Findings**	
SHBG	↓	
DHEAS (adrenal androgen)	↑	
Total testosterone (ovarian)	↑ but <200; ♀ ULN = 40–60 ng/dL	
Morning 17-OHP	Normal (<200 ng/dL); obtain in first 10 d of menstrual cycle	
TSH, PRL	Normal	
Other	No role for LH/FSH in diagnosis of PCOS; can help with Ddx of amenorrhea (see "*Menstrual Disorders*")	
PCOS Differential Diagnosis (Adapted from *JCEM* 2013;98:4565)		
	Distinguishing Features	**Laboratory Findings**
Disorders to Always Exclude		
Thyroid disease	See "*Thyroid*"	TSH ↑ or ↓
PRL excess	See "*Hyperprolactinemia"*	PRL ↑
Nonclassical congenital adrenal hyperplasia	Family hx infertility or hirsutism; Ashkenazi Jewish heritage	17-OHP >200 ng/dL (AM, early follicular phase); confirm with stimulation test

Medications	Anabolic steroids, valproic acid, cyclosporine	None
Disorders to Consider Excluding (see "Menstrual Disorders: Amenorrhea")		
Pregnancy	Amenorrhea, breast fullness, nausea, uterine cramping	⊕ β-HCG
Hypothalamic amenorrhea	Amenorrhea + low BMI, excessive exercise or stress	↓ FSH, ↓ estradiol
Primary ovarian insufficiency	Amenorrhea + hot flashes, vaginal dryness; autoimmunity	↑ FSH, ↓ estradiol
Androgen-secreting tumor	Rapid onset of severe hyperandrogenism (e.g., Δ voice, clitoromegaly)	↑↑ Total testosterone, DHEAS, obtain vaginal u/s, MRI adrenals
Cushing syndrome	Easy bruising, violaceous striae, myopathy, plethora	24-h urine free cortisol, see "Cushing's"
Acromegaly	Increased shoe/glove size, frontal bossing, macrognathia	↑ IGF-1

(*NEJM* 2005;352:1223; *JCEM* 2013;98:4565)

- **Progesterone:** If concern for anovulation, may obtain a week before anticipated bleed (usually ~day 21); should be ≥3–4 ng/mL; if low, pt warrants progesterone tx (to protect uterus against unopposed estrogen)
- **Imaging:** Pelvic ultrasound recommended if hyperandrogenism with regular menses or suspicion for ovarian tumor (rapid onset, T >200 ng/dL)

Management (*Am J Med* 2007;120:128; *NEJM* 2005;352:1223)

- **CV risk stratification:** BMI, waist circumference, blood pressure, 2-h 75-g oral glucose tolerance test (preferred to HbA1c), lipid panel
- **Medical therapy** (see below)
- **Weight loss and exercise** to improve metabolic dysfunction; may also reduce androgen levels and restore ovulation
- **When to refer:** Refer to a specialist if fertility desired, if tx below ineffective, or dx uncertain

PCOS Medical Therapies		
Medication	**Mechanism and Effects**	**Considerations**

Estrogen/progestin combined contraceptives (**1st-line therapy**, includes OCPs, patch, vaginal ring)	↓ LH → ↓ ovarian androgens ↑ SHBG → ↓ bioavailable androgens Endometrial protection	Provides contraception ↑ risk of VTE (esp if older, smoker, obese) No specific formulation proven superior; norgestimate is progestin with low androgenic potential and lower risk of VTE
Spironolactone (for severe hirsutism refractory to hormonal contraceptives)	Androgen receptor antagonist	Uptitrate to 100 mg twice a day Pregnancy must be avoided (teratogenic)
Metformin (for impaired glucose tolerance)	↓ Insulin resistance May ↑ ovulation	Gradually uptitrate to minimize gastrointestinal side effects
Progestin (episodic)	Endometrial protection	Induce withdrawal bleed every 1–3 mo
Levonorgestrel-releasing IUD	Endometrial protection	Provides contraception

(*NEJM* 2016;375:54; *NEJM* 2005;352:1223)

FEMALE 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 mo, 72% w/in 6 mo, 85% w/in 1 y (*Obstet Gynecol Clin N Am* 2015;42:15)
- **Definitions:**
  - *Infertility:* Failure to conceive by heterosexual couple despite regular, unprotected intercourse for defined period; timeframe is based on the age of ♀ partner: ♀ <35 y = failure to conceive after 1 y, ♀ ≥35 y = failure to conceive after 6 mo
  - *Impaired fecundity:* Physical difficulty becoming pregnant and/or carrying a pregnancy to live birth (e.g., includes miscarriage/stillbirth) (*Natl Health Stat Report* 2014;67:1)
- **Epidemiology:** 6% of married US ♀ 15–44 y meet definition of

infertility, 11% of all US ♀ 15–44 y have impaired fecundity (*Natl Health Stat Report* 2014;67:1; 2014;73:1)

- **Etiology:** May be caused by endocrine, genetic, structural, immunologic, or infectious causes in either partner; infertility rates correlate w/ **age** in ♀ > ♂, w/ ↓ fecundity for ♀ at age 32 y and ↓↓ age >37 y 2/2 ↓ oocyte numbers/quality and ↑ incidence of tubal disease, endometriosis, other structural problems; ~ 20–25% of all cases of infertility are unexplained; when known, ♀ factors contribute to 50–75% of cases, ♂ factors contribute to 25–50%, >1 factor may be present

Selected Female Infertility Etiologies	
Category	**Diagnoses**
Ovulatory dysfunction (32%) See "Abnormal Uterine Bleeding" and "Amenorrhea" in Menstrual Disorders	Hypothalamic–pituitary dysfunction (↑ stress, eating d/o, ↑ exercise) Anovulation (~80% related to PCOS, see *"Polycystic Ovary Syndrome"*) Endocrinopathy (↑ PRL, thyroid disease, metabolic syndrome, obesity) Ovarian insufficiency (idiopathic, age-related, medication-related, s/p ovarian surgery, s/p viral illness, h/o chemo/XRT)
Tubal pathology (22%)	Occlusion or other abnormalities, often in setting of prior PID or intra-abdominal surgery
Endometriosis (15%)	Anatomic distortion; possible effect of cytokine release interfering 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 s/p prior procedure *Genetic:* Turner syndrome, androgen insensitivity syndrome *Immunologic:* SLE, APLAS, celiac disease; *Meds:* OCPs, progestins, Ψ medications, corticosteroids, chemotherapeutics

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

Evaluation (*Clin Ob Gyn* 2012;55:692; *Womens Health* 2010;6:753)

- **General approach:** Consider as a problem affecting couples rather individuals; ♂ infertility assoc w/ ↑ pt risk of genetic abnormalities,

CA, potentially heritable conditions *(Fertil Steril* 2013;100:681–685) **∴ both partners should be evaluated, even if IVF planned** (see "*Men's Health"*)

- **History:** (*Can Fam Physician* 2003;49:1465)

  Reproductive hx: Age (**both partners**); duration of infertility, frequency of coitus, sexual dysfunction (both partners), pregnancy/paternity hx, menstrual hx (age at menarche, cycle length, frequency, regularity), h/o PID, h/o abnl Pap, h/o gyn procedure, prior contraception

  PMHx: H/o chemo/XRT, endocrinologic disease, celiac disease, autoimmune disease

  Medications: Include herbal preparations, OTC, vitamins

  FHx: Early menopause, endometriosis; both partners: infertility, birth defects, CF, genetic mutations, developmental delay

  Social hx (for **both partners**, if known): EtOH, tobacco, illicits, stress, toxic exposures

  ROS: ⊕ PMS sx (suggest ovulatory cycles), ↓ estrogen (vaginal dryness, hot flashes), galactorrhea, sx of hyperandrogenism

- **Exam:** BMI, BP, HR, general appearance, secondary sex characteristics, thyroid exam, breast exam (galactorrhea), 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)

Studies to Evaluate Female Infertility	
Lab/Study	**Notes**
TSH, PRL	If both elevated, tx hypothyroidism 1st (see "Thyroid Disorders" & "Prolactinemia")
FSH/estradiol in early follicular phase (d 3 of cycle)	Evaluates ovarian reserve: estradiol >60–80 pg/mL + nl FSH (<10 IU/L) consistent w/ ↓ ovarian reserve, ↑ FSH + ↑ estradiol = likely poor response to assisted reproductive technology (ART)
Hysterosalpingogram	Assess tubal patency, uterine cavity (e.g., fibroids)
PCOS evaluation	(see *"Polycystic Ovary Syndrome"*), d 21–25 progesterone level → level >3 ng/mL confirms ovulation

STI testing	Including chlamydia Ab; as indicated by Hx/PE

(*NEJM* 2010;363:965; *Obstet Gynecol Clin N Am* 2015;42:15)

Treatment (*Am J Obstet Gynecol* 2008;199:596; *Obstet Gynecol Clin N Am* 2015;42:15)

- Treat underlying cause as indicated; *Lifestyle modifications as indicated:* Weight loss/gain, mod exercise, smoking cessation, ↓ EtOH, ↓ stress, ↓ caffeine (note that data lacking/inconclusive w/ exception of maintaining nl weight); *PCOS:* Consider metformin vs. clomiphene +/- other anti-estrogenic therapies in conjunction w/ specialist, although inconclusive data re: efficacy for fertility (*Cochrane Database Syst Rev* 2016;12:CD002249)
- **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 to ↓ risk of neural tube defects; male partners should avoid ejaculatory abstinence of >2 d; avoid water-based lubricants (e.g., K-Y) as these may ↓ sperm motility (*J Reprod Med* 2004;49:289; *PLoS One* 2012;7:e46276)
- **When to refer:** Consider gyn referral in all pts; genetics referral as per Hx/PE

  Infertility specialist: Prompt referral for pts >35 y, pts w/ ↓ ovarian reserve or pts w/ suspected POI for additional testing of ovarian reserve (e.g., clomiphene citrate challenge test, inhibin B, antimullerian hormone); refer for other pts requiring advanced tx, incl further evaluation of structural causes, or possible ART (including ovarian hyperstimulation, intrauterine insemination, in vitro fertilization)
- **Patient information:** acog.org/Patients/FAQs/Evaluating-Infertility

CONTRACEPTION

Background

- Almost **half** of all US pregnancies are unintended (pregnancy not desired at time of conception); 33% of women use contraception inconsistently, incorrectly, or not at all → 95% of unintended pregnancies, resulting in increased morbidity, mortality, and

healthcare costs (*Perspect Sex Repro Health* 2006;38:90; guttmacher.org; *AFP* 2016;94:942)

- Half of US women are 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 w/↑ health risks from unintended pregnancy:** Estrogen-sensitive CA, cyanotic CHD, recent bariatric surgery, transplant, epilepsy, HTN, SLE, APS, sickle-cell

Choosing a Method

- Counsel pt to choose most effective method she and partner able to *use successfully*
- **Women w/ medical issues:** Refer to CDC US Medical Eligibility Criteria for Contraceptive Use, 2016: *MMWR Recomm Rep* 2016;65:1

First-Year Contraceptive Failure Rates (Selected)		
	Annual # of pregnancies/100 using method	
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; guttmacher.org/pubs/fb_contr_use.html)

Long-Acting Reversible Contraception

Background (*Obstet Gynecol* 2011;118:184; *AFP* 2012;85:403; *MMWR* 2016;65:1)

- **Long-acting reversible contraception (LARC):** 3 methods available in US: (1) copper IUD (ParaGard), (2) levonorgestrel IUD (Mirena, Skyla, Liletta), and (3) etonogestrel-containing contraceptive implant (Nexplanon)
- **Benefits: Very effective, no maintenance;** good option for women who desire to avoid pregnancy for >3 y; avoids estrogen exposure; no evidence of subsequent long-term fertility problems
- **Onset of efficacy:** Copper IUD is effective immediately; all other forms of LARC take ~7 d to achieve efficacy, pts may continue prior form of contraception or be counseled to use barrier methods for this period
- **Risk of ectopic pregnancy:** ↓ overall risk compared with pts who do not use contraceptives, but ↑ risk *if* pregnancy occurs (*Am J Obstet Gynecol* 2004;190:50)

Evaluation

- **Prior to placement:** β-hCG generally recommended; STI testing should be offered, but is not required unless clinical suspicion; antibiotic ppx unnecessary; for IUD, pre-placement misoprostol not generally thought to offer benefit
- **Contraindication for IUDs:** Uterine distortion, active pelvic infection (wait 3 mo before insertion), pregnancy, unexplained serious uterine bleeding, active cervical/endometrial CA; pelvic TB; postpartum sepsis; ***not* contraindicated in adolescents/young adults, nulliparous women, or during breastfeeding;** may be placed immediately postpartum
- **Training:** Must be performed by trained providers; training opportunities/information at acog.org/-

/media/Departments/LARC/Clinical-Training-Opportunities.pdf

Long-Acting Reversible Contraceptives		
Class	**Mechanism**	**Notes**
Levonorgestrel-releasing IUD	Interferes w/ sperm migration, inhibits ova fertilization; partially inhibits ovulation	S/e: irregular bleeding Benefits: ↓ menstrual bleeding (amenorrhea for many women w/ higher dose formulations), ↓ dysmenorrhea
Copper T-380A IUD	Interferes w/ sperm migration, prevents fertilization	S/e: heavier menses
Nexplanon subdermal implant	Continuous-release progestin (etonogestrel) inhibits ovulation	*S/e:* irregular bleeding (1° reason for discontinuation); can cause menses to be heavier or lighter Fertility returns soon after removal

LARC Duration of Use	
Trade Name (active ingredient)	**Duration**
Mirena (levonorgestrel 52 mg)	Approved for 5 y, likely effective longer
Liletta (levonorgestrel 52 mg)	Approved for 3 y, likely effective longer
Kyleena (levonorgestrel 19.5 mg)	Approved for 5 y
Skyla (levonorgestrel 13.5 mg)	Approved for 3 y
ParaGard (Copper)	Approved for 10 y, likely effective longer
Nexplanon (etonogestrel 62 mg)	Approved for 3 y

(*Int J Women's Health* 2016;8:589)

Combined Hormonal Contraception

Background (*NEJM* 2003;349:1443)

- **Definition**: Synthetic **estrogen** (usually ethinyl estradiol [EE]) **and progestin** (multiple types); can be delivered orally, transdermally (patch), or transvaginally (ring)
- **Estrogen** suppresses gonadotropin surge → prevents ovulation
- **Progestin** affects cervical mucus, tubal peristalsis, endometrial lining → ↓ sperm motility, prevents egg fertilization/implantation; also

inhibits GnRH → ↓ ovulation (*Contraception* 2002;65:21)

- **Benefits:** Improvement in menorrhagia, dysmenorrhea, anemia, PMS, acne, hirsutism; ↓ risk ovarian/endometrial cancer
- **Risks:** HTN, venous thromboembolic disease (up to 3–4x ↑ risk if no underlying RFs; up to 1.8x further ↑ w/ 3rd- and 4th-gen progestins; absolute VTE risk low, much < risk than pregnancy), MI, CVA; risks ↑ w/ older preparations (EE >50 µg)
- **Efficacy in overweight/obese pts:** Some studies suggest 50–70% higher failure rates in women w/ BMI >25 (*Womens Health* 2013;9:453)
- **Absolute contraindications:** Include h/o DVT/PE, CVA, MI, uncontrolled HTN, known thrombogenic mutations, migraine w/ aura or neuro s/sx, smokers ≥35 y, active liver disease, known/suspected estrogen-dependent tumor, SLE, h/o solid-organ transplant (*CDC MMWR* 2016;65:1)

Transdermal & Vaginal Hormonal Contraception

- **Vaginal ring:** NuvaRing (15 µg EE, 150 µg etonogestrel); flexible plastic ring inserted by pt; intravaginal × 3 wk, remove × 1 wk; high pt satisfaction rates
- **Transdermal patch:** Ortho Evra/Xulane (35 µg EE, 150 µg norelgestromin/d); apply q1wk; ↓ efficacy in pts >90 kg (*Fertil Steril* 2002;77:S13); ↑ systemic estrogen exposure w/ patch than w/ OCP of equivalent EE dose; ↑ **risk VTE**

Combination Oral Contraceptive Pills (OCPs)

- **Initiating OCPs:** Obtain BP, careful review PMHx for contraindications; confirm not pregnant via hx ± β-hCG; no role for pelvic exam (for this purpose); prescribe 1 y Rx at a time (1 28-d supply + 12 refills)
- **Contraindications:** Include **women ≥35 y who smoke**; HTN (esp uncontrolled) those w/ estrogen contraindications (incl hx VTE, thrombophilia), complicated valvular heart disease, advanced DM, **migraine with aura**, known ASCVD or at ↑↑ risk, cirrhosis (*MMWR Recomm Rep* 2016;65:1)
- **General approach** to prescribing: After review of PMHx and contraindications (above):

  (1) Decide on planned pattern of use (cyclic vs. extended cycle vs. continuous)

(2) Select estrogen dose
(3) Select progesterone formulation
(4) Set initiation plan w/ pt (quick vs. 1st day vs. Sunday start)
(5) Discuss indications for backup methods
(6) Counsel re: s/e

- **Pattern of use:** *Cyclical*: 21 active pills → 7 hormone-free pills or 24 active pills → 4 hormone-free pills (possible ↑ efficacy, ↑ breakthrough bleeding)

  Extended-cycle regimen: Typically 84 active pills → 7 hormone-free pills,

  Extended/Continuous: May be preferred in women w/ premenstrual sx or for lifestyle; efficacy, safety equivalent to cyclic use
- **Notes on formulations:** In general, all OCPs equally effective; **no evidence of benefit for multiphasic compared to monophasic**; preparations w/name ending in "Fe" include iron; preparations with "Tri" in name usually multiphasic
- **Estrogen formulations:** Ethinyl estradiol (EE) most common: Low-dose (10–20 µg) to high-dose (50 µg) formulations; **standard = 20–35 µg**; breakthrough bleeding may ↑ w/ doses ≤20 µg; 50 µg mestranol considered equivalent to 30–35 µg EE
- **Progestin formulations:** Multiple options, vary in androgenic activity (least → most by generation: 4th → 3rd → 1st → 2nd); note different progestins *not* equivalent on a mg basis; 3rd/4th gen may have relative ↑VTE risk (drospirenone higher risk, LNG lower risk)

  1st gen: Norethindrone acetate, norethindrone, ethynodiol
  2nd gen: Levonorgestrel (↑ androgenic), norgestrel
  3rd gen: Norgestimate, desogestrel (least androgenic)
  4th gen: Drospirenone (antiandrogenic + antimineralocorticoid activity), dienogest
- **Sample Rx:** Norgestimate 0.25 mg/ethinyl estradiol 30 µg a reasonable initial Rx for most pts

Selected OCP Formulations (*Med Letter* 2015;57:e133)			
Progestin	**Estrogen**	**Sample Rx**	**Notes**
Norethindrone	EE	Necon 1/35 or 0.5/35	Chewable

(NE)			available
Multiphasic Norethindrone	EE	Necon 10/11 (10 d of 0.5 mg NE → 11 d mg of 1 NE) Nortrel, Ortho-Novum	
Norethindrone	Mestranol	Necon 1/50	
Norethindrone acetate (NEA)	EE	Loestrin 1.5/30	24-d available
Multiphasic Norethindrone acetate	EE	Lo Loestrin (1/10) (no generic)	Lowest dose of EE available
Norethindrone acetate	Multiphasic EE	Estrostep FE (5 d of 20 µg EE → 7 d of 30 µg EE → 9 d of 35 µg EE)	Approved for acne
Ethynodiol	EE	Kelnor, 1/35	
Levonorgestrel	EE	Amethyst (has 20 µg EE, 0.09 mg LNG) Seasonale (84 d of 30 µg EE /0.15 mg LNG)	Amethyst intended for continuous use
Levonorgestrel	multiphasic EE	Seasonique (84 d of 30 µg EE/0.15 mg LNG → 7 d of 0.1 µg EE LoSeasonique (84 d of 20 µg EE/0.15 mg LNG →7 d of 0.1 µg EE)	Intended for 91-d cycles
Multiphasic Levonorgestrel	Multiphasic EE	Enpresse, Trivora	
Norgestrel	EE	Cryselle, Lo-Ogestrel, Ogestrel	
Norgestimate	EE	Ortho-Cyclen 35 µg EE/0.25 mg NG	
Multiphasic Norgestimate	EE	Ortho Tri-Cyclen (7 d of 35 µg EE/0.18 NG → 7 d of 35 µg EE/0.215 NG → 7 d 35 µg EE/0.250 NG)	Approved for acne
Desogestrel (DG)	EE	Apri (30 µg EE/0.15 DG)	
Multiphasic Desogestrel	Multiphasic EE	Kariva, Viorele	
Drospirenone	EE	Loryna, Ocella, Yasmin, Yaz	All indicated for acne
Dienogest	Estradiol Valerate	Natazia	Both multiphasic; no generic

- **Initiation Plan:** multiple options available
  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
- **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 of interaction w/ other abx, case reports w/ PCN, tetracyclines (*Obstet Gynecol* 2001;98:853)
- **Side effects/monitoring:**
  S/e: Counsel pts re: anticipated s/e (see below), typically resolve w/in 2–3 mo; also discuss risk/benefits of combined hormonal tx (above)
  F/u: Consider f/u at 3 mo to check BP, evaluate for tolerance and 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, reassure pt no adverse outcome assoc w/ using OCPs at time of conception

Adjusting OCP Formulation for Side Effects (*AFP* 2010;82:1499)

Side Effects	Cause	Adjustment
HA, nausea, mastalgia	Estrogen excess	Try dosing QHS vs. low EE pill (↑ risk breakthrough bleeding); consider LARC
Hirsutism, acne, weight gain	Progestin and/or androgen excess	→ 3rd/4th-gen progestin
Mood changes, ↓ libido	Progestin excess	→ 3rd-gen progestin or LARC
Breakthrough bleeding	Often multifactorial	Consider alternate etiology (polyp/infection), missed dose Early cycle/continuous: → ↑ EE **or** consider LARC

		Late cycle bleeding: → ↑ progestin (desogestrel > norgestimate) **or** change to multiphasic preparation vs. LARC
Amenorrhea	Pregnancy; nonpathologic suppression of endometrial shedding	Pregnancy test: If ⊕, d/c OCP; if ⊖, reassure; if pt desires menses → ↑ EE **or** choose progestin w/ ↑ endometrial activity (e.g., 1 mg norethindrone → 5 mg); multiphasic pill may be effective

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Other Contraception Methods

Barrier Methods

- **Condoms:** Consistent, correct use **protects from STI transmission**; latex condoms ↓ HIV risk 80–95% (*Cochrane Data* 2001:CD003255; *Soc Sci Med* 1997;44:1303)
  - *Latex allergy:* 1–6% of US; synthetic and natural membrane available but ↓ 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

Sterilization

- **Tubal obstruction:** Permanent; prevents pregnancy by disrupting tubal patency via tubal ligation or hysteroscopic sterilization device (Essure); 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*

Progestin-Only Methods

- **Progestin-only ("mini-") pills (norethindrone; Camila, Micronor):** Option for pts w/ contraindication to estrogen (including lactation); ↑ risk breakthrough bleeding; must take at same time every day

- **Injectable:** Depot medroxyprogesterone acetate (DMPA); IM/SC injection q 3mo

  Benefits: No need for daily pt adherence, amenorrhea w/ ongoing use, ↓ endometrial CA; no need for specialized provider training; *S/e:* Irregular bleeding (frequent cause for discontinuation of this method), ↑ weight, HA; **can ↓ BMD**, esp in adolescents (FDA Black Box Warning)

Emergency Contraception

Background (*ACOG Practice Bulletin* 152. 2015)

- **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)
- **Efficacy:** ↓ pregnancy risk up to 88% (levonorgestrel EC); does *not* interrupt established pregnancy
- **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

Management

- **Who:** anyone of childbearing age; contraindications (VTE, migraines, liver disease) to daily OCPs do NOT apply to EC
- **Options:** May refer pts to **www.not-2-late.com**

  Levonorgestrel EC: 1 (1.5 mg) dose **(Plan B One-Step, Take Action, Next Choice One Dose, My Way)** or 2 × 0.75 mg taken 12 h apart; *single dose as effective;* safer, more effective than Yuzpe regimen w/ ↓ rates of N/V, but **minimally** effective for women >154 lb (70 kg) (*Contraception* 2014;91:97)

  ***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, especially in women >154 lb;* pregnancy rate = 1.3% w/

ulipristal acetate vs. 2.2% w/ levonorgestrel (use 0–120 h after intercourse) (*Lancet* 2010;375:555; *Contraception* 2014;91:97)

Copper IUD: Most effective form of EC (>10× efficacy of pills), provides continuing contraception; insert w/in 5 d of intercourse; avoid w/ active gonorrhea/chlamydial infection (*CDC MMWR* 2010;59:64; *Hum Reprod* 2012;27:1994)

- **Counseling:** Emphasize regular contraception use (can start OCPs immediately after EC or schedule LARC placement); consider screen for sexual assault; "I'm glad you came in to get help. Can I ask if the sex happened with your consent?" consider screening for STIs; ✓ pregnancy test if no menses in 3–4 wk

PELVIC INFLAMMATORY DISEASE

Background (*CDC MMWR* 2015;64:1; *AFP* 2012;85:791)

- **Definition:** Acute infection of the **upper genital tract** in women; includes endometritis, salpingitis, TOA, pelvic peritonitis; may 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, ***N. gonorrhoeae, C. trachomatis* most common***;* can also be due to 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:** ~1 million pts diagnosed w/ PID annually in US; most common among pts 15–29 y & most frequent Gyn cause for ED visits, though many episodes go undiagnosed; subclinical PID (endometritis) equally common as clinically diagnosed PID, can → same rate of complications (*Infect Dis Obstet Gyn* 2011;2011:561909)
- **Complications/sequelae: Tubo-ovarian abscess (TOA), chronic pelvic pain** (up to 30%) (*Am J Obstet Gynecol* 2002;186:929), **infertility, ectopic pregnancy;** risk ↑ w/ number/severity of episodes (sx >3 d), delays in care, infection 2/2 Chlamydia; recurrent PID assoc w/ 2x ↑

in infertility & 4x ↑ in chronic pelvic pain (*Sex Transm Dis* 2011;38:879)

Evaluation (*AFP* 2012;85:791; *Lancet* 1992;339:785)

- **History:** Sx include **lower abdominal pain** (usually bilateral, ↑ w/ intercourse, palpation, or Valsalva), dyspareunia, fever, chills, back pain, vomiting, & sx of lower genital tract infection (abnl vaginal d/c or bleeding, itching, odor); sx may be mild or absent
- **Risk factors:** Age <25 y; multiple, new, or symptomatic partners; h/o PID or STIs; lack of barrier contraception, IUD (↑ risk *only* w/in 3 wk of insertion), douching
- **Physical exam:** *VS:* only 50% present w/ fever
  Abd: Tenderness in lower quadrants; if RUQ pain, suggests perihepatitis/Fitz–Hugh–Curtis syndrome
  Pelvic exam: Purulent endocervical d/c and/or acute cervical motion tenderness or 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; 95% NPV if no WBCs), CBC, GC/CT, CRP/ESR (Se = 74–93%); HIV, HBV SAg/Ab, syphilis
- **Imaging:** TVUS indicated to dx TOA if clinically ill, severe pain, or adnexal mass; thickened, fluid-filled tubes on TVUS definitive for PID; do not delay tx for imaging
- **Differential diagnosis:** Consider "neighboring structures" (appendix, colon, bladder, urinary tract), other gynecologic phenomena (miscarriage, ectopic, ovarian pathology); see *"Pelvic Pain"*

Treatment (*CDC MMWR* 2015;64:1)

- **Treatment:** 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 minimal 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 cephalosporins **not** recommended due to ↑↑ gonorrhea resistance; consider adding MNZ to treat coexisting BV

CDC 2015 Recommendations for PID Treatment	
Oral/IM Re-evaluate at 72 h; if not responding → IV abx, inpt or outpt	Ceftriaxone 250 mg IM × 1 **and** doxycycline 100 mg PO BID (± MNZ 500 mg PO BID) × 14 d **OR** Cefoxitin 2 g IM × 1 **and** probenecid 1 g PO and doxycycline 100 mg PO BID (± MNZ 500 mg PO BID) × 14 d **OR** Other parenteral 3rd-gen ceph (e.g., ceftizoxime or cefotaxime) × 1 **and** doxycycline 100 mg PO BID (± MNZ 500 mg PO BID) × 14 d
Parenteral	Cefotetan 2 g IV q12h OR cefoxitin 2 g IV q6h **and** doxycycline 100 mg PO or IV q12h **OR** Clindamycin 900 mg IV q8h **&** gentamicin IV / IM 2mg/kg loading dose → 1.5 mg/kg q8h

(https://www.cdc.gov/std/tg2015/pid.htm)

- **Sex partners:** Examine/treat ♂ partners from previous 60 days (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; discuss safe sex practices, offer HPV immunization for pts aged <26 y; regular screening for GC/CT in pts <26 y (see *"STIs," "Screening," and "Immunizations"*)
- **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)

- **Definition:** Vaginal inflammation 2/2 infectious or noninfectious cause; may be associated with unusual discharge, pruritus, and/or 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%

Evaluation (*AFP* 2011;83:816; CDC 2015 STD Treatment Guidelines; *CID* 2008;47:1426)

- **General approach:** S/sx often nonspecific; demographics, PE, diagnostic studies are key
- **History:** *HPI:* Sx: Onset, nature of d/c (see *Exam*), pruritus (vaginal candidiasis [VS], 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); h/o 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, 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 and 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 varies

- **Point-of-care testing:** Vaginal wet mount preparation ("wet prep"): when prepared, can take 5–10 min to complete and may offer definitive dx

Vaginal Wet Prep Examination Process	
Equipment	Cotton swab, test tube with 0.5-mL sterile saline, 2 glass slides, 2 cover slips, microscope
Exam room	Obtain sample of vaginal discharge and place swab in test tube
Sample prep + Whiff test	*Saline sample:* Using swab, place drop of solution onto glass slide, then cover w/ coverslip *KOH sample:* Using swab, place drop of solution onto glass side, add 1 drop 10% KOH; sniff immediately and evaluate for fishy odor ("whiff test"—BV or trichomonas), then cover w/ coverslip
Microscope	Start w/10x, focus & adjust condenser/diaphragm level to ensure good contrast, scan field for areas of interest, then adjust to 40x
Saline sample	May observe squamous cells (normal), PMNs (suggest inflammation), clue cells (BV—squamous cells that look "**pressed in sand**"), or trichomonads (**jerky motion**, ↓ w/ time since sample collected, flagellae often *not* visible)
KOH sample	May observe pseudohyphae and budding yeast (KOH lyses cell walls of cells seen in saline sample, allows clearer view of Candida)

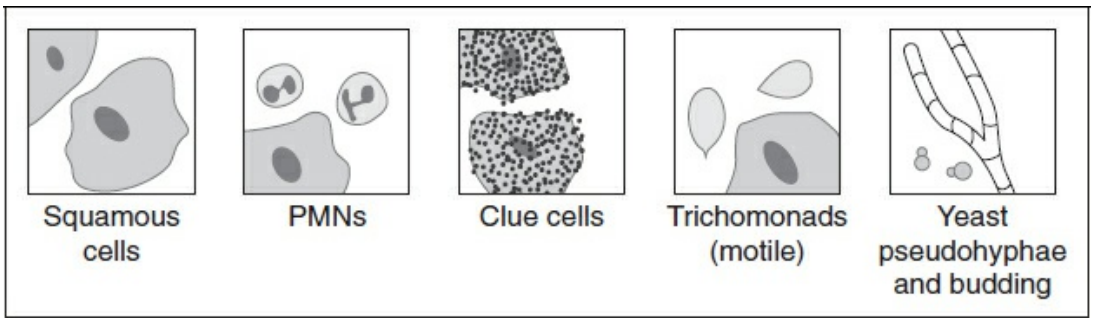


Figure 15-3. Common findings on Wet Mount Microscopy

- **Treatment considerations:** Consider effectiveness/preference of PO vs. topical preparations, pregnancy status, need to Rx sexual partner(s) (see below)

- **When to refer:** If sx persist despite Rx, dx unclear, or "other" causes (see below)

Bacterial Vaginosis (*AFP* 2011;83:816; *AFP* 2004;70:2125; CDC 2015 STD Treatment Guidelines)

- **Background:** Most prevalent cause of vaginal d/c or malodor, often chronic; >50% ♀ w/ BV are asx; may develop into posthysterectomy cuff cellulitis
- **Pathogens:** *Gardnerella vaginalis*, *Lactobacillus*, *Mobiluncus*, *M. hominis*, anaerobic GNRs, polymicrobial
- **Expected findings:** pH >4.5, Whiff test ⊕
- **Microscopy:** >20% clue cells w/ addition of NS
- **Other tests:** No role for cx or cervical cytology; consider PCR if microscopy unavailable
- **Treatment:** Metronidazole (MNZ) is standard; recurrence risk highest w/in 1 y,
  - *Recommended tx:* MNZ 500 mg PO BID × 7 d, counsel against EtOH use during Rx; intravaginal MNZ (0.75 gel, QD × 5 d) vs. clindamycin (2% crm, QD × 7 d) ~equivalent efficacy but ↑ recurrence rates
  - *Alt:* Tinidazole 2 g PO daily × 2 d **or** 1 g PO daily × 5 d; PO clindamycin/intravaginal clindamycin ovules ↓ effective; single-dose PO MNZ (2 g) **not** recommended
  - *Sex partners:* Tx not recommended

Vaginal Candidiasis (*AFP* 2011;83:816; *AFP* 2004;70:2125; CDC 2015 STD Treatment Guidelines)

- **Background:** Highest incidence, 75% of women have ≥1 episode
- **Pathogens:** *C. albicans* > *C. glabrata*, *C. tropicalis*
- **Expected findings:** pH 4–4.5, Whiff test ⊖
- **Microscopy:** Hyphae/pseudohyphae visible w/ addition of 10% KOH
- **Other tests:** Pap smear ↑ Sp but ↓ Se; OTC rapid yeast detection kit convenient, inexpensive; PCR ↑ Se but expensive; Cx if recurrent sx w/ ⊖ microscopy
- **Treatment:** Determine if uncomplicated vs. complicated:
  - *Uncomplicated* (healthy, nonpregnant, mild–mod disease, <4 episodes/y, ⊕ hyphae): Short antifungal course; PO

(fluconazole 150 mg × 1) or topical preparations (multiple azole agents, most 1-, 3-, & 7-d course) similarly effective

Complicated (recurrent, pregnancy, systemic sx, immunocompromise): see below

Recurrent (>4 episodes/y): Consider suppression w/ fluconazole 150 mg q72h × 3 doses, followed by fluconazole 150 mg weekly × 6 mo; if recurrence: repeat regimen but weekly dosing × 1y; repeat PRN, low incidence of resistance

Pregnancy: Topical agents (clotrimazole or miconazole) preferred over PO; 7-d course

Systemic/severe symptoms: Fluconazole 150 mg q72h × 3 doses

Immunocompromise: Fluconazole 150 mg q72h × 3 doses; alert pt that worsening sx may require hospitalization.

Sex partners: Tx **not** recommended

Trichomonas (*AFP* 2011;83:816; *AFP* 2004;70:2125; CDC 2015 STD Treatment Guidelines)

- **Background:** Highly transmissible, frequent coinfection w/ other STIs; may develop into posthysterectomy cuff cellulitis
- **Pathogen:** Trichomonas vaginalis
- **Expected findings:** pH >5.4, Whiff test ⊕
- **Microscopy:** ⊕ trichomonads; leukocytes > epithelial cells
- **Other tests:** Cx, rapid Ag ↑ Se compared w/ microscopy (operator dependent); PCR most Se/expensive
- **Treatment:** Cure rate 90% w/ most PO nitroimidazoles

  Initial tx: MNZ 2 g PO × 1 effective but ↑ GI sx, metallic taste; 500 mg BID × 7 d or tinidazole 2 g PO × 1 ↓ s/e; intravaginal tx **not** recommended due to ↓ cure rate

  Resistant: MNZ 2–4 g/d × 7–14 d; PO **and** intravaginal Rx more effective than PO alone

  Sex partners: **Should be treated** simultaneously; counsel to avoid intercourse until both pt and partner have completed Rx and are asx

Other Vaginitis Etiologies	
Causative Factor/Pathogen	**Notes**

N. gonorrhoeae* or *Chlamydia trachomatis	Often asx; test all pts <25 y w/ vaginal sx; test/tx all pts w/ sx + multiple partners or PID sx (see *"Pelvic Inflammatory Disease," "Sexually Transmitted Infections"*)
Mycoplasma genitalium	Most strongly assoc w/ cervicitis and PID; assoc w/ urethritis in ♂; common co-infxn w/ other pathogens, esp *C. trachomatis*. *Tx:* Azithro 1 g PO × 1; *Alt:* Moxifloxacin 400 mg × 7, 10, or 14 d; *Sex partners:* Tx **not** recommended
Dermatitis (Allergic, Contact)	Diseased vulvar skin more prone to irritation; irritation dermatitis > allergic (*Dermatol Clin* 2010;28:639) *Irritants*: Excessive washing, cleansers/deodorizers, condoms, topical antibacterial/antifungals *Allergens*: Latex, antifungals
Atrophic vaginitis	10–40% of postmenopausal ♀; ↓ Estrogen → vaginal atrophy, ↓ secretions (see *"Menopause"*)
Other	Lichen planus, pemphigus vulgaris, cicatricial pemphigoid, desquamative inflammatory vaginitis, Behcet syndrome, foreign bodies (retained tampons) GYN, derm, or rheum referral, as appropriate

PELVIC PAIN

Background (*AFP* 2010;82:148; *AFP* 2016;93:380)

- **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; no dx found in up to ~1/3 of acute cases
- **General approach:** Distinguish **acute** (≤3 mo) vs. **chronic** (≥6 mo); 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	R/o most common emergent causes: PID, appendicitis, ovarian torsion, ectopic pregnancy, cyst rupture	Up to 40% have >1 dx; dysmenorrhea, dyspareunia & IBS are frequently reported comorbidities

GYN	PID/TOA, ruptured ovarian cyst, ectopic pregnancy, ovarian torsion, miscarriage, torsion/degeneration of uterine fibroid, endometriosis, mittelschmerz	Endometriosis, dysmenorrhea, chronic PID/endometritis, adhesions, adenomyosis, uterine fibroid, pelvic congestion syndrome, ovarian cyst, malignancy
Non-GYN	*GI:* Appendicitis, diverticulitis, bowel obstruction, mesenteric venous thrombosis, IBD flare, perirectal abscess *GU:* Cystitis, pyelonephritis, nephrolithiasis *Ψ/neuro:* Somatization d/o (anxiety, depression, physical or sexual abuse: see *"Somatoform Disorders"*) *Note:* Malignancy must be considered if postmenopausal	*GU:* Interstitial cystitis, radiation cystitis, recurrent UTI, bladder CA *GI:* IBS, IBD, constipation, inguinal hernia, celiac disease, diverticulitis, colitis, colon CA *MSK:* Fibromyalgia, coccydynia, piriformis syndrome, levator ani syndrome, hip arthritis, DJD, stress fx *Neuro:* Abdominal cutaneous nerve entrapment syndrome *Ψ:* Depression, sleep d/o, somatization

Evaluation (*AFP* 2010;82:148; *AFP* 2008;77:1535; *AFP* 2016;93:41; *AFP* 2016;93:380)

- **History:** *Onset* (acute vs. chronic); age, *location* (radiating: appendicitis, kidney stone, ovarian torsion, discitis); quality, exacerbating & alleviating factors; *assoc sx* (menses, constipation, diarrhea, hematochezia, hematuria, dysuria, vaginal d/c, postmenopausal bleeding); PMHx, PSHx; *FHx* (sickle cell, coagulation d/o); *Social hx* (trauma; h/o 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 β-hCG if premenopausal; GC/CT; U/A ± UCx; CBC w/ diff; vaginal wet prep /Cx (see *"Vaginitis"*); 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; *AFP* 2016;93:380)

Treatment of Pelvic Pain, by Etiology	
Treatment	**Therapy**
PID, TOA	See *"Pelvic Inflammatory Disease";* early surgical c/s and inpt mgmt for TOA
Genital HSV	See *"Herpes Simplex Virus"*
Dysmenorrhea	See *"Menstural Diorders";* OCPs + NSAIDs vs. APAP
Endometriosis	OCP (monthly → if inadequate improvement, trial continuous); consider medroxyprogesterone acetate (continuous progestin), GYN referral for possible GnRH agonist (leuprolide), danazol (progestin-like effects), or laparoscopy for dx & tx; levonorgestrel-releasing IUD may ↓ recurrence after laparoscopic tx
Adhesions	Evidence inconsistent re: laparoscopy for adhesiolysis
Chronic pelvic pain	*Surgical:* No shown benefit over nonsurgical (except adenomyosis) *Nonsurgical:* Trial empiric tx for endometriosis (above) *Other modalities:* NSAIDs, consider SSRI for concomitant depression, TCAs, SNRIs or anticonvulsants for neuropathic pain *Multidisciplinary:* Pelvic floor PT, trigger point injections, topical analgesics, heat, acupuncture, somatocognitive tx, 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 or not responsive to initial Rx → GYN; pts w/ unresponsive chronic pelvic pain may benefit from multidisciplinary pain center referral
- **Patient information:** familydoctor.org/condition/chronic-pelvic-pain/ (Chronic Pelvic Pain)

INTIMATE PARTNER VIOLENCE

Background (*AFP* 2013;87:577; 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 IPV in their lifetime, and 14% of men; ♂ → ♀ 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
- **Associations:** Higher prevalence of chronic pain, neurologic disorders, GI disorders, migraine headaches, depression and SI, among those experiencing IPV
- **Screening:** USPSTF recommends screening all women of childbearing age; evidence insufficient for other groups (*Ann Intern Med* 2013;158:478)

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 treatment
- **Screening: 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?"
- **History:** Severity, frequency, type of abuse (incl forced sex); screen for comorbid psych disease, SUD; safety of others in household; assess immediate safety
- **Exam:** Bruises at different stages of healing, unwitnessed head, neck, and facial injuries (*Trauma Violence Abuse* 2010;11:71) "baby zone" injuries (breasts/abdomen), inner thigh bruising (sexual trauma);

photograph injuries
- **Workup:** STI, HIV testing

Management (*JAMA* 2003;289:589; 601)

- Evidence for benefit of counseling, information cards, community service referrals, and mentoring support (*Ann Intern Med* 2012;156:796)
- **Contraception:** Self-empowering methods (i.e., ring, IUD, ♀ condom, diaphragm, hormone injection)
- **Referrals:** Psychiatry as needed, social work for all pts, financial services
- **Pre-exposure HIV prophylaxis:** Consider in high-risk situations
- **Emergency resources:** Provide contact info pt can use in an emergency
- **Mandatory reporting:** Typically not applicable unless also involves abuse of a child (<18), or disabled person (physical or mental); injury involving a firearm or knife may be reportable in some states
- **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:** thehotline.org, 1–800–799-SAFE, futureswithoutviolence.com

BPH AND LOWER URINARY TRACT SYMPTOMS

Background (*AFP* 2014;90:769; *JAMA* 2014;312:535; *NEJM* 2012;367:248)

- **Lower urinary tract symptoms (LUTS):** *Storage:* Frequency, nocturia, urgency, incontinence; *Voiding:* Incomplete emptying, intermittency, straining, dysuria, weak stream, hesitancy; *Polyuria:* ≥3 L UOP/24 h; nocturnal polyuria: ≥33% UOP at night
- **Benign prostatic hyperplasia (BPH):** Prostatic enlargement due to ↑ smooth muscle & epithelial cells within the prostatic transition zone, can lead to LUTS; complications include CKD, urinary retention, recurrent UTI, disturbed sleep, bladder stones, hematuria
- **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 (decongestants, opiates, antipsychotics, antihistamines); urgent catheterization for bladder decompression ± nontitratable a-blockers, 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 (OAB):** Urinary urgency & frequency ± incontinence; may be 2/2 neurologic disorder (stroke, PD) or nonneurologic causes (BPH, bladder stones); storage sx are more prominent in OAB compared to voiding sx seen in BPH
- **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 dx:** Prostate/bladder cancer, bladder stone, UTI, prostatitis, neurogenic bladder, urethral or bladder neck stricture

Evaluation and Prognosis (*J Urol* 2009;181:1779; *NEJM* 2012;367:248)

- **History:** LUTS, pain, dysuria, hematuria, sexual function; ask which sx interfere most w/ QoL; fluid intake, caffeine intake. How many times each night do you wake up to urinate?

  PMHx/PSHx: Including neuro (stroke, PD, dementia, MS), DM (polyuria, polydipsia)

  Medications: Diuretics, antidepressants, bronchodilators, antihistamines, anticholinergics (↓ bladder function/ ↑ urinary sphincter tone), a-agonists (↑ prostatic smooth muscle tone)

  Frequency–volume chart: Record time/volume of every void for 72 h

  IPSS score: Quantitates LUTS sx at 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 if hematuria/irritative sx); check serum PSA as a surrogate marker for prostate size & response to medical Rx (different than PSA screening for asx pt)

  Post-void residual: To r/o silent urinary retention (nl <100 mL)

Uroflowmetry: Measures urine volume/time to quantify urine flow (can't distinguish obstruction from decreased bladder contractility)

Treatment (*AFP* 2008;77:1403; *BJU Int* 2004;94:738; *NEJM* 2012;367:248)

- **Conservative management:** Appropriate if mild sx or sx not bothersome to pt; *adjust meds* (avoid a-agonists, anticholinergics, diuretics), *adjust fluid intake* (UOP goal 1 L/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)

  α-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 wk 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 planning cataract surgery given risk of intraoperative floppy iris syndrome; use caution when combining with PDE5 inhibitors due to orthostasis; tamsulosin 0.4 mg/d preferred in men on sildenafil

  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/ larger prostate (>30 g, PSA ≥1.5); reassess efficacy using IPSS 3 mo after initiating tx; *may take up to 1* y *to show full 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, ✓ PSA prior to initiation (*J Urol* 2005;174:877)

Anticholinergics: Treat LUTS due to OAB; useful in BPH w/ irritative LUTS 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 wk 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 LUTS 2/2 BPH; use caution in pts w/ CrCl <30 mL/min, or who are on a-blockers; may take up to 4 wk 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:** Should be considered if medical therapy insufficient; Transurethral resection, laser ablation, simple prostatectomy, transurethral radiofrequency needle ablation, microwave tx, Uro-Lift; botulinum toxin injection (bladder overactivity)

Commonly Used α-Adrenergic Receptor Antagonists				
Name	**Selectivity**	**Titration**	**Starting Dose**	**Max Dose/d**
Terazosin	Nonselective	Yes	1 mg PO QHS	10 mg
Doxazosin IR	Nonselective	IR: Yes ER: Maybe	IR: 1 mg PO daily ER: 4 mg PO	8 mg

			QD[a]	
Alfuzosin	Nonselective	No	10 mg PO daily[b]	10 mg
Tamsulosin	α-1A selective	Maybe	0.4 mg PO daily[b]	0.8 mg
Silodosin	α-1A selective	No	8 mg PO daily[c]	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

[a]Before breakfast.
[b]After meal.
[c]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 a-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**

MALE SEXUAL DYSFUNCTION

Background (*Eur Urol* 2010;57:804; *Lancet* 2013;381:153; *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
  - **Epidemiology:** ↑ w/ age (5% complete 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: Obesity, 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

- ↓ **libido:** 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 20–30%; multinational studies show average ejaculatory latency 5–6 min (*J Sex Med* 2010;7:2947); may be comorbid w/ ED; if present, tx ED first
- **Priapism:** Painful erection lasting >4 h; requires immediate tx (→ ED)
- **Dyspareunia:** Pain w/ intercourse for >3 mo; may be related to chronic pelvic pain syndrome, Peyronie disease, phimosis (inability to retract foreskin over glans), UTI/cystitis, psychological (h/o abuse)
- **Hematospermia:** Blood in ejaculate; usually benign; ✓ U/A, UCx, gonorrhea/chlamydia based on clinical suspicion; consider PSA, referral to Urology for reassurance; may be present for 4+ wk after prostate bx

Evaluation (*AFP* 2016;94:820; *J Urol* 2005;174:230)

- **History:** Δ in desire, ejaculation, orgasm, penile curvature, genital pain; nocturnal/AM erections, ability to achieve erection/ejaculation from masturbation; distinguish complaints about ejaculation/orgasm from ED; ED severity (e.g., International Index of Erectile Function [IIEF-5]), chronology of sx; LUTS; Y hx, sexual orientation, hx of

sexual abuse, relationship problems, partner's sexual function; may be helpful to interview partner when feasible; screen for CV disease; EtOH/illicit use; presence of spontaneous erections suggests against a vascular or neurologic cause of ED

- **Exam:** *Gen:* 2° sexual characteristics; *Neuro:* Visual fields (pituitary tumor), genital/perianal sensation, LE sensation/strength; *Chest:* Gynecomastia, *CV:* Femoral/LE pulses; *GU:* Penis (phimosis, plaques); testicles (size, firmness), DRE (rectal tone, prostate size/consistency)

  Cremasteric reflex: Contraction of ipsilateral scrotum upon stroking inner thigh → assesses genitofemoral nerve and integrity of thoracolumbar erection center

- **Workup:** Comorbid conditions (e.g., HbA1c, serum lipids), AM testosterone (if ↓ see *"Male Hypogonadism"*); ✓ PSA if prostate pathology suspected (e.g., abnl DRE, LUTS) or plan for testosterone tx (need to discuss risks/benefits of prostate CA dx/tx [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 and 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, can be trialed after PDE5i) → surgery (penile prosthesis)

- **Lifestyle modification:** Smoking cessation, diet, wt loss, ↑ exercise, ↓ EtOH, medication modification, psychotherapy
- **SSRI-related ED:** Usually causes delayed ejaculation, resulting in prolonged stimulation needed for orgasm; tx: ↓ dose, substitute another SSRI or non-SSRI (mirtazapine, bupropion), drug holidays, Rx PDE5i (below); Duloxetine and desvenlafaxine may be less commonly associated with male sexual dysfunction, and PCPs

probably often consider SNRIs as next-line agents if SSRIs are causing sexual side effects

- **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 → ↑ penile blood flow/erection in response to sexual stimuli; onset ~60 min, but as early as 20 min; 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 (rare), vision loss (nonarteritic anterior ischemic neuropathy) & visual disturbance (blue hue; sildenafil, vardenafil)
  - **Cautions/Contraindications:** Caution in pts on a-blockers (e.g., tamsulosin) antihypertensives, or EtOH use as may worsen orthostasis; 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 drug w/in class; discuss risks/benefits of other therapies

PDE5 Inhibitors						
	Starting Dose		Dose Range			
Name	PRN	Daily	PRN	Daily	Duration	Notes
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

Rapid onset of action (~30 min): Avanafil, ODT vardenafil. **Longest acting:** Tadalafil
No food interaction: Tadalafil, avanafil. **Relieves LUTS due to BPH:** Tadalafil
Notes: (1) Absorption ↓ by fatty food; (2) May have visual s/e; (3) Avoid if hx/risk of ↑ QT. Also available as an orally disintegrating tablet; (4) May cause back pain & myalgia due to PDE11 inhibition. Most rapid onset of action.

- **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 (more common than PDE5i), penile pain; also component of Trimix
- **Yohimbine:** ? placebo effect; not recommended by AUA due to concerns about effectiveness & safety (dizziness, HA, nausea, flushing, tachycardia, HTN)
- **Vacuum erection device:** Vacuum↓ intracavernosal pressure →↑ penile blood flow (maintained by elastic band)
- **Penile prosthesis:** Include semirigid, inflatable; high satisfaction rate, but tx of last resort as permanently destroys erectile tissue
- **Testosterone supplementation therapy:** See *"Male Hypogonadism"*; contraindicated in hx prostate/breast CA; may be beneficial when combined w/ PDE5i; **not indicated for tx of ED in setting of nl serum T;** *should NOT be used in men planning on having children as shuts down HPT axis and impairs spermatogenesis*
- **Premature ejaculation:** Pause & squeeze technique, stop–start technique, masturbation prior to sex, desensitizing agents/topical anesthetics (lidocaine–prilocaine, condoms), low-dose 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), consideration of PDE5i if concomitant ED (tx ED first); 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; *JAMA* 2016;316:1838

MALE HYPOGONADISM

Background (*JCEM* 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; normal, mild age-related decline in serum T of unclear significance (*NEJM* 2004;350:482; *JCEM* 2001;86:724)
- **Physiology:** (*NEJM* 2013;369:1011) 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)

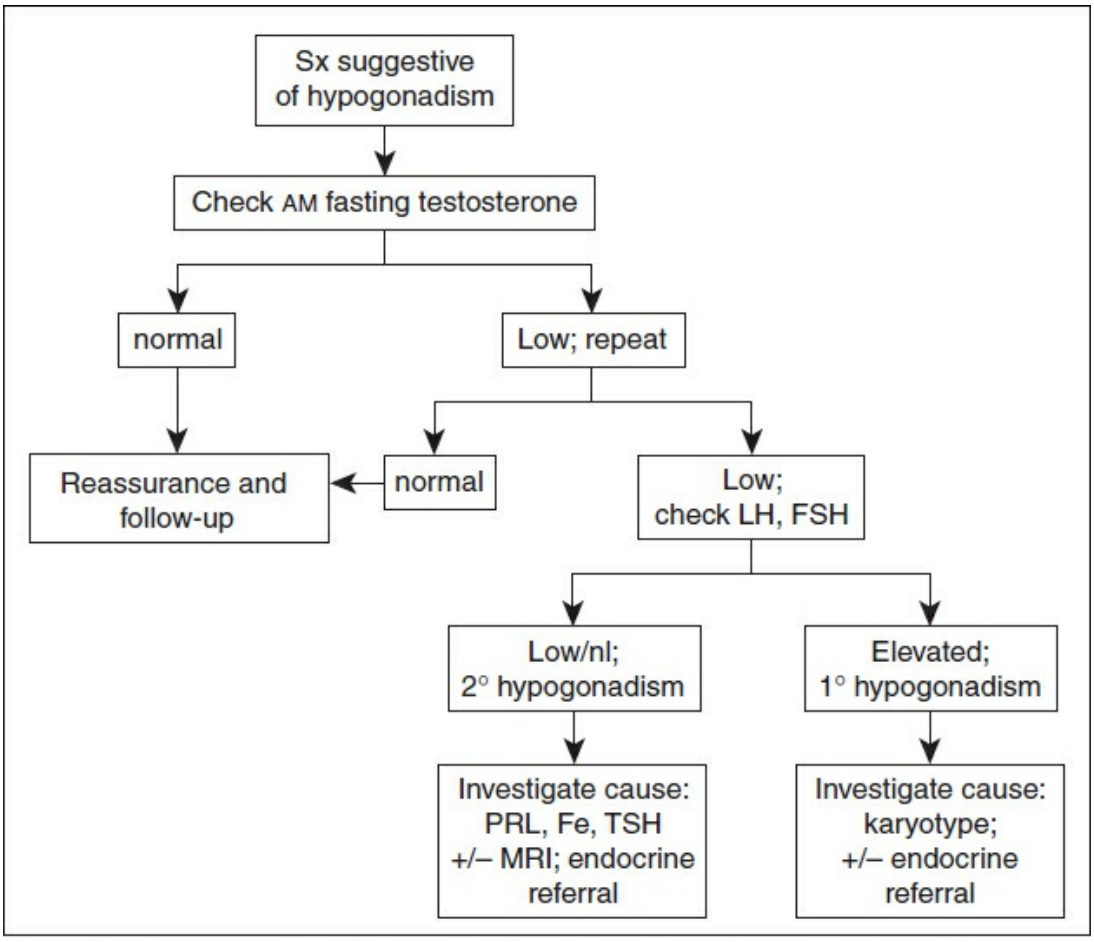
Selected Causes of Hypogonadism	
Cause	**Example/Notes**
Congenital	*1°*: **Klinefelter syndrome;** 46,XY/XO; 47,XXY (common, 1 in 500 ♂), cryptorchidism, d/o of androgen biosynthesis; 2/2: LH, FSH, or GnRH receptor mutations; Kallmann, Prader–Willi
1° acquired	Autoimmune; chemotherapy; medications (ketoconazole); infection (HIV, mumps); bilateral orchiectomy; radiation; torsion; trauma
2° acquired	**DM; obesity;** medications (**GnRH agonists, opioids**); critical illness; ↑ PRL; CNS tumors; pituitary disease; 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/Y;* ↓ **energy, depression,** concentration/memory; sleep disturbances; *Sexual:* ↓ **Libido**, ED; *MSK:* ↓ Muscle bulk/strength, ↑ body fat, ↓ **physical stamina;** *Heme:* Mild normocytic anemia
- **History:** Also attempt to assess age of onset, fertility, & etiologic 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, SHBG, iron studies, CBC/PSA, and ± estradiol
- **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 infertility, see *"Infertility";* PRL, iron studies if 2° hypogonadism & no clear etiology (DM, obesity); pituitary MRI indicated if 2° hypogonadism & severe ↓ T (total T <150) 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) *Advantages:* Standardized values, reflects free & "bioavailable" levels *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



(Adapted from Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *JCEM* 2010;95(6):2536–2559. Copyright © 2010 by The Endocrine Society. With permission.)

Figure 16-1. Testing algorithm

Management (*NEJM* 2004;350:482)

- **Comorbidities:** In pts w/ diseases known to lead 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, poorly controlled BPH/LUTS–see *"BPH & LUTS"*), CHF, untreated 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 q2–3wk; *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:** Only useful to check if symptoms fail to improve on therapy
- **Monitoring:** At 1–2 mo, then q6mo × 2, then yearly: Assess response to tx, perform DRE; *Labs:* check HCT q6mo then annually, PSA; if baseline >0.6 ng/mL, check at 3 & 6 mo, 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

MALE INFERTILITY

Background (*Lancet* 1997;349:787)

- **Definition:** Failure to conceive after 12 mo of unprotected intercourse (6 mo if ♀ partner >35 y); affects 15% of couples; ~20%

d/t ♂ only, 30-40% d/t both ♂ and ♀; also eval ♀ partner, see *"Women's Health."* ♂ infertility assoc w/ ↑ rate of genetic abn, CA, other serious medical conditions in the ♂ himself; ∴eval ♂ even if known ♀ factor or planned IVF, as may improve health/identify heritable conditions (*Fertil Steril* 2013;100:681)

- **Indications for evaluation:** Infertility or concerns for ♂ fertility/future fertility (e.g., h/o cryptorchidism, varicocele)
- **Causes:** Unknown (40–50%), testicular dz (30–40%, i.e., hypogonadism, primary spermatogenesis failure), defective sperm transport (10–20%, i.e., retrograde ejaculation, epidiymal obstruction), endocrine (1–2%, secondary hypogonadism); spermatogenesis takes ~72–81 d;∴events (e.g., febrile illness) w/in previous 3 mo can impact sperm production; changes may take >2–3 mo before reflected in semen parameters. Exogenous testosterone, testosterone-like products/anabolic steroids can shut down HPT axis for mo/y following discontinuation

Evaluation

Basic Reproductive Hx	Detailed Medical Hx
Coital frequency/timing Duration of infertility/prior fertility Childhood illnesses/development Systemic medical illnesses Prior surgeries Sexual hx (incl sexual function, STI) Gonadal toxin exposure (e.g., heat, chemo) (*Andrology* 2016;4:648)	Basic reproductive history Complete ROS Medication use Family reproductive history Detailed social history (incl tobacco, EtOH and anabolic steroid/illicit drug use) (Adapted from *Fertil Steril* 2015;103:e18)

- **Exam:** Habitus, secondary sexual characteristics (body hair distribution, gynecomastia), genital exam (penis, location of meatus, testicle location/consistency/size, epididymides, vasa deferentia, varicocele), DRE as indicated
  - **Varicocele:** Present in 15% of ♂ population, ~40% of infertile ♂; subclinical (detectable on u/s but not physical exam) not clinically relevant (*Fertil Steril* 2014;102:1556)
- **Workup:** Basic reproductive hx and semen analysis (2 if 1st semen analysis abn); refer to urologist or specialist in ♂ infertility if abnl
  - **Semen analysis (SA):** Generally ♂ infertility associated with abnl

SA; nl SA doesn't r/o ♂ factor/guarantee fertility, abnl SA doesn't guarantee infertility; performed after 2–5 d abstinence, by masturbation in clinic where it will be analyzed; can collect at home (masturbation or collection condom) and transport at body temp to lab w/in 1 h but less reliable; frequent ejaculation (q1–2d) doesn't ↓sperm concentration, can ↓ ejaculatory volume, may ↑sperm quality; abstinence >10 d assoc w/ ↓ quality/motility

Endocrine: Usually NOT the cause of ♂ infertility; eval indicated if abn SA, impaired sexual function; *Screening:* AM testosterone, FSH; abn T should prompt further eval, see "*Hypogonadism*"; Do NOT give T to pts interested in fertility → suppresses HPT axis/↓ spermatogenesis; ↑ FSH suggests testicular failure

Specialized testing: Limited clinical utility, defer to urologist or ♂ infertility specialist; defer genetic testing (e.g., karyotype, CFTR mutation, Y-chromosome microdeletion testing) to specialist

Imaging: Generally not indicated; scrotal u/s if irregular testes/concern for mass or if congenital bilateral absence of vas deferens/varicocele are being considered

Semen Analysis Reference Values (WHO 2010)	
Volume	>1.5 mL
pH	>7.2
Sperm concentration	>15 × 10^6/mL
Total sperm count	>39 × 10^6/ejaculate
Percent motility	>40%
Forward motility	>32%
Normal morphology*	>4%

*Based on Krueger strict morphology.

Management (*Fertil Steril* 2013;100:631)

- **Indications for referral:** Abn reproductive hx, abn SA, abn endocrine profile, persistent infertility despite neg ♀ eval/tx, clinical varicocele assoc w/ abn SA or future interest in fertility, concern for genetic abn; treatment options include intrauterine insemination (i.e.,

injection of washed sperm into the uterus), IVF, removal of sperm from testes by microdissection, correction of hormonal problems

- **Recs for ↑ chances of conception while awaiting referral** (*Fertil Steril* 2013;100:631)
  - **Education:** Intercourse frequency (q1–2d) and timing (6 d leading up to ovulation, see *"Women's Health"*), avoid lubricants (incl olive oil, saliva; can use canola/mineral oil, hydroxyethylcellulose-based products, if needed), avoid gonadotoxins/heat exposure
  - **Lifestyle:** Heart-healthy diet, moderate exercise, weight loss, ↓ EtOH, stop tobacco/marijuana/illicit drug use, ↓ stress
  - **Supplements:** Limited evidence supporting use; daily MVI/? CoQ_{10} may have benefit; stop testosterone-like products
  - **Optimize chronic medical conditions** (e.g., diabetes), sexual function
- **Patient information:** *JAMA* 2015;313:320;1770

PROSTATITIS

Bacterial Prostatitis (*AFP* 2010;82:397; *JAMA* 1999;282:236; *NEJM* 2006;355:1690)

- **Prostatitis:** Acute or chronic (>3 mo) 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); GC/CT can infect the prostate
  - **Complications:** Bacteremia, pelvic abscess, metastatic infection, epididymitis
  - **Risk factors:** Prostate biopsy, immunocompromise, anatomic abnormalities, urinary catheters/instrumentation, sexual activity
  - **Ddx:** UTI, cystitis, urethritis, BPH, chronic pelvic pain syndrome, epididymoorchitis

	Acute Bacterial Prostatitis	Chronic Bacterial Prostatitis

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); ✓ GC/CT	Compare midstream U/A, UCx, gram stain before & after 1 min prostate massage (⊕ if bacteria only in post, or post >10x pre-massage Ucx); ✓ GC/CT
Therapy	**Empiric Tx (IV abx if acutely ill):** **Gram ⊖ organisms:** Ciprofloxacin 500 mg PO BID, levofloxacin 500 mg PO QD, or TMP-SMX DS PO BID; **Gram ⊕**: Cephalexin 500 mg PO q6h; **GC/CT:** see *"STI"* Tx 4–6 wk, adjust abx based on culture; β-lactams & nitrofurantoin have poor prostate penetration; for recurrent infections, treat w/ longer course (3 mo) w/ different abx	
Referral indications: Urinary retention, severe sx, suspicion for prostatic abscess (e.g., fever for >36 h after appropriate abx tx initiated)		

- **Patient information:** *JAMA* 2012;307:527

Chronic Prostatitis/Chronic Pelvic Pain Syndrome

- Chronic pelvic pain for ≥3 of 6 mo; may be inflammatory or noninflammatory w/o infection; unclear if related to h/o bacterial or ongoing cryptic infection; usually dx of exclusion, so likely heterogeneous group of disorders rather than a single disorder
- **Ddx:** BPH, urethral stricture, prostatic abscess, prostate cancer, urethritis, epididymoorchitis, 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 h/o UTIs; screen for sexual dysfunction, h/o abuse, depression/Ψ; ± pain w/ erections/ejaculation; consider UPOINT classification to guide dx/tx (www.upointmd.com)

- **Exam:** Abdomen, back/spine, rectal exam (prostate/pelvic muscle tenderness), detailed genital exam; ✓ for hernias, scrotal masses, hemorrhoids
- **Workup:** U/A, UCx (pre- and postprostate massage), STI testing; imaging guided by sx; prostate massage is typically done in a urologist's office
- **Treatment** (*AFP* 2010;82:397; *NEJM* 2006;355:1690): Difficult to tx as likely a collection of different disorders; UPOINT classification can help guide tx (www.upointmd.com)
  - **Symptomatic treatment:** NSAIDs or celecoxib useful if pain is primary symptom
  - **Antibiotics:** Controversial but commonly used; RCT fail to show benefit, & no clear guidelines exist (often used >1 mo), may improve pain if bacterial source
  - **α–blockers é 5α-reductase inhibitors:** Controversial but commonly used (*JAMA* 2011;305:78); RCT of alfuzosin failed to show benefit (*NEJM* 2008;359:2663); however, α-blockers ± 5α-reductase often trialed at least 3 mo, may be used w/ or w/o abx
  - **Other:** Quercetin, pregabalin, gabapentin, nortriptyline; pelvic floor physical therapy; psychotherapy; referral to chronic pain specialist
  - **Urology referral:** Persistent or severe pain/LUTS

SCROTAL & TESTICULAR LESIONS

Background (*AFP* 2014;89:273)

- 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, 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 injury, torsion, strangulated inguinal hernia

Fournier gangrene (Emergent): Necrotizing fasciitis of perineum; painful/swelling/ induration of penis/scrotum/perineum, cellulitis/edema, ± crepitus, fever → ED

Testicular torsion (Emergent): Testis twists around spermatic cord → hypoxia → ED

Suspected cancer (Urgent): Intratesticular masses are CA until proven o/w → urology

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Acute Epididymoorchitis

- Most common cause of scrotal pain; usually d/t infection (spread from urinary tract) or ischemia; orchitis alone rare unless viral
- **Causes:** *Infectious:* Bacterial (<35 y: STI; >35 y: *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

  Cremasteric reflex: Contraction of ipsilateral scrotum upon stroking inner thigh → assesses genitofemoral nerve; may be absent in torsion

- **Workup:** H&P, midstream U/A, UCx, STI testing (if at risk); urethral swab cx/GS if d/c
  - **Scrotal U/S:** Usually not necessary (recommended for orchitis, r/o tumor/torsion)
- **Treatment:** Scrotal support, analgesics (NSAIDS, ± opiates), ice, empiric abx
  - **GC/CT suspected:** Ceftriaxone + azithromycin/doxycycline, see *"STI"*
  - **If STI unlikely:** Levofloxacin 500 mg PO QD × 10 d, tailor based on cx results
- **Follow-up:** Pain/fever usually resolves within 3 d, induration may last wk/mo; if no improvement: Re-evaluate, repeat cx, scrotal U/S; if STI, tx sexual partners, see *"STI"*

Chronic Epididymoorchitis/Orchalgia/Epididymalgia (*Rev Urol* 2003;5:209)

- **Definition:** Scrotal pain >3 mo; may be intermittent, bilateral, mild–severe pain, often part of chronic prostatitis/CPPS, see *"Chronic Prostatitis/Chronic Pelvic Pain Syndrome"*
- **Risk factors:** ? STI; often dx of exclusion so likely heterogeneous group of problems
- **Exam:** Epididymal tenderness (up to 50% will have nl exam); check external genitals, DRE (prostate/muscle tenderness), inguinal/lower abdomen, back/spine
- **Workup:** Assess LUTS, midstream U/A, UCx, STI testing; urethral swab cx/GS if d/c
  - **Scrotal ultrasound:** Esp if indurated epididymis or difficult exam 2/2 pain/habitus
- **Treatment:** Typically self-limited, may take mo/y to resolve, very difficult to tx (limited data d/t heterogeneity); consider UPOINT classification to guide tx (www.upointmd.com)
  - **Conservative mgmt:** NSAIDs, scrotal support, avoid painful activities, warm compresses, pelvic floor PT (if pelvic muscle tenderness)

Opiates: Avoid d/t chronic nature of pain, strongly consider referral to pain specialist
Empiric abx: 4–6 wk; evidence lacking for effectiveness/regimen
Referral: For consideration of spermatic cord block (can repeat every couple of mo 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:** Nontender swelling behind/above (i.e., separate) from testicle, compression → pain
- **Workup:** U/S if dx in question
- **Treatment:** Typically asx → reassurance (may continue to grow); If sx → urology referral

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Hydrocele

- **Definition:** Fluid collection within tunica vaginalis; often present at birth, most resolve by 1 y; can spontaneously occur/recur/↑ size
- **Risk factors:** Scrotal trauma, scrotal infection, STI
- **Exam:** Painless swelling involving testicles, transilluminates
- **Workup:** U/S if doesn't fully transilluminate, can't assess testicle or other scrotal contents
- **Treatment:** Generally asx, no tx required; if pain or size limit activity → urology referral

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Varicocele

- **Definition:** Dilation of testicular veins; very common, majority L side or b/l; unilateral R side rare; may be associated with infertility
- **Exam:** "Bag of worms" in scrotum, ↑ size w/ standing/Valsalva; may

c/o dull pain/heaviness

- **Workup:** Consider abdominal CT or U/S to r/o retroperitoneal mass if unilateral R side or sudden onset/worsening
- **Treatment:** Generally asx; refer to urologist if painful, assoc w/ infertility or discrepant testicular size prior to attempting to conceive

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Testicular Cancer (*AFP* 2008;77:469; *NEJM* 2014;371:2005)

- **Pathology:** Germ cell tumors (95%, seminoma/nonseminoma), sex cord stromal tumors
- **Epidemiology:** Most common tumor in ♂ 15–35 y; ~8000 cases/y in US, ~400 deaths/y (*CA Cancer J Clin* 2013;63:11)
- **Risk factors:** Cryptorchidism (surgery ↓ CA risk & facilitates monitoring), testicular dysgenesis, FHx, HIV (seminoma) (*JCO* 2003;21:1922)
- **Screening:** USPSTF recommends *against* routine screening in asx pts (*Ann Intern Med* 2011;154:483) d/t high cure rate and unclear mortality benefit (*Cochrane Database Syst Rev* 2011:CD007853); consider screening in pts w/ risk factors
- **Exam:** Intratesticular mass ± pain/swelling/hardness; does not transilluminate; usually unilateral, R > L; bilateral likely lymphoma; ✓ for gynecomastia
- **Workup:** Assume testicular mass CA until proven o/w → Color duplex U/S, ✓ tumor markers (AFP, LDH, β-hCG) → urgent urology referral

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Other Causes of Scrotal Pain/Masses

- **Strangulated inguinal hernia:** Surgical emergency → 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:** Must r/o testicular torsion; sudden onset pain often localized to superior aspect of testicle ± “blue dot

sign" (40%), cremasteric reflex intact; Tx: Self-limited, none
- **Mumps orchitis:** Fever, HA, myalgia, parotid swelling

PROSTATE CANCER

Background (*JAMA* 2014;311:1143; 2015;314:825; 2073; *NEJM* 2011;365:2013)

- **Clinical heterogeneity:** Varies from indolent (majority) to aggressive, rapidly lethal disease
- **Epidemiology:** Annually ~240,000 US men dx, ~30,000 deaths; 1 in 6 lifetime risk of dx, but 30% men >50 & 70–90% >80 y have prostate CA on autopsy; only ~3% die from prostate CA (*CA Cancer J Clin* 1997;47:273)
- **Presentation:** Most cases asx, detected by abnl PSA or DRE; urinary sx are usually a late finding ∴ LUTS usually not d/t prostate CA
- **Risk factors:**↑ age, African ancestry (earlier onset/more aggressive), obesity, family hx (1° >2° relative (esp if dx <65 y), BRCA1/2 carrier, Lynch syndrome
- **Prevention:** No recommended tx; 5a-reductase inhibitors (off label) ↓ incidence low grade but slight ↑ in high-grade CA, unclear benefit (*NEJM* 2011;365:97); vitamins do not ↓ risk (SELECT, *JAMA* 2009;301:39; 52)
- **PSA:** Secreted by nl prostate cells, good surrogate for prostate size; prostate CA, inflammation, trauma disrupt normal architecture → ↑ PSA; if ↑ PSA r/o benign causes repeat several wk later; 5a-reductase inhibitors ↓ PSA by ~50% and should be taken into account when interpreting PSA (*J Urol* 2005;174:877); role of PSA velocity, density, fractionation in detection of prostate CA unclear (*Cancer* 2007;109:1689)

  Factors that alter PSA: Increase: Age; ejaculation (up to 0.8 ng/mL for 48 h), prostatitis (PSA returns to baseline after 6–8 wk), prostate biopsy or TURP (levels may take 2–4 wk to normalize), acute urinary retention; DRE may increase PSA by 0.26–0.4 ng/mL; **Decrease:** Finasteride, dutasteride

  Interpretation: Cut-off for upper limit of normal controversial, and a value of 4.0 ng/mL typically used (Se 21%, Sp 91%, PPV

30%) (*CA Cancer J Clin* 2010;60:70); NPV 85% if PSA ≤4.0 (*NEJM* 2004;350:2239); role of PSA velocity, density, fractionation in detection of prostate CA unclear (*Cancer* 2007;109:1689)

- **Digital rectal exam:** Detects peripheral zone tumors, but ~30% of tumors arise in other parts of prostate; prostate CA may manifest as induration, a nodule, or asymmetry; Se 59%, Sp 94%, PPV 28%, NPV 99% (*Fam Pract* 1999;16:621)
- **PSA/DRE are not diagnostic:** CA found in 22% of PSA btw 2.6–9.9 ng/mL, 67% >10 ng/mL (*JAMA* 1997;277:1452; *NEJM* 1991;324:1156); no PSA completely r/o CA

Benefits of Screening (*Ann Int Med* 2015;163:ITC1; *NEJM* 2011;365:2013)
Early detection & tx, some studies show CA-specific survival benefit, esp in pts at ↑ risk
⊖ Results may provide reassurance
Risks of Screening
Bx and tx of tumors assoc with low but nonzero rates of impotence, incontinence, bowel problems, infection, pain, & mortality. Tumors might not 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 & decision is not urgent
(3) Inform pt that some trials found a mortality benefit w/ screening; discuss that evidence is mixed w/ some experts in favor & some against; review major society guidelines
(4) Inform pt that many prostate CA detected by screening might 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 CA; if the PSA or DRE are abnl a bx may be necessary & even this may not conclusively r/o cancer; PSA may be elevated for other reasons
(6) Tx of prostate CA, even if detected early, may entail surgery or radiation, which have significant s/e

- **Documentation:** Discussion of risks/benefits of screening & shared decision-making esp if pt declines screening
- **Refer for biopsy:** Abnl DRE and/or PSA (usually ≥4 ng/mL, or

significant ↑); consider referral to urologist if strong family hx or high risk

- **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/prostate((USPSTF); http://www.mayoclinic.com/health/prostate-cancer/HQ01273 (Mayo Clinic)

Prostate CA Screening Guidelines
(Adapted from *Ann Intern Med* 2013;158:761; *NEJM* 2011;365:2013)

Recommendation	USPSTF	AUA	ACP	ACS
Shared decision-making	On pt request (*Ann Intern Med* 2012;157:120)	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[a]
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	q1–2 y	PSA >2.5 q1 y	PSA >2.5 q1 y PSA <2.5 q2 y
Criteria for bx referral	N/A	Consider age, FHx, race, DRE, PSA (total, free, velocity, density), prior bx, PMHx		PSA ≥4, abnl DRE PSA 2.5–4, individualized risk eval

[a]African-American pts & those w/ 1st-degree relatives w/ prostate cancer diagnosed before 65 y.

ABBREVIATIONS

1°	primary
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
17-OHP	17-hydroxyprogesterone
Aϕ	alkaline phosphatase
α1AT	α-1 antitrypsin
A1c	hemoglobin A1c
AA	Alcoholics Anonymous amyloid A
AAA	abdominal aortic aneurysm
AAD	antiarrhythmic drug
AAFP	American Academy of Family Physicians
αB	alpha-blocker
Ab	antibody
ABE	acute bacterial endocarditis
ABG	arterial blood gas
ABI	ankle-brachial index
abnl	abnormal
ABPA	allergic bronchopulmonary aspergillosis

ABPM	ambulatory blood pressure monitoring
ABRS	acute bacterial rhinosinusitis
abx	antibiotics
A/C	air conditioning
AC	acromioclavicular
	anticholinergic
ACC	adrenal cortical carcinoma
	American College of Cardiology
ACCP	American College of Chest Physicians
ACD	allergic contact dermatitis
ACE	angiotensin-converting enzyme
ACEI	ACE inhibitor
ACHD	adult congenital heart disease
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
	Alzheimer 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
AERD	aspirin exacerbated respiratory disease
AF	atrial fibrillation
AFB	acid-fast bacilli
AFib	atrial fibrillation
AFL	atrial flutter
AFP	α-fetoprotein
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
AKI	acute kidney injury
AL	amyloid light chain
alb	albumin
ALF	acute liver failure
ALL	acute lymphoblastic leukemia
ALS	amyotrophic lateral sclerosis
alt	alternative

ALT alanine aminotransferase
AM anti-muscarinic
AMA anti-mitochondrial antibody
AMD age-related macular degeneration
AMH asymptomatic microscopic hematuria
AMI anterior myocardial infarction
AML acute myelogenous leukemia
AMS altered mental status
AN anorexia nervosa
ANA antinuclear antibody
ANC absolute neutrophil count
ANCA antineutrophilic cytoplasmic antibody
angio angiogram
AOE average onset
AOM acute otitis media
AoV aortic valve
AP anterior–posterior antipsychotic
APAP acetaminophen
APC activated protein C
APL acute promyelocytic 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
ARNI angiotensin receptor neprilysin inhibtor
ARS Acute retroviral syndrome
acute retroviral syndrome (HIV)
ART antiretroviral therapy
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
ASCVD atherosclerotic cardiovascular disease
ASD acute stress disorder
atrial septal defect
ASIS anterior superior iliac spine
ASO anti-streptolysin O
assoc w/ associated with
AST aspartate aminotransferase
average survival time
ASTHM American Society of Tropical Medicine and Hygiene
asx asymptomatic
AT atrial tachycardia
ATG antithymocyte globulin
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
AUD alcohol use disorder
AV atrioventricular
AVA aortic valve area
AVB atrioventricular block

	AV block
avg	average
AVM	arteriovenous malformation
AVN	avascular necrosis
AVNRT	AV nodal reentrant tachycardia
AVR	aortic valve replacement
AVRT	AV reciprocating tachycardia
AZA	azathioprine
AZT	zidovudine
b/c	because
b/l	bilateral
BAL	blood alcohol
	bronchoalveolar lavage
BAV	bicuspid aortic valve
βB	beta-blocker
BBB	bundle branch block
BCC	basal cell carcinoma
BCx	blood culture
BD	bile duct
BG	blood glucose
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
bili	bilirubin
BiPAP	bilevel positive airway pressure
BiV	biventricular
BM	bone marrow
	bowel movement
BmBx	bone marrow biopsy
BMD	bone mineral density

BMI	body mass index
BMP	basic metabolic panel (Chem-7)
BMS	bare metal stent
BMT	bone marrow transplant
BN	bulimia nervosa
BNP	B-type natriuretic peptide
BOOP	bronchiolitis obliterans with organizing pneumonia
BP	blood pressure
BPAD	bipolar affective disorder
BPH	benign prostatichypertrophy
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/f	concern for
c/o	complains of
c/w	compared with
	consistent with
Ca	calcium
CA	cancer
CAA	cerebral amyloid angiopathy
CABG	coronary artery bypass grafting

CAD	coronary artery disease
CAH	congenital adrenal hyperplasia
cal	calorie
CALLA	common ALL antigen
CAM	complementary 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 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
CFTR	cystic fibrosis transmembrane conductance regulator
Cftx	ceftriaxone
CFU	colony forming units

cGMP	cyclic guanosine monophosphate
CHB	complete heart block
CHD	congenital heart disease
CHF	congestive heart failure
CHL	conductive hearing loss
CHO	carbohydrate
CI	cardiac index
	cholinesterase inhibitor
	contraindicated
	contraindications
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
CM	contingency management
CMC	carpalmetacarpal (joint)
CML	chronic myelogenous leukemia
CMML	chronic myelomonocytic leukemia
CMP	cardiomyopathy
CMT	Charcot Marie Tooth
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

CPPS chronic pelvic pain syndrome

Cr creatinine

CRA central retinal artery

CRC colorectal cancer

CrCl creatinine clearance

CREST calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias

CRH cortisol-releasing hormone

crm cream

CRP C-reactive protein

CRS chronic rhinosinusitis

CRT cardiac resynchronization therapy

CRV central retinal vein

CsA cyclosporine A

CSF cerebrospinal fluid

CSM carotid sinus massage

CSOM chronic suppurative otitis media

CSS clinical stabilization service

CT chlamydia trachomatis
computed tomography

CTA CT angiogram

CTD connective tissue disease

CTS carpal tunnel syndrome

CV	cardiovascular
CVA	cerebrovascular accident (stroke)
	costovertebral angle
CVAT	costovertebral 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
CYC	cyclophosphamide

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
DAPT	dual antiplatelet therapy
DASH	dietary approaches to stop hypertension
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
def deficiency
def'n definition
derm dermatologic
DES drug-eluting stent
diethylstilbestrol
dry eye syndrome
DFA direct fluorescent antigen detection
DFE dilated fundus exam
DFI diabetic foot infection
DGI disseminated gonococcal infection
DGP deamidated gliadin peptide
DHEA dehydroepiandrosterone
DHT dihydrotestosterone
DI diabetes insipidus
DIC disseminated intravascular coagulation
diff. differential
DILI Drug-Induced Liver Injury
DIP desquamative interstitial pneumonitis
distal interphalangeal (joint)
DJD degenerative joint disease
DKA diabetic ketoacidosis
DLCO 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

DOAC direct oral anticoagulant
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
dSSC diffuse systemic sclerosis/scleroderma
DST dexamethasone suppression test
d/t due to
DTR deep tendon reflex
DU duodenal ulcer
DUB dysfunctional uterine bleeding
DVT deep vein thrombosis
dx diagnosis
DXA dual-energy x-ray absorptiometry (DEXA)

EAC external auditory canal
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 esophagogastrod-uodenoscopy
EGFR epidermal growth factor receptor
eGFR estimated GFR
EGPA Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
EHEC enterohemorrhagic *E. coli*
EI entry inhibitor
EIA enzyme-linked immunoassay
EIB exercise-induced bronchospasm
EIC epidermal inclusion cyst
EKC epidemic keratoconjunctivitis
ELISA enzyme-linked immunosorbent assay
EM erythema migrans

EMA endomysial antibody
EMB ethambutol
EMDR eye movement desensitization and reprocessing
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
extrapyramidal side-effects
ER emergency room
extended release
ERCP endoscopic retrograde cholangiopancre-atography
ERV expiratory reserve volume
ESA erythropoiesis stimulating agent
ESC European Society of Cardiology
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
fx Fracture

G6PD glucose-6-phosphate dehydrogenase
GAD generalized anxiety disorder
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
GCS Glasgow coma scale
G-CSF granulocyte colony stimulating factor
GDM gestational diabetes mellitus
GDMT guideline directed medical therapy
GE gastroesophageal
gen generation
GERD gastroesophageal reflux disease
GFD gluten-free diet
GFR glomerular filtration rate
GGT γ-glutamyl transpeptidase

GH	glenohumeral (joint)
	growth hormone
GI	gastrointestinal
GIB	gastrointestinal bleed
GIOP	glucocorticoid-induced osteoporosis
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	drop
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
HBIG	hepatitis B immune globulin
HBV	hepatitis B virus

HC	hemorrhagic cystitis
HCAP	healthcare-associated pneumonia
HCC	hepatocellular carcinoma
HCMP	hypertrophic cardiomyopathy
HCQ	hydroxychloroquine
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
HepA	hepatitis A vaccine
HepB	hepatitis B vaccine
HEV	hepatitis E virus
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
Hgb	hemoglobin
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
HMG-	β-Hydroxy β-methylglutaryl-CoA

CoA

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

IBM inclusion body myositis

IBS irritable bowel syndrome

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
I+ CT	CT with iodinated intravenous contrast
ICU	intensive care unit
IDDM	insulin-dependent diabetes mellitus
IDSA	Infectious Diseases Society of America
IDU	injection drug use
IDV	indinavir
IE	infective endocarditis
IF	intrinsic factor
IFIS	intraoperative floppy iris syndrome
IFN	interferon
Ig, IG	immunoglobulin
IGF	insulin-like growth factor
IGRA	interferon-γ release assay
IHD	ischemic heart disease
II	integrase inhibitor
IIP	idiopathic interstitial pneumonia
ILD	interstitial lung disease
ILI	influenza-like illness
ILR	implantable loop recorder
IM	intramuscular
IMI	inferior myocardial infarction
incl	including

inh	inhaled
INH	isoniazid
INR	international normalized ratio
IOM	Institute of Medicine (US)
IOP	intensive outpatient intraocular pressure
IPD	invasive pneumococcal disease
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
IV	intravenous
IVB	intravenous bolus
IVC	inferior vena cava
IVCD	intraventricular conduction delay
IVF	in vitro fertilization intravenous fluids
IVIg	intravenous immunoglobulin
JVD	jugular venous distention
JVP	jugular venous pulse
KOH	potassium hydroxide
KS	Kaposi sarcoma
KUB	kidneys, ureters, & bladder (radiograph)

LA left atrium
long-acting
lupus anticoagulant

LAA left atrial abnormality
left atrial appendage

LABA long-acting β_2-agonist

LAD left anterior descending coronary artery
left axis deviation
lymphadenopathy

LAE left atrial enlargement

LAN lymphadenopathy

LAP left atrial pressure
leukocyte alkaline phosphatase

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
LOE	level of evidence
LOS	length of stay
LP	lumbar puncture light perception
LpA	lipoprotein A
lpf	low power field
LPFB	left posterior fascicular block
LQTS	long QT syndrome
LR	lactated Ringer's likelihood ratio
LRI	Lower respiratory infection
LSD	lysergic acid diethylamide
LSIL	low-grade squamous intraepithelial lesion
lSSC	limited systemic sclerosis/scleroderma
LTBI	latent tuberculosis infection
LTRA	leukotriene receptor antagonist
LUSB	left upper sternal border
LUTS	lower urinary tract symptoms
LV	left ventricle
LVAD	LV assist device
LVEDP	LV end-diastolic pressure
LVEDV	LV end-diastolic volume
LVEF	left ventricular ejection fraction
LVESD	LV end systolic diameter

LVH left ventricular hypertrophy
LVOT left ventricular outflow tract
LVP large volume paracentesis
LVSD LV systolic dimension

M million
MAC mitral annular calcification
Mycobacterium avium complex
MACE major adverse cardiac event
MAHA microangiopathic hemolytic anemia
MALT mucosa-associated lymphoid tissue
MAOI 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-methylenedioxy-methamphetamine (Ecstasy)
MDR multidrug resistant
MDS myelodysplastic syndrome
MELD model for end-stage liver disease
MEN multiple endocrine neoplasia

MET	metabolic equivalent
MG	myasthenia gravis
MGD	Meibomian gland dysfunction
mgmt	management
MGUS	monoclonal gammopathy of uncertain significance
MH	male hypogonadism
MI	myocardial infarction
MIBI	sestamibi
MIC	minimum inhibitory concentration
mil	million
min	minute
	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
MOCA	Montreal cognitive assessment
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
MPGN	membranoproliferative glomerulonephritis
MPN	myeloproliferative neoplasm

MPTP methylphenyl tetrahydropyridine
MR magnetic resonance
mitral regurgitation
MRA magnetic resonance angiography
MRCP magnetic resonance cholangiopan-creatography
MRI magnetic resonance imaging
MRSA methicillin-resistant *S. aureus*
MRV magnetic resonance venography
MS mental status
mitral stenosis
multiple sclerosis
MSD male sexual dysfunction
MSK musculoskeletal
MSM men who have sex with men
MSSA methicillin-sensitive *S. Aureus*
MSU monosodium urate
MT metatarsal
MTb *Mycobacterium tuberculosis*
MTP metatarsal phalangeal joint
MTX methotrexate
MUI mixed urinary incontinence
MV mitral valve
MVA mitral valve area
MVC motor vehicle crash
maraviroc
MVI multivitamin
MVP mitral valve prolapse
MVR mitral valve replacement
M_{Φ} macrophage

NA	narcotics anonymous
Na	sodium
NAAT	nucleic acid amplification testing
NAC	N-acetylcysteine
NADPH	nicotinamide adenine dinucleotide phosphate
NAFLD	nonalcoholic fatty liver disease
NAION	nonarteritic ischemic anterior ischemic optic neuropathy
NAM	necrotizing autoimmune myositis
NAMCS	National Ambulatory Medical Care Survey
NASH	nonalcoholic 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 lymphoma
NIDA	National Institute on Drug Abuse
NIDDM	non–insulin-dependent diabetes mellitus
NIF	negative inspiratory force
NIHL	noise-induced hearing loss
NIPPV	noninvasive positive pressure ventilation
NJ	nasojejunal
nl	normal
NLP	no light perception
N/V	nausea and/or vomiting
N/V/D	nausea/vomiting/diarrhea

NM neuromuscular
NMDA *N*-methyl *D*-aspartate
NMJ neuromuscular junction
NNH number needed to harm
NNRTI nonnucleoside reverse transcriptase inhibitor
NNS number needed to screen
NNT number needed to treat
NO nitric oxide
NOAC new oral anticoagulant
NOS not otherwise specified
NPDR nonproliferative diabetic retinopathy
NPJT nonparoxysmal 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
NSG neurosurgery
NSIP nonspecific interstitial pneumonia
NSR normal sinus rhythm
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
ODT	orally disintegrating tablet
OG	osmolal gap
OGT	orogastric tube
OGTT	oral glucose tolerance test
OHS	obesity hypoventilation syndrome
OI	opportunistic infection
OK	okay
OM	obtuse marginal coronary artery
OME	otitis media with effusion
OMFS	oral and maxillofacial surgery
ONH	optic nerve head
ONJ	osteonecrosis of the jaw
OP	oropharynx
OR	odds ratio
	operating room
OROS	oral release osmotic system
OSA	obstructive sleep apnea
OTC	over-the-counter
OTP	opioid treatment program

OU	both eyes
p/w	present(s) with
PA	pulmonary artery
PAC	premature atrial contraction
	pulmonary artery catheter
PAD	peripheral arterial disease
PAN	polyarteritis nodosa
PAPA	pyogenic arthritis, pyoderma gangrenosum, acne syndrome
para	paracentesis
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
PCSK9	roprotein convertase subtilisin/kexin type 9
PCT	porphyria cutanea tarda
	proximal convoluted tubule
PCV	polycythemia vera
PCWP	pulmonary capillary wedge pressure
PD	Parkinson disease
	peritoneal dialysis
PDA	patent ductus arteriosus

	posterior descending coronary artery
PDE	phosphodiesterase
PDE5	Phosphodiesterase 5 inhibitor
PDGF (R)	platelet-derived growth factor (receptor)
PDR	proliferative diabetic retinopathy
PE	pulmonary embolism
	physical exam
	pulmonary embolus
PEA	pulseless electrical activity
PEEP	positive end-expiratory pressure
PEF	peak expiratory flow
PEG	polyethylene glycol
PEP	postexposure 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)
PJP	*Pneumocystis* pneumonia
PKD	polycystic kidney disease
PKU	phenylketonuria
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
PRN	as needed
PRPP	phosphoribosyl-1- pyrophosphate
PRWP	poor R wave progression
PS	pulmonic stenosis
PSA	prostate-specific antigen
PsA	psoriatic arthritis
PSAP	personal sound amplification product
PSC	primary sclerosing cholangitis
PSG	polysomnography
PSGN	post streptococcal glomerulonephritis
PSHx	past surgical history
PSV	pressure support ventilation
psych	psychiatric
Pt	patient
PT	prothrombin time
	physical therapy
PTA	percutaneous transluminal angioplasty
PTH	parathyroid hormone
PTH-rP	parathyroid hormone–related peptide
pts	patients
	points
PTSD	posttraumatic stress disorder
PTT	partial thromboplastin time
	posterior tibial tendon
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 vitreous detachment
PVE	prosthetic valve endocarditis
PVR	post-void residual pulmonary vascular resistance
PWID	people who inject drugs
PZA	pyrazinamide
qac	before every meal
qhs	every bedtime
QID	four times daily
QOD	every other day
QoL	quality of life
Qw	Q wave
r/i	rule in
r/o	rule out
RA	refractory anemia right atrium rheumatoid arthritis
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 recurrent acute rhinosinusitis
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
RDA recommended daily allowance
RDW red cell distribution width
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
RHF right heart failure
RI reticulocyte index
RIBA recombinant immunoblot assay
RIF rifampin
RLSB right lower sternal border

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
rPMI	radionucleotide myocardial perfusion imaging
RPR	rapid plasma reagent
RPR	rapid plasma reagin
RPV	rilpivirine
RR	relative risk
	response rate
	respiratory rate
RRT	renal replacement therapy
RTA	renal tubular acidosis
RtHF	right heart failure
RTV	ritonavir
RTX	rituximab
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	semen analysis
	sinoatrial
	short-acting
SAAG	serum-ascites albumin gradient
SABA	short-acting β_2-agonist
SAH	subarachnoid hemorrhage
SAPHO	synovitis, acne, pustulosis, hyperostosis, osteitis syndrome
SARS	severe acute respiratory syndrome
SBE	subacute bacterial endocarditis
	self breast exam
SBO	small bowel obstruction
SBP	spontaneous bacterial peritonitis
	systolic blood pressure
SBT	spontaneous breathing trial
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
SES	socioeconomic status
sev	severe
SG	specific gravity
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
SLICC	Systemic Lupus International Collaborating Clinics Classification Criteria
SLP	speech language pathology therapist
SMA	smooth muscle antibody
	superior mesenteric artery
SMV	superior mesenteric vein
SNF	skilled nursing facility
SNHL	sensorineural hearing loss
SNRI	serotonin-norepinephrine reuptake inhibitor
SNS	Sympathetic nervous system
SOB	shortness of breath
soln	solution
Sp	specificity
SPEP	serum protein electrophoresis
SPK	superficial punctate keratopathy
SPN	solitary pulmonary nodule
SQV	saquinavir
SR	sinus rhythm
	sustained release
ss	single strength
SSc	systemic sclerosis
SSRI	selective serotonin reuptake inhibitor

SSS sick sinus syndrome
SSTI skin + soft tissue infection
SSZ sulfasalazine
ST sinus tachycardia
STARI Southern tick-associated rash illness
STC slow transit constipation
STD sexually transmitted disease
ST depression
STE ST segment elevation
STEMI ST elevation myocardial infarction
STI sexually transmitted infection
STS Society of Thoracic Surgeons
SU sulfonylurea
subQ subcutaneous
SUD substance use disorder
SUI stress urinary incontinence
SV stroke volume
SVC superior vena cava
SVR systemic vascular resistance
SVT supraventricular tachycardia
sx symptom(s)
sz seizure
T testosterone
T3RU T_3 resin uptake

TA temporal artery
TAA thoracic aortic aneurysm
TAC trigeminal autonomic cephalgia
TB tuberculosis
total bilirubin
TBG thyroid binding globulin

TBI	toe brachial index
TBST	TB skin test
TBW	total body weight
TC	total cholesterol
TCA	tricyclic antidepressant
TCD	transcranial doppler
TD	therapeutic dose
	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
THC	marijuana
TIA	transient ischemic attack
TIBC	total iron binding capacity
TID	three times daily
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	temporomandibular joint
TMNG	toxic multinodular goiter
TMP-SMX	trimethoprim-sulfamethoxazole

TMPT thiopurine methyl transferase
Tn troponin
TNF tumor necrosis factor
TOA tubo-ovarian abscess
TOF Tetralogy of Fallot
TOP topical
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
transitional support service
TST tuberculin skin test
TTE transthoracic echo
TTG tissue transglutaminase
TTKG transtubular potassium gradient

TTP	tender to palpation
TV	tricuspid valve
TVR	tricuspid valve repair
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	unconjugated (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 pneumonia
	usual interstitial pneumonitis
UL	upper lobe

ULN upper limit of normal
UMN upper motor neuron
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
UTox urine toxicology
UUI urge urinary incontinence
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
VS	vital signs
VSD	ventricular septal defect
VST	venous sinus thrombosis
VT	tidal volume
VT	ventricular tachycardia
VTE	venous thromboembolus
VU	vesicoureteral reflux
vWD	von Willebrand disease
vWF	von Willebrand factor
VZV	varicella zoster virus
w/	with
w/d	withdraw, withdrawal
w/in	within
w/o	without
w/u	workup
WB	weight bearing
WBAT	weight bearing as tolerated
WBC	white blood cell (count)
WCT	wide-complex tachycardia
WHO	World Health Organization
wk	week
WM	Waldenström macroglobulinemia
WMA	wall motion abnormality
WPW	Wolff–Parkinson–White syndrome
wt	weight
XR	extended release
XRT	radiation therapy

y	year(s)
yo	year old
♂	male
♀	female
✓	check
ψ	psychiatric

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