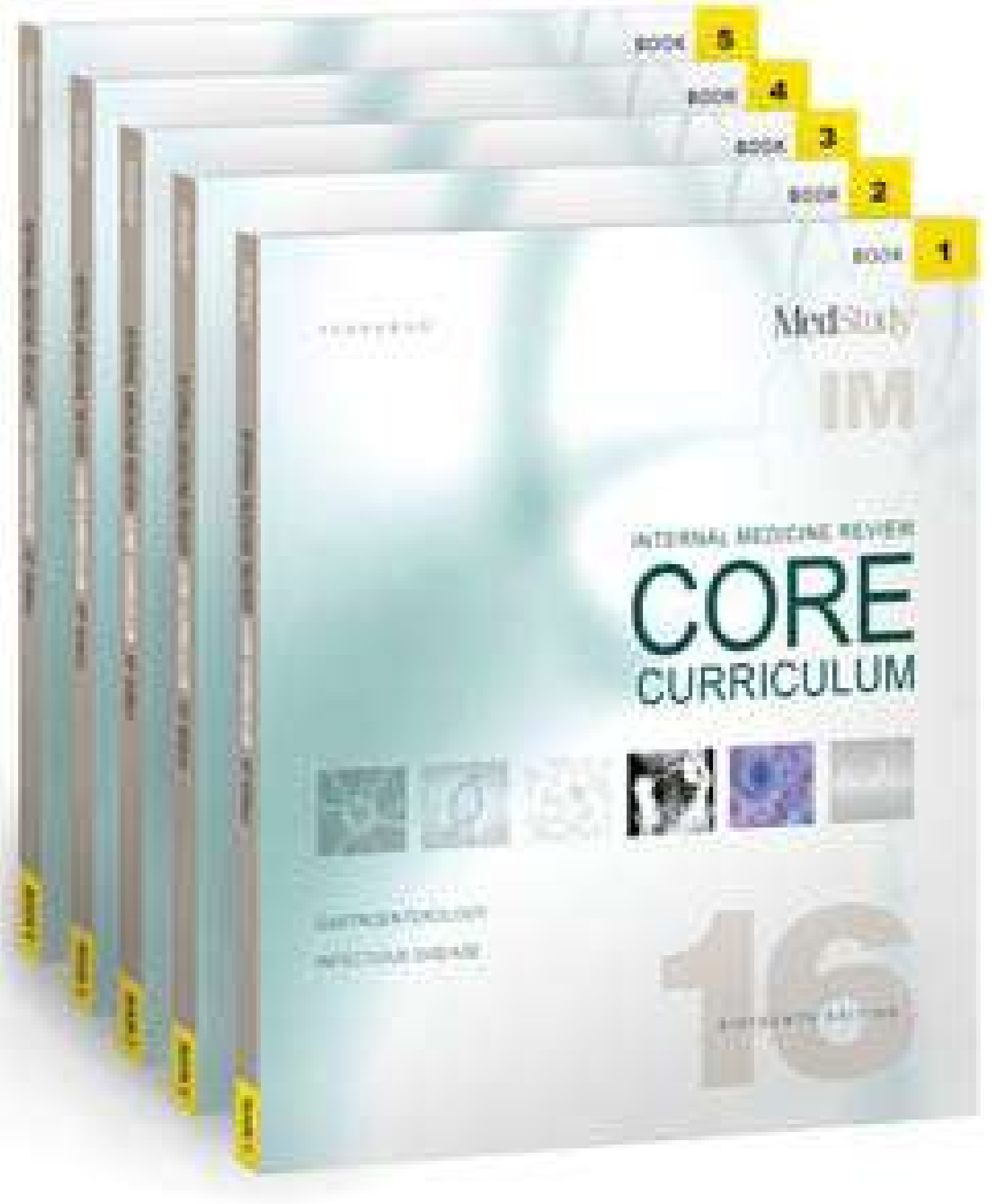
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CORE CURRICULUM

SIXTEENTH EDITION

Book 1 of 5

Topics in this volume:

Gastroenterology

Infectious Disease

Robert A. Hannaman, MD
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Gastroenterology

GI PROCEDURES

Relative contraindications to GI endoscopy include a recent MI, combative patient, and intestinal perforation.

Esophagogastroduodenoscopy (EGD) is the procedure of choice for:

- Evaluation of painful swallowing (odynophagia)
- Determining presence of a peptic ulcer—either instead of upper gastrointestinal (UGI) series or when the UGI is equivocal or negative—and always before peptic ulcer disease (PUD) surgery
- Workup of gastroesophageal reflux disease (GERD) if initial treatment fails, or if there are alarm signals (see GERD on page 1-6)
- UGI bleed
- Dysphagia (if needed after the barium swallow!)
- Evaluation/removal of an ingested foreign body
- Evaluation of small bowel disease (celiac disease)
- Persistent dyspepsia despite treatment (A normal EGD is a prerequisite for diagnosing non-ulcer dyspepsia.)
- Placement of feeding or drainage tubes

Endoscopic retrograde cholangiopancreatography (ERCP): Asymptomatic elevations in amylase occur frequently following ERCP; however, acute pancreatitis develops in 2–5% (< 0.2% severe). Treat patients with possible bile duct obstruction with antibiotics before ERCP. Indications for ERCP include:

- Suspected biliary obstruction
- Discovery of otherwise undetectable common duct stone
- Diagnosis and treatment of pancreatic duct obstruction
- Diagnosis of primary sclerosing cholangitis (PSC) —MRCP (magnetic resonance cholangiopancreatography) is a non-invasive, safe alternative
- Treatment of choledocholithiasis with cholangitis
- Further evaluation of abnormal biliary or pancreatic duct imaging (from CT/MRCP/EUS)

ERCP is contraindicated in acute pancreatitis, except in the following conditions:

- Impacted gallstones
- Ascending cholangitis (bacterial infection causing cholangitis)

MRCP can be used to:

- Diagnose bile duct obstruction
- Diagnose chronic pancreatitis
- Assess a lack of clinical improvement in acute pancreatitis
- Test of choice for primary sclerosing cholangitis (PSC)

Retrograde cholangiography visualizes the bile tract. (Percutaneous transhepatic cholangiography [PTC], U/S, CT scan, and HIDA scans are also used.) Retrograde pancreatography is used to visualize the pancreatic duct. Colonoscopy is discussed later.

Endoscopic ultrasonography (EUS) is done via a high-frequency ultrasound probe that is passed through the biopsy channel of the endoscope—allowing for exact placement. Indications for EUS include:

- Staging of malignancy of the GI tract, biliary tree, and pancreas
- Diagnosis of chronic pancreatitis
- Diagnosis and treatment of complications of pancreatitis
- Tissue sampling of organs adjacent to the GI tract
- Providing access to pancreatic duct or biliary tree

ESOPHAGUS

DYSPHAGIA

Normal swallowing (deglutition) is a voluntary action that leads to involuntary upper esophageal sphincter (UES) relaxation and epiglottis closure. The smooth muscle in the esophageal body then generates a peristaltic contraction, propelling the food bolus distally. The lower esophageal sphincter (LES) relaxes to allow the bolus to enter the gastric fundus.

Swallowing that does not proceed appropriately for any reason is termed dysphagia. The history often gives important clues as to the etiology of dysphagia. Distinguish dysphagia from odynophagia, where the patient experiences pain when the food bolus traverses the esophagus.

The causes of dysphagia can be categorized into 3 types:

1) **Transfer** disorders (oropharyngeal): This is due to neurologic deficits, which leads to oropharyngeal muscle dysfunction and results in difficulty transferring food from the mouth to the esophagus. Symptoms include coughing, gagging, and nasal regurgitating immediately upon swallowing. Common causes include stroke, Parkinson disease, and amyotrophic lateral sclerosis (ALS).
2) **Anatomic** or **structural** disorders: physical obstruction of the esophageal lumen.
3) **Motility** disorders: trouble with transporting food from the upper esophagus to the stomach. This can be a failure of effective peristalsis and/or failure of LES relaxation. These disorders have endogenous or exogenous causes.

See Figure 1-1 and Table 1-1 on the next page.

Diagnosis: Always work up dysphagia. Do not treat empirically.

1) The **barium swallow** is usually the 1st test performed in the workup of esophageal dysphagia, unless the etiology is known from past evaluations. It is definitely done as the 1st test if symptoms are severe or

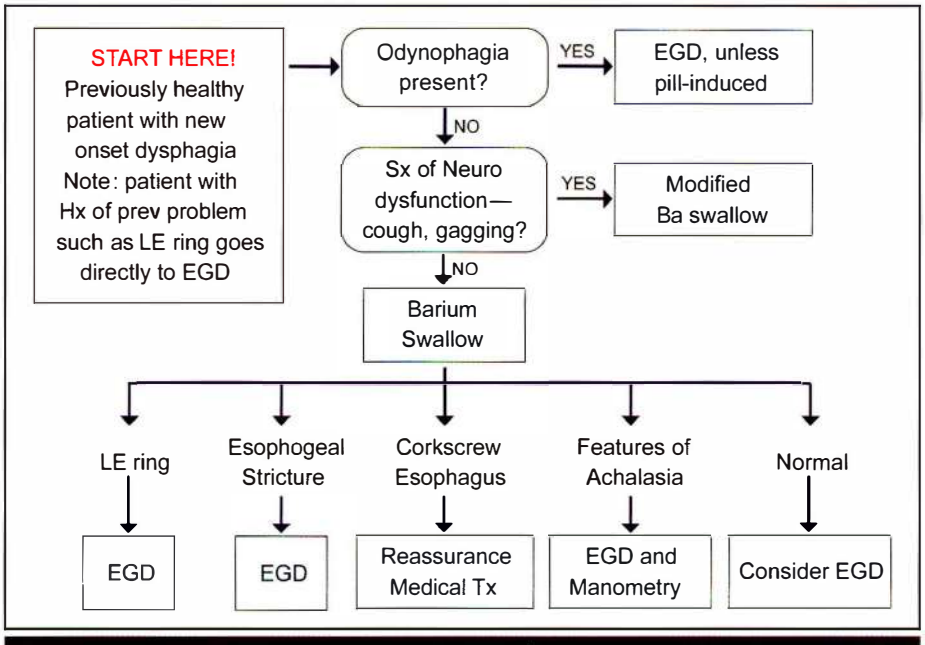


Figure 1-1: Dysphagia Workup

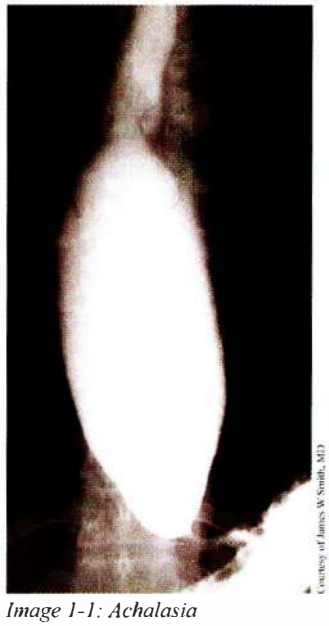


Image 1-1: Achalasia

if there is new-onset dysphagia with liquids. Barium swallow is generally done before endoscopy for the following reasons:

- There is a risk of perforation when endoscoping a patient with diverticula or high-grade obstruction.
- Information from the barium swallow may preclude the need for endoscopy.
- Information from the barium swallow provides the endoscopist a general idea of the type and severity of the underlying lesion.

2) **EGD** generally follows barium swallow if needed. But know that EGD can be done 1st if the patient has a history of reflux and presents with slight-to-moderate dysphagia for solids, because the pretest probability is high for stricture secondary to chronic reflux. Esophageal dilation can be done along with the EGD.

3) **Esophageal manometry** is generally done only if dysphagia persists after negative barium swallow and EGD studies.

Again, workup of dysphagia: 1 = barium swallow, 2 = endoscopy if needed, 3 = manometry studies if needed.

High-resolution manometry, using multiple ports, which may be combined with measurements of esophageal impedance, may provide more information than traditional esophageal manometry alone.

Table 1-1: Causes and Symptoms of Dysphagia

Disease	Main Problem	Symptoms are ...	Symptoms precipitated by ...
Schatzki ring	Anatomic	Intermittent	Solids
Stricture	Anatomic	Progressive	Solids, then liquids
Cancer	Anatomic	Progressive	Solids, then liquids
Achalasia	Motility/ Neurologic	Longstanding	Solids and liquids
DES	Motility/ Neurologic	Intermittent	Solids and liquids (esp. cold)
Systemic sclerosis	Various	Progressive	Solids and liquids

ACHALASIA

Achalasia is of unknown pathogenesis, but it has characteristic and diagnostic features. Neuronal denervation and ganglion cell degeneration of myenteric plexus lead to the following findings:

- Absence of organized peristalsis in the esophageal body.
- The lower esophageal sphincter (LES) does not relax completely with swallowing.
- Often the LES has an elevated resting pressure.

The characteristic features of the history include:

- Dysphagia for solids and liquids
- Long-standing symptoms, usually years
- Regurgitation of food, especially at night
- Chest pain
- No age or gender predilection

QuickQuiz

- What are the indications for an EGD?
- What is the 1st test usually performed in the workup of dysphagia?
- What is the preferred treatment for achalasia?
- A classic corkscrew pattern seen on barium swallow is indicative of what disorder?

The diagnosis of achalasia can be made by various tests, commonly in this order:

1) **Barium swallow**: The esophagus appears dilated and is often fluid-filled. The barium may take a long time to empty into the stomach, even if the patient is upright. There is a "bird-beak" narrowing distally, which represents the tight LES (Image 1-1).
2) **EGD**: generally the 2nd test ordered. It is done mainly to confirm the diagnosis and to exclude a tumor at the esophagogastric junction ("pseudoachalasia").
3) **Esophageal manometry**: generally done as a last test to confirm the diagnosis before treatment is offered. This test clearly shows the absence of normal peristalsis, often with a non-relaxing LES. The use of high resolution manometry with impedance has revealed 3 distinct subtypes of achalasia: traditional aperistalsis, esophageal compression, or generalized spasm. Each subtype may have a different long-term outcome.

Remember the 3 tests for achalasia: barium swallow, endoscopy, and manometry.

Also remember pseudoachalasia and secondary achalasia. A tumor at the esophagogastric junction can mimic the history and diagnostic findings of achalasia. Especially consider this diagnosis if onset of symptoms is rapid, patient is > 60 years, and symptoms are progressive and include profound weight loss.

Complications of achalasia include aspiration pneumonia and weight loss.

Focus treatment for achalasia on opening the LES, usually by pneumatic dilation although onabotulinumtoxinA (Botox®) may be an alternative. A large, 3–4-cm diameter balloon is inflated within the LES to tear the sphincter muscle fibers. This balloon is much larger and generates higher pressure than the balloons used to treat esophageal rings and strictures. There is a 5% risk of perforation. Surgical myotomy is also very effective and can be done via laparoscope. Botulinum toxin is effective in 65% of cases but requires repeat therapy within 6–12 months. It is an alternative therapy in high-risk surgical patients. Calcium channel blockers and nitrates have been used with minimal relief.

DIFFUSE ESOPHAGEAL SPASM

Diffuse esophageal spasm (DES) is a simultaneous, nonperistaltic contraction of the esophagus, often precipitated by cold or carbonated liquids. This may be a cause of dysphagia, chest pain, or both. The chest pain is atypical in description, but cardiac causes should be investigated. Occult reflux causes esophageal spasms even in the absence of typical reflux symptoms.

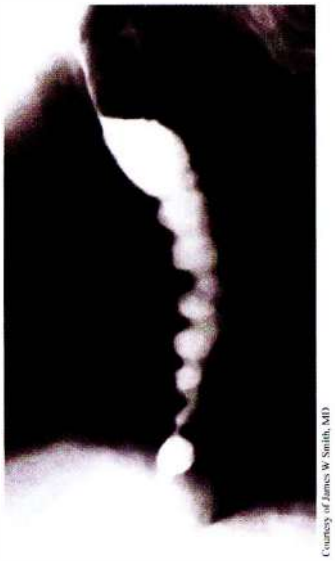


Image 1-2: Corkscrew esophagus

Barium swallow is generally normal but may show the classic corkscrew pattern (Image 1-2). High resolution manometry confirms the diagnosis as Type 3 achalasia by revealing excess, simultaneous (nonperistaltic) contractions in the distal esophagus with normal LES relaxation.

LES pressure may be low, normal, or high (i.e., nonspecific).

Endoscopy is rarely helpful in the workup of DES. Even in those patients with spasm due to reflux, there is usually no obvious or gross reflux esophagitis. If reflux is considered a possible cause of the diffuse esophageal spasm, order a 24-hour esophageal pH recording or give twice-daily proton pump inhibitors (PPIs) for 3 months.

Treatment: Think of DES as irritable bowel of the esophagus. Reassurance is the most important part of therapy.

However, if reassurance is not effective or the patient requests specific therapy, recommend these in this order:

1st line: diltiazem or imipramine
2nd line: isosorbide or sildenafil
3rd line: botulinum toxin injection

Obviously, avoiding certain foods, like cold beverages, may be important. PPIs if GERD is suspected (half of pH studies are abnormal). Some patients report benefit from empiric esophageal dilation, although the rationale for this is difficult to understand, and a benefit over placebo is hard to prove. There may be a role for the use of botulinum toxin for some types of DES, based on specific manometric patterns.

ANATOMIC OBSTRUCTION

Overview

Anatomic obstruction causes a slowly progressive dysphagia—initially to solids, then to liquids when

severe. Depending on the cause, this slowly progressive dysphagia may be intermittent or constant.

In younger patients, slowly progressive dysphagia is typically caused by a Schatzki ring (lower esophageal ring), whereas in older patients, it is usually due to cancer (esophageal or extrinsic compression) or peptic stricture.

Lower Esophageal Ring (Schatzki Ring)

The lower esophageal ring (LE ring or Schatzki ring) is a common cause of dysphagia, especially in younger patients. Patients often give a classic history of very slowly progressive, intermittent, solid food dysphagia, especially for meat and bread. They may have to regurgitate the impacted bolus for relief. LE ring is always associated with a hiatal hernia, and, although reflux may have a role in pathogenesis, at endoscopy there is generally no obvious esophagitis. The ring is usually 13 mm or less in diameter to cause symptoms. Treatment is dilation using either the bougie method or a through-the-scope hydrostatic balloon. Patients are placed on PPIs after dilation (Image 1-3).

Esophageal Stricture

Esophageal stricture presents with a history of slowly progressive, constant (not intermittent) dysphagia for solid foods. Commonly the stricture is due to a long history of incompletely treated acid reflux. The incidence of stricture has decreased sharply with the use of PPIs. It can also be due to prolonged nasogastric tube placement or lye ingestion (rare today, except in those who ingested lye decades ago; these have a chronic stricture and an increased risk of esophageal cancer). Barium swallow shows narrowing, typically at the esophagogastric junction. Treatment is dilation.

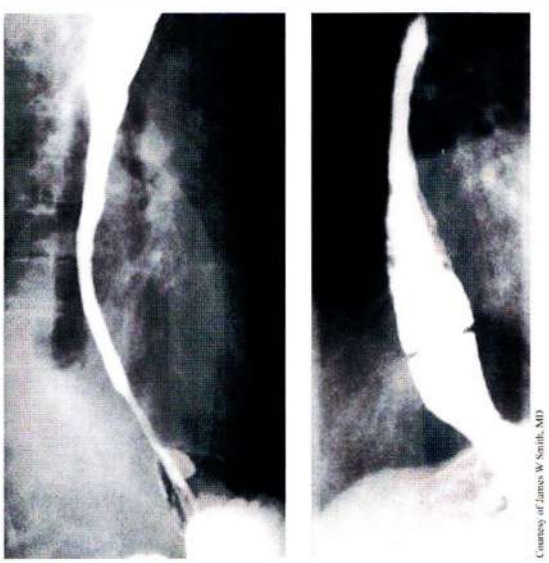


Image 1-3: Severe esophageal stricture on the left; Schatzki ring on the right

Malignant Obstruction

Malignant obstruction can be due to esophageal adenocarcinoma, squamous cell carcinoma, or extrinsic compression from nonesophageal primary cancers. Usually the history is of progression of symptoms: solid food dysphagia to soft food difficulties and finally to problems with liquids (Image 1-4). Dysphagia with weight loss represents esophageal malignancy until proven otherwise.

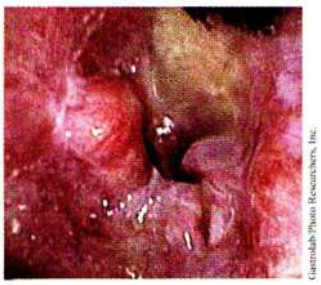


Image 1-4: Esophageal cancer

Plummer-Vinson Syndrome

Plummer-Vinson syndrome, a rare disorder, results in dysphagia due to an upper esophageal web. An esophageal web is a thin fold of tissue covered with squamous epithelium that protrudes into the lumen. It is generally found in postmenopausal women in association with iron-deficiency anemia—the reason for this association is unknown. Patients with Plummer-Vinson syndrome have a slightly increased risk of squamous cell esophageal cancer.

NEUROLOGIC DYSFUNCTION

Neurologic problems involving the swallowing and/or esophageal peristaltic mechanism cause dysphagia to both solids and liquids from time of onset. Examples include stroke, parkinsonism, bulbar palsy (lower motor neuron—ALS, MS), and pseudobulbar palsy (upper motor neuron—ALS).

Bulbar palsy causes dysphagia due to weakness, whereas pseudobulbar palsy causes dysphagia due to disordered contractions. Any type of dysphagia can cause aspiration.

This aspiration is often well tolerated and does not need treatment, unless pulmonary problems arise. These patients may complain of choking, gagging, and nasal regurgitation.

If you suspect aspiration, perform a modified or 3-phase barium swallow to confirm the diagnosis. Tracheostomy does not prevent chronic aspiration. A percutaneous endoscopic gastrostomy (PEG) or percutaneous endoscopic jejunostomy (PEJ) tube may be required. Video swallowing studies are also useful in evaluating neurologic dysfunction.

SCLERODERMA AND SYSTEMIC SCLEROSIS

Scleroderma is the term for shiny, hard, thickened skin. Scleroderma may occur alone, but when the sclerosis involves internal organs, it is called "systemic sclerosis"

Quick Quiz

- What type of problem causes slowly progressive dysphagia for solids and then liquids?
- What is a likely cause of anatomic obstruction of the esophagus in younger patients? In older patients?
- What anatomic problem causes slowly progressive intermittent dysphagia to solid food?
- What type of problem presents with dysphagia to both solids and liquids?
- What is the LES pressure in patients with dysphagia due to SSc?

(SSc). SSc itself can be diffuse or limited in its expression—hence the terms "diffuse SSc" and "limited SSc."

Diffuse SSc is the most common connective tissue disease involving the esophagus. More than 80% of patients have involvement of the esophagus. When the esophagus is involved, the patient has very weak-to-absent esophageal peristalsis in the distal 2/3 of the esophagus. The LES is "wide open" with low or no tone or pressure, resulting in severe acid reflux damage to the esophagus.

Dysphagia can be due to any 1 or a combination of the following 3 problems:

1) Esophagitis
2) Stricture
3) Impaired motility

So, workup requires a barium swallow followed by EGD to look for all 3 of these possibilities.

If esophagitis is present, begin aggressive PPI therapy. Perform a follow-up endoscopy at 2–3 months to confirm healing and to assure adequacy of the PPI dose. Any stricture can be safely dilated using standard techniques.

Note: Polymyositis and dermatomyositis can have similar effects on the esophagus.

EOSINOPHILIC (ALLERGIC) ESOPHAGITIS

Primary eosinophilic esophagitis (EoE) is an immune-mediated chronic eosinophil-predominant inflammatory disorder of the esophagus. Its pathogenesis involves interleukin-5 (IL-5) in a central role in concert with eotaxin.

EoE occurs most commonly in men age 20–40 years.

There is a strong association with allergies—environmental, food, asthma, and atopy. IgE is elevated in 2/3 of patients.

The leading symptom is recurrent attacks of dysphagia with food impaction. On average, patients have symptoms for 4–5 years before diagnosis. Symptoms are more pronounced in those with a peripheral eosinophilia, which is found in ~ 30% of patients.

The "classic" EGD finding is a scalloped appearance with ridges or rings (trachealization) in the esophagus. Diagnosis is confirmed by esophageal biopsies showing a dense eosinophilic infiltration of the esophageal epithelium (> 15 eos/HPF). GERD patients may have increased eosinophils as well (Image 1-5).

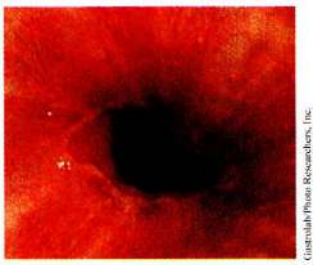


Image 1-5: Esophagitis

Treatment is difficult. Most gastroenterologists refer for allergy testing with subsequent avoidance of potential allergens. Swallowed fluticasone (bid) or viscous budesonide usually results in a response within a week. Long-term therapy is typically required, and relapses are common when steroids are discontinued. PPI therapy may be helpful in those with concomitant reflux or PPI-responsive eosinophilic esophagitis.

MISCELLANEOUS CAUSES OF ESOPHAGITIS

Odynophagia (painful swallowing) is usually due to either pill-induced esophagitis or opportunistic infections.

Pill-Induced Esophagitis

Pill-induced esophagitis is most likely when pills are taken with little or no water or before lying down. It is especially seen in patients taking doxycycline (teenager with acne), KCl, ASA, NSAIDs, iron, bisphosphonates (alendronate), and quinidine. The pain can be severe.

Diagnosis can be made based solely on history! If the history is typical, with abrupt onset of symptoms and an obvious offending medication, no EGD is needed.

Treatment: Stop the offending medicine and reassure the patient that the condition will improve. Educate your patients to take medications in the upright position with plenty of water.

Opportunistic Infections

Opportunistic infections (OIs) can occur in any immunocompromised patient, such as those with diabetes or HIV, but can also occur in otherwise immunocompetent patients who are taking corticosteroids. Common OIs are *Candida*, herpes simplex virus, and cytomegalovirus. If you see thrush in the mouth, you can assume that the esophagitis is also due to *Candida*; treat the patient empirically with fluconazole. If there is no improvement, or you're unsure of the diagnosis, EGD with biopsy is the procedure of choice. Rarely is dilation needed or helpful.

PROTON PUMP INHIBITORS

Proton pump inhibitors (PPIs) are more commonly used today than H_2 receptor blockers because they are more effective.

Efficacy of the PPIs depends on plasma levels. They are all metabolized via the cytochrome P450 pathway with CYP2C19 being the main enzyme. There is a genetic mutation for this enzyme that results in a person being a "slow metabolizer." Heterozygotes are moderate metabolizers, and the people without the mutation (i.e., wild type) are rapid metabolizers. The proportion of slow metabolizers varies by ethnicity. For instance, among Caucasians, it is 5%, 30%, 65%; slow to fast. Slow metabolizers of PPIs have much better results than fast metabolizers.

PPIs cause hypergastrinemia, achlorhydria, and possibly gastric atrophy. Short-term and long-term effects of PPIs are becoming known.

Short-term: Community-acquired pneumonia (CAP) appears more likely to occur within 30 days of starting PPIs—and especially within 48 hours.

Long-term:

- Fracture risk appears increased
- Hypomagnesemia (muscle spasms, arrhythmias, seizures)

Although long-term PPI use leads to parietal cell hyperplasia, no dysplasia or neoplasia has been seen.

Rebound acid hypersecretion occurs when PPIs are stopped abruptly after several months—especially in *H. pylori*-negative patients.

Long-term use of PPIs is now discouraged unless necessary (e.g., Barrett esophagus), and patients should be maintained on the lowest tolerable dose.

Drug interactions with PPIs:

PPIs interact with few drugs and are generally well tolerated. They decrease absorption and serum levels of thyroxine and itraconazole/ketoconazole and increase absorption of digoxin.

A controversy regarding use of clopidogrel with omeprazole has been resolved by the COGENT trial and a subsequent consensus statement (ACC/AHA/ACG in December 2010) which states:

- There is no significant cardiovascular harm found.
- There is potential GI protective effect.
- Further study is needed for the slow metabolizers of clopidogrel.

GE REFLUX DISEASE (GERD)

Overview

GE reflux is generally a result of transient relaxation of the lower esophageal sphincter (LES). The transient relaxation is a vagally mediated reflex, which is the physiologic mechanism of belching. Transient relaxations occur at increased frequency with gastric distension and in the upright position. Hiatal hernia is risk factor for factor for GERD.

LES pressure is increased by motilin, acetylcholine, and possibly gastrin. Therefore, drugs that increase these mediators tend to decrease reflux. LES pressure is decreased by progesterone (pregnancy increases GE reflux), chocolate, smoking, and some medications, especially those with anticholinergic properties.

Suspect GE reflux disease (GERD) in patients with a persistent, nonproductive cough, especially with hoarseness, continual clearing of the throat, and a feeling of fullness in the throat. This cough is commonly worse at night when the patient is supine.

Most non-cardiac chest pains (70%) are caused by GERD! Most other GI-related chest pains are due to motility disorders. Note: These pains are not necessarily associated with pyrosis (heartburn) or dysphagia.

Extraesophageal manifestations of GERD:

- Nocturnal cough
- Frequent sore throat
- Hoarseness, laryngitis, clearing of the throat
- Loss of dental enamel
- Exacerbation of asthma
- VCD (vocal cord dysfunction)

GERD is associated with two respiratory disorders: asthma and VCD.

Some asthma patients, even without symptoms of GERD, have improvement of their asthma symptoms with GERD treatment. In the workup of GERD, always ask about asthma symptoms—especially those occurring at night. Note: A recent study showed that treatment of asymptomatic GERD in patients with severe asthma did not improve asthma control. More in the Pulmonary section, Book 2.

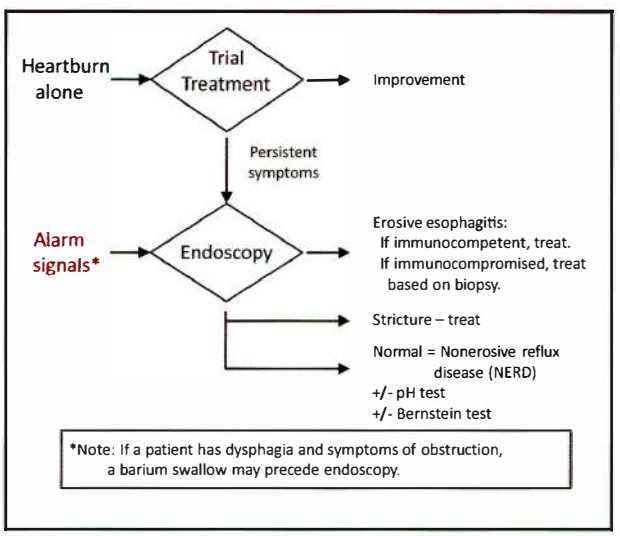


Figure 1-2: Workup of Suspected GERD

QuickQuiz

- Which drugs interact with PPIs?
- What is the clinical presentation of GERD?
- What are the "alarm" signals in a patient with GERD symptoms? These indicate the need for what?
- What diagnostic test may be helpful for atypical GERD?
- For how long is severe GERD treated? And with what?

Do not assume asthma is the culprit in patients who complain of nocturnal symptoms. VCD is spasm of the vocal cords with associated inspiratory stridor. Patients will tell you that they are wheezing at night and may not really know if it is inspiratory or expiratory. Pulmonary function testing may be necessary to help distinguish vocal cord dysfunction from asthma. VCD is not always due to GERD; it is more typically seen in young adults who engage in competitive sports and is thought to be a stress reaction. About 10% of exercise-induced "asthma" is now thought to be misdiagnosed VCD.

Increased body mass index (BMI) is associated with increased incidence of both GERD and asthma.

Complications: esophageal ulcers, stricture, bleeding, and Barrett esophagus (discussed on page 1-8).

Diagnosis of GERD

If the patient has only the classic symptoms of heartburn without alarm signals, the diagnostic workup starts with a therapeutic trial of PPIs—EGD is indicated only if this trial fails (Figure 1-2).

Alarm signals in GERD indicating the need for EGD:

- Nausea/Emesis
- Blood in the stool
- Family history of PUD
- Weight loss
- Anorexia
- Iron deficiency anemia
- Abnormal physical exam
- Long duration of frequent symptoms, especially in Caucasian males > 50 years old
- Failure to respond to full doses of a PPI
- Dysphagia/Odynophagia

EGD also is done if you suspect Barrett esophagus.

If the patient has obstructive symptoms, you can do a barium swallow before endoscopy.

Note: 62% of patients with GERD symptoms have a normal esophagus. This is termed nonerosive reflux disease or NERD!

Conduct the 24-hour esophageal pH monitor for atypical cases with impedance, such as:

- Refractory symptoms and a normal EGD
- Hoarseness, coughing, or atypical chest pain, but no classic symptoms of GERD
- Failure to respond to PPIs

The pH monitor is similar to a Holter monitor in that the patient keeps a diary of symptoms. You then analyze the diary logs and pH monitor results for correlation.

The combination of esophageal pH with ambulatory esophageal impedance has resulted in increased ability to identify types of GERD, including non-acid GERD.

Treatment of GERD

Treatment of mild-to-moderate GERD:

Initial:

- Raise head of bed.
- Encourage weight loss of > 10 lb if overweight or if there was recent weight gain.
- Small meals; no fatty meals in the evening; eat dinner at least 3 hours before bedtime; no sweets, especially chocolate, at bedtime.
- Stop smoking.
- Antacids as needed.
- Avoid alcoholic and acidic beverages before bedtime (e.g., colas, orange juice, wine).

In clinical trials, only raising the head of the bed and weight loss have been shown to be effective; the remaining are mechanistically plausible but unproven.

If the above is unsuccessful, try antisecretory drugs.

Overall healing of patients with endoscopic evidence of esophagitis (not necessarily GERD!):

- Placebo: 25%
- H_2 blockers and prokinetic drugs: 50%
- PPIs: 80–95%

H_2 blockers may heal mild cases of GERD, but treatment of severe GERD (i.e., grade B or worse esophagitis) requires PPIs, such as omeprazole or lansoprazole, continued indefinitely*, unless the patient has corrective surgery.

PPIs in particular are indicated for long-term therapy* in patients with EGD evidence of esophagitis.

*Note the concerns with the long-term use of PPIs in the previous topic, Proton Pump Inhibitors.

In patients with GERD symptoms who do not respond to PPIs, check for other medications that may delay gastric emptying and thus promote reflux---especially calcium channel blockers, antihistamines, narcotics, tricyclics, and anticholinergics.

Consider antireflux surgery (fundoplication, now mostly laparoscopic) in patients with severe GERD because

it has a reasonable success rate. Indications: patients refractory to medical treatment, young patients with severe disease, and as an alternative to long-term PPIs. Outcome of antireflux surgery is best in patients responding to PPIs. However, even after reflux surgery, 60% still require PPI therapy. With Nissen fundoplication, the lower esophagus is wrapped in a sleeve of the stomach. Side effects of this surgery are bloating, dysphagia, and an inability to belch. You must do a motility study prior to antireflux surgery—because the results may influence the performance of the fundoplication. Patients with very poor peristalsis are at risk for postoperative dysphagia. Endoscopic antireflux procedures are not ready for routine use.

Treat peptic strictures secondary to GERD with dilation and then PPIs. Note: Metoclopramide (due to too many side effects) and sucralfate (not very effective) have little use in treatment of GE reflux.

Maintenance therapy consists of PPIs for moderate-to-severe cases. Long-term use of H_2 receptor blockers is typically ineffective.

Be aware that patients with GERD-related cough/hoarseness require longer treatment and higher doses (e.g., bid) for symptomatic improvement than those with run-of-the-mill heartburn.

BARRETT ESOPHAGUS

Barrett esophagus is a change in cell type—from esophageal squamous to specialized intestinal metaplasia (columnar epithelium with goblet cells)—caused by chronic GE reflux. Even though GERD is the cause, many patients with Barrett esophagus lack reflux symptoms.

10–20% of men and 2% of women who undergo endoscopy for chronic reflux have Barrett esophagus!

The need for screening for Barrett's is a controversial topic because of the absence of randomized clinical trials that prove a decrease in mortality with screening. Current guidelines recommend screening based on the presence of risk factors (Caucasian males > 50, long-standing GERD, elevated BMI); screening of the general population is not recommended.

Barrett esophagus is associated only with adenocarcinoma (not squamous cell carcinoma). Incidence of adenocarcinoma in patients with Barrett esophagus is 30x the normal rate. The risk of adenocarcinoma is related to the length of Barrett esophagus, presence of a hiatal hernia, degree of dysplasia, and concurrent smoking. Risk of adenocarcinoma is 0.52% per year in patients with Barrett esophagus (Image 1-6).

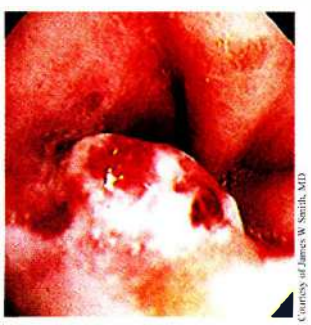


Image 1-6: Barrett esophagus

Neither antireflux medication nor surgery reverses the epithelial changes of Barrett esophagus—or eliminates the cancer risk.

If Barrett esophagus is found, do follow-up endoscopic surveillance as follows (2011 ACG guidelines):

- No dysplasia: 3–5 years
- Low-grade dysplasia: 6–12 months
- High-grade dysplasia in the absence of eradication therapy: 3 months

Endoscopic surveillance includes 4-quadrant biopsies every 2 cm if no dysplasia, every 1 cm for known dysplasia.

For any high-grade dysplasia, eradication therapy is now recommended over surveillance. It is done with radiofrequency ablation (RFA) or endoscopic mucosal resection (EMR). Photodynamic therapy (PDT) is occasionally used as well.

Esophagectomy is an alternative treatment for patients with high-grade dysplasia but has higher morbidity and should be done by centers that specialize in this type of surgery.

ESOPHAGEAL CANCER

There are 2 types of esophageal cancer:

1) **Adenocarcinoma** of the esophagus has been on the rise (from Barrett esophagus) and now occurs more commonly than squamous cell; it occurs in the distal 1/3 of the esophagus. See more in previous discussion.
2) **Squamous cell** esophageal cancer generally occurs in the proximal 2/3 of the esophagus, and it is caused by smoking and alcohol (especially hard liquor). It is associated with other cancers of the head or neck and is rarely associated with achalasia, lye stricture, or Plummer-Vinson syndrome (see page 1-4).

Smoking and alcohol have a synergistic (a multiplicative, not additive) carcinogenic effect on the esophagus. Incidence of squamous cancer has a marked geographic variation, and its occurrence appears to be strongly associated with diet and environment.

Diagnosis of esophageal cancer is accomplished with a number of tests. Dysphagia is the usual presenting symptom, so a barium swallow during the workup may suggest cancer. EGD is always done to allow confirmation via biopsy. Use CT scan and endoscopic ultrasound for staging.

If small and localized, treat with surgical resection. If large or metastasized, treat with combination chemotherapy (cisplatin + 5FU) plus radiation prior to surgery. This combination results in a 2-year survival of 38% vs. 10% with radiation alone.

QuickQuiz

- In patients with GERD, what study must be done before antireflux surgery?
- What is the pathologic definition of Barrett esophagus?
- What cancer is associated with Barrett's?
- What follow-up is indicated in patients with Barrett's?
- What is the treatment of choice for Barrett's with high-grade dysplasia?
- Discuss the differences between adeno and squamous cell cancer of the esophagus.
- Name the risk factors for esophageal cancer.

ZENKER DIVERTICULUM

Zenker diverticulum is an outpouching of the upper esophagus. Patients have foul-smelling breath and may regurgitate food eaten several days earlier. This is the most common cause of transfer dysphagia (trouble initiating swallowing) for solid foods, but it can also cause transport dysphagia. These patients are often elderly. Treatment is surgery.

[Know the indications for EGD, ERCP, pH monitor, and motility studies!]

STOMACH

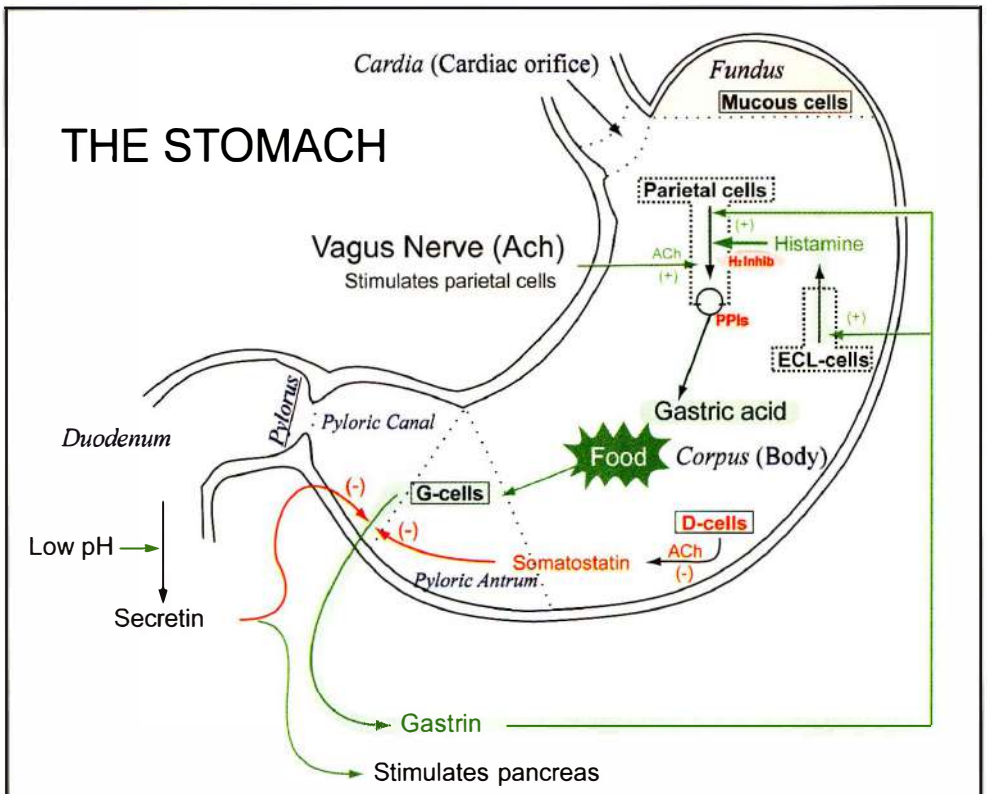
NORMAL PHYSIOLOGY

First, a quick review of normal stomach physiology as it relates to gastritis and peptic ulcer disease (PUD). See Figure 1-3. The light green highlight shows the main pathway used in production of gastric acid.

G cells are in the pyloric antrum. Parasympathetic vagal stimulation, presence of amino acids (from food breakdown), and pyloric distension cause the G cells to release gastrin, which, like acetylcholine (ACh) and histamine, interacts with specific receptors on the parietal cells in the fundus—stimulating them to secrete (via the proton pump) HCL (gastric acid) into the lumen. More importantly, gastrin stimulates enterochromaffin-like (ECL) cells to produce histamine.

The proton pump is the final common pathway for the action of these three receptors, which explains why PPIs are the strongest anti-gastric acid drugs.

Gastrin is released into the circulation and is therefore an endocrinal stimulus for gastric acid release. Gastrin is the dominant mediator of postprandial gastric acid production.



Note: Low pH decreases gastrin by stimulating the D-cells to produce somatostatin and the duodenum to produce secretin.

Figure 1-3: Stomach Physiology

Histamine is released by the ECL cells in the corpus (especially due to gastrin stimulation), and it has a local paracrine effect via the H_2 receptors of the parietal cells.

Gastrin-releasing peptide is released onto G cells by parasympathetic stimulation of the vagus nerve (a neurocrine effect).

Therefore, parietal cells are affected by endocrine, neurocrine, and paracrine stimuli.

Somatostatin and **secretin** both decrease the production of gastrin (and therefore gastric acid), and the production of both of these is stimulated by low pH—hence, they are the negative feedback portions of the regulatory mechanism for maintaining stomach pH. A stomach pH < 3 causes production of somatostatin by corpus D cells. Secretin is produced in the duodenum in response to the acidified output of the stomach; it decreases gastrin production and it stimulates output of bicarbonate from the pancreas. Again, two inhibitors of gastrin (and therefore gastric acid) production are somatostatin (from low stomach pH) and secretin (from low duodenum pH).

Note: In patients with achlorhydria (as in autoimmune gastritis) or pernicious anemia, the serum gastrin level skyrockets because of the loss of this inhibitory effect. PPIs, in the setting of achlorhydria, can lead to a markedly elevated gastrin level (> 500 pg/mL).

Both gastric acid and pepsin (made from pepsinogen in the presence of acid) not only digest food but also attack the mucosal defenses.

Things to know about the mechanical actions of mixing and grinding:

- This is best studied with a gastric emptying scan.
- Only particles < 1–2 mm can pass through the pylorus.
- Controlled at three levels (ANS, enteric, and smooth muscle).

DYSPEPSIA

Dyspepsia is a nonspecific term that refers to recurrent upper abdominal pain or discomfort especially after meals. It includes epigastric fullness, belching, bloating, gnawing pain, and heartburn. It generally does not apply to severe pain. Most dyspepsias are functional or caused by medications (e.g., Fe, ASA, NSAIDs), but if onset is recent, there are no medicines involved, and the patient is > 40–50 years, consider an organic cause; i.e., consider an EGD.

For patients < 55 years of age, test for *H. pylori* and treat if positive (more below).

Organic causes of dyspepsia include PUD, gastritis, GERD, biliary colic, gastroparesis, pancreatitis, and cancer. EGD is usually normal. Dyspepsia is generally classified by symptoms: GERD-like, ulcer-like (improves on anti-ulcer therapy), and dysmotility-type (improves on promotility drugs, such as metoclopramide). There can also be overlaps in the types.

"Non-ulcer dyspepsia" is defined by recurrent upper abdominal pain with a normal EGD.

So, how do we handle dyspepsia? Do the following:

- Discontinue NSAIDs
- Test and treat if *H. pylori*+
- Conduct a PPI treatment trial
- Order EGD if alarm symptoms or failure of therapy

GASTRITIS

Classification Schemes

Gastritis is generally classified by histology or etiology.

Classification by Histology

A neutrophil infiltrate is seen in acute gastritis, while a lymphocyte and plasma cell infiltrate occurs with chronic gastritis. Histologic classification reflects the findings throughout the possible life of the disease:

- Superficial gastritis (early, neutrophils)
- Atrophic gastritis (mid, lymphocytes)
- Gastric atrophy (late, gastropathy)—also called metaplastic atrophic gastritis

Some lump mid and late disease into a single term, "chronic gastritis," which is not quite correct—the inflammation has "burned out" in the late phase, so it is not really gastritis. Biopsy of gastropathy shows atrophy of gastric glands with fibrosis but no inflammatory infiltrate.

Classification by Etiology

Type A: **A**utoimmune, **A**trophic, pernicious **A**nemia, **A**chlorhydria. It affects the proximal stomach—fundus and body only. (Note: "Antrum" is not one of the "A" words!) Autoantibodies against both intrinsic factor and the parietal cells cause a progression to pernicious anemia and to achlorhydria, with secondary hypergastrinemia (levels often > 1,000 pg/mL). Metaplasia is a universal feature of atrophic gastritis; it appears before, and is associated with, both pernicious anemia and gastric carcinoma. Even so, the incidence of gastric cancer is so low with atrophic gastritis that, if there is no cancer or dysplasia on initial endoscopic exam, periodic endoscopic exams are not warranted!

Type B is the most common form of chronic gastritis (80%). It is usually due to a treatable infection caused by *Helicobacter pylori*. Symptoms and findings can mimic Type A gastritis.

But … successful treatment of the infection results in resolution of gastritis symptoms in only half of the patients!

Depending on chronicity and location of infection, gastric acid secretion can decrease with increased degree of *H. pylori* gastritis. Oral meds such as itraconazole, ketoconazole, and thyroxine require gastric acid for optimal absorption. Note: 50% of AIDS patients have decreased stomach acid and are especially prone to

Quick Quiz

- What is the clinical presentation of dyspepsia?
- What are the possible diagnostic/treatment approaches to dyspepsia?
- When should you test for *H. pylori*?
- Is the CLOtest® accurate if a patient is taking a PPI? What other *H. pylori* tests are affected by PPIs?
- Which type of *H. pylori* test is not good for checking effectiveness of treatment?

itraconazole failure. Fluconazole does not require gastric acid for proper absorption.

Especially remember thyroxine because this is a widely used drug.

Erosive Gastropathy

Erosive gastropathy, frequently with subepithelial hemorrhage, may be caused by NSAIDs, alcohol, or severe physiologic stress (Image 1-7).

Note that gastritis, by definition, means there is an inflammatory response; however, there is not one in this setting. So, calling this gastritis, as is commonly done, is technically wrong.

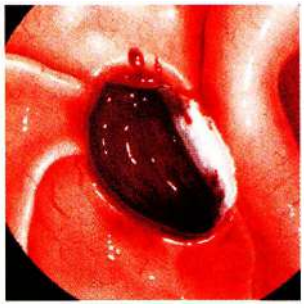


Image 1-7: Acute erosive gastritis

Onset of erosive gastropathy in the ICU suggests stress-related mucosal damage (SRMD), which is due to severe physiologic stress, such as that induced by major surgery or burns. Having severe CNS injuries, being on a ventilator, or having a coagulopathy are also major risk factors. Just about anything works to prevent SRMD: H_2 receptor antagonists, antacids, PPIs, sucralfate, and even early feedings.

Continuous infusion of an H_2 receptor antagonist or PPI is the most effective treatment for SRMD. It has been proposed that decreased acidity in the stomach allows colonization and increases the risk of aspiration pneumonia in patients receiving acid-suppressive therapy. Studies are ongoing to further evaluate this risk.

MORE ON *H. PYLORI*

Overview

H. pylori infection can cause gastritis, PUD, gastric adenocarcinoma, and gastric B-cell (MALT) lymphoma.

Chronic gastritis occurs in almost all adults infected with *H. pylori*, although only a minority has symptoms. Treat only symptomatic patients: those with history of gastric/duodenal ulcer, personal/family history of gastric cancer, or personal history of MALT lymphoma.

Virtually everyone in third world countries is infected with *H. pylori*. In the U.S., the incidence is ~ 50% in older patients and 30% overall. It is generally acquired in childhood. Incidence is decreasing in the U.S.

Testing for *H. pylori*

[Know!] Test for *H. pylori* when:

- there is any prior history of PUD, complicated or uncomplicated, and especially duodenal ulcer;
- current findings on EGD show ulcer disease, erosive gastritis, or duodenitis;
- MALT lymphoma is present; and/or
- there is a family history of gastric cancer.

The strategy is "test and treat" in dyspeptic patients < 55 years of age even with no alarm symptoms/features.

Invasive tests:

- The gold standard for *H. pylori* testing is histologic examination of biopsied antral mucosa—obtained during EGD.
- Urease tests are based on the finding that *H. pylori* breaks down urea into ammonia and CO_2. Urease tests are good for checking for active disease and for response to therapy. These tests are sensitive (95%) and specific (95%). For the CLOtest® and other rapid urease tests (RUT), the biopsy sample is placed on an agar medium containing urea and a pH reagent. Any ammonia then produced causes an increase in pH, which changes the color of the medium. Urease tests are less sensitive if the patient is on a drug that may blunt the effect of *H. pylori* infection, such as PPIs and antibiotics. In such patients, it is appropriate to obtain biopsies for histologic evaluation with or without RUT or to plan testing with a urea breath test or fecal antigen test later (after withholding the offending agents for 2–4 weeks).

Noninvasive tests include a urea breath test, a fecal antigen test, and a serologic test:

- A urea breath test (UBT), which uses labeled urea, is the 1st choice for checking effectiveness of treatment.
- A fecal antigen test (FAT) is a good method for primary diagnosis, and if the patient is on PPIs, it is the best test for checking effectiveness of treatment (S&S = 94% & 98%).
- Serologic tests are no longer recommended due to their low PPV (positive predictive value; < 50%). Also, serum tests are poor for checking effectiveness of treatment as they can stay positive for years after eradication.

Again:

PPIs interfere with any urease test (CLOtest and urease breath test). Stop PPIs 2 weeks before the breath test.

Serologic tests are discouraged due to poor positive predictive value for *H. pylori*.

PPIs and *H. pylori* pangastritis cause decreased gastric acid production which, in turn, interferes with absorption of some medications (thyroxine, azole antifungals).

H. pylori Treatment

H. pylori treatment is the same whether the patient has gastritis or PUD: Usually, triple-drug therapy is used—2 antibiotics and a PPI. A good one with an eradication rate of ~ 80% is **O-CLAM** (**o**meprazole 20 mg + **cl**arithromycin 500 mg + **am**oxicillin 1 g—all bid x 10–14 d).

Recurrence rate is very low. Increasing resistance to clarithromycin is leading to increasing numbers of treatment failure.

Because of resistance to clarithromycin, levofloxacin is now being substituted on a 3-day regimen. Sequential therapy with a PPI and amoxicillin for 7 days followed by a PPI, metronidazole, and clarithromycin for 7 days has been shown to be superior to a 3-day regimen. A 4-drug regimen (PPI, tetracycline, metronidazole, and bismuth) is also effective.

[Know:] The more drugs the better! Single- and dual-drug therapies are ineffective.

Note: *H. pylori* develops resistance to metronidazole and clarithromycin. Previous macrolide antibiotic use precludes the use of clarithromycin. Metronidazole resistance can be overcome with increased dose (500 mg bid). If the first course of therapy (PPI and 2 antibiotics) fails to eradicate *H. pylori*, then some recommend PPI + amoxicillin + levofloxacin or quadruple therapy using bismuth + 2 antibiotics + PPI.

Universal post-treatment testing is not recommended. The accepted indications include the following:

- History of *H. pylori*-associated ulcer
- Persistent dyspepsia despite the test-and-treat strategy
- *H. pylori*-associated MALT lymphoma
- Resection of early gastric carcinoma

When confirmation is necessary, testing should be performed no sooner than 4 weeks after the completion of therapy. In general, noninvasive tests (not serology) should be done for post-treatment testing unless there is a need for repeat EGD.

PEPTIC ULCER DISEASE

ETIOLOGY

Peptic ulcer disease (PUD) has 4 well-confirmed causes:

1) *Helicobacter pylori* infection is still the most common cause of PUD—especially duodenal ulcer disease (50%, but incidence is decreasing in the U.S.). Lifetime ulcer risk for a person with *H. pylori* infection is 10–15% (higher for men). If *H. pylori* can be eradicated, ulcers virtually never recur, and the *H. pylori* recurrence rate is very small. The trouble is getting rid of it! If the ulcer does recur, suspect NSAIDs. See earlier discussion of *H. pylori* testing.
2) NSAIDs cause the majority of peptic ulcers not caused by *H. pylori*. The prevalence of ulcers in patients on NSAIDs is ~ 25% (!) although many are < 5 mm and asymptomatic. NSAIDs cause both gastric and duodenal ulcers—but typically gastric. If NSAIDs are required, and the patient is having or has had trouble, use any of the following:
   - Nonacetylated NSAIDs (e.g., salsalate).
   - NSAIDs that are non-acidic prodrugs (e.g., nabumetone; Relafen®).
   - NSAIDs with a PPI or prostaglandin E analog (e.g., misoprostol). PPIs are superior to H_2 blockers and sucralfate in the prevention of NSAID-induced ulcers.
   - COX-2 NSAIDs (see page 1-14).
3) High acid-secreting states, such as Zollinger-Ellison (1–3% of duodenal ulcers).
4) Crohn disease of the duodenum/stomach.

Enteric-coated NSAIDs have been recommended in the past; but the 2008 ACC/ACG guidelines on NSAIDs in patients with coronary artery disease highlights data that demonstrates no increased benefit of enteric-coated formulations in reduction of GI adverse events.

Risk factors for conventional NSAID-induced PUD include: first 3 months of use, high doses, elderly patient, history of ulcer disease or prior UGI bleed, cardiac disease, concurrent steroid use, serious illness, and concurrent ASA use.

What about smoking? In gastric and duodenal ulcer disease, smoking exacerbates the ulcer. For non-*H. pylori* ulcers, smoking also decreases the healing rate and increases recurrence and perforation rate. Commonly, these recurrences are asymptomatic.

Previously, the incidence of PUD was higher in men, but now the male-to-female ratio is approaching 1. Type of diet, personality, and occupation are not significant risk factors for PUD! Weight loss is uncommon in PUD.

Notes: Alcohol is not ulcerogenic! Corticosteroids alone are not ulcerogenic, but they double the risk of serious NSAID-associated gastrointestinal complication—risk of bleeding may be 10-fold!

QuickQuiz

- What is a common medical regimen for *H. pylori* infection?
- What is the most common cause of peptic ulcer disease?
- What is the relationship between NSAIDs and PUD?
- How does smoking affect PUD?
- What is the relationship of steroids to PUD? Alcohol?
- How are peptic ulcers diagnosed? If perforated?
- Name at least 3 indications for surgery in a patient with PUD.

DIAGNOSIS OF PUD

The following are currently approved strategies for diagnosing PUD:

- For the younger, healthy patient with classic symptoms, no diagnostic protocol is required—empiric treatment with an H_2 blocker or PPI is acceptable.
- For this same younger, healthy group, *H. pylori* "test-and-treat" also is acceptable.
- EGD is done for all other patients, particularly in older patients or in patients of any age who present with melena, heme+ stools, early satiety, or iron deficiency anemia.

EGD is always indicated in the workup of PUD in the following situations:

- If symptoms include dysphagia and odynophagia
- UGI bleeding
- Abnormal UGI (barium swallow) or CT scan
- Family history of duodenal ulcer disease

(EGD is also done for follow-up of a healing gastric ulcer and for evaluation of a swallowed foreign body.)

The upper gastrointestinal series (UGI) is less sensitive than the EGD and rarely done today to diagnose PUD. If an ulcer is found, serum gastrin levels may be indicated (specifics discussed under the type of ulcer). Diagnose the presence of *H. pylori*, as described in the Gastritis section, page 1-10.

Perforated gastric and duodenal ulcers often cause free air in the peritoneal space, which can be seen on an upright abdominal x-ray. If a perforated ulcer is suspected, do the upright x-ray first! EGD and UGI are contraindicated until perforation is excluded.

[Know:] The pain of an ulcer tends to be gnawing, whereas that of a perforated ulcer is usually severe.

TREATMENT OF NONBLEEDING PUD

Treatment of PUD targets combinations of 3 main strategies:

1) *H. pylori* treatment
2) Decrease acid secretion (H_2 receptor antagonists, PPIs)
3) Stop exacerbating processes (smoking, taking NSAIDs)

Less frequently used are mucosal protection (sucralfate) and acid neutralization with antacids.

Treat *H. pylori* infection associated with PUD. This is discussed on page 1-12.

If the patient tests negative for *H. pylori* infection, and if exacerbating factors such as NSAIDs have been addressed, then use antisecretory drugs and antacids.

Sucralfate is an effective treatment of non-*H. pylori* PUD, but patients do not care for the qid dosage; so PPIs are preferred. Sucralfate binds bile salts and forms a barrier at the ulcer site that prevents acid penetration. Sucralfate is a short-term drug of choice in renal patients because it also binds PO_4. However, it should not be used long term in patients with advanced chronic kidney disease because it can cause aluminum accumulation and metabolic bone disease.

Stop smoking—smoking increases the risk of recurrence and perforation in ulcers not associated with *H. pylori* or in untreated *H. pylori* ulcers.

Indications for surgery in PUD:

- **UGI bleed**—most common—active bleed unable to stop via endoscopic therapy. Surgery is required in 5% of UGI bleeds.
- **Gastric outlet obstruction**—initial treatment is balloon dilation. Surgery required in ~ 25%.
- **Perforation**—laparoscopic repair may be possible.
- **Recurrent/refractory ulcers** (rare).
- **Zollinger-Ellison syndrome** (ZES)—surgery is for underlying gastrinoma.

DUODENAL vs. GASTRIC ULCER

Duodenal ulcers: Again, the common causes are NSAIDs and *H. pylori*, and only 1–3% are due to increased acid secretion (ZES). See Image 1-8 and Image 1-9.

Gastric ulcers not associated with *H. pylori* are treated for 3 months. PPIs and misoprostol (a synthetic prostaglandin) are superior to H_2 blockers and sucralfate in the prevention of NSAID-induced ulcers.

Although gastric ulcers were once thought to increase gastric cancer risk, studies have not shown this to be true! On the other hand, examine all nonhealing gastric ulcers via endoscopy with a cytologic exam of at least 6 biopsy samples to rule out gastric cancer.

BLEEDING PEPTIC ULCERS

NSAIDs

NSAIDs are the leading cause of bleeding ulcers in the U.S. Gastrointestinal bleeding may be the only presenting symptom. The bleeding risk is dose-related. As mentioned previously, corticosteroids alone are not ulcerogenic, but they may increase the NSAID-associated bleeding 10-fold!

Risk of bleeding with conventional NSAIDs:

- General population: 1%
- In those using aspirin concurrently as preventive medicine: 1.5%
- History of PUD/UGI bleed: 3%

NSAID-related ulcer risk is higher in females and in any patient > 70 years of age.

If you add cardiac disease to any of the above factors, the risk increases 3-fold. Note that there is no perfectly safe dose of aspirin.

Risk of bleeding with COX-2 NSAIDs:

- COX-2 used alone has close to normal risk of GI bleeding (0.5%).
- COX-2 with low-dose (81 mg) aspirin has the same risk as regular doses of NSAIDs (1%)! Baby aspirin used alone has near-normal risk of GI bleeding.

COX-2 NSAIDs block the action of cyclooxygenase (COX), an enzyme that converts arachidonic acid to prostaglandin. COX-1 is the constitutive enzyme, while COX-2 is inducible. COX-1 produces protective prostaglandins in the stomach, whereas the inducible COX-2 is involved in inflammatory response. COX-2 inhibitors (celecoxib, Celebrex®; meloxicam, Mobic®) appear to have decreased GI side effects (compared to conventional nonselective NSAIDs), while retaining the antiinflammatory and pain relief effects.

All NSAIDs (including COX-2 inhibitors) appear to have some dose-related cardiovascular risks (thrombosis and MIs).

All NSAIDs now have an FDA-mandated boxed warning highlighting the potential for increased risk of death from cardiovascular events and GI bleeding.

Workup of Bleeding Peptic Ulcers

Signs indicating a severe bleed and high risk of rebleed:

- Hemodynamic instability
- Recurrent red-colored hematemesis or hematochezia

EGD is the diagnostic and treatment procedure of choice for UGI bleeding. It should be done emergently if the patient has any of the above findings.

EGD is done for 2 reasons:

1) To treat the current bleed
2) To assess the risk for rebleed

EGD findings that indicate increased chance of rebleeding:

1) Larger size of the ulcer.
2) Active bleeding at time of endoscopy (risk of rebleed 55%).
3) Visible vessels on a non-bleeding ulcer (increase the risk for rebleed to 43%). See Image 1-10.
4) Visible clot = 22%.

Conversely, an ulcer with a clean base (i.e., no bleeding, no clot, and no visible vessels) has a very low chance of rebleed (< 10%). These patients are typically sent home the same or next day—unless they have 1 of the 4 signs of severe bleed mentioned above.

Treatment of Bleeding Peptic Ulcers

What does not work: Gastric lavage does not stop bleeding or prevent rebleeding. IV vasoconstrictors also are ineffective.

The purpose of gastric lavage is to look for blood in the effluent. Blood in the effluent indicates that the stomach is the source of bleeding. But, remember that the absence of blood does not rule out peptic ulcer as the source, because it may have stopped bleeding.

Increasing the gastric pH to > 6.0 reduces the risk of rebleeding—PPIs given either IV or orally bid achieve this. Most patients with a bleeding ulcer get prompt IV PPI treatment before endoscopic therapy; this is continued until they are able to switch to oral bid therapy.

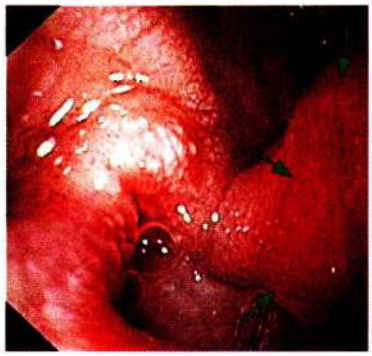


Image 1-8: Duodenal ulcer

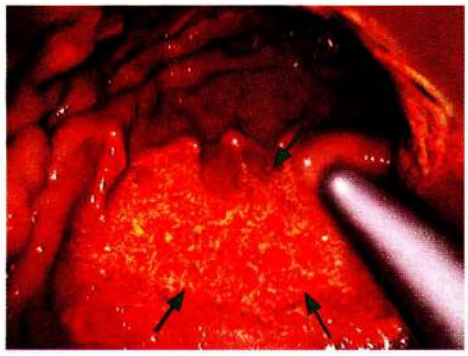


Image 1-9: Gastric ulcer

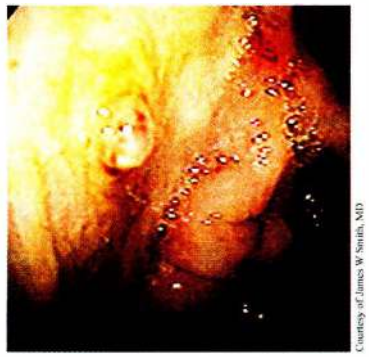


Image 1-10: Ulcer with visible vessel

Quick Quiz

- What is the main cause of bleeding ulcers in the U.S.?
- Name 4 EGD findings that indicate increased risk for rebleed of a peptic ulcer.
- What is the most common presentation of ZES?
- What is the usual cause of gastric carcinoid?

Initial treatment of actively bleeding ulcers (or adherent clot/visible vessel) shows best results with combination therapy consisting of injection (epinephrine or sclerosant) followed by either thermal/laser coagulation or a hemoclip.

NON-ULCER CAUSES OF UGI BLEEDS

Osler-Weber-Rendu (hereditary hemorrhagic telangiectasia) causes telangiectasias on the skin, buccal and nasal mucosa, and throughout the GI tract, lungs, and brain. Occasionally, arteriovenous malformations (AVMs) occur and have the propensity to bleed. In the GI tract, these AVMs are generally in the stomach or duodenum.

Peutz-Jeghers syndrome (PJS) causes dark melanin spots on the lips, buccal mucosa, and the hands and feet. Most patients have hamartomatous polyps that can occur anywhere from the stomach to the rectum. These polyps may cause acute or chronic GI bleeds.

ZOLLINGER-ELLISON SYNDROME

Zollinger-Ellison syndrome (ZES) occurs when a gastrinoma, which produces gastrin continuously, causes refractory (usually duodenal bulb) ulcers and diarrhea +/– steatorrhea. The most common presentation of ZES is diarrhea. The diarrhea/steatorrhea is from the large volume of gastric juice causing acidification of duodenal contents and resultant inactivation of pancreatic enzymes and damage to the intestinal villi (maldigestion/malabsorption).

Gastrinomas most frequently occur in the duodenum (~ 50%) or pancreas (~ 25%), and less frequently in the stomach, lymph nodes, and spleen. 90% are found in what is called the "ZE triangle"—which includes the porta hepatis, mid-duodenum, and the head of the pancreas. 80% are of the sporadic form; 20% are associated with MEN Type 1.

Consider ZES in patients with:

- Severe esophagitis and chronic diarrhea
- Ulcer (especially duodenal ulcer) and chronic diarrhea
- Duodenal ulcer and big folds in the stomach (from parietal cell hyperplasia)
- Recurrent ulcers and no other risk factors
- Recurrent complicated ulcers
- Post-bulbar duodenal ulcers

To evaluate ZES, first order a serum gastrin while patient is off PPI therapy. If the gastrin level is elevated in a patient with gastric ulcer, workup typically requires abdominal CT, endoscopic ultrasound, and somatostatin receptor imaging.

Treatment: All patients with newly diagnosed ZES without evidence of metastatic disease warrant surgical exploration. 1/2 are cured by resection of the primary tumor. Even with metastatic disease, treat ZES aggressively with resection of the primary tumor, because the mass effect of the tumor tissue can eventually cause problems (obstruction).

A PPI is the drug of choice for medical treatment of ZES, although the dose is higher than usual and often must be increased with long-term therapy.

Remember: Other conditions associated with an elevated gastrin level are vitiligo, renal failure, hyperthyroidism, and achlorhydria caused by PPI use or chronic Type A gastritis (see page 1-10). Also remember that persistent high gastrin levels can cause gastric carcinoids.

GASTRIC CARCINOIDS

Gastric carcinoids are rare (0.5% of gastric tumors) and typically caused by chronic hypergastrinemic states. The types of carcinoids are based on the causes of the hypergastrinemic state:

- Type 1 (70–80%): Autoimmune gastritis/pernicious anemia
- Type 2 (5%): ZES, when it occurs as part of multiple endocrine neoplasia—MEN1
- Type 3 (20%): Spontaneous (most aggressive)

Sometimes gastric carcinoids occur in patients with vitiligo.

Gastrin is trophic to the enterochromaffin-like (ECL) cells of the stomach, leading to hyperplasia and occasionally to gastric carcinoids.

Note: The PPI omeprazole has not been shown to cause carcinoids in humans (> 10 years worth of data), although it does increase the circulating gastrin level.

It is unusual for gastric carcinoids to metastasize or to be symptomatic. They are slow growing and almost never cause carcinoid syndrome. See page 1-26 for more on carcinoids.

GASTRIC CANCER

There are 4 significant malignancies of the stomach:

1) Adenocarcinoma (most common—95%!)
2) Carcinoids (just discussed)
3) Lymphoma
4) GIST (gastrointestinal stromal tumors; e.g., leiomyosarcoma)

There are 2 distinct forms of gastric adenocarcinoma: a proximal diffuse type and a distal intestinal type. The incidence of distal gastric cancer had been decreasing until about 20 years ago; since then, its incidence has been holding steady. The proximal type has been steadily increasing. See Image 1-11.

The risk factors and associations with gastric cancer include:

- Chronic *H. pylori* infection
- Metaplastic (chronic) atrophic gastritis
- Ménétrier disease (= large stomach folds from epithelial cell hyperplasia)
- Adenomatous gastric polyps (rare)

It appears that distal gastric cancer is most strongly associated and observed with environmental factors, especially:

- A diet low in fruits and vegetables and high in dried, smoked, and salted foods
- Foods rich in nitrates and nitrites (animal studies)

Acanthosis nigricans is a reactive skin condition with velvety dark plaques in the intertriginous areas (areas where opposing skin surfaces touch and rub). It is usually due to Type 2 diabetes and obesity, but it is also associated with various GI and lung malignancies. Of these malignancies, acanthosis nigricans is most often associated with gastric cancer.

Note that with *H. pylori* infection, some patients may develop MALT (extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue … er, like I said, MALT). This is diagnosed by EGD with biopsy. When the *H. pylori* infection is treated, the MALT may resolve. Close endoscopic follow-up is necessary.

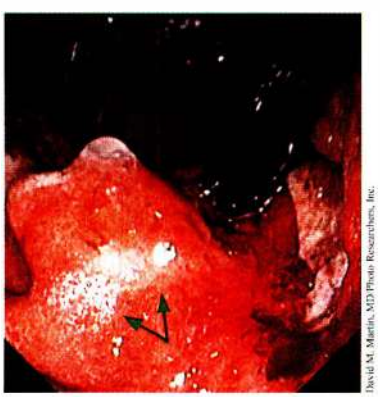


Image 1-11: Gastric adenocarcinoma

Neither alcohol consumption nor gastric ulcers has been proven to cause gastric cancer—as previously thought—even though gastric cancer can present as an ulcer.

Diagnosis of gastric cancer: Often an ulcer is picked up on EGD or barium contrast study (double contrast is better). If it appears benign, it can be treated. Biopsy of gastric ulcers is recommended, especially nonhealing ulcers, if clear etiology is not found (*H. pylori*/NSAID).

For a nonhealing ulcer, endoscopy with multiple biopsies is the diagnostic procedure of choice. Tumor markers, such as carcinoembryonic antigen (CEA) and alpha fetoprotein (AFP), are not useful as early markers for gastric cancer.

Prognosis is determined by stage (TNM classification), using CT scan and endoscopic ultrasound. Because it is largely asymptomatic until advanced, < 10% are found in the early gastric cancer stage (EGC, confined to the mucosa and submucosa, T1N0M0).

The 5-year survival rate is 85–90% for treated EGC and only 3% for treated invasive, metastatic gastric cancer.

Treatment consists of surgical removal of the cancer and adjacent lymph nodes. Adjuvant combination chemoradiation prolongs survival.

OTHER GASTRIC SYNDROMES

POSTGASTRECTOMY SYNDROMES

Overview

Postgastrectomy syndromes include dumping syndrome, blind loop syndrome, and afferent loop syndrome. All are now infrequent because < 5% of PUD cases warrant surgery.

Dumping Syndrome

Dumping syndrome consists of postprandial vasomotor symptoms: palpitations, sweating, and lightheadedness. There are 2 types. The early type occurs 30 minutes after eating and is of uncertain etiology (hyperosmolality of food and fluid shifts in the small bowel). The late type occurs 90 minutes or more after eating and is probably due to hypoglycemia. Treat both types identically: Restrict sweets and lactose-containing foods, separate liquid and solid intake by at least 30 minutes, and encourage frequent small meals that are high in protein and complex carbohydrates.

Blind Loop Syndrome

Blind loop syndrome is bacterial overgrowth in a loop (generally in patients with prior gastrectomy or Billroth II gastrojejunostomy) manifested by fat and B_{12} malabsorption, and a low D-xylose absorption test (bacterial overgrowth and with small bowel mucosal problems).

QuickQuiz

- What are the clinical and environmental risk factors for gastric cancer?
- Carcinoid may be associated with which skin condition?
- What is the relationship of alcohol to gastric cancer?
- How do you rule out gastric cancer in a patient with a nonhealing gastric ulcer?
- What is the best diagnostic test for suspected gastroparesis?
- When are barium enemas contraindicated in IBD?

Afferent Loop Syndrome

With a gastrojejunostomy, an anastomosis is formed between the stomach and the jejunum. The "afferent loop" is the portion that is bypassed and through which bile and pancreatic fluids still flow toward the jejunum. Occasionally these patients get "afferent loop syndrome."

Presentation is abdominal bloating and pain 20 minutes to 1 hour after eating; vomiting often relieves symptoms. The emesis is often bile-colored. Many believe the cause is an incompletely draining afferent loop, which fills with the biliary and pancreatic secretions. Studies of anatomy (using barium) and physiology (using radiolabeled meals) may help further identify the specific pathophysiology involved in a patient with symptoms of dumping syndrome.

Gastroparesis

Gastroparesis, strictly defined as delayed gastric emptying, is increasingly identified in patients who present with symptoms of nausea, vomiting, and abdominal pain among other complaints. Recent guidelines have better defined this syndrome and its characteristics, diagnosis, and therapies.

Gastroparesis in Diabetics

Highly variable gastric emptying is seen in diabetics. Emptying may be slow, normal, or fast. However, long-term diabetics tend to develop gastroparesis. This occurs much more commonly in Type 1 than in Type 2.

Blood glucose > 200 mg/dL has been shown to result in decreased antral motility and delayed gastric emptying. Hyperglycemia may also have a negative long-term direct effect on gastric motility.

Conversely, slowed gastric emptying itself tends to increase blood glucose because of the delay of insulinemic and glycemic responses to the carbohydrates, which leads to a vicious cycle. Treat by maintaining tight glucose control.

Clinical presentation is nausea, vomiting, early satiety, and a predisposition for bezoars.

Other Causes of Gastroparesis

Aside from diabetic neuropathy, gastroparesis can be caused by:

- Autonomic dysfunction—amyloid neuropathy
- An infiltrative process of the smooth muscles—scleroderma, amyloidosis
- An antecedent viral infection (particularly norovirus and rotavirus)
- A CNS disorder (stress, MS, parkinsonism, tumor, cord injuries)
- Post-vagotomy
- Opioid analgesics

Workup of suspected delayed gastric emptying requires that you rule out obstruction first. Then diagnosis is confirmed with a radiolabeled solid meal (gastric emptying study).

Treat with:

- good hydration;
- dietary modification (low-fat, low-residue; multiple small meals);
- tight control of blood glucose;
- symptom management (anti-emetics);
- metoclopramide (FDA warning, though, for long-term use—extrapyramidal side effects may become permanent!); and
- domperidone (widely used outside the U.S.).

IV erythromycin, which is very similar in structure to motilin, stimulates gastric motility but is not very useful as a long-term therapy. It can, however, be used in the acute setting when oral intake is inhibited by severe stasis.

Gastric electrical stimulation has been approved for drug refractory gastroparesis since 2000 in the U.S. and may be a therapeutic option for selected patients.

INFLAMMATORY BOWEL DISEASE

COMMON FACTORS

Inflammatory bowel disease (IBD) comprises **Crohn disease** (CD) and **ulcerative colitis** (UC). In both, family members are at increased risk of IBD, and the patient has an increased risk of GI cancer—but the risk of cancer is much higher in long-standing UC than in CD.

Toxic megacolon is a complication in both, so a barium enema is contraindicated if the patient is having an acute exacerbation.

Infectious colitis, early CD, and UC can appear identical on sigmoidoscopy. Stool examination for blood, WBCs, O&P, C&S, and *C. difficile* toxin assay are included in the initial workup. Refer to Table 1-2 as you review the diagnosis of CD and UC. See Table 1-3 on page 1-22 for a comparison between treatments of CD and UC.

Smokers are more likely than the normal population to develop CD. UC, however, is uncommon in smokers—only 10% of UC patients are smokers!

Colonoscopy is the usual method used to assess IBD. Barium enema is not used anymore, but CT enterography can be helpful in diagnosis of small bowel as well as colonic disease.

The main drugs used to treat IBD include:

- Mesalamine (5-aminosalicylate or 5-ASA preparations)
- Sulfasalazine
- Metronidazole
- Budesonide
- Azathioprine and its metabolite, 6-mercaptopurine
- Infliximab, adalimumab, and certolizumab (monoclonal antibody to TNF-α)
- Prednisone

Methotrexate and cyclosporine are also available.

COMMON DRUGS FOR IBD

Mesalamine (5-aminosalicylic acid, 5-ASA) is normally rapidly absorbed from the upper digestive tract, but different oral formulations release mesalamine into the distal ileum and colon. For colonic disease, it is given either rectally—as an enema (proctosigmoiditis) or suppository (for proctitis only)—or in a formulation designed to delay absorption of the drug.

Sulfasalazine is split, by bacterial action in the colon, into mesalamine (active component) and sulfapyridine.

Because this takes place in the colon, sulfasalazine is ineffective for CD of the small bowel. The other breakdown product, sulfapyridine, is absorbed in the colon, acetylated in the liver, and excreted in the urine. Sulfapyridine is a highly reactive sulfa moiety, which is responsible for most of the side effects of sulfasalazine—such as reversible infertility in men, leukopenia, and headache.

Metronidazole is beneficial for perianal abscesses and fistulas in CD. Long-term use is hampered by the side effect of peripheral sensory neuropathy (particularly if the dose is > 10 mg/kg).

Budesonide is an enteric-coated corticosteroid that is released mostly in the ileum and ascending colon. It metabolizes in the liver to inactive products. It has a 90% first-pass effect—thus, much fewer systemic side effects than prednisone. It was previously used specifically for small bowel CD. A new preparation of extended-release budesonide, which targets the full length of the colon, was recently approved for the treatment of mild-to-moderate UC. As with other corticosteroids, bone mineral density should be monitored yearly. At this point, it is uncertain whether budesonide has less effect than prednisone on bone density.

6-mercaptopurine (6-MP) and **azathioprine** (which metabolizes to 6-MP) are prednisone-sparing drugs useful in both Crohn's and UC, but they usually take 3–4 months to show an effect. Also, because these 2 drugs have bone marrow suppressive effects, monitor CBC monthly. There is no report of increased malignancy with long-term use of either drug.

Infliximab (Remicade®), **certolizumab pegol** (Cimzia®), and **adalimumab** (Humira®) are monoclonal antibodies to TNF-α. They are given for moderate-to-severe Crohn disease, fistulous Crohn disease, and refractory UC. Know that TB may reactivate with usage, but the most common side effect is actually URI. Patients should be assessed for latent TB and hepatitis B and have all recommended age-appropriate vaccinations before initiation of therapy.

Note: Monoclonal antibodies (mAb) are immunomodulators that are identical antibodies derived from clones of a single parent cell. The standard recombinant DNA procedure produces mouse (murine) Ab. The human body reacts against these foreign Ab with an inflammatory response. To overcome this, a portion of mouse DNA that codes for the binding site is combined with human DNA. The result is a chimeric (human-murine) Ab or a humanized (mostly human) Ab. The more human, the less reaction. Fully human antibodies have been developed using transgenic mice. Monoclonal Ab's generic names always end in "mab" (mAb, get it?) with the preceding letters further defining what type of antibody it is—chimeric (-ximab), humanized (-zumab), or human (-umab).

Drugs proven to decrease the relapse rate in CD are azathioprine, 6-mercaptopurine, MTX, and also infliximab.

Table 1-2: Comparison of CD and UC

	Crohn Disease	Ulcerative Colitis
Lesions	Focal, skip, deep	Shallow, continuous
Clinical Course	Indolent	More acute
Prednisone*	Less responsive	Very responsive
Granulomas	Pathognomonic	None
Rectal Involvement	Rectal sparing in 50%	Rectum always involved
Perianal Disease	Abscesses, fistulas	None
Small Bowel Involvement	> 50%	Backwash ileitis in < 10%

** For flares. Not for long-term maintenance therapy.*

QuickQuiz

- Sulfasalazine is ineffective in which types of CD?
- What are the side effects of metronidazole?
- When is budesonide used for CD? for UC?
- What are the indications for monoclonal antibodies in patients with IBD?
- What is the relationship of Crohn disease to cancer?
- What are the colonoscopy and biopsy findings in Crohn's?
- What is the significance of an "apple-core" lesion? How does it differ from the "string sign"?

(Infliximab reduces relapse only in infliximab-induced remission.) Note that all of the standard drugs decrease the relapse rate in UC! Mesalamine drugs and corticosteroids are good for inducing remission in CD but not for maintaining it.

Smoking cessation decreases relapse rate in CD and increases it in UC.

Use in pregnancy:

- FDA risk category B (no evidence of risk in humans): metronidazole (although, because of insufficient data, contraindicated in 1st trimester), prednisone, sulfasalazine, and mesalamine.
- FDA risk category C (risk cannot be ruled out): olsalazine.

CROHN DISEASE

Overview

Although most patients present with Crohn disease (regional enteritis) in their 20s or 30s, the disease can present at any age. There is a second, smaller peak of incidence in 70–80-year-olds. The incidence of CD is rising. There is an increased risk of GI cancer with CD, especially with long-standing disease and Crohn colitis; screen long-term (> 8 years) CD patients every other year for cancer.

CD tends to be more indolent than UC and therefore also tends to be less responsive to treatment. It is harder to get these patients off steroids. Patients with CD are more likely to have perianal fistulae and abscesses. They are also more likely to have strictures, inflammatory masses, and associated obstruction. One big problem with CD is the high rate of recurrence. It was once thought to be 50% at 10 years, but this is the symptomatic recurrence rate. Radiologic/endoscopic recurrence rate is 75% at 3 years!

Osteoporosis is common in patients with Crohn disease. About 70% have abnormal bone density—due to chronic disease, vitamin D deficiency, and/or steroids.

Diagnosis

CD is diagnosed by finding patchy, focal, and aphthous ulcers and deep transmural ulcers with occasional strictures and fistula formation. Granulomas, infrequently found on biopsy specimen of these ulcers, are pathognomonic. See Image 1-12 through Image 1-14.

A tetrad to remember for "Crohn colitis":

1) Rectal sparing
2) Skip lesions
3) Perianal disease
4) Ileocecal involvement

Patients with CD may present with fever, abdominal pain, and systemic symptoms. One classic but uncommon feature is the string sign, which may be seen in the terminal ileum during a small bowel follow-through. The terminal ileum is so edematous and/or fibrotic that the lumen is compressed and can be visualized only as a "string" of contrast. If you see this narrowing of the lumen elsewhere in the colon, with or without CD, it is called an apple-core lesion, which suggests cancer. Bowel involvement in CD: 30% colon only, 30% small bowel only, and 30–50% both.

Initially, a definitive diagnosis cannot be established in up to 15% of patients with IBD. Serologic tests (p-ANCA and ASCA, anti-saccharomyces antibody) can be useful in indeterminant cases. p-ANCA is associated

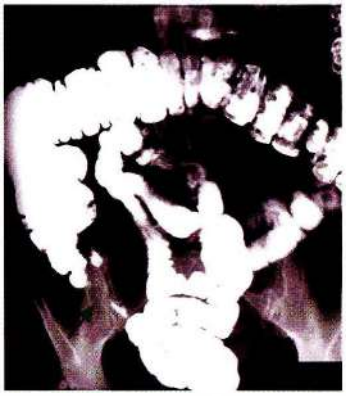


Image 1-12: Crohn colitis with "string sign" in RLQ

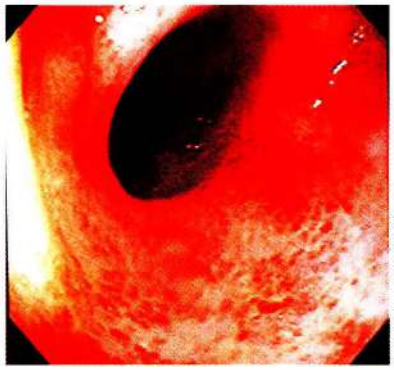


Image 1-13: Crohn proctitis

Image 1-14: Crohn disease with submucosal edema causing cobblestone appearance

with UC and ASCA with CD. Panels containing additional serologic markers, which increase sensitivity/specificity, are commercially available.

Extraintestinal Manifestations of CD

The extraintestinal manifestations occur primarily in CD involving the colon. These manifestations are identical to those of UC (which involves only the colon). So, these are discussed later under Extraintestinal Manifestations of UC on page 1-21.

Terminal Ileum Problems in CD

Problems related to disease/resection of the terminal ileum are found in CD—but ordinarily not in UC. These problems include:

- Calcium oxalate kidney stones
- Steatorrhea
- Gallstones
- B_{12} deficiency
- Hypocalcemia (from vitamin D malabsorption)
- Bile acid-induced diarrhea
- Nutrient malabsorption

What type of gallstones occurs? Pigment gallstones are the usual type, and the risk appears to correlate with the amount of ileal disease or resection.

Note that anytime > 60 cm of terminal ileum is resected, patients have B_{12} malabsorption.

Bile acid-induced diarrhea is usually the cause of diarrhea in Crohn patients when < 100 cm of distal ileum is resected. Some of the bile acids escape absorption in the terminal ileum and go on to stimulate colonic salt and H_2O secretion by the colon. Treat with bile acid sequestrants (e.g., cholestyramine, colestipol), which bind and inactivate bile acids.

When > 100 cm of distal ileum is resected, the patient gets steatorrhea from greatly decreased proximal gut concentration of bile salts. (Synthesis does not keep up with GI losses with the loss of distal ileum resorption.) Treat these patients with a low-fat diet. Sometimes, the low-fat diet does not allow them to get enough calories. In this case, give them supplemental medium-chain triglycerides (MCT).

Treatment Overview for CD

Medical treatment of CD includes many of the same drugs as that for UC. See more detail on these medications on page 1-21.

Medical treatment of CD:

- 5-aminosalicylate (5-ASA, mesalamine—slow-release formulations)
- Olsalazine
- Corticosteroids (prednisone, budesonide)
- Infliximab, adalimumab, and certolizumab pegol
- Metronidazole
- Ciprofloxacin
- Azathioprine (and its metabolite, 6-mercaptopurine)

[Know Table 1-3 on page 1-22. And know:]

- In general, treatment for mild disease is a slow-release oral 5-ASA formulation with progression to other drugs if response is not adequate. 5-ASA analogs are more effective in CD with colon disease only vs. ileal or ileocolic disease.
- Prednisone is more effective in UC than CD—again, probably due to the indolent nature of CD. In CD, prednisone is more effective than sulfasalazine when CD affects only the small intestine. Prednisone is best used only for flares; long-term use (> 3 months) should be discouraged because of side effects.
- Budesonide is a 1st line drug for mild-to-moderate CD of the ileum or ileocecal disease.
- Infliximab is helpful in patients with fistulas, and it also facilitates withdrawal from corticosteroids. Before starting this agent (or adalimumab, below), screen all patients for tuberculosis and hepatitis B. The most common adverse reactions are development of a positive ANA in 55% and URIs in 32%. Severe fungal infections, in addition to tuberculosis, can be seen while on therapy. Additionally, lymphoma and multiple sclerosis have been described.
- Metronidazole is effective, especially for fistulas and perianal CD (used for UC only when there is fulminant disease with peritonitis). Long-term use is hampered by neuropathy.
- Ciprofloxacin is also occasionally used for fistulous or perianal Crohn disease.
- 6-mercaptopurine (6-MP) and azathioprine are used with Crohn patients who cannot be weaned off prednisone. Note: Long-term treatment with 6-MP and azathioprine has been shown to decrease recurrence rates in CD.

Like 6-MP and azathioprine, mesalamine may also decrease the relapse rate in CD. Prednisone and metronidazole do not affect relapse rate.

Surgery and Recurrence in CD

Surgery is only for intractable disease and specific serious complications. Previously, 60% of Crohn patients required surgery in the first 5 years and then again after ~ 8 years. These numbers are decreasing with improved medical therapy options (especially 6-MP, infliximab).

The incidence of recurrence after surgery depends on:

- Site—ileocolic is highest.
- Nature of the complication—obstruction, perforation, and abscesses have a higher rate of recurrence.

Essentially, the worse the disease is where you cut, the more likely is the recurrence at that site. Colectomy and ileostomy provide the best results for Crohn colitis when there is no ileal inflammation (> 60% have no recurrence).

QuickQuiz

- What GU complication can arise in a patient with Crohn's of the terminal ileum?
- What is the usual etiology of diarrhea in CD patients with > 100 cm of distal ileum removed? With < 100 cm of distal ileum removed? What is the treatment for each?
- What additional screening should be done in patients with Crohn's who have been treated with chronic steroids?
- What are the findings of UC on colonoscopy?
- What serological marker may be found in 70–80% of patients with UC?
- Describe the extraintestinal manifestations of UC.

Treatment Scenarios for CD

Colon only: sulfasalazine or mesalamine tablets/enemas. Sulfasalazine is about $30/month vs. $300+/month for mesalamine and other drugs. Therefore, sulfasalazine is the 1st choice—then 5-ASA drugs, if required because of intolerance to the side effects of sulfasalazine.

Any ileum or small bowel involvement: slow-release mesalamine.

Only ileum or small bowel involvement: slow-release mesalamine or budesonide.

Fistula or perianal: infliximab (or other immunomodulators), metronidazole, or ciprofloxacin. 6-MP also used.

Steroid-dependent: 6-MP, azathioprine, mAb.

Corticosteroids are a 1st line drug for incomplete acute small bowel obstruction. Otherwise, they are used for flares and only if there is inadequate response to the 5-ASA drugs.

Note: Be sure to screen CD patients for osteoporosis. About 70% have abnormal bone density due to chronic disease and/or steroids.

ULCERATIVE COLITIS

Overview

Ulcerative colitis (UC) consists of uniform, contiguous mucosal inflammation with shallow ulcers. The inflammation always starts in the rectum, extends proximally, and always is confined to the colon (Image 1-15). There is typically a sharp margin between the area of involvement and the normal mucosa. The area of involvement tends to remain the same from the time of diagnosis but does extend more proximally in 10%.

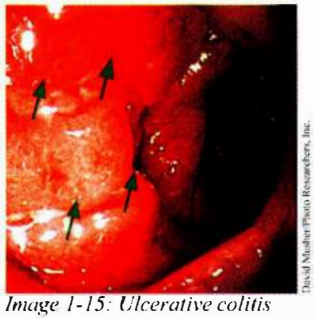


Image 1-15: Ulcerative colitis

70–80% of UC patients are p-ANCA–positive, although this test is of little use clinically (low sensitivity and specificity). ESR and C-reactive protein (CRP) are often elevated.

The main symptoms of UC are abdominal pain and bloody diarrhea. Clinical course and degree of involvement are variable—from mild ulcerative proctitis (rectal area only) with minimal symptoms to severe colitis of the entire colon with bad cramps, liquid stools containing blood and pus, anemia, extraintestinal manifestations (below), and constitutional symptoms. Occasionally, tenesmus (painful anal sphincter spasm with no bowel movement) and constipation may be the major clinical presentation.

You must rule out infectious causes of colitis:

- *E. coli* O157:H7 (EHEC)
- *Shigella*
- *Salmonella*
- *Yersinia*
- *Campylobacter*
- *C. difficile*
- *E. histolytica* (amebiasis)

Especially *Campylobacter*—since it can have a chronic, relapsing course that mimics UC.

Consider *C. difficile* infection in a flare-up—it is generally thought of as an acute disease, but it can manifest as diarrhea 1–3 months after antibiotic use! Don't forget that *C. difficile* can occur even without preceding antibiotic use.

Diagnosis is made with colonoscopy or sigmoidoscopy.

Extraintestinal Manifestations of UC

Extraintestinal manifestations of IBD are usually seen in IBD patients with colitis (so they are typically associated with UC, although they can be seen in CD involving the colon).

These extraintestinal manifestations include:

- RF-negative peripheral polyarthritis (types 1 and 2)
- Ankylosing spondylitis (also HLA-B27+)
- Skin lesions—Erythema nodosum and pyoderma gangrenosum—which correlate with disease activity
- Iritis/episcleritis/uveitis (HLA-B27+)
- Venous thrombosis
- Pericholangitis
- Primary sclerosing cholangitis (PSC, HLA-B8+; see page 1-48)
- Aphthous ulcers of the mouth

The complications associated with HLA antigens tend not to improve with improvement of colitis, whereas the other problems mentioned here usually get better as colitis improves!

Type 2 peripheral arthritis (polyarticular)—predominantly MCP; independent of disease activity.

Type 1 peripheral arthritis (pauciarticular)—parallels disease activity.

So, what disease do you think of if a patient with UC develops jaundice, itching, and cholestatic LFTs?

Note that the JSEM mnemonic leaves out primary sclerosing cholangitis, the answer to this question! PSC occurs in 5% of UC patients. As with any newly increased LFTs, do an ultrasound first, then do MRCP (shows "string of beads," multifocal strictures of intrahepatic bile ducts) to confirm the diagnosis of PSC.

Check LFTs, especially alkaline phosphatase, initially and periodically. If the alkaline phosphatase becomes 2 x nl and persists, work up for sclerosing cholangitis.

Cancer in UC

Risk of cancer in patients with UC is high. Risk starts increasing about 8 years after onset of symptoms in patients with pancolitis. It is up to 5–10% at 20 years and up to 12–20% at 50 years. Risk increases with:

- Duration of UC
- Extent of UC—pancolitis has the highest risk, whereas ulcerative proctitis has no increased risk
- Concurrent PSC
- Persistent mucosal inflammation (disease activity)
- Dysplasia

Any patient who has had pancolitis for 8 years or left-sided colitis for 15 years should have a colonoscopy with multiple biopsy samples to check for dysplasia. Once started, routine colonoscopy screening for cancer every 1–2 years should be continued.

Table 1-3: Comparison of Treatments Used for Ulcerative Colitis and Crohn Disease

Ulcerative Colitis

Severity:		**Mild**	**Moderate**	**Severe**	**Fulminant**	**Remission**
... definition of severity	Stools/d	< 4	Between mild and severe	> 6	> 10	Normal
	KUB	Normal		Air, edema, thumbprinting	Bowel dilation	
	Physical exam	Normal; but h/o intermittent fecal blood		Fever, Abd tenderness, freq fecal blood	Fever, Abd tenderness, and distention	
Treatment:		Distal disease: Rectal corticosteroids; oral or rectal aminosalicylates Extensive colon involvement: Oral aminosalicylates		Distal disease: Oral or rectal corticosteroids Extensive colon involvment: Oral corticosteroids	IV corticosteroids IV cyclosporine or infliximab if resistant to corticosteroids	Colonic release budesonide; infliximab (Remicade®) and adalimumab (Humira®) as maintenance therapy

Crohn Disease

Severity: Definitions same as for UC	**Mild**	**Moderate**	**Severe/Fulminant**	**Post-Op**	**Remission**
Treatment:	Oral aminosalicylates; metronidazole	Oral corticosteroids (short term < 3 months); budesonide, azathioprine, 6-MP, or methotrexate if steroid dependent or refractory	IV corticosteroids; IV infliximab; Elemental diet or TPN = transient benefit	Metronidazole (delays anastomotic recurrence—danger of neuropathy)	Oral aminosalicylate; azathioprine or 6-MP especially if steroid dependent or refractory; 6-MP or azathioprine is standard maintenance therapy. Infliximab and adalimumab are frequently used to maintain remission

Note the differences and similarities in these treatments! Metronidazole and diet (bowel rest) are ineffective in UC. Rectal preparations are used only in UC of the distal colon.

QuickQuiz

- What is the relationship of UC to cancer?
- What is the treatment for UC with high-grade dysplasia?
- What is the treatment for moderate-to-severe UC?
- Associate these "buzzwords" with UC or CD: a) tenesmus, b) rectal bleeding, c) fecal soiling, d) pneumaturia.
- How is diarrhea classified?
- What tests are done for the workup of acute diarrhea?

Treatment of UC

UC is cured with surgery! But it may be a difficult surgery, so reserve it for findings of cancer or dysplasia! UC colectomy is recommended for patients with dysplasia in a mass lesion and for high-grade dysplasia in flat mucosa. Repeat colonoscopy in 6 months if there is low-grade dysplasia without inflammation. Some authorities recommend colectomy if low-grade dysplasia without inflammation is confirmed on 2 biopsies within 6 months. Repeat in 6–12 months for dysplasia with inflammation (usually not precancerous).

Other indications for UC surgery besides cancer are:

- Intractable disease
- Perforation
- Growth retardation in children
- Toxic megacolon
- Stricture
- Steroid dependence
- Exsanguinating hemorrhage
- Complication from therapy

Know all the treatments for UC! Therapy for UC is changing due to the advent of 5-ASA compounds without sulfa, newer immunomodulators, and short-term use of corticosteroids. UC, a more acute inflammatory process, responds to steroids much better than CD (Table 1-3).

For mild disease, there are several options:

- Oral sulfasalazine
- Oral mesalamine
- Rectal mesalamine (suppository for proctitis; enema for proctosigmoiditis)
- Hydrocortisone enemas

All have similar efficacy—75% response and 30% remission after 2 months. The HC enemas have few side effects and lead to quicker symptom relief than mesalamine.

For moderate-to-severe UC, initial therapy is oral prednisone. Hospitalize patients with fulminant UC and treat with IV corticosteroids, infliximab, or cyclosporine; the patient may need a colectomy if fulminant symptoms persist for > 48 hours.

Maintenance therapy after remission:

- Sulfasalazine or mesalamine daily for 2 or more years.
- Azathioprine and 6-mercaptopurine for frequent recurrences/steroid dependence; treatment may take 3–4 months to show an effect.
- Cyclosporine provides short-term remission in 40–50% of patients with severe colitis, but long-term remission in only 20–30%. Long-term remission is improved when adjuvant azathioprine is used.
- Immunomodulators

A few buzzwords:

- Tenesmus (UC)
- Rectal bleeding (UC)
- Fecal soiling (think fistula = CD)
- Hydronephrosis without stones (obstruction from inflammatory mass = CD)
- Pneumaturia (think fistula to the bladder = CD)

DIARRHEA

OVERVIEW

Diarrhea is defined variably as > 200–250 g/day of stool. Normal average daily output is 150–180 grams. Note: Small-volume, loose stools are not considered diarrhea. Normal bowel frequency varies from 3 to 21 stools/week.

Diarrhea is typically categorized by duration of symptoms. Acute is < 2 weeks, persistent is 2–4 weeks, and chronic is > 1 month.

ACUTE DIARRHEA

The infectious causes of acute diarrhea are covered in the Infectious Disease section, Book 1, under Common ID Syndromes: Gastrointestinal.

Introduction

Acute diarrhea commonly has an infectious etiology, but it may also be caused by food poisoning or drug side effects. Infectious diarrhea may be invasive or noninvasive.

Diagnosis of Acute Diarrhea

Do the simple things first! Check diet and travel history.

Lab: First, check stool for blood (guaiac test) and fecal WBCs. The invasive types usually are positive for fecal WBCs.

Table 1-4: Osmotic vs. Secretory Diarrhea

	Osmotic	Secretory
Volume/day	< 1 L	> 1 L
Effect of Fasting on Diarrhea	Decreases > 50%	Decreases < 20%
Serum (= Total Stool) Osmolality	290	290
Example $[Na^+]$ Example $[K^+]$ So $[Na^+] + [K^+]$ =	40 20 60	105 40 145
$2([Na^+] + [K^+])$	120	290
Osmotic Gap	> 50	< 25

If these are elevated, do:

- Culture + Sensitivity exam (C+S)
- Ova + Parasite exam (O+P) (especially with positive travel history)
- +/– Sigmoidoscopy with biopsy

If you suspect *E. coli* O157:H7 (enterohemorrhagic *E. coli*; EHEC), specifically ask for MacConkey-sorbitol agar for the stool culture media. If you suspect *Clostridium difficile*, also add *C. difficile* toxin assay.

Rectal/colonic biopsies can be useful in differentiating infectious colitis from inflammatory bowel disease. Crypt abscesses may be found in both, but crypt distortions are found only in inflammatory bowel disease.

Treatment of Acute Diarrhea

Generally, invasive diarrhea is treated with quinolones (especially ciprofloxacin), but use macrolides for *Campylobacter* (high quinolone resistance) and metronidazole for amebiasis. Antibiotics may prolong *Salmonella* infections and, therefore, are typically not used.

Another big exception is *E. coli* O157:H7 infection (EHEC), which is treated only symptomatically; antibiotics are contraindicated!

Before reading further, see Infectious Disease, Book 1, to review more detail on the specific organisms and treatments.

CHRONIC DIARRHEA

Mechanisms of Chronic Diarrhea

Overview

Again, chronic diarrhea is defined as loose stools > 200–250 g/day for > 1 month.

Chronic diarrhea can be classified according to 3 mechanisms: osmotic, secretory, and increased motility. First, let's compare and contrast osmotic and secretory mechanisms. In this section, when discussing ion concentrations, note that "[x]" means "concentration of x."

In normal bowel contents, the cations are equal to the anions:

$$[Na^+] + [K^+] = [Cl^-] + [HCO_3^-] + \text{other anions}$$

(The "other anions" are mostly short-chained fatty acids that are usually absorbed early in bowel transit.)

You can calculate stool osmolality using only the Na^+ and K^+ concentrations:

$$\text{Stool osmolality}_{calc} = 2[Na^+ + K^+]$$

For normal stool and for diarrhea of any cause:

$$\text{Stool osmolality} = \text{serum osmolality}$$

But! ... Depending on the cause of the diarrhea, the amount of unmeasured anions may vary from normal to high.

Note: Serum osmolality is typically 280–300 mOsm/L—or, for the equations, 290 mOsm/L.

Because the fluid in secretory diarrhea is, in essence, an ultrafiltrate of the serum, secretory diarrhea is similar to normal stool in that $2[Na^+ + K^+] = 290$ mOsm/L.

With osmotic diarrhea, part of the osmolality is due to unmeasured, nonabsorbable, osmotically active molecules—so the $2[Na^+ + K^+]$ is much less than 290 mOsm/L. This difference is usually > 50 mOsm/L.

Summary: Here are the pertinent equations again. Learn them, and you should be able to handle this topic:

$$\text{Stool Osm}_{calc} = 2 \times (\text{stool } [Na^+] + \text{stool } [K^+])$$

$$\text{Stool Osmolar Gap} = 290 - \text{Stool Osm}_{calc}$$

If SOG > 50, the gap is increased, and added osmoles are present that are causing diarrhea.

When the SOG < 25, the stool is either normal, or the diarrhea is secretory.

These calculations are very academic and work in straightforward situations, but many causes of diarrhea have both secretory and osmotic components. At the bedside, the calculations are less useful. For a Board exam, though, definitely know how to do this.

Make sure this makes sense to you before you move on!

Secretory Diarrhea

In secretory diarrhea, $2[Na^+ + K^+]$ of the stool is ~ 290 mOsm/L; i.e., measured serum osmolality (SOG is < 25). There is more stool volume in secretory diarrhea than in osmotic diarrhea, often > 1 L/d, so there is obviously an increased secretion of electrolytes; thus, the patient is at risk for an electrolyte deficiency.

There are many causes of secretory diarrhea:

- Enterotoxins from *E. coli*, cholera, and *S. aureus*
- Villous adenomas (rare cause)
- Gastrinomas
- Microscopic colitis

Quick Quiz

- What are the treatments generally used for invasive diarrhea?
- Which cause of invasive diarrhea should not be treated with antibiotics?
- What is the osmolar gap in patients with osmotic diarrhea?
- Will a 24-hour fast stop osmotic diarrhea?
- In an AIDS patient with fever and diarrhea, what organisms are on your differential list?

- Collagenous colitis
- Bile acids
- VIPomas that produce vasoactive intestinal peptide (VIP)

A 24–48-hour fast does not decrease secretory diarrhea, except in fatty acid- and bile acid-related diarrheas. See Table 1-4.

Osmotic Diarrhea

In osmotic diarrhea, ([290] – 2[Na^+ + K^+]) is > 50. So, there is at least a 50 mOsm/L osmotic gap that is due to a nonabsorbable osmotic agent. A 24-hour fast does resolve or greatly improve the diarrhea. Lactase deficiency is one of the most common causes of osmotic diarrhea. Other common causes are: Mg-containing laxatives and antacids, non- or poorly absorbable carbohydrates (xylitol, lactulose, sorbitol, fructose), and nutrient malabsorption; i.e., pancreatic insufficiency, celiac disease, bacterial overgrowth. If an osmotic diarrhea persists despite a 24-hour fast, suspect surreptitious ingestion of an Mg-containing antacid. Most laxatives, including castor oil, cause an osmotic diarrhea.

Diarrhea 2° Increased Motility

The last mechanism of diarrhea is increased motility. The dysmotility syndromes include antibiotic-associated diarrhea, hyperthyroidism, carcinoid, and irritable bowel. Treatment for most antibiotic-associated diarrhea is simply to stop the drug. *C. difficile* diarrhea is a different animal (discussed later).

Different mechanisms of diarrhea may occur together in certain diseases. In celiac disease, for example, osmotic and secretory mechanisms coexist because there is malabsorption of carbohydrates (osmotic) and fat (secretory). Exudative diarrhea (i.e., high fecal WBCs; includes invasive bacteria and IBD) contains all 3 mechanisms: Inflammation causes altered motility, and malabsorption can cause both osmotic and secretory components.

Causes of Chronic Diarrhea

AIDS

[Know!] With the advent of highly active antiretroviral therapy (HAART), infectious causes of diarrhea in AIDS patients have reduced dramatically from > 50% to 13%. Despite HAART, diarrhea still occurs frequently. If the patient with AIDS has diarrhea and weight loss without fever but has a low CD4 count, suspect one of these noninvasive organisms: *Cryptosporidia* (usual cause), *E. histolytica*, *Giardia*, *Isospora*, *Strongyloides*, or AIDS enteropathy.

With fever, think *Mycobacterium*, *Campylobacter*, *Salmonella*, *Cryptococcus*, *Histoplasma*, and CMV. (These are covered in Infectious Disease, Book 1, under Common ID Syndromes: Gastrointestinal.)

Volume is a big clue in AIDS-associated diarrhea; > 1 L/d suggests a small bowel cause.

A CD4 count < 200, especially if accompanied by weight loss, points to an infectious etiology rather than AIDS enteropathy.

IBD

[Know!] Chronic inflammatory diseases of the colon (UC and Crohn colitis) cause loose stools with many WBCs and histologic damage. Volume may be greater or less than 200 g/day. Chronic bloody stools suggest UC. Chronic loose stools associated with chronic RLQ abdominal cramping, especially palpation of thickened bowel in the RLQ, suggest CD.

Note: Fecal WBCs and blood are found in both invasive diarrhea and UC. See page 1-17 for more on IBD.

Diabetes

Diabetic diarrhea may be caused by:

- Use of dietetic foods rich in sorbitol (erroneously labeled "sugarless")
- Visceral autonomic neuropathy (Especially suspect this in the incontinent diabetic patient.)
- Malabsorption (less common) due to celiac disease (present in 5% of diabetics), pancreatic insufficiency, or bacterial overgrowth (treat with metronidazole and amoxicillin-clavulanate)
- Pancreatic exocrine insufficiency (more common in DM due to pancreatic disease)

Carbohydrate Intolerance

Consider carbohydrate intolerance in all patients with chronic diarrhea who excessively ingest beverages rich in sorbitol and fructose. Note: Coke/Pepsi has 40 g of fructose per 16 oz (480 mL).

Carcinoid

There are several types of carcinoid tumors (GI, lungs, kidneys, ovaries), and they can present with carcinoid syndrome or symptoms associated with tumor growth, such as pain or obstruction.

Carcinoid syndrome is the neuroendocrine manifestation caused by release of vasoactive mediators, including 5-hydroxytryptophan, 5-hydroxytryptamine, histamine, kallikrein, and prostaglandins.

With GI tumors, carcinoid syndrome occurs only when the primary tumor has metastasized to the liver. In other tumors, the liver deactivates the vasoactive mediators, so symptoms don't occur. But, with liver mets, the vasoactive mediators are released directly into the circulation from the liver and, thus, are not deactivated. Some bronchial carcinoids can present with carcinoid syndrome, but it's extremely rare!

So, when you see carcinoid syndrome, think GI primary with hepatic metastases!

Most carcinoids are asymptomatic, are found in the GI track outside of the midgut, and do not metastasize. Most symptomatic carcinoids are associated with a primary tumor in the midgut (ileum and proximal colon).

Carcinoid is an uncommon cause of chronic diarrhea. Gastric carcinoids are related to hypergastrinemic states (discussed on page 1-15).

Carcinoid syndrome presents as paroxysmal flushing; crampy, explosive diarrhea; and hypotensive tachycardia. The flushing is often bright red to violaceous, with well-defined borders, and can be on the whole body—including palms and soles.

Because tryptophan, a precursor of niacin, is used up in carcinoid syndrome, niacin deficiency (pellagra) may occur (scaly rash, thickened tongue, angular cheilitis, and mental status changes).

Diagnosis of carcinoid: Check 24-hour urine for 5-hydroxyindoleacetic acid (5-HIAA)—a breakdown product of 5-hydroxytryptamine. Normal is < 10 mg/d; with carcinoid, patient has > 25 mg/d. In patients with carcinoid syndrome from a primary GI tumor, CT of liver should show metastatic lesions.

Visceral Autonomic Neuropathy (Diabetes, Amyloidosis)

Visceral autonomic neuropathy is characterized by:

- Delayed gastric emptying (i.e., gastroparesis)
- Postural decrease in blood pressure
- Anhidrosis (inability to tolerate heat, lack of functioning sweat glands)—especially in lower extremities
- Fecal incontinence
- Impotence (men)
- Urinary overflow incontinence

Patients may exhibit any one or all of the above!

Microscopic Colitis

Microscopic colitis consists of both collagenous colitis and lymphocytic colitis. These patients have grossly normal-looking mucosa but abnormal findings on mucosa biopsy (hence the name microscopic colitis). These patients have a chronic secretory, watery diarrhea.

Colonoscopy is normal, but mucosal biopsy of the normal-looking mucosa shows a lymphocytic infiltrate or a collagenous band in the submucosa. [Know:] These entities do not progress to IBD. Budesonide is the 1st line treatment.

Other

Other causes of chronic diarrhea include:

- Steatorrhea (discussed further below)
- Endocrinopathies (hyper- and hypothyroidism, adrenal insufficiency)
- Colon cancer
- Radiation-induced disease
- Fecal incontinence (radiation; diabetes; rectal surgery; and childbirth injury to anal sphincter, especially forceps delivery)

Patients may not want to mention that they have fecal incontinence. They frequently tiptoe around the issue by asking "for medication to control the diarrhea." Ask patients with diarrhea if they experience fecal incontinence more than once a week. If so, the differential diagnosis includes the items listed previously.

Chronic Loose Stools

The following may cause loose stools < 200 g/day, so they do not meet the criteria of diarrhea:

- Lactase deficiency (lactose intolerance) is a common cause of loose stools, although the volume is generally < 200 g/day.
- Irritable bowel syndrome (IBS) has loose stools with normal daily volume. See page 1-32 for more on IBS.

Diagnosis of Chronic Diarrhea

Know the following 3 stages of diagnosis:

Stage 1

- Stool O&P
- Fecal leukocytes x 3
- Serum chemistry and thyroid profile
- *C. difficile* toxin assay
- Stool pH
- Weight of stool/day
- 3-day fecal fat (or if Sudan stain is positive, do the fecal fat)
- Lactose-free diet if lactase deficiency is at all suggested by history

Quick Quiz

- What tumor causes the majority of cases of carcinoid syndrome?
- What is the clinical presentation of carcinoid syndrome?
- How do you diagnose carcinoid?
- Explain each of the 3 stages used in the workup of chronic diarrhea.
- What lab tests are done in the workup of malabsorption?
- What are the extraintestinal manifestations of celiac disease?

Stage 2

- Immunoabsorbent assay for giardiasis.
- If steatorrhea is confirmed, order ultrasound or CT scan for pancreatic calcification (further tests for steatorrhea discussed in detail on page 1-30).
- If diabetic has suggestive history: Do either a lactulose breath test for bacterial overgrowth or (more often) just treat empirically.
- If > 1,000 cc/day of stool, check vasoactive intestinal polypeptide.
- Check for laxative abuse by:
  - Specific urine tests for bisacodyl, anthraquinones, and phenolphthalein
  - Stool osmotic gap > 100 mOsm/L (magnesium-containing)
  - Stool measurement of phosphate and sulfate
- If the stool osmolality is < 290, the patient could be adding water or urine to the stool.

Stage 3

- EGD and colonoscopy

A significant number of patients have no discernible cause of the diarrhea and have no abdominal pain and normal EGD and colonoscopy. These patients have idiopathic chronic diarrhea.

Often, a hospital stay is required after stage 3 to redo the previous tests with better controls. Suspect occult bile acid diarrhea if the patient has loose watery stool but no abdominal pain.

Loose Stools and Fecal Impaction

Watery stool may leak around a fecal impaction, causing small-volume watery effluent. See more on fecal impaction on page 1-32.

MALABSORPTION

Overview

Malabsorption may be short-lived, but patients often present with chronic diarrhea.

The "Big 6" blood tests are those done in the routine workup for malabsorption. These tests are albumin, Ca++, cholesterol, carotene, serum iron (all low), and PT (prolonged).

These are discussed later in this section, but first let's discuss the causes of malabsorption—which can be divided into decreased mucosal transport (something wrong with intestinal uptake) or decreased digestion (not enough digestive enzymes).

Malabsorption Due to Decreased Mucosal Transport

Introduction

Decreased mucosal transport may be caused by celiac disease, tropical sprue, common variable immune deficiency with hypogammaglobulinemia, Whipple disease, intestinal lymphoma, eosinophilic gastroenteritis, bacterial overgrowth, and other small bowel disease. These are discussed below.

Celiac Disease

Celiac disease (gluten-sensitive enteropathy, previously celiac sprue, nontropical sprue) is one of the most commonly undiagnosed disorders. It occurs in up to 1% of the population of most countries.

Celiac disease is an autoimmune intestinal disorder in which there is an altered gut mucosal response to dietary gluten, which is in wheat, barley, malt, and rye, resulting in small bowel villous atrophy and crypt hypertrophy with resulting malabsorption. It can cause growth retardation in children and is associated with HLA-DQ2 and HLA-DQ8. It may go into remission during adolescence, and then recur. If detected early, the patient may have only mild symptoms such as bloating and loose stools.

Extraintestinal manifestations of celiac disease:

- Iron deficiency anemia (most common presentation; iron is absorbed mostly in the duodenum): low Hgb, MCV, and ferritin
- Abnormal serum aminotransferases
- Dermatitis herpetiformis—discussed below
- Osteoporosis
- Osteomalacia
- Neuropsychiatric symptoms
- Dental enamel defects

Primary intestinal lymphoma is a rare, late complication of celiac disease.

Deficiencies caused by celiac disease:

- Iron
- Folic acid
- Calcium
- Vitamin D
- Vitamin B_{12} (rarely)
- Vitamin K

There is a wide spectrum of presentations. Patients often have little or no GI symptoms and may present with only a psychiatric disorder, osteomalacia, or a purulent pustular rash.

Dermatitis herpetiformis is a manifestation of celiac disease. It is characterized by intensely itchy vesiculopapular eruptions on the face, trunk, buttocks, sacrum, and extensor surfaces of elbows and knees (Image 1-16).

Most patients with dermatitis herpetiformis do not have abdominal symptoms, although 85% have the characteristic findings on intestinal wall biopsy.

Diagnosis of celiac disease includes these 4 criteria:

1) Evidence of malabsorption (steatorrhea, weight loss, iron deficiency anemia)
2) Many patients with latent celiac disease may have only a positive tissue transglutaminase antibody test (90+% sensitivity) or positive antiendomysial antibody test
3) A positive response to a gluten-free diet (clinical, chemical, histological, and immunologic)
4) Abnormal small bowel biopsy to clinch the diagnosis

The best antibody tests are:

- Tissue transglutaminase (tTG) antibody
- IgA antiendomysial Ab (but not good with IgA deficiency)

Antigliadin antibodies (AGA) are sensitive but not specific and are superseded by tTG antibody or antiendomysial Ab. Because IgA deficiency occurs in 1–2% of U.S. population, if IgA tTG antibody is negative in the setting of a strong suspicion of sprue, check serum IgA levels. These antibody tests may also be useful for determining latent celiac disease or as a measure of compliance with the gluten-free diet.

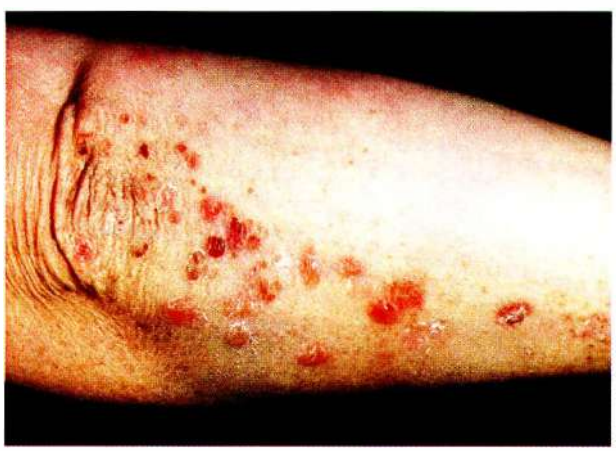


Image 1-16: Dermatitis herpetiformis

If there is a high suspicion for celiac disease, serology in conjunction with early EGD with small bowel biopsy is often utilized for diagnosis.

Note: The small bowel biopsy results are characteristic but not pathognomonic, since you may see similar villous atrophy with hypogammaglobulinemia ("hypogammaglobulinemic sprue"), small intestinal bacterial overgrowth, lactose intolerance, giardiasis, peptic duodenitis, and tropical sprue! Many small bowel disease processes can cause villous atrophy.

Treat celiac disease with a gluten-free diet (GFD).

80% eventually respond. For those patients who do not, consider:

- Dietary noncompliance (most common)
- Intestinal lymphoma
- Microscopic colitis
- T-cell enteropathy
- Lactose intolerance 2° to lactase deficiency (damaged mucosa)
- Pancreatic insufficiency
- Collagenous sprue (see below)
- Ulcerative jejunoileitis

Emphasize to the patient the need for lifetime gluten restriction.

One can test for compliance by doing repeat tests for tissue transglutaminase antibody (tTg).

Now that you know about celiac disease, what test will you remember to order in the following patients?

A 16-year-old presents with a diagnosis of bipolar disorder.

A 33-year-old presents with bone pain in his spine and legs.

A 28-year-old presents with a pruritic papulovesicular eruption on her extensor elbows and knees.

A 30-year-old presents with heme-negative stool and low Hgb, MCV, and ferritin.

Good! tTG or IgA antiendomysial Ab for celiac disease. Celiac disease is a commonly missed diagnosis.

Collagenous Sprue

Collagenous sprue is an unusual, possible variant of celiac disease in which the small bowel biopsy shows flattened mucosa with large masses of subepithelial eosinophilic hyaline material in the lamina propria. Collagenous sprue is one cause of failure to respond to GFD treatment.

Tropical Sprue

Tropical sprue causes malabsorption with partial villous atrophy and is probably caused by a still-unknown infectious organism. It is endemic in areas of the Caribbean, South Africa, Venezuela, India, and South East Asia (i.e., the equatorial areas). Patients often have megaloblastic anemia.

Quick Quiz

- How do you diagnose celiac disease?
- What is the clinical presentation of Whipple disease?
- What must be ruled out in a patient older than 55 with pancreatic insufficiency?

Treatment: tetracycline or doxycycline for 3–6 months. Folic acid replacement can also be effective either alone or as adjunctive treatment.

Whipple Disease

Whipple disease is a seemingly rare disease (< 1,000 cases total; probably under-reported) caused by *Tropheryma whipplei*, a gram-positive actinomycete.

The cardinal tetrad of symptoms:

1) Arthralgias—the most common symptom preceding diagnosis! (Much more so than abdominal problems!)
2) Abdominal pain
3) Weight loss
4) Diarrhea

Patients may have severe malabsorption—often with marked hypoalbuminemia and neurologic symptoms (depression, paranoia, dementia). Some of these symptoms are the result of lymphatic obstruction.

Upper endoscopy with small intestine biopsy is the diagnostic procedure of choice. Small bowel biopsy shows specific foamy macrophages that are positive for PAS staining bacterial remnants. You can also check CSF for *T. whipplei* by PCR, which is diagnostic if found.

Treat with ceftriaxone or IV PCN for 14 days and then treat with TMP/SMX for 1 year. Relapse often manifests with CNS symptoms.

DDx: Similar symptoms also may be caused by lymphatic blockage from primary intestinal (or other) lymphoma.

Eosinophilic Gastroenteritis

Eosinophilic gastroenteritis can mimic intestinal lymphoma and regional enteritis. Patients have N/V, diarrhea, abdominal pain, weight loss, albumin wasting, and iron deficiency anemia. They often have a peripheral eosinophilia; and even though it is thought to be due to an allergy to certain foods—which would be mediated by IgE—only 20% have specific food allergies with an increased IgE.

Treat with corticosteroids for 2–6 weeks and avoidance of the causative foods (commonly 7-food elimination diet—soy, milk, seafood, wheat, corn, egg, and peanut). *Strongyloides* can also cause a peripheral eosinophilia (*Giardia does* not), so be sure to rule this out before you start the steroids!

Short Bowel Syndrome

Short bowel syndrome occurs after massive resection of the small bowel, generally due to:

- severe ischemic injury,
- surgery for small bowel volvulus,
- jejunoileal bypass for morbid obesity, or
- multiple surgeries for Crohn disease.

Short bowel syndrome is likely when there is (roughly) < 2 feet (60 cm) of remaining small bowel, especially when the proximal jejunum and/or distal ileum are removed. Lifelong total parenteral nutrition (TPN) is likely to be required if the remaining small bowel is < 100 cm and there is loss of the ileocecal valve.

These patients are susceptible to calcium oxalate kidney stones (2° steatorrhea) and gastric acid hypersecretion.

Treat short bowel syndrome with a low-fat diet, small frequent meals, and vitamin supplements. TPN may be needed after large resection and/or while waiting for bowel adaptation after surgery.

Malabsorption Due to Decreased Digestion

There are 2 main causes:

1) **Pancreatic insufficiency**: can be seen in chronic pancreatitis, pancreatic cancer, and cystic fibrosis. Determine pancreatic insufficiency by qualitative stool exam, revealing undigested muscle fibers, neural fat, split fat, and low levels of fecal elastase.
   - The undigested muscle fibers indicate impaired digestion.
   - Low fecal elastase is characteristic of pancreatic insufficiency steatorrhea.
   - Further confirm impaired digestion by a positive response to treatment with pancreatic enzymes. The d-xylose absorption test may also be done during the workup (discussed below) and is normal.
   - You must rule out pancreatic cancer if there is evidence of pancreatic insufficiency in patients > 55 years of age. CT scan frequently shows pancreatic abnormalities.
2) **Bile acid deficiency**:
   - Ileal resection (> 100 cm— see page 1-31) or disease that decreases bile acid uptake
   - Severe liver disease, which decreases production of bile acids
   - Zollinger-Ellison syndrome (ZES), in which the patient has increased acidity in the small bowel that causes precipitation of bile acids
   - Bacterial overgrowth resulting in the breakdown of bile acids, making them useless for fat digestion (discussed on next page)

Steatorrhea is the best indicator of malabsorption because it commonly is the most prominent problem:

- The 3-day, quantitative fecal fat measurement is the "gold standard" for determining steatorrhea. Steatorrhea is defined as > 14 g/d of fecal fat.
- Sudan stain of the stool tests for fat, which is the best screening test.
- Serum carotene levels are a less specific indicator for malabsorption (see next).

Steatorrhea from pancreatic insufficiency causes the most fecal fat (can be > 50 g/d). Any patient having > 40 g/d of fecal fat almost certainly has pancreatic insufficiency—barring history of intestinal resection, which can also increase fecal fat to these levels.

Diagnosing the Cause: Transport vs. Digestion

First, determine whether it is a small bowel mucosal problem or a digestive problem by testing directly for celiac disease and chronic pancreatitis. Other common causes of malabsorption are Crohn disease and bacterial overgrowth. A small bowel biopsy may be needed.

The xylose (D-xylose) absorption test is not used much. Still, it is frequently a quiz topic and is still useful for differentiating disorders in carbohydrate absorption.

D-xylose requires normal transmucosal transport; but to be absorbed, it does not require digestion by pancreatic enzymes. Therefore, a normal test result in a patient with steatorrhea tells you that mucosal transport is normal. Diffuse small bowel disease can be excluded (i.e., CD, short bowel syndrome) and pancreatic insufficiency is more likely. These patients are often empirically treated with pancreatic enzymes. Resolution of the symptoms with treatment confirms the diagnosis.

On the other hand, low D-xylose absorption is not specific. It can be caused not only by small bowel disease, but also by many other conditions, including poor gastric emptying, bacterial overgrowth, ascites, renal insufficiency, and old age. But, if the patient definitely has steatorrhea, the diagnosis probably is small bowel disease since most of the other causes of an abnormal xylose test do not cause steatorrhea. So if the xylose test is low, do a small bowel biopsy!

Again, normal D-xylose = normal small bowel. In which case, pancreatic insufficiency is probably the cause of steatorrhea.

The absorption of carotene, vitamin K, vitamin D, folate, and iron also are independent of pancreatic enzyme digestion. So low serum carotene, hypocalcemia, hypoprothrombinemia, and/or Fe deficiency anemia in the patient with steatorrhea suggests a small bowel malabsorption problem rather than a pancreatic disorder. This is true only if steatorrhea is chronic and the patient has a normal dietary intake. Conversely, chronic diarrhea and normal levels of the above indicate pancreatic insufficiency.

An alcoholic who has an elevated prothrombin time easily corrected by vitamin K more likely has malabsorption as the cause of the high PT—not liver disease!

Summary

When malabsorption occurs with steatorrhea:

- Low "anything" suggests small bowel mucosal problem or bacterial overgrowth.
- Normal xylose absorption test with normal carotene, calcium, and prothrombin suggests pancreatic insufficiency—especially if there is very high fecal fat.

Bacterial Overgrowth

There can be combined causes of malabsorption, as in bacterial overgrowth, which results in bile acid deconjugation and patchy destruction of intestinal villi.

Patients with bacterial overgrowth usually have moderate steatorrhea, but their presenting complaint is often abdominal distention. The overgrowth of bacteria makes more folate but decreases absorption of B_{12}, so you can get the odd finding of macrocytosis with high folate and low B_{12} levels.

Bacterial overgrowth occurs in a variety of conditions:

- **Structural abnormalities**—diverticula, fistulae, strictures, after ileocecal resection.
- **Motility disorders**—peristalsis is a major mechanism for clearing the small intestine of bacteria. (Peristalsis may be defective in diabetes and scleroderma and a number of other conditions.)
- **Achlorhydria**—acid in the stomach kills bacteria before it enters the small bowel.
- **Immune disorders**—immunoglobulins secreted in the small bowel may decrease bacterial growth.

There are data showing a direct causative relationship between bacterial overgrowth and rosacea! In this study, almost 50% of patients with rosacea had bacterial overgrowth and 100% of these patients had long-term resolution when their bacterial overgrowth was resolved with a 10-day course of rifaximin—a nonabsorbable antibiotic.

Diagnose bacterial overgrowth with the lactulose hydrogen breath test (or simply, hydrogen breath test) and sometimes a C14-glycocholate breath test. It can also be diagnosed by quantitative culture from small bowel aspirate during EGD. Also remember the high folate levels, low B_{12}, and macrocytosis. CT or UGI may show any small bowel diverticula (usually from scleroderma) and dilated small bowel.

The specific overgrowth tests are generally available only at large medical centers. Bacterial overgrowth is often treated empirically with antibiotics after suggestive history and lab findings with:

- rifaximin (a nonabsorbable antibiotic that stays in the digestive tract), or
- amoxicillin-clavulanate, or

Quick Quiz

- Steatorrhea is the best indicator of _____.
- What is the best screening test for steatorrhea? What is the "gold standard" test?
- What is the significance of a normal D-xylose absorption test in a patient with steatorrhea? Low D-xylose?
- What are some important causes of bacterial overgrowth?
- Bacterial overgrowth is associated with which dermatologic condition?
- How do you diagnose bacterial overgrowth as a cause of diarrhea?
- Most cases of constipation are due to what?
- What common gynecologic surgery leads to constipation in 5% of patients?

- combination antibiotics (usually cephalexin + metronidazole) that cover both anaerobes and aerobes, or
- doxycycline.

Appropriate antibiotic treatment regimens for bacterial overgrowth: on antibiotics for 2 weeks, off antibiotics for 1 week, and repeat indefinitely. If symptoms recur while on a given antibiotic, switch antibiotics.

Bowel Resection and Diarrhea

Massive resection of small bowel can cause malabsorption (short bowel syndrome), especially if the terminal ileum and ileocecal valve are resected. The ileum absorbs specific nutrients, especially B_{12} and bile acids. Know the following:

> 60 cm of terminal ileum resected: B_{12} deficiency.

< 100 cm of terminal ileum resected: Bile acid uptake capacity is decreased, causing bile acid to make it to the colon and cause a bile acid-induced diarrhea.

> 100 cm of terminal ileum resected: Bile acid uptake capacity is lost. Synthesis cannot keep up with loss, resulting in bile acid deficiency and subsequent fat malabsorption. See Crohn Disease, Terminal Ileum Problems in CD on page 1-20.

CONSTIPATION

CAUSES

Causes of chronic constipation are many, but they usually result in:

- generalized or regional colonic inertia, and
- pelvic floor muscle dysfunction.

The large majority of cases are idiopathic! Lifestyle habits, such as a change to low-fiber diet; sudden, prolonged inactivity; and high stress may result in constipation.

Recent onset of constipation without change in lifestyle habits (e.g., no changes to diet, no new medications) suggests an obstructing lesion (neoplasm, stricture, foreign body). Pelvic floor dysfunction acts like outlet obstruction. Hysterectomy leads to refractory constipation in 5% of patients.

Neurologic causes affecting the parasympathetic innervation of the distal colon and rectum cause acquired megacolon; e.g., traumatic sacral nerve damage, MS, Chagas disease, or aganglionic megacolon (Hirschsprung's). Chagas disease is found in Central and South America. It is caused by infection with *Trypanosoma cruzi*, resulting in achalasia, cardiomyopathy, and acquired megacolon. Aganglionic megacolon (Hirschsprung disease) is typically diagnosed within the first 6 months of life, but a milder variant may present in adults.

Drugs with anticholinergic properties are common causes of constipation. These include antipsychotics, antidepressants, 1st generation antihistamines, anticholinergic cold medications, and especially most narcotics. Other causes include iron preparations, calcium supplements, calcium channel blockers, and antacids containing aluminum or calcium. Dehydration is one of the most common causes of constipation, especially in the elderly.

Endocrine disorders, such as diabetes mellitus (DM) and hypothyroidism, often cause mild constipation. Myxedema may result in acquired megacolon. The altered progesterone and estrogen levels are the probable cause of constipation in pregnancy.

Collagen vascular diseases, especially progressive systemic sclerosis, also cause constipation.

Many of these causes of constipation can be determined with a careful history.

DIAGNOSIS

Whom do you work up for constipation? Patients with constipation who additionally have weight loss, rectal bleeding, or anemia should get:

- A colonoscopy (to exclude structural disease; e.g., cancer, strictures)
- Serum Ca^{++} and TSH (to exclude hyper/hypocalcemia and hypothyroidism; DM is usually evident from the history)

For intractable constipation, test for colonic transit function. 24 radio-opaque markers ("Sitz markers") are taken by capsule, and a flat plate of the abdomen is done 5 days later. Normally, most markers are gone. It is abnormal for ≥ 5 to be retained. If the markers are spread throughout the colon, the cause is generalized colonic

inertia. Clustering of markers in the rectosigmoid colon indicates pelvic floor dysfunction.

Other tests for chronic constipation include evaluation of pelvic floor function, often by anorectal manometry with or without anal EMG, and by defecograms, which look for underlying abnormalities such as intussusception. These tests should be reserved for refractory constipation.

TREATMENT

Treatment of constipation consists of correcting any reversible causes. If idiopathic or irreversible, treat by increasing dietary fiber to > 20 g/day and encourage adequate fluid intake (to avoid dehydration).

Note: Fiber or bulking agents often help with colonic inertia but not with pelvic floor dysfunction, which often responds to pelvic floor retraining (+/– biofeedback). Fiber can also cause bloating and abdominal cramping (especially in female patients).

Increase exercise.

Short-term use of an osmotic laxative and/or stool softener is okay. Avoid stimulant laxatives.

Pelvic floor retraining, using modified Kegel exercise, can be quite helpful in refractory cases of constipation.

Difficult cases generally respond well to daily use of polyethylene glycol powder with water or the recently approved lubiprostone (Amitiza®) or linaclotide (Linzess®). Surgical treatment is indicated for Hirschsprung disease. In patients with constipation related to narcotic use, mu-opioid antagonists can be used to counteract peripheral effects of narcotics on the bowel without affecting pain-killing properties.

Osmotic laxatives (polyethylene glycol, sorbitol, glycerine, etc.) cause increased fluid movement into the lumen, increasing fecal bulk.

Stimulant laxatives (senna or bisacodyl) cause colonic muscles to contract. They are indicated only for short-term use.

Prophylaxis: When you initiate narcotic treatment, also start a stool softener + fiber supplement "bowel regimen" to reduce the risk of iatrogenic constipation.

FECAL INCONTINENCE

Fecal incontinence is a major health problem, especially in the elderly as well as women who have had childbirth-related pelvic floor injuries. The diagnostic evaluation is similar to constipation using the same diagnostic tests: transit studies, defogram, and anorectal manometry +/– EMG. Most therapies have aimed to increase stool bulk and/or to decrease diarrhea, which can contribute to fecal incontinence. Several new therapies for refractory cases have become available, including injection of a submucosal bulking agent (Solesta®) to increase anal tone and sacral nerve stimulation (InterStim®) to improve function of the anal sphincter and pelvic floor muscles.

FECAL IMPACTION

Fecal impaction is a large mass of dry, hard stool in the rectum causing constipation. Those at greatest risk are elderly persons with inadequate fluid intake who are also on narcotics or anticholinergics or who have decreased mobility.

Often, more proximal watery stool leaks around the impaction causing a watery fecal incontinence. Presentation is sudden onset of watery stools/incontinence in a person with chronic constipation.

Treatment is to remove the impaction. Initially, you can try a mineral oil enema, but often the impaction must be manually removed by breaking off small pieces until the obstruction is cleared. Longer-term treatment focuses on remedying the constipation: docusate stool softeners and bulk-forming agents used along with a bowel-training program (daily/regular BMs).

IRRITABLE BOWEL SYNDROME

OVERVIEW

A large part of a gastroenterologist's practice consists of functional complaints. Around 15% of the population has signs/symptoms of irritable bowel syndrome (IBS), and women are diagnosed with it more often than men (2:1). IBS has characteristic symptoms of abdominal pain or discomfort associated with disturbed defecation. Abdominal pain is improved with defecation. These symptoms may be either continuous or intermittent. There are no nocturnal or organic symptoms. Patients generally have an increased bowel motor response to emotional and physical stimuli, but these motor patterns are not specific to IBS. Patients with IBS are more likely to have experienced psychological or physical trauma in childhood.

DIAGNOSIS OF IBS

Overview

Establish diagnosis of IBS by:

- excluding other diseases, and
- looking for characteristic symptoms.

Rarely, invasive evaluation with colonoscopy or sigmoidoscopy is required.

These patients are more likely to have psychosocial dysfunction that doesn't meet criteria for major disorders. They may have neuroses, anxiety, or depression. As mentioned, they are also more likely to have a history of physical or psychological trauma.

Quick Quiz

- What are common causes of fecal incontinence?
- What is the clinical presentation of fecal impaction?
- What other diagnoses should be excluded prior to diagnosing a patient with irritable bowel syndrome?

Patients > 50 years of age with new-onset IBS-like symptoms should prompt consideration and workup for an alternative, organic cause.

Exclude Other Diseases

Celiac disease: 2–4% of patients with a diagnosis of IBS, especially those referred to a secondary center, actually have celiac disease (page 1-27). In this population, screening with tissue transglutaminase Ab or antiendomysial Ab testing may be helpful.

Lactose intolerance: Rule out lactose intolerance. Also, consider that 33% of patients with lactose intolerance do not improve on a lactose-restricted diet because they have concurrent IBS!

Bacterial overgrowth has been implicated in some cases.

Sorbitol: Rule out excessive sorbitol intake from excess ingestion of "sugarless" candies, mints, gums.

Look for Characteristic Symptoms

The characteristic symptom pattern of abdominal pain and altered bowel habits has been formalized into the International Classification for Irritable Bowel Syndrome—commonly called the Rome criteria.

The Rome criteria are at least 3 months of continuous or recurrent (at least 3 days out of the month):

- Abdominal pain relieved by defecation or accompanied by a change in frequency or consistency of stool, and
- Disturbed defecation at least 25% of the time, consisting of 2 or more:
  - Altered frequency
  - Altered consistency
  - Passage of mucus
  - Altered stool passage
  - Abdominal distention

  and ...
- No constitutional signs or symptoms, such as fever, weight loss, anorexia, and anemia. Specifically, no nocturnal symptoms!

TREATMENT OF IBS

Know the following:

Reassurance is paramount, as evidenced by the very impressive 60–70% (!) response to placebo by these patients—although only 30% have adequate relief with placebo. It is critical to form a therapeutic physician-patient relationship.

Diet: Take a diet history and advise against "sugar free" or "sugarless" foods that contain sorbitol. Have the patient keep a diet log to identify putative foods causing diarrhea.

Behavioral and **cognitive** therapies help the psychosocial issues.

Fiber supplementation is a traditional standard of care, although it is more helpful in constipation-predominant IBS and can actually worsen bloating.

Probiotics, such as *Lactobacillus,* acidophilus, and *Bifidobacterium longum*, can be tried.

Antispasmodic agents used for IBS are anticholinergics (dicyclomine, hyoscyamine). Long term, these have more side effects than benefits. They are, however, acceptable for short-term or intermittent use.

Tricyclic antidepressants (TCA) in low doses work well for IBS, especially if patients have loose stools, because TCAs slow bowel motility and may improve neuropathic pain.

Motility drugs: Loperamide decreases motility, increases sphincter tone, and is good for loose stools.

Lubiprostone (Amitiza®) is effective for constipation-predominant IBS.

Linaclotide (Linzess®) is newly approved for constipation-predominant IBS. It is a guanyl cyclase agonist that stimulates intestinal fluid secretion and transit.

Low FODMAP diet: Limited data suggests symptomatic benefit from avoiding fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs). Both physicians and patients can obtain FODMAP diets from a number of online sources.

5-hydroxytryptamine-3 receptor antagonists cause complications such as ischemic colitis and severe constipation. Alosetron was withdrawn from the market and now is back, but with an FDA boxed warning. Other agents include ondansetron and granisetron.

5-hydroxytryptamine-4 receptor agonists have had even more issues (cardiac side effects!), and the only agent in this class—tegaserod—was withdrawn by the FDA in March of 2007. It is now back, under investigational use.

Alternating diarrhea and constipation may be due to patients' use of "stoppers," such as loperamide (e.g., Imodium®), and "starters," such as laxatives.

COLON CANCER

OVERVIEW

Colon cancer risk factors:

- Age > 50
- Adenomatous polyps (current or past)
- Ulcerative colitis
- Crohn colitis
- *BRCA1* mutation
- Acromegaly
- Obesity
- Smoking
- Diets high in calories and animal fat

Hereditary risk factors:

- 1st degree relatives with colon cancer or adenomatous polyps
- Familial polyposis syndromes (see next page)
- Hereditary, nonpolyposis colon cancer (HNPCC—see below)

Lifetime risk of colon cancer is 6% in average-risk persons.

Diagnostic flags for colon cancer:

- Anorexia
- Weight loss
- Anemia
- Fever
- Heme+ stools
- Change in bowel habits, especially with nocturnal stools
- Onset of symptoms after age 45

Remember: Endocarditis caused by either *Streptococcus bovis* or *Clostridium septicum* is often associated with colon cancer, so perform a colonoscopy in these patients.

Aspirin reduces the risk of both colonic adenomas and carcinoma. In some series, the protective effect did not become evident until after 10 years of use. Low-dose aspirin has now been shown to reduce the risk of right-sided colon cancer. Aspirin also reduces the risk of development of recurrent colon cancer, and evolving data suggest a reduction in carcinomas and adenomas after resection. Protective effect of aspirin is thought to be related to:

- Dose of aspirin
- Frequency of use per week
- Duration of use (years)
- Ongoing investigation into the appropriate dose and potential benefit of aspirin continues.

Most GI cancers arise from adenomas (Image 1-17, Image 1-18). 25% of colorectal cancers are located distal to the splenic flexure.

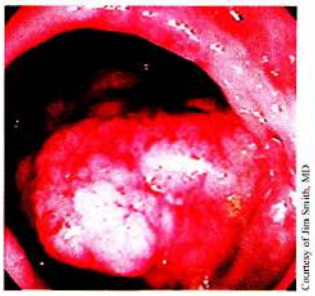


Image 1-17: Colon cancer

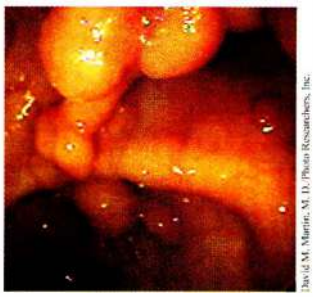


Image 1-18: Polyps in the colon

Adenomas with "advanced" features are defined as any of the following:

- Presence of high-grade dysplasia
- Presence of villous histology
- Size > 10 mm

"Advanced" means likely to develop into cancer. Progression to cancer from an early adenoma takes 5–10 years. Diet plays a role in GI cancer—possible dietary factors include high animal protein and fats, low fiber, and low calcium. Be sure and discuss these important considerations with patients on a "low-carb" diet!

Again, large or villous adenomatous polyps are likely to harbor or progress to cancer (Table 1-5).

Perspective: ~ 30% of people > 40 years old have adenomatous polyps, but only 1% of adenomatous polyps ever become malignant.

Hyperplastic polyps have no malignant potential and contain no features of dysplasia. This makes sense because hyperplasia, by definition, is increased growth of normal tissue.

After polyps are found, follow-up depends on the type of polyp, size, number, and family history. Only adenomatous polyps require specific follow-up. Hyperplastic polyps, if < 1 cm (except for those with a hyperplastic polyposis syndrome), have the same follow-up as no polyp (10 years).

The 2008 American Cancer Society (ACS) guidelines recommend the following:

- Patients with 1 or 2 small tubular adenomas with low-grade dysplasia should have repeat colonoscopy 5–10 years after initial polypectomy.
- Patients with 3–10 adenomas, or 1 adenoma > 1 cm, or any adenoma with villous features or high-grade dysplasia should have repeat colonoscopy in 3 years.

Table 1-5: Malignant Potential vs. Polyp Size

	< 1 cm	1–2 cm	> 2 cm
Tubular	1%	10%	34%
Mixed (TV)	4%	9%	45%
Villous	10%	10%	54%

Quick Quiz

- Endocarditis due to _____ or _____ (organisms) warrants a colonoscopy to search for colon cancer.
- What size and histologic features of colon adenomas are considered "advanced features" with increased malignant potential?
- What is the relationship between hyperplastic polyps and colon cancer?
- Know the 2008 ACS guidelines for recommendations on follow-up intervals based on type and number of polyps.
- Which 2 familial polyposis syndromes have the highest risk of carcinoma? Which has no risk of carcinoma?
- What is the risk of cancer in a patient with Peutz-Jeghers syndrome?
- At what age does screening begin for HNPCC?

- Patients with > 10 adenomas should have repeat colonoscopy < 3 years. (Consider the possibility of an underlying familial syndrome—see below.)
- Patients with sessile adenomas that are removed piecemeal require repeat colonoscopy in 2–6 months to verify complete removal.

The American Gastroenterology Association (AGA) published similar guidelines in 2012.

INHERITED COLON CANCER

Overview

Inherited colon cancer can be categorized into either polyposis or non-polyposis syndromes.

Familial Polyposis Syndromes

The familial (or hereditary) polyposis syndromes are all autosomal dominant (AD).

The 4 types are listed here in order of decreasing cancer potential. The first 2 are adenomatous, the second 2 are hamartomatous:

1) **Familial adenomatous polyposis** (FAP)—hundreds of adenomas in the colon—100% risk of cancer if not treated. These patients often require a prophylactic proctocolectomy by age 20! They can also get some duodenal adenomas, which also have a high risk of cancer. After colectomy, patients with FAP tend to get duodenal cancer. They are also at increased risk of developing secondary tumors (ampullary adenomas and carcinomas). Giant stomach tumors are common in patients with FAP, but they are benign.
2) **Gardner syndrome**—a variant of FAP with more extraintestinal benign growths. The adenomas have the same risk of cancer as FAP (100%). These patients often have bone lesions (osteomas) and soft tissue tumors. Treatment is the same as FAP. Question: Patient has multiple osteomas found incidentally on an x-ray. What do you do? Colonoscopy!
3) **Peutz-Jeghers syndrome**—multiple hamartomatous polyps throughout the small bowel, and occasionally in the colorectum and stomach, plus melanotic pigmentation (freckles) on the lips and buccal mucosa. The most common presentation is with abdominal pain due to intussusception or bowel obstruction by a large polyp. Even though these polyps are hamartomas, which have no risk of cancer, these patients still have a higher than baseline risk of cancer because they occasionally develop adenomas that can become carcinomas. Risk of cancer is 50% by 60 years of age.
4) **Juvenile polyposis** also consists of hamartomas (> 10 juvenile polyps – juvenile polyposis syndrome). To date, no specific guidelines for screening/surveillance have been established in the U.S. for juvenile polyposis.

Hereditary Nonpolyposis Colon Cancer

As the name suggests, most patients with this form of cancer do not have a familial polyposis; rather, the cancer arises from normal-appearing epithelium.

Hereditary nonpolyposis colon cancer (HNPCC, a.k.a. Lynch syndrome) can be defined as "the occurrence of a HNPCC-associated cancer (colorectal, endometrial, small bowel, ureter or renal pelvis) in at least 3 (one is a 1st degree relative of the other two) 1st degree relatives over at least 2 generations, and with at least 1 person diagnosed < age 50." These rather loose diagnostic criteria suggest that Lynch syndrome is responsible for cancer in as many as 1 in 20 (5%) patients with colon cancer! Women in families with HNPCC have an increased incidence of ovarian and endometrial cancer as well as renal, ureteral, stomach, pancreatic, and biliary tree cancers.

Start screening those with HNPCC risk profile at age 25.

SCREENING

Review

Current screening recommendations are also covered in General Internal Medicine, Book 5, under Screening Tests. In general, do yearly fecal immunohistochemical testing (FIT) in average-risk patients.

Low-risk patients: The 2008 American Cancer Society guidelines for colorectal cancer screening for asymptomatic adults ≥ 50 years of age with a negative family history for colon cancer or adenomatous polyps have broken down the tests into the following 2 areas:

1) Tests that detect adenomatous polyps and cancer (preferred by the guideline-writing committee):

- Colonoscopy every 10 years, or
- Flexible sigmoidoscopy every 5 years, and
- FOBT yearly, or
- CT colonography every 5 years

2) Tests that primarily detect cancer:
- Annual fecal immunochemical test with high sensitivity for cancer, or
- Annual guaiac-based fecal occult blood test with high sensitivity for cancer, or
- Stool DNA test with high sensitivity for cancer, interval uncertain

Each strategy has inherent strengths and weaknesses. FOBT is the most inexpensive and obviously least invasive, but it may miss ~ 1/3 of advanced cancers. Colonoscopy has the highest yield of finding polyps and cancers, but is most costly and invasive. Guidelines recommend that any positive test (other than colonoscopy) should be followed up by a full colonoscopy with biopsy of any identified abnormalities/polyps. The 2008 USPSTF guidelines generally agree with the American Cancer Society guidelines except that the USPSTF recommends against screening in those > 85 years of age.

Repeat colonoscopy timing based on polyp pathology (see page 1-34).

Increased-risk patients: Surveillance (colonoscopy) should begin at age 40 years or 10 years before age at which the index case is diagnosed—whichever is first.

For example: Start at age 40 if a 1st degree relative was diagnosed with an adenoma or colon cancer at age 52; start at age 20 if several 1st degree relatives had colon cancer at age 30.

Colonoscopy is the screening procedure of choice in patients with any 1st degree relatives with either colon cancer or an adenomatous polyp. It is also the screening method of choice in patients who have a history of an adenomatous polyp. Time between surveillance colonoscopies depends upon the cancer potential of the polyp—see previous discussion, under Colon Cancer Overview on page 1-34.

Virtual colonoscopy or CT colonography is a CT scan with special software. It has high yield for detecting larger polyps and cancers. Areas of adherent stool can be mistaken for small polyps. However, it is an excellent test for a patient who cannot complete a standard colonoscopy to visualize the entirety of the colon. If abnormalities are found on CT colonography, the guidelines recommend proceeding to colonoscopy if possible (since the patient has already been prepped).

Sigmoid colon cancer can perforate the bowel wall and simulate diverticulitis. So, screen for colon cancer after an episode of diverticulitis in older patients. To avoid risk of perforation, wait for resolution of acute inflammation (6 weeks after episode of diverticulitis) before proceeding with colonoscopy. See Table 1-6 for the most common indications for colonoscopy.

FOBT

Fecal occult blood testing (FOBT) is positive 2% of the time. This varies with age; > 5% after 60 years of age. Of positive FOBTs, 2% have GI cancer.

Remember: The FOBT is negative in up to 66% of patients with colon cancer. Using 6 Hemoccult● cards (the full FOBT series) will detect advanced colonic cancer in only about 25% of patients. This makes it a pretty poor screening test, but it is used (annually or biennially) because it is quick and cheap.

Even if one FOBT is positive, do a colonoscopy.

A flex-sig + ACBE (air-contrast barium enema) is also acceptable but clearly less desirable.

CEA

Note: Carcinoembryonic antigen (CEA) levels are useful only for surveillance for recurrence of colon cancer—and only if levels were elevated before surgery and reduced after surgery. CEA may also be mildly elevated in patients who smoke or who have benign biliary disease, sclerosing cholangitis, or IBD.

STAGING OF COLON CANCER

TNM Classification

The 2 methods for staging colon cancer are TNM and Duke's. They are similar, but TNM classification, which was updated in 2010, is the preferred method.

Table 1-6: Indications for Colonoscopy

Occult bleeding
Fe deficiency anemia unless other explanation
Gross lower GI bleeding except bright red blood in a younger person
Abnormal barium enema
Adenomatous polyp—initially and for all follow-ups
History of colon cancer
1st degree relative with colon cancer
Familial polyposis syndromes, HNPCC/Lynch syndrome
IBD: Suspicion, follow-up, surveillance
Strep bovis, *Clostridium septicum* bacteremia
Ischemic colitis
Persistent diarrhea with negative blood tests and not meeting criteria for diagnosis of IBS
4–8 weeks after new-onset, presumed diverticulitis to rule out colon cancer

Quick Quiz

- Under what circumstances should periodic colonoscopy be started at age 40?
- What common colon problem in older patients is an indication for colonoscopy?
- Are CEA levels useful for primary diagnosis, recurrence, or both in colon carcinoma? Why?
- Surgery for cure is the rule in colon cancer. When is adjuvant chemotherapy used? When is radiation used?

In general, the cancer stage becomes more advanced as the tumor enlarges and invades the colonic wall:

- TNM stage I: extends into submucosa (T1) or muscularis (T2); no nodal involvement; no metastases
- TNM stage II (subclassifications A, B, C): extends past muscularis into tissues around the colorectal area (T3) or into visceral peritoneum (T4a) or is directly invasive (T4b); no nodal involvement; no metastases
- TNM stage III (subclassifications A, B, and C): any combination of T1–T4b with nodal involvement and no metastases
- TNM stage IV: any combination of T1–T4b, any N, with distant metastases

Colon cancer virtually always metastasizes to the liver first (via portal circulation). However, if it involves only the rectum, the blood supply bypasses the portal circulation, so the patient may have lung, bone, and brain mets without liver mets.

TREATMENT OF COLON CANCER

Surgical resection is the 1st treatment option and is potentially curative. Recurrences after surgery are probably due to micrometastases.

Adjuvant chemotherapy consists of a 5FU–based therapy. Typically, 5FU plus leucovorin (LV) is used. Trials have shown benefit from oxaliplatin being added to this regimen. This protocol is called FOLFOX.

Adjuvant chemo is effective only for stage III or locally advanced II.

Radiation therapy prior to surgery is helpful for rectal lesions only.

Hepatic resection increases survival with solitary liver mets.

If you remove a cancerous polyp, you must do a bowel resection if the cancer extends to either a blood vessel or the cautery line.

DIVERTICULAR DISEASE AND LOWER GI BLEED

DIVERTICULAR DISEASE

Types of Diverticular Disease

There are 4 types of diverticular disease (see Image 1-19 and Image 1-20):

1) Asymptomatic diverticulosis (most common)
2) Painful diverticulosis (contraction of hypertrophied colonic muscle)
3) Diverticular bleeding
4) Diverticulitis

Asymptomatic Diverticulosis

Diverticulosis is the presence of one or more diverticula in the colon. Incidence increases with age. About 80–85% are asymptomatic. It has been assumed that diverticulosis is caused by a low-fiber diet and can be warded off by a high-fiber diet. A 2011 study casts doubt on this theory. Current guidelines still recommend high-fiber diet for those with asymptomatic and symptomatic diverticulosis. Recent work on the pathophysiology of diverticular disease has focused on the inflammatory etiology of diverticular formation and the possible role of antiinflammatory agents in retarding diverticular formation. However, no new guidelines have been issued in this regard.

Symptomatic Diverticulosis

Painful diverticulosis is due to hypertrophy of both circular and longitudinal colonic musculature myochosis, which leads to luminal narrowing, pencil-thin stools, and bouts of colicky pain often relieved by passing flatus or having a bowel movement. This occurs in about 10–15% of diverticulosis patients. Another helpful clue in establishing a diagnosis of colonic myochosis is a palpable and thickened sigmoid and left colon.

Treat with bulking agents which typically contain psyllium or methylcellulose. Probiotics may be beneficial as well.

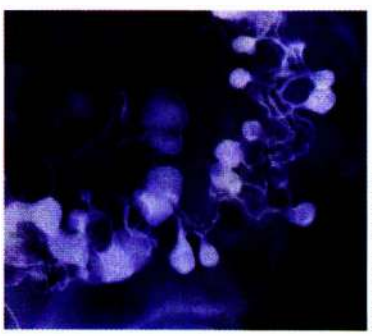


Image 1-19: Intestinal diverticulosis, x-ray

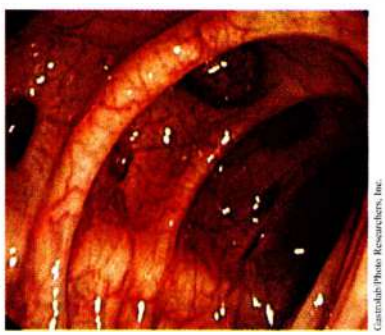


Image 1-20: Diverticular disease

Diverticular Bleeding

Diverticular bleeding occurs in only a small percentage of patients with diverticulosis. Even so, diverticular bleeding is the most common cause of colonic bleeding in the elderly; angiodysplasia is next on the list and often results in more severe bleeds. Diverticular bleeding usually originates in the right colon, and typically stops spontaneously.

Patients classically present with "painless, maroon stool," but color can actually vary from red to black.

Treatment for diverticular bleeding: Stabilize patient with IV crystalloid and give packed red blood cell transfusion if needed. Rule out UGI bleed. Correct any coagulopathies and discontinue any medications that worsen bleeding. Colonoscopy is indicated only if bleeding does not stop.

Note: UGI bleed is suggested by a BUN/Cr ratio > 30:1, which indicates blood is being digested and breakdown products are being absorbed.

Diagnose diverticular bleeding with colonoscopy or technetium-tagged RBC scan. Angiography with embolization can be performed if bleeding is severe or continuous. See Table 1-7 for common indications for GI angiography.

Diverticulitis

Diverticulitis, as the word suggests, is caused by inflamed diverticula. It is typically due to microperforations. It occurs in < 5% of patients with diverticulosis. Signs and symptoms include:

- LLQ pain
- Fever
- High WBC
- LLQ tenderness
- No bleeding!

The LLQ tenderness, and sometimes rebound tenderness, is usually localized. Look for a sigmoid mass (i.e., palpable, tender sigmoid) on physical exam, on U/S, or on CT. CT is most useful in assessing diverticulitis: It may show areas of thickened sigmoid colon or pericolic fluid accumulation. Avoid colonoscopy on any patient with diverticulitis (due to risk of perforation).

Table 1-7: Angiography in GI Disease

Chronic and acute mesenteric ischemia
Severe lower GI bleed
Rarely used for UGI bleed—some duodenal ulcers
TIPS in variceal bleeding
Therapeutic uses: embolization, vasopressin

Treatment of diverticulitis should cover both aerobic and anaerobic gram-negative organisms.

Treat mild diverticulitis in a patient able to drink and without peritoneal signs with outpatient metronidazole (for gram-negative anaerobic coverage) plus either ciprofloxacin or TMP/SMX (for gram-negative aerobic coverage) and follow up closely.

Treatment of moderate-to-severe diverticulitis:

Inpatient parenteral treatment for those with peritoneal signs may consist of dual- or single-drug therapy:

1) Dual-drug therapy (best!), such as:
   - aminoglycoside or ciprofloxacin (gram-negative aerobic)

   plus

   - clindamycin or metronidazole (gram-negative anaerobic)
2) Single-drug therapy, such as:
   - Ticarcillin/clavulanic acid
   - Piperacillin/tazobactam
   - Imipenem/cilastatin
   - Ampicillin/sulbactam
   - Cefotetan

Note that all of these single-drug therapies cover both aerobic and anaerobic gram-negative organisms.

Drain abscesses percutaneously.

Perforation from sigmoid colon cancer can present similarly to diverticulitis, so follow up patients > 50 years of age with a flex-sig/colonoscopy 4–8 weeks after the acute condition resolves.

Meckel diverticulum is the most common congenital GI anomaly. Although < 1/2 of these diverticula have gastric mucosa, only these ulcerate and bleed. Meckel diverticula cause 1/2 of all GI bleeds in children; they can also cause obstruction and intussusception. They may be seen with the technetium scan ("Meckel's scan"). Technetium is taken up by gastric mucosa.

ANGIODYSPLASIA AND LOWER GI BLEED

Angiodysplasia (= vascular ectasia, = AVM) is the 2nd most common cause of lower GI bleeding in the elderly (diverticular bleeding is 1st). Think of these as spider nevi of the GI tract.

Bleeding in angiodysplasia may be occult to severe. The usual bleeding site is the right colon (cecum, ascending).

AVMs typically are not cauterized unless they are bleeding significantly.

Hereditary hemorrhagic telangiectasias (HHT = Osler-Weber-Rendu) is a hereditary condition in which there are multiple AVMs affecting all the organs, including brain, lung, skin, and mucous membranes and the GI tract—especially in the upper GI tract (AVM is usually lower). Patients with HHT often have a history of epistaxis.

Quick Quiz

- What may be seen on abdominal CT scan in a patient with diverticulitis?
- What is the treatment of moderate-to-severe diverticulitis?
- What is "thumbprinting," and when is it seen?

Angiography may be used in workup of severe disease (again, see Table 1-7).

Endoscopic treatment can help, although there are often many lesions and not all can be treated.

ISCHEMIC COLITIS

Ischemic colitis (CI; a.k.a. colonic ischemia) causes abdominal pain (from the ischemia) and maroon stools. This is covered fully under Intestinal Ischemia.

VIDEO CAPSULE ENDOSCOPY

Okay, with EGD you can see the upper GI tract, and there is colonoscopy for the lower GI tract. We now have the wireless video capsule endoscopy (VCE), which is used to visualize the previously unvisualizable small bowel. It is especially useful in working up small bowel bleeds or occult blood loss without an obvious cause.

[Know:] A patient presenting with recurrent melanotic stools, with negative EGDs and colonoscopies, should undergo wireless video capsule endoscopy.

The VCE is also becoming useful for other small bowel problems; e.g., assessing tumors, Crohn disease, and celiac disease.

A similar capsule to VCE is now available that measures pressure, temperature, and pH and may have a role in the evaluation of transit disorders.

BALLOON-ASSISTED ENTEROSCOPY

Single and double balloon-assisted enteroscopy allows for evaluation and treatment of small bowel lesions which were previously out of reach of standard endoscopes.

BOWEL OBSTRUCTION

The most common cause of small intestine obstruction is postoperative adhesions. The most common causes of colonic obstruction are (in decreasing frequency): carcinoma, diverticulitis, and volvulus.

The diagnosis of obstruction is suggested in the setting of persistent vomiting, obstipation, and constipation. The diagnosis is confirmed radiographically with a flat and upright abdominal film showing (typically) excessive amounts of air in the small bowel with no air in the colon. The presence of air fluid levels is helpful when there are "J-loops," in which the air fluid levels are at different heights on either side of the same loop of bowel. This signifies a dynamic obstruction. If the fluid levels are the same height on either side of the loop, paralytic ileus is the more likely diagnosis.

Treat with IV fluids and NG suction. Further workup is indicated if the symptoms do not resolve in 1–2 days. Gastrografin enema can be helpful if the obstruction is thought to be of colonic origin.

INTESTINAL ISCHEMIA

TYPES

There are 4 types of intestinal ischemia:

1) Ischemic colitis (most common)
2) Chronic mesenteric ischemia
3) Acute mesenteric ischemia (70% mortality!)
4) Mesenteric venous thrombosis

ISCHEMIC COLITIS

Ischemic colitis is the most common form of intestinal ischemia. It is due to a nonocclusive ischemia—mostly involving some portions of the splenic flexure, descending colon, and/or sigmoid colon; i.e., inferior mesenteric circulation. Most often, no specific cause for the ischemia is found. It is a disease primarily of the elderly and may be seen post-op (colonic surgery and aortic aneurysmectomy); it is occasionally associated with low-flow conditions (CHF), medications/cocaine, and hypercoagulable states. Because this condition is virtually never embolic, patients are not likely to have valvular heart disease or cardiac arrhythmia. In many cases, an evaluation of underlying coagulation disorders may be indicated.

Symptoms of ischemic colitis: typically a sudden LLQ pain with an urge to defecate, followed by passage of red-to-maroon stool within 1 day. Also think of this in extreme athletes; e.g., marathon runner with abdominal pain and hematochezia after a long race.

Mildest injury: mucosal and submucosal hemorrhage and edema—which is completely reversible. More severe injury ranges from replacement of mucosa and submucosa with granulation tissue to transmural infarction and fulminant colitis.

Submucosal hemorrhage and edema (mildest injury) are seen on abdominal x-ray (KUB) or barium enema (BE) as "thumbprinting." This thumbprinting lasts only a few days and is not specific for the type of ischemia, just for submucosal edema or hemorrhage. CT scan is generally the 1st diagnostic test. Portal venous gas on CT is indicative of transmural necrosis/injury.

If there are peritoneal signs, diagnose with colonoscopy (which is usually done without bowel prep to reduce risk of decreasing blood flow due to use of dehydrating agents). Sigmoidoscopy is also acceptable. Angiography is not usually done.

The usual treatment for colonic ischemia is bowel rest, fluids, and antibiotics. Most cases resolve with conservative measures. Rarely, strictures or acute abdomen develop.

CHRONIC MESENTERIC ISCHEMIA

Chronic mesenteric ischemia is also called intestinal angina. Patients may require further evaluation if they have the classic triad:

1) Abdominal pain after meals
2) Abdominal bruit
3) Weight loss (from tolerating only smaller meals)

The pain is due to episodes of inadequate blood flow brought on by digestion.

Suspect mesenteric vascular ischemia in the above setting, especially if abdominal pain is out of proportion to any physical findings.

Symptoms are 1–3 hours of dull, gnawing abdominal pain ~ 30 minutes after eating. The etiology is atherosclerosis of the mesenteric arteries, with the symptoms caused by gastric "steal" after eating. Patients often have signs of other types of peripheral vascular disease (PVD) and often have a history of smoking (no clear association).

Diagnosis is mainly based on symptoms. The next step is commonly an MRA (magnetic resonance angiogram) or CT angiogram. These have good sensitivity for proximal lesions, such as superior mesenteric or celiac arteries, but are much less sensitive as the involved lesion becomes more distal. Splanchnic angiography is then done if these are abnormal.

Treatment is surgical bypass or angioplasty.

ACUTE MESENTERIC ISCHEMIA

Acute mesenteric ischemia is the most severe and life-threatening form of intestinal ischemia, with a mortality rate of 70% –even with treatment! It is caused by the lodging of a thromboembolus in a mesenteric artery, leading to acute loss of blood flow to the corresponding small intestine and/or ascending colon.

Acute mesenteric ischemia is seen in older patients with a history of CHF, recent MI, cardiac arrhythmias, or hypotensive episodes.

Patients often have symptoms of intestinal angina (above) for months before the acute event. Because this condition is commonly due to emboli, patients are likely to have concomitant valvular heart disease or cardiac arrhythmia. These patients are acutely ill with vomiting, diarrhea, and rectal blood.

Bowel infarction leads to lactic acidosis. In the early stages, excruciating abdominal pain (from ischemia) may be disproportionate to the abdominal exam, which can be relatively benign.

Do CT angiography unless there is evidence of perforation (e.g., rigid abdomen, lactic acidosis, intra peritoneal air)—in which case the patient goes directly to surgery for dead-bowel resection and possible embolectomy.

MESENTERIC VENOUS THROMBOSIS

Mesenteric venous thrombosis (MVT) is associated with hypercoagulable states, such as deficiencies of antithrombin III, prothrombin 20210A (a gene variant), protein S, protein C, and *Factor V Leiden* defect.

MVT is also linked to any of the following:

- Pancreatitis
- Liver disease (cirrhosis)
- Intraabdominal sepsis
- Sickle cell disease
- Paroxysmal nocturnal hemoglobinuria (PNH)

MVT may be acute, subacute, or chronic. Like mesenteric infarction, the pain of MVT is often out of proportion to the abdominal exam. If the portal or splenic veins are involved in chronic MVT, there may be bleeding from gastroesophageal varices. Cirrhosis patients with coagulopathy can still develop MVT.

CT is the diagnostic procedure of choice—with CT, > 90% of MVT can be diagnosed.

Treat acute MVT with thrombolytics and long-term anticoagulants; patients may require surgery if peritoneal signs are present. Treatment of chronic MVT is focused on minimizing bleeding from varices with sclerotherapy, portosystemic shunts, or similar devices.

PANCREAS

ACUTE PANCREATITIS

Overview

Acute pancreatitis is frequently caused by either alcohol abuse or gallstones; these are the #1 and #2 etiologies in the U.S. In Europe, the reverse appears to be true. These are not firm conclusions; results from studies are influenced by where they are done. For example, if the study is done in a VA hospital, the primary cause is probably alcohol abuse; whereas, if it is done in a community hospital, gallstones are more likely to cause the majority of cases.

Endoscopic retrograde cholangiopancreatography (ERCP) causes acute pancreatitis (see page 1-1) in 2–5% of patients. Other causes of acute pancreatitis are acidosis (as in DKA), hypertriglyceridemia, hypercalcemia, trauma, and other problems that result in obstruction of the ampulla of Vater (e.g., pancreatic cancer).

Quick Quiz

- What is the clinical presentation of chronic mesenteric ischemia?
- What is the clinical presentation of acute mesenteric ischemia?
- What are the most common causes of pancreatitis in the U.S.?
- What happens to serum amylase and lipase levels over time with acute pancreatitis?
- What 2 relationships do high triglyceride levels have with acute pancreatitis?
- Know the Atlanta classification of acute pancreatitis.
- What physical findings reflect severe pancreatic necrosis with multiple organ failure?
- What is Cullen sign? What is Turner sign?

Always check medications. Quite a few drugs can cause acute pancreatitis:

- Diuretics: furosemide and thiazides
- Estrogens
- Azathioprine
- 5-ASA derivatives
- Antibiotics: tetracycline and sulfonamides
- Anti-HIV drugs; e.g., pentamidine and didanosine
- Oral hypoglycemics
- 6-mercaptopurine, L-asparaginase, and valproic acid

Many cases of "idiopathic" pancreatitis are actually secondary to biliary microlithiasis, cystic fibrosis, hereditary pancreatitis, or hypertriglyceridemia.

With acute pancreatitis, amylase and lipase are generally elevated. The serum amylase level is almost always elevated early on (> 3x N is almost always due to pancreatitis) but decreases within 2–3 days after disease onset. Remember, amylase is less specific than lipase because there are other etiologies for hyperamylasemia (see below). The lipase level increases later and stays elevated longer than the amylase (beyond day 7).

High triglyceride levels in the setting of acute pancreatitis may cause a spuriously normal amylase level!

Additionally, triglyceride levels > 1,000 mg/dL can cause pancreatitis.

The 2012 revision of the Atlanta classification for acute pancreatitis identifies that 2 of the following must be present:

1) Upper abdominal pain radiating through to the back
2) Serum amylase or lipase 3x the upper limit of normal
3) Cross sectional imaging consistent with acute pancreatitis

Severity of Pancreatitis

Factors and Results

The severity of acute pancreatitis is directly related to the degree of pancreatic necrosis (10-25% have necrosis) and whether this necrotic tissue is infected (mortality = 30%) or not (mortality = 10%). Overall, mortality rate for acute pancreatitis = 5–10%!

Severe pancreatitis causes shock and multiorgan failure. These multiorgan failure indicators are used in several methods of assessment for severity:

- Hemoconcentration
- Heart: systolic BP < 90 mmHg; tachycardia > 130 bpm
- Lungs: PO_2 < 60 mmHg
- Renal: progressive azotemia or oliguria to < 50 mL/hr
- CNS: altered sensorium
- Metabolic: low calcium (< 8 mg/dL) and albumin < 3.2 g/dL

Assessing Severity

Skin Signs

Okay, so we know severity of pancreatitis is associated with the degree of necrosis and signs of multiple organ failure. How do we determine severity on admission?

Good clues are the skin signs that may be seen with severe acute pancreatitis:

- The most common skin finding is an erythema of the flanks caused by extravasated pancreatic exudates.
- Cullen sign and Turner sign, when seen (unusual), indicate a severe necrotizing pancreatitis:
  - Cullen sign, a faint blue discoloration around the umbilicus, indicates hemoperitoneum.
  - Turner (or Grey-Turner) sign, a bluish-reddish-purple or greenish-brown discoloration of the flanks, results from tissue catabolism of hemoglobin from retroperitoneal blood dissecting along tissue planes.
  - Cullen and Turner signs are characteristic but not pathognomonic for acute pancreatitis. Cullen sign is also seen with intraperitoneal bleeding (especially ruptured ectopic pregnancy), and Turner sign is seen with other causes of retroperitoneal bleeding.

Severity Scoring Systems

Multiple systems have been developed over the years, including Ranson and Glasgow. However, neither of these scoring systems has been validated in larger trials.

Newer systems are the Apache II and the BISAP score:

APACHE II has been shown to have good sensitivity and specificity, although adding body mass index (APACHE 0) has produced conflicting results. In addition, APACHE II scoring requires calculators to perform.

BISAP (BUN > 25, impaired mental status, SIRS, age > 60 years, pleural effusion) has similar reliability for mortality (but not other indices) to the APACHE II—with the added benefit that BISAP can be done at the bedside.

SIRS (systemic inflammatory response syndrome score) has been validated in smaller studies, is also easily done at the bedside, and can be repeated daily. It is typically used for inpatient daily follow-up assessment.

SIRS is a measurement of the body's physiologic response to an undefined insult (infectious or not) and does not necessarily imply multiple organ failure. SIRS is part of a somewhat newer method of categorizing severe illnesses. For instance, sepsis is defined as SIRS plus a documented or presumed infection.

SIRS requires 2 or more of the following:

- Temperature < 36° C (96.8° F) or > 38° C (100.4° F)
- Tachycardia (HR > 90)
- Tachypnea (RR > 20 or pCO_2 < 32)
- WBC abnormal (> 12 K or < 4 K or > 10% bands)

Current AGA Recommendations

Currently, the AGA recommends the following to assess severity:

- Use the APACHE II score ≥ 8 as a cutoff for severe disease. Patients with ≥ 8 or those with organ failure at 72 hours should undergo CT to assess for necrosis.
- Clinical judgment is still important.

Independent risk factors include:

- Morbid obesity (BMI > 30) is associated with a 2x increase in mortality.
- Hemoconcentration (> 44%) that is persistent despite fluid resuscitation; however, studies are inconsistent regarding the significance of this finding.
- Age > 75.
- Organ failure.

Pancreatic necrosis is best confirmed by dynamic CT scan or MRI (at some centers). It is considered severe if ≥ 30% of the pancreas is necrotic.

When following after admission, do a SIRS evaluation daily and look for signs of multiple organ failure. Worsening indicators equal worsening severity. ICUs may also use the APACHE system.

Fluid / Masses in Acute Pancreatitis

Types of fluid collections and masses found in acute pancreatitis:

Acute fluid collections with high amylase levels appear in up to 50% of patients within 48 hours of pain onset. They usually resolve spontaneously. A sympathetic transudative left pleural effusion frequently occurs. Rarely, a diaphragmatic defect into the pleural space causes an effusion high in amylase (Figure 1-4).

Necrotic tissue: Inflamed, edematous, necrotic pancreas occurs in the first 1–2 weeks and may simulate a pseudocyst (which typically occurs later; discussed below). Necrotic tissue can be differentiated from a pseudocyst with the aid of ultrasonography. Pancreatic necrosis is serious and may require drainage.

Infected necrosis: Infected pancreatic necrosis generally requires either drainage (endoscopic or CT-guided) or surgery (infrequent nowadays) within 2 weeks of the episode. You can diagnose by CT-guided aspiration of necrotic pancreas with Gram stain and culture.

Pseudocyst: A pancreatic pseudocyst develops in less than 10% of patients with acute pancreatitis. It requires a minimum of 4 weeks to develop after the acute attack. It is now recognized that walled-off necrosis can mimic a pseudocyst. Basically, it is a collection of pancreatic fluid, which, if small enough, resolves spontaneously. A size > 5 cm suggests it may not resolve on its own. If the pseudocyst persists > 3–6 months and causes symptoms, it may require surgical, radiologic, or endoscopic drainage. Remove enlarging, symptomatic pseudocysts because they are associated with serious complications—especially fistula, pseudo-aneurysms, rupture, and hemorrhage. Rupture without hemorrhage = 15% mortality, while rupture with hemorrhage = 60% mortality! Consider this in a patient who is recovering normally and then suddenly gets worse. Most experts, consistent with newly emerged data, recommend early intervening in symptomatic patients.

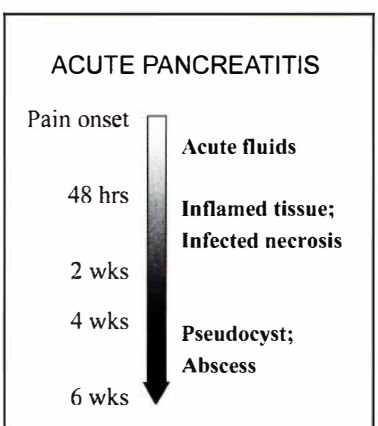


Figure 1-4: Timeline of Complications

Abscess: A pancreatic abscess occurs 4–6 weeks after onset of acute severe pancreatitis—in which there is severe pancreatic necrosis. It may be seen as a "soap bubble sign" on upright abdominal x-ray. This is a very serious condition that may present with fever and septic shock.

Diagnose pancreatic abscess with Gram stain of a CT-guided percutaneous aspirate, which is 90% accurate. This allows for immediate surgical or radiologic debridement and drainage.

Quick Quiz

- What is the APACHE II score that indicates severe pancreatitis?
- How is pancreatic necrosis best confirmed?
- What masses may develop due to acute pancreatitis? What is their timeline, and what is their treatment?
- Symptomatic pseudocysts persisting for more than 3–6 months generally require what intervention(s)?
- What is the 1st test in the workup of the etiology of acute pancreatitis?
- What is the clinical presentation of chronic pancreatitis?
- What is the classic diagnostic triad for chronic pancreatitis?

Diagnosis of Pancreatitis

In working up the cause of acute pancreatitis, the 1st and often only test is gallbladder ultrasonography to rule out gallstones. Diagnosis is otherwise often based mainly on history.

Treatment of Acute Pancreatitis

With supportive care, ~90% resolve spontaneously within a few days. Patients must be made NPO for a variable period of time, but NG suction is generally not required. Provide vigorous IV crystalloid fluid hydration plus colloids as needed. Early enteral feeds have been shown to be superior to TPN in maintaining nutritional status in patients with protracted acute pancreatitis. High-protein, low-fat, semi-elemental formulas via nasojejunal tube are recommended.

Give systemic antibiotics only if there is established infection. Give 20 mL/kg bolus of lactated Ringer followed by continuous infusion at a rate of 3 mL/kg/hr for the next 6–8 hours. At 8 hours, if the patient is fluid responsive, continue 1.5 mg/kg/hr; if patient is fluid refractory, give another 20 mL/kg bolus followed by a continuous infusion at a rate of 3 mg/kg/hr. Recheck at 16 hours.

Watch for antibiotic-associated fungal infections.

Pearls of Acute Pancreatitis

If the amylase is still elevated after 10 days, think of something else going on, such as a leaking pseudocyst. With large fluid collections, consider a disrupted pancreatic duct leaking fluid. This can be treated by ERCP with stenting of the duct. Recurrent acute pancreatitis with no evidence of gallstones or alcohol abuse may be due to microlithiasis; so, consider an elective cholecystectomy.

Gastric varices, in the absence of esophageal varices, occur only in the setting of splenic vein thrombosis, which is a complication of both severe acute pancreatitis and chronic pancreatitis.

ERCP is not done acutely unless a patient has biliary sepsis. Use MRCP after the acute period to diagnose suspected common bile duct stones; e.g., the bilirubin is > 2.5 and rising or the ultrasound shows a dilated common duct. Do therapeutic ERCP to treat ductal obstructions found on MRCP. Perform cholecystectomy ASAP after gallstone pancreatitis —after the inflammation has resolved.

Criteria for resumption of oral feeds in acute pancreatitis:

- Bowel sounds present and passing flatus/stools.
- Not requiring narcotics.
- Patient is hungry and wants to eat!

Question: What conditions can cause abdominal pain with an elevated amylase? Answer: Acute pancreatitis, acute cholecystitis, intestinal infarction, diabetic ketoacidosis, perforated ulcer, salpingitis, and ectopic pregnancy. Other causes of hyperamylasemia are increased salivary amylase and macroamylasemia (benign condition due to a low urinary excretion of amylase).

CHRONIC PANCREATITIS

Overview

In developed countries, chronic pancreatitis is commonly (60–70%) a result of chronic alcohol ingestion—typically > 10 years. Next in frequency is idiopathic (30%). About 10% are rare hereditary disorders (lack of cationic trypsinogen activator inhibitor, SPINK abnormality) and other causes such as cystic fibrosis, pancreas divisum, tumor, and hyperparathyroidism. Autoimmune pancreatitis is a newly described, rare disorder that accounts for 1–5% of cases (see page 1-45).

Chronic pancreatitis has an initial, asymptomatic phase, followed by recurrent bouts of abdominal pain. Late in the disease, when > 80–90% of the endocrine and exocrine pancreatic function is lost, patients develop steatorrhea and diabetes mellitus. The fecal fat in late-stage patients is elevated—it may be > 100 g/day. More than 40 g/day is highly suggestive of chronic pancreatitis. Ultimately, 40–80% of patients with chronic pancreatitis develop diabetes, and 50–80% develop exocrine insufficiency. Chronic pancreatitis also increases the risk of pancreatic cancer 2-fold (4% lifetime risk)—but not enough to support screening.

Diagnosis of Chronic Pancreatitis

The classic diagnostic triad for chronic pancreatitis is:

1) Pancreatic calcification
2) Diabetes
3) Steatorrhea

But this triad is present in < 20% of cases and usually is found only during late-stage disease.

Diagnosis can be difficult, so begin evaluation with simple, noninvasive tests that detect advanced forms of chronic pancreatitis. First, get a CT of the abdomen —if the pancreas is calcified, or if the pancreatic duct is dilated, or if the pancreas is atrophic, you have made the diagnosis of chronic pancreatitis!

Initial tests used in the diagnosis of chronic pancreatitis:

- Abdominal CT has 80–85% sensitivity and specificity and is the initial procedure of choice.
- Endoscopic ultrasound (EU/S) is very sensitive and may be the best test yet, but it requires a very skilled gastroenterologist. It is the procedure of choice in some centers.
- Abdominal U/S.
- Plain radiograph of the abdomen showing pancreatic calcification (only 30% sensitive, but very specific).
- Secretin stimulation test (see below).

Follow-up tests. If results from the tests above are negative, and you still have suspicions, do either magnetic resonance cholangiopancreatography (MRCP; preferred) or ERCP:

- MRCP is accurate in diagnosing chronic pancreatitis without the risk of causing pancreatitis (unlike ERCP, below). Additionally, MRCP allows for visualization of the biliary tree and can also be useful in cases of suspected bile duct stones or other biliary diseases like PSC. MRCP is the preferred 2nd level test, and some centers advocate secretin-stimulated MRCP.
- ERCP may induce pancreatitis (2–5%). The only advantage ERCP has over MRCP is the potential for endoscopic removal of calcific stones, which may be located within the duct and, hence, can be reached with the endoscope.

Both MRCP and ERCP can show large duct disease and small duct disease. With large duct disease, the pancreatic duct has stenoses and dilations, which visualize as an irregular "chain of lakes."

Dilation of the common bile duct can be caused by chronic pancreatitis but also by pancreatic cancer. Either can compress the common bile duct as it passes through the head of the pancreas.

The **secretin test** is the most sensitive test for pancreatic exocrine function; however, it is complicated, so it is generally performed only in major medical centers, and only when there is still a high "index of suspicion" after negative follow-up tests. (This does vary—in some places with ready access, it is done before ERCP.) IV infusion of secretin (+/– cholecystokinin [CCK]) causes a direct stimulation of the pancreas. Duodenal pancreatic secretions are then measured via a duodenal catheter. The bicarbonate concentration should be > 80 mEq/L. CCK stimulates lipase, amylase, trypsin, and chymotrypsin, all of which can be measured. An endoscopic secretin test is also now available. Fecal elastase, in addition to a fecal fat, can also be used to evaluate for malabsorption.

Complications of Chronic Pancreatitis

A major complication is persistent and severe abdominal pain. In this setting:

- Rule out continued EtOH use.
- Rule out pseudocyst.
- Do MRCP, EUS, or MRCP with secretin to define duct anatomy.

Pancreatic cancer develops in 4% of patients with chronic pancreatitis > 20 years.

Complications of chronic pancreatitis include gastric varices (from splenic vein thrombosis), B_{12} malabsorption, jaundice, pleural effusion, and brittle diabetes mellitus.

The only skin involvement is tender red nodules from fat necrosis; this is uncommon, but can simulate erythema nodosum.

The diabetes associated with chronic pancreatitis is different from the usual DM. It occurs when > 80% of the pancreas is destroyed. There is a decrease in production of insulin and glucagon.

Because the pancreas is producing so little glucagon, the patient is very prone to hypoglycemia. Therefore, less stringent control of hyperglycemia is recommended to decrease the chance of life-threatening hypoglycemia.

These patients do not commonly develop retinopathy and nephropathy associated with the usual DM. They commonly have neuropathy, but this more likely secondary to alcoholism and/or malnutrition.

Treatment of Chronic Pancreatitis

Treatment includes:

- Alcohol and tobacco cessation
- Pancreatic enzymes (a minimum 60,000–80,000 units of lipase per meal and snacks) supplementation
- Decreasing dietary fat
- Antioxidants

Pancreatic enzymes must either have an enteric coating or be given with antacids/H_2 blockers because gastric acid destroys enzymes. Alcohol consumption must be avoided. Discontinuation of smoking is very important because smoking accelerates the development of pancreatic calcification and makes pain management more difficult.

Analgesia is sometimes required. Most try a short-term opioid with amitriptyline. There is no therapy proven to show benefit if the pain persists.

Quick Quiz

- What is the preferred initial test used in the workup of chronic pancreatitis?
- When is ERCP considered over MRCP as a 2nd level test in the workup of chronic pancreatitis?
- What are the classic symptoms of pancreatic carcinoma?
- How is pancreatic cancer treated if there are metastases? Without metastases?
- When is ERCP indicated in pancreatic cancer?

Other therapeutic options include: pancreatic sphincterotomy, pancreatic duct stenting, pancreatic duct stone extraction, nerve blocks, surgical duct drainage, and Whipple procedure.

AUTOIMMUNE PANCREATITIS (AIP)

You should know this entity, even though it occurs in < 5% of cases of chronic pancreatitis. It is interesting in that its presentation often simulates cancer of the pancreas.

What to know:

- 50% present with obstructive jaundice (simulating cancer of the pancreas).
- CT can show a mass in the head of the pancreas (again simulating cancer) or diffuse enlargement (sausage-shaped pancreas).
- There may be bile duct and pancreatic duct strictures.
- Serum IgG4 level is usually ≥ 2x normal.

Histology shows a dense lymphoplasmacytic infiltrate. Treat with prednisone at an initial dose of 40 mg/day with a taper of 5 mg/week. In patients who relapse on corticosteroids, immunomodulators (azathioprine, rituximab) are often added. AIP is now recognized as an IgG4 systemic disease which, in addition to autoimmune pancreatitis, can include any or all of the following:

1) Mediastinal fibrosis and adenopathy
2) Retroperitoneal fibrosis
3) Chronic periaortitis
4) Tubulointerstitial nephritis
5) IgG4 associated cholangitis

PANCREATIC NEOPLASMS

Pancreatic Cancer

Pancreatic cancer is astonishingly aggressive. 80% of patients present with advanced disease. Heavy smokers have 2x the baseline risk. Other risk factors include DM, pancreatic cancer in 2 first-degree relatives, hereditary pancreatitis, and chronic pancreatitis.

Patients frequently present with some combination of jaundice, unexplained upper abdominal pain, and/or weight loss.

Tumor location affects presenting signs and stage:

- Head: Painless jaundice tends to be the presenting sign with early-stage cancers of the head of the pancreas.
- Body and tail: These patients are more likely to present with pain and weight loss (jaundice in only ~ 30%) and with the cancer at a much more advanced stage.

Pain and weight loss are indications of advanced disease. The pain typically has a gnawing quality, is not relieved by eating, and occasionally radiates to the back.

Diagnosis is made with helical CT, CT angiography, endoscopic ultrasound (EUS)-guided FNA biopsy, and laparoscopy.

The most-used serum marker is cancer-associated antigen 19-9 (CA 19-9).

Treatment of pancreatic cancer: Resection is the only hope for cure.

Most common reasons for tumor unresectability:

- Distant metastases
- Local invasion of major vessel (portal vessel or superior mesenteric vein or artery)

If the patient is a surgical candidate, the mass is in the head of the pancreas, and the cancer appears resectable, do a pancreaticoduodenectomy (Whipple resection). Evaluate lymph nodes for evidence of metastasis.

There is a modest survival benefit (survival increased 3+ months) with specific chemoradiotherapy (especially with 5FU or gemcitabine).

If noninvasive workup shows that the cancer has already metastasized, avoid surgery—provide supportive care or give experimental chemotherapy (especially gemcitabine) only. Place a stent using ERCP to palliate biliary obstruction. This is the only time you use ERCP for pancreatic cancer.

Post-surgical prognosis: 5-year survival is 30% if node-negative and 10% if node-positive.

Glucagonoma

A glucagonoma is a glucagon-secreting, alpha-cell tumor of the pancreas that causes a unique set of clinical findings:

- Scaly necrolytic erythema
- Weight loss
- Anemia
- Diarrhea
- Persistent hyperglycemia
- Plasma glucagon (by RIA) usually > 1,000 pg/dL

Insulinoma

Insulinoma is a very rare, insulin-secreting beta-cell tumor of the pancreas. This is covered in Endocrinology, Book 4, under Hypoglycemia.

Gastrinoma

Gastrinomas are discussed under ZES on page 1-15. Most (50%) are found in the duodenum, 24% in the pancreas. This diagnosis is likely when the serum gastrin is > 500 in a patient who is able to secrete gastric acid (not on PPI, no prior peptic ulcer surgery).

VIPoma

VIPomas are tumors that secrete vasoactive intestinal peptide (VIP). 2/3 occur in the pancreas, and > 1/2 of these are malignant. They cause a profuse secretory diarrhea ("pancreatic cholera"). Diagnosis: increased serum VIP level and hypokalemia.

BILIARY SYSTEM

CHOLELITHIASIS

Overview

Cholelithiasis is widespread—20% of women and 8% of men—and typically asymptomatic. It is not associated with hypercholesterolemia.

The pathophysiology of cholelithiasis involves 1 or more of the following 3 factors:

1) Abnormal bile secreted by the liver (lithogenic—supersaturated with cholesterol)
2) Accelerated nucleation of microcrystals to macrocrystals
3) Defective gallbladder emptying

Cholelithiasis has been associated with obesity, oral contraceptive use, clofibrate treatment, and ileal disease or resection. 75% of gallstones are composed of radiolucent cholesterol (pure or mixed); the rest are bile pigment gallstones.

Profile for **cholesterol** stones: rapid weight loss in obese patient (these stones prevented by aspirin or ursodeoxycholic acid), Native American, octreotide use.

Profile for **pigment** stones: ileal resection (as in Crohn disease), sickle cell disease, or anything else that causes hemolysis; e.g., *Clonorchis sinensis* (biliary dwelling trematode).

Symptoms: RUQ pain lasting 20–60 minutes—especially after a fatty meal. But fatty food intolerance is a very nonspecific finding.

Diagnosis of Cholelithiasis

To detect the presence of stones, do an ultrasound (90% sensitive). A normal ultrasound in the presence of normal bilirubin and liver enzymes is sensitive for excluding common duct stones. If the ultrasound is technically inadequate, consider MRCP or oral cholecystogram. The usual procedures used for diagnosing common duct obstruction are MRCP, ERCP, and transhepatic cholangiography.

The HIDA scan (cholescintigraphy) is the best test for confirming acute cystic duct obstruction (i.e., acute cholecystitis) by imaging of the bile duct but not the gallbladder. HIDA scan is rarely used because ultrasound has characteristic findings for acute cholecystitis.

Note: About half of pigment stones are radiopaque, whereas cholesterol stones are radiolucent.

Treatment of Cholelithiasis

If the patient has gallstones and is symptomatic, do an elective cholecystectomy because 70% of these patients will have recurrent symptoms if not treated.

Do not treat asymptomatic cholelithiasis because only 20% of patients go on to develop symptoms within 10–20 years. Don't mistake symptoms of reflux for that of cholelithiasis, even if you incidentally find stones in the gallbladder.

Supplemental oral bile acid (ursodeoxycholic acid) may be used in the treatment of gallstones for those who are too ill to have surgery or refuse surgery. Lithotripsy can be effective, but few centers have the expertise necessary to perform this procedure.

Acalculous cholecystitis occurs only in seriously ill patients; e.g., major trauma, burns, after major surgeries. Diagnosis may be assisted by ultrasound or CT showing no stones, but a large, tense, often thickened gallbladder with pericholecystic fluid (or no stones and a HIDA scan showing cystic duct obstruction). Treatment is cholecystectomy, but cholecystostomy (percutaneous drainage) can be done if the patient is too sick for surgery.

Common Duct Stones

Alkaline phosphatase and bilirubin are generally not elevated in typical gallbladder cases because the gallstones block only the exit to the gallbladder. Increasing levels of alkaline phosphatase and bilirubin (bilirubin > 4 mg/dL) suggest the presence of a common duct stone. Consider common duct stones in the gallbladder patient with increased alkaline phosphatase and bili or the post-cholecystectomy patient with persistent pain. Common duct blockage also can cause cholangitis (next page).

Common duct stones are removed by ERCP with prn endoscopic sphincterotomy.

CHOLESTASIS

Cholestasis can be obstructive (as with common duct stones) or hepatocellular. In both cases, there is retention of the substances normally released into bile. In both cases, there is a cholestatic pattern jaundice with

QuickQuiz

- What are the 3 causative factors of cholelithiasis?
- What should you investigate in the patient who persists in having RUQ pain after cholecystectomy or with symptoms of cholangitis?
- What is the "hallmark" test for primary biliary cirrhosis? How do you confirm the diagnosis?

increased alkaline phosphatase and conjugated bilirubin with bilirubinuria. More on bilirubin on page 1-61.

CHOLANGITIS

Cholangitis is a complication of common bile duct blockage—usually from bile duct stone or cancer.

Acute cholangitis is suggested by the triad of biliary colic, fever, and jaundice (Charcot's triad). Suppurative cholangitis additionally has mental confusion, bacteremia, and septic shock.

Treatment is with parenteral antibiotics, IV hydration, and biliary drainage; antibiotics alone are not sufficient. When you suspect suppurative cholangitis, the best procedure for both diagnosis and treatment is ERCP with endoscopic sphincterotomy. If ERCP is unavailable, surgery or percutaneous transhepatic cholangiography with drain placement should be considered.

Emphysematous cholecystitis requires emergent laparotomy with cholecystectomy and antibiotics. In both suppurative cholangitis and emphysematous cholecystitis, the antibiotics must be effective against both gram-negative and anaerobic organisms. Do not use ceftriaxone—it can cause biliary sludge and has no (zero!) anaerobic coverage.

PORCELAIN GALLBLADDER

X-ray showing a gallbladder with a calcified outline ("porcelain gallbladder") suggests the possibility of cancer, and an open cholecystectomy is indicated.

PRIMARY BILIARY CIRRHOSIS

Overview

Primary biliary cirrhosis (PBC): slow onset. 95% are women—typically middle-aged. PBC is characterized by a nonsuppurative, progressive, destructive cholangiolitis. The florid duct lesion on liver biopsy is pathognomonic. However, it is seen only in small numbers in early stages.

The bile ducts become chronically inflamed and eventually cause obstructive jaundice and liver cirrhosis.

The cause of PBC is unknown, but 70% have associated autoimmune diseases (e.g., Sjögren's, scleroderma, autoimmune thyroiditis, limited scleroderma). The disease does tend to run in families. 90% have a positive antimitochondrial antibody test (> 1:40), but degree of elevation does not correlate with severity of disease.

PBC patients who present with symptoms have advanced disease. Most patients present asymptomatically or with fatigue and are worked up because of a high alkaline phosphatase noted on a liver enzyme screening. If they have symptoms, patients initially complain of itching—first in the palms and soles and later throughout the body.

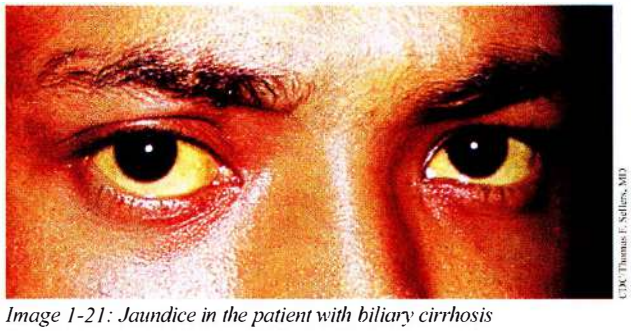
Later, patients develop jaundice, hyperpigmentation, inflammatory arthropathy, keratoconjunctivitis and/or xerostomia, and accelerated osteoporosis. Patients can develop xanthomas and xanthelasma from associated hypercholesterolemia, but this does not convey increased risk of CAD (not an atherosclerogenic lipid pattern). (See Image 1-21 and Image 1-22.)

PBC is indolent, but relentlessly progressive. Symptomatic patients previously had a median survival of 7 years, and asymptomatic 10–16 years. These numbers are increasing significantly as patients are diagnosed earlier and all patients are treated with ursodiol (ursodeoxycholate; see Treatment on next page).

When the bilirubin increases to > 2, the disease accelerates. Most die within 2 years after the bilirubin reaches 10 unless the patient undergoes liver transplantation.

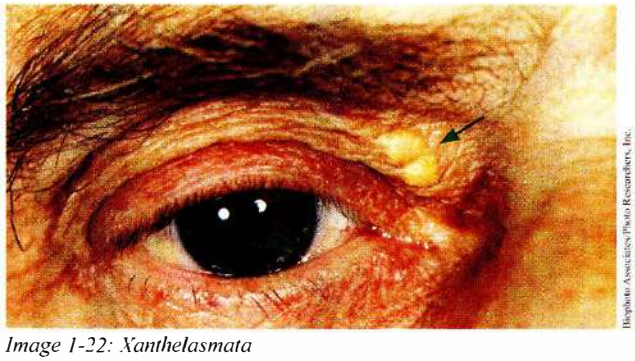
Incidental discovery of a 2–5x increase in serum alkaline phosphatase has been the primary reason for the increase in PBC diagnoses. High levels of alkaline phosphatase occur in up to 95% of patients with PBC.

Note: The antimitochondrial antibody test is the hallmark test for PBC. Even so, it is not a good indicator



CDC/Thomas F. Sellers, MD

Image 1-21: Jaundice in the patient with biliary cirrhosis



Biophoto Associates/Photo Researchers, Inc.

Image 1-22: Xanthelasmata

of the severity of PBC. The antimitochondrial antibody test is occasionally positive in both autoimmune hepatitis and drug-induced chronic hepatitis; a high titer in a patient with autoimmune hepatitis suggests an overlap syndrome (Table 1-8).

Diagnosis of Biliary Cirrhosis

Diagnosis is confirmed only with a liver biopsy, which may show granulomas (florid duct lesions); often findings are nonspecific. PBC patients also have a high hepatic copper level (as do patients with primary sclerosing cholangitis and Wilson disease).

Treatment of Biliary Cirrhosis

Ursodiol (ursodeoxycholate—a synthetic bile acid) 13–15 mg/kg/day is the best proven treatment available for PBC. It improves LFTs and decreases symptoms, and it significantly slows progression of the disease. Patients who have a biochemical response to ursodiol (defined as a decrease in alkaline phosphatase, AST, and/or bilirubin to much lower level at 1 year) have dramatic slowing of the progression.

Additionally, symptomatic treatment includes:

- Pruritus: cholestyramine
- Osteomalacia: vitamin D and calcium
- Malabsorption: decreased dietary fat

Treatment has no effect on late disease. For late disease, liver transplantation is recommended. It has been shown to significantly improve survival in late PBC. PBC is one of the most common indications for liver transplantation; hepatitis C is the most common indication. The "**AAAABCs** of PBC" are: **Antimitochondrial Antibody Attack** increases **Alk phos** and causes **obstructive Biliary lesions** and **liver Cirrhosis.**

Table 1-8: Serologic Markers in PBC and CAH

	Primary Biliary Cirrhosis	Drug-induced CAH*	Auto-immune CAH*
Antimitochondrial Ab	90–95% Positive	occ Positive	occ Positive (low titers)—think overlap syndrome
Anti-Smooth muscle Ab	Negative	Negative	Positive
Antinuclear Ab	usually Negative	Negative	Positive

* chronic active hepatitis

PRIMARY SCLEROSING CHOLANGITIS

Overview

Primary sclerosing cholangitis (PSC): also indolent. It primarily occurs in males (70%) with average age of 45.

PSC is strongly associated with colitis—so it is mainly seen in ulcerative colitis (up to 75% of PSC patients have UC!), but it can occur in patients with Crohn colitis as well. Incidence of PSC has no relationship to the severity of colitis.

PSC occurs in 5% of UC patients and perhaps 2% of Crohn patients. UC may precede the diagnosis of PSC, but not necessarily. So, all PSC patients should have a colonoscopy.

Conversely, PSC may precede the diagnosis of UC; therefore, any UC patients with a persistent, ≥ 2x increase in alkaline phosphatase should be screened for PSC.

Cause is unknown. Patients develop inflammation and sclerosis of the entire biliary tract (intra- and extrahepatic), leading to obstructive jaundice and eventually cirrhosis.

Patients are initially asymptomatic but eventually, with advanced disease, develop weakness and fatigue, abdominal pain, itching, and jaundice.

Bilirubin and alkaline phosphatase levels are elevated (cholestatic pattern). There is an elevated hepatic copper level (as in primary biliary cirrhosis and Wilson disease), but the antimitochondrial antibody is negative. The total protein level gives an idea of how much the disease has affected liver function.

8–15% of PSC patients develop cholangiocarcinoma. One-third have cholangiocarcinoma when first diagnosed with PSC! Suspect cholangiocarcinoma if symptoms of PSC abruptly worsen. CA 19-9 is elevated in 80% of patients with cholangiocarcinoma .

Diagnosis of Sclerosing Cholangitis

Diagnosis of PSC is made with MRCP, ERCP, or transhepatic cholangiography. These reveal irregularly narrowed bile ducts with small bile duct ballooning just prior to obstructions, producing the typical "beaded" appearance. With ERCP, if a dominant stricture exists, it can be dilated. Liver biopsy shows "onion skin" fibrosis in portal triads.

In small duct PSC, the extrahepatic and intrahepatic biliary system may be nondiagnostic, but liver biopsy abnormalities establish the diagnosis.

Secondary causes of sclerosing cholangitis must be ruled out. These include: bacterial cholangitis (stones or bile duct stricture), atypical anatomy (congenital or previous surgery), bile duct neoplasms, and AIDS-associated cholangiopathy.

QuickQuiz

- PBC: What is the best, proven treatment for early disease? For late disease?
- List the similarities and differences between PBC and PSC. These are commonly confused diseases. [Know!] What are the alk phos, bilirubin, hepatic copper, and antimitochondrial antibody tests in PBC and PSC?
- A patient presents with cholestatic jaundice and a history of IBD (or a history of chronic diarrhea). Which of the following do you include in your differential—PBC or PSC? Why?

Treatment of Sclerosing Cholangitis

The only sure treatment for PSC is liver transplantation. Colectomy cures ulcerative colitis, but does not alter the course of PSC.

[Know:] High-dose ursodeoxycholic acid (UDCA, 20–25 mg/kg) was recommended in the past, but a 2010 guideline from the American Association for the Study of Liver Diseases now recommends against UDCA because of lack of efficacy and increased risk of adverse effects! If patients are already on UDCA because of past recommendations, some authorities now recommend discontinuing it.

Remember: When a patient presents with jaundice and increased alkaline phosphatase and has a history of chronic diarrhea or IBD, especially UC, rule out PSC with MRCP or ERCP!

Again, PSC: sclerosing cholangitis, colitis, high cholestatic bili, and alkaline phosphatase levels; negative antimitochondrial antibody, cirrhosis, and liver failure. Abnormal magnetic or endoscopic retrograde cholangiopancreatography (MRCP, ERCP).

PBC vs. PSC

These two conditions are often confused because they have similar abbreviations and both affect the bile tracts and have high alkaline phosphatase and elevated hepatic copper level. Both eventually cause obstructive jaundice and cirrhosis. (Hmm. Why the confusion?)

Table 1-9: PBC vs. PSC

	Sex	IBD	Cancer	UDCA effective?
PBC	Female	No	Rare	Yes
PSC	Male	Yes	(UC) 8-15% risk of cholangiocarcinoma	No

To help remember the differences, drop the abbreviations and think:

- Biliary cirrhosis: 55-year-old woman named Hillary C. Roses with fatigue and pruritus. Antimitochondrial Ab+.
- Sclerosing cholangitis: 45-year-old man with UC.

Also review Table 1-9.

LIVER

HEPATITIS NOTES

Regarding ALT (SGPT) and AST (SGOT), know:

- To remember that ALT is more liver-specific than AST, think of "**L-L**" (A**L**T-**L**iver):
- With alcoholic hepatitis, the AST:ALT is about 3:1 because the alcohol damages mitochondria, which then release the AST. Mitochondrial damage is less liver-specific.
- With viral hepatitis, the ALT is generally greater than the AST because its toxicity is more liver-specific. Table 1-10 is a review of serologic testing for viral hepatitis.
- Nonalcoholic fatty liver disease (NAFLD) is also more liver-specific and has an ALT:AST ratio > 2:1.
- Acute viral hepatitis has histologic characteristics of diffuse liver cell injury and swelling, increased macrophages, accelerated apoptosis (the normal programmed cell death is accelerated by viral hepatitis), and inflammatory periportal infiltrates (mostly lymphocytic).

Chronic viral hepatitis has histologic characteristics of interface hepatitis (formerly known as piecemeal necrosis) and fibrosis.

EVALUATION OF ABNORMAL LIVER BIOCHEMICAL TESTS

Increased Transaminases

An abnormal laboratory value should be confirmed before ordering follow-up tests. To confirm, order a full set of liver biochemical tests, including alkaline phosphatase, total and direct bilirubin, albumin, PT, and CBC. If the transaminases are still elevated, order more specific tests for hepatitis A, B, and C—and tests for hemochromatosis with iron studies and ferritin level.

Increased Alkaline Phosphatase

Remember that alkaline phosphatase comes from liver and bones. Gamma glutamyl transpeptidase (GGT) typically rises in parallel with alkaline phosphatase from the liver and should be checked in cases of increased alkaline phosphatase with normal bilirubin and transaminases. Generally, the next test is abdominal ultrasound to look for dilated biliary ducts or metastatic liver lesions. In appropriate patients, also order antimitochondrial antibody test (to screen for PBC).

Table 1-10: Hepatitis — Serological Tests

	Anti-HAV IgM	Anti-HAV IgG	HBsAg	Anti-HBs IgG	Anti-HBc IgG	Anti-HBc IgM	HBeAg	Anti-HDV
Acute hepatitis A	+	–	–					
Previous HAV	–	+	–					
Acute HBV	–		+ early	–	–	+	+	–
Acute HBV—window			–	–	–	+	–	–
Chronic active HBV			+	–	+	–	usu +	–
Remote HBV (immune)			–	+	+	–	–	–
Vaccinated (immune)			–	+	–	–	–	–
Acute hepatitis D (w/ acute HB)			+ early	–	–	+	+	+
Acute hepatitis D (w/ CAH)			+	rarely	+	–	usu +	+

HEPATITIS A

Hepatitis A is an RNA virus. It is easily transmitted by the fecal-oral route—commonly via food or water. It can also be sexually transmitted. There is no transplacental transmission! There are no carrier or persistent states, although, occasionally, these patients get prolonged cholestasis (with increased bili and alkaline phosphatase) for up to 4 months. Incubation period is 15–50 days. See Figure 1-5.

Symptoms are unusual in children and very common in adults (70%). Complications are rare; there is ~ 1% chance of fulminant hepatitis. Immune globulin (IG) is good prophylaxis only against HAV (use HBIG for hepatitis B).

Diagnosis of acute infection: high titers of anti-HAV IgM in serum. (IgG indicates only a previous infection.)

The incidence of hepatitis A has fallen dramatically due to immunization.

Hepatitis A vaccine (Havrix® and Vaqta®) is for use in patients > 1 year of age and is given as 2 doses, 6+ months apart. Virtually all of those completing the series develop protective antibodies (anti-HAV IgG). Trends, based on what is now known about antibody levels, suggest protection for up to 20 years in those who complete the series. If completion of the 2-dose series is delayed, there is no need to start the series over again.

Indications for use of HAV vaccine:

- High-risk sexual behavior (see hepatitis C section).
- IV drug use.
- Universally recommended for all > 1 year of age.
- Chronic liver disease.

Table 1-11: Interpretation of Hepatitis B Tests

HBsAg	Anti-HBc	Anti-HBs	Interpretation
+	–	–	Acute infection
+	+	–	3 possibilities: 1) Acute infection (IgM anti-HBc) 2) Chronic Hep B (high ALT, IgG anti-HBc) 3) Inactive carrier (normal enzymes, IgG anti-HBc)
–	–	+	2 possibilities: 1) Remote infection 2) Immunized
–	+	+	Remote infection
–	+	–	3 possibilities: 1) Window disease 2) Remote infection 3) False positive
+	+	+	More than 1 infection; e.g., IV drug user or renal dialysis patient with both acute and chronic hepatitis B (infected with different strains of hepatitis B)

Quick Quiz

- With what coinfections can hepatitis A become fulminant?
- How do you confirm that a hepatitis B vaccine was immunogenic?
- Regarding HBsAg, HBcAg, and HBeAg: Which is the best marker for infectivity? Which is the best marker for past infection?
- What is the "window" period for hepatitis B infection?
- Polyarteritis nodosa is associated with which hepatitis virus?

- Travel to high-risk countries.
- HAV vaccine is also given to all patients with chronic hepatitis B and hepatitis C; if these patients get hepatitis A, it can be fulminant.
- Also now (since 2007) recommended for post-exposure prophylaxis instead of immunoglobulins.

Note: Onset of jaundice is 3 weeks with hepatitis A and 3 months with hepatitis B—an important diagnostic clue!

HEPATITIS B

Overview

The 5 main serological markers in hepatitis B are HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb (Table 1-10 and Table 1-11).

HBsAg: There are 3 HBsAg+ proteins seen in the serum in patients with hepatitis B: one large, double-shelled 42 nm particle that is the intact virion and two smaller 22 nm spherical or rod-shaped protein particles that outnumber the large particle by up to 1,000 to 1! These 22 nm HBsAg+ particles are thought to be just excess viral coat protein. Having HBsAg means you are producing hepatitis B virus.

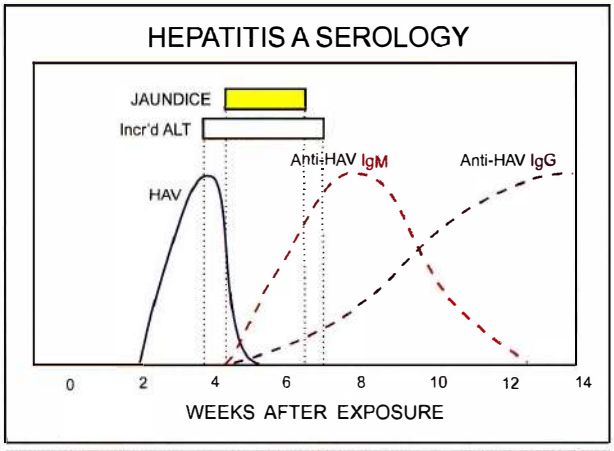


Figure 1-5: Hepatitis A Serology vs. Time after Exposure

HBsAb: Finding HBsAb in the serum indicates past exposure to either hepatitis B virion or to the vaccine. Usually it indicates immunity.

HBcAg is the inner shell protein of the above 42 nm virion. This protein is retained in the hepatocyte until it is covered with HBsAg+ nucleocapsid outer shell, which then incorporates the DNA. Free HBcAg does not circulate in the serum. Antibody to HBcAg appears early in the disease (initially IgM, then IgG) and persists for life, so HBcAb IgG is the best marker for previous exposure to HBV. However, it does not distinguish between active or "cured" infection.

HBeAg is a soluble protein made from the same gene as HBcAg, but, unlike HBcAg, HBeAg is secreted from the hepatocytes and circulated in the serum. HBeAg correlates with the quantity of intact virus and, therefore, with infectivity and liver inflammation. The HBe antibody (HBeAb) appears several weeks after the illness. Detecting HBsAg and HBeAg indicates active virions and high infectivity (more so than HBsAg+ and HBeAg–). The tests for HBeAg and HBeAb are often not available locally.

Confused? Reread the highlighted text and remember:

- **HBsAg+** means a patient is making hepatitis B virus. Levels may be low or very high. It can be acute or chronic.
- **HBsAb+** almost always means the patient is "cured" of previous hepatitis B infection or, if this is the only marker (specifically no IgG HBcAb), then the patient was vaccinated.
- **HBeAg+** means the patient is highly infectious and actively making hepatitis B virus.

Hepatitis B is the only hepatitis virus composed of DNA. Incubation period is 1–6 months. It is transmitted by contaminated blood products. Once infected, the 1st marker detectable in the serum is the antigen HBsAg. This is followed by the appearance of antibody to the core antigen (HBcAb IgM). After HBsAg becomes undetectable, there is a period of weeks to months before the HBsAb antibody becomes detectable. This is called the "window," and you must perform an HBcAb IgM test during this period to confirm acute hepatitis B (Figure 1-6 and Table 1-10).

Hepatitis B is strongly associated with polyarteritis nodosa (PAN). The surface antigen is found in 20–30% of these patients. It appears that the hepatitis B infection precipitates an autoimmune reaction resulting in PAN.

Clinical: First, there are prodromal constitutional symptoms, which typically resolve at the time jaundice becomes apparent. Occasionally (10–15%), the prodromal symptoms are serum sickness-like with fever, arthritis, urticaria, and angioedema. This seems to be caused by circulating immune complexes (especially "HBsAg—HBsAb" immune complex) which activate

the complement system. With the onset of jaundice, the patient generally feels much better but may have liver swelling and tenderness and cholestatic symptoms.

Removal of HBV is T-cell–mediated, and the only purpose of HBsAb is to prevent reinfection.

Hepatitis B immune globulin (HBIG; HBsAb) provides some protection against hepatitis B, although it appears to only decrease the severity of illness rather than protect the patient from disease.

HBIG is effective both as short-term prophylaxis and when given in early infection.

Hepatitis B Vaccines

The 2 hepatitis B vaccines are composed of HBsAg. They are equally effective and are safe for pregnant patients. It is best if the hepatitis B vaccine is given before the patient is exposed to HBV. 95% of immunocompetent patients develop antibodies, whereas only about 50% of dialysis patients do (even though dialysis patients also are given a much higher dose of the vaccine).

To ensure effectiveness after the course of vaccine has been given, check for HBsAb, which is produced in response to the vaccine. There is no HBcAb.

Indications for hepatitis B vaccine in adults include persons engaging in high-risk sexual behavior, those with chronic liver disease, persons with HIV infection, healthcare personnel, and dialysis patients. There is universal preschool vaccination in the U.S.

Hepatitis B Treatment Scenarios

Scenarios:

- Give a newborn of a mother with hepatitis B both hepatitis B immune globulin (HBIG) and hepatitis B vaccination. There is a 5–10% transplacental transmission of HBV.

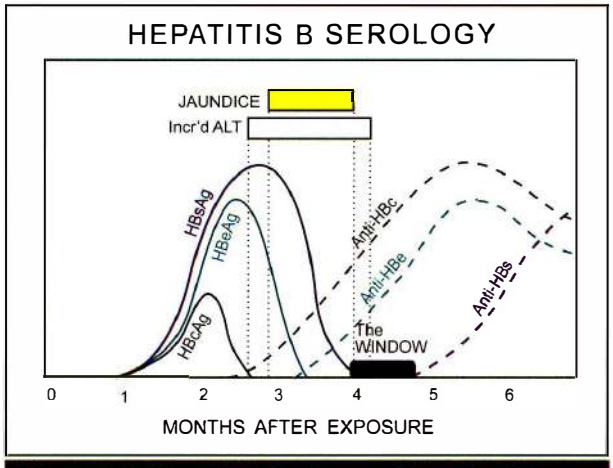


Figure 1-6: Hepatitis B Serology vs. Time after Exposure

- If an asymptomatic patient has HBsAg in the serum, it means either the patient is a carrier or the patient has early hepatitis B—so initial action is only to follow closely. (Once the patient is infected, neither vaccine nor HBIG helps.)
- Sexual contacts and infants cared for by a patient with acute HBV infection should be given HBIG followed by a complete course of HBV vaccinations. Pregnant women are treated the same.

Note: Several months after an episode of hepatitis B infection, check for loss of HBsAg and HBV-DNA to ensure that it has not become a chronic infection.

Chronic Hepatitis B

The likelihood of developing chronic HBV is inversely related to age. Chronic HBV occurs in 90% of infants infected at birth, 25–50% in children age 1–5 years, and 5% in older children and adults. Note that comorbid conditions (hemochromatosis, AIDS/HIV, alcohol) worsen course and response to treatment. Less than 1% of patients with hepatitis B develop fulminant hepatitis, but 5–7% develop chronic carrier states.

There are 2 types of hepatitis B carrier states:

1) Inactive carrier state (asymptomatic with normal liver enzymes)
2) Chronic active hepatitis B (abnormal enzymes)

A liver biopsy is usually required to confirm the diagnosis of chronic hepatitis B.

Patients with inactive carrier states can develop severe exacerbations of hepatitis B if they become immunocompromised. For example, a woman with breast cancer who also has an inactive carrier state with hepatitis B is to be started on chemotherapy. What other drug is given? Lamivudine (or lamivudine + adefovir) is given with her chemotherapy to blunt viral replication.

Chronic hepatitis B is a serious illness. It often progresses to cirrhosis and is strongly associated with hepatocellular carcinoma (HCC; 2% conversion per year). Lifetime risk for HCC is 20%.

Screen for HCC every 6 months with abdominal ultrasound irrespective of cirrhosis. Helical CT or MRI can also be used (more sensitive but much more expensive).

Note: Previously, an alpha-fetoprotein test was also used for screening, but the 2010 AASLD HCC guideline notes that alpha-fetoprotein does not have adequate sensitivity or specificity to support its use for every-6-months HCC surveillance. This new guideline supports an ultrasound-alone strategy.

Treatment of Chronic Active Hepatitis B

Who Should Be Treated

Use HBV DNA, ALT, HBeAg, and degree of cirrhosis to determine when to treat.

QuickQuiz

- Are hepatitis B vaccines safe for pregnant patients?

Treatment is recommended for those with HBV DNA > 20,000 and ALT > 2 x ULN:

- Treatment is started immediately for HBeAg–.
- Treatment is delayed 3–6 months for newly diagnosed HBeAg+ patients to see if seroconversion takes place.

The presence of cirrhosis requires less HBV DNA to initiate treatment. Treat:

- Compensated cirrhosis when HBV DNA > 2,000
- Decompensated cirrhosis when HBV DNA > 200

See Table 1-12 for treatment options for chronic active hepatitis B. Lamuvidine used to be a main treatment option, but it is less desirable now because the drugs shown in the table develop resistance at a lower rate.

Liver transplantation is the only treatment for end-stage liver disease. The HBV recurs in the transplanted liver, but an antiviral treatment program can help.

HEPATITIS C

Overview

Hepatitis C: single-strand RNA virus. It is one of the most common liver diseases in the U.S. [Know this section well!] It is second only to NAFLD (nonalcoholic fatty liver disease, see page 1-57). Hepatitis C has blood-borne transmission and was the cause of 90% of transfusion-associated hepatitis prior to the early 1990s. Since then, especially with the 2nd generation HCV Ab assays, the incidence of transfusion-related hepatitis has become very rare.

Hepatitis C genotypes are 1a, 1b, 2, 3, 4, 5, and 6. Genotypes influence response to treatment. Most HCV infections in the U.S. (> 70%) are genotype 1, which happens to be less responsive to treatment than the other genotypes.

Increased risk for hepatitis C:

- IV drug abuse; common in prisons
- High-risk sexual behavior: with STD, sex with prostitutes, > 5 sexual partners per year
- Blood transfusion/transplant recipients before 1992
- Tattoos, body piercing
- Shared razors and toothbrushes
- Snorting cocaine
- Needle stick injuries
- Renal dialysis personnel
- Children born to HCV infected mothers

The hepatitis C "rule of 2s":

- 2% of U.S. population
- 2% risk of needlestick transmission (though some say 5%+)
- 2% risk of neonatal transmission
- 2% risk of spousal transmission
- 2% cirrhotics with hepatitis C develop hepatoma each year

HIV and Hepatitis C

In the U.S., 25% of patients with HIV are coinfected with HCV. These patients progress faster to cirrhosis than those with HCV alone. Best treatment of HCV for HIV-infected patients is combination therapy: pegylated interferon and ribavirin (with the addition of HCV specific protease inhibitors in genotype 1). Refer to a specialist for treatment.

Extrahepatic Disease with Hepatitis C

Extrahepatic disease includes:

- Small vessel vasculitis with glomerulonephritis and neuropathy
- Mixed cryoglobulinemia (discussed under Chronic Hepatitis C, next page)
- Porphyria cutanea tarda (PCT)

PCT is associated only with hepatitis C (and not B).

So, skin blisters? Think C!

Table 1-12: Treatment of Chronic Active Hepatitis B

Treatment	Benefits	Disadvantages	Used for
Tenofovir	Resistance is rare. Drug of choice for lamivudine-resistant HBV	Limited experience on using in adefovir-resistant disease	Primary treatment
Entecavir	Low drug resistance; Potent antiviral	Not for lamivudine-resistant HBV	Primary treatment
Telbivudine	Slightly more potent than adefovir and entecavir	Same resistance profile as lamivudine	Not used much
Adefovir	Active against lamivudine-resistant HBV	Low viral suppression	Lamivudine-resistant HBV
Interferon	Limited duration of therapy; 35% complete remission; No resistance; Potent	Side effects may be severe; Contraindicated in decompensated liver disease	Primary treatment for young patients and women contemplating pregnancy

Serology and Hepatitis C

Within 2–4 months after an exposure or episode of hepatitis C, recheck for loss of HCV RNA (PCR) to ensure that the disease has not become chronic. Note: This HCV RNA test is not quantitative—but it is sensitive and can determine if there are more than 200 IU/mL of HCV RNA present.

In a person positive for HCV Ab, check for active virus with HCV RNA. This is necessary because the HCV Ab does not confer immunity (as does the HBV antibody to HB).

Chronic Hepatitis C

Whereas < 5% of adults with hepatitis B develop chronic disease, 70–80% of acute HCV infections become chronic! Hepatitis B has high virus counts, whereas hepatitis C has lower virus counts, as evidenced by hepatitis C viral RNA (units/mL).

These low virus counts are consistent with the more insidious nature of hepatitis C:

- Only 25% of acute infections are symptomatic.
- HCV infection has an increased likelihood to become chronic.
- The chronic form is relatively benign. (25% are only carriers; 50% have no symptoms but have abnormal LFTs; 25% have chronic active disease with symptoms.)
- Low rates of sexual transmission are seen in monogamous couples—2% after 10–20 years! This is low, but it does occur—so safe sex is required! Sexual transmission increases with multiple sexual partners.
- Needlestick transmission from a known infected patient is 2–6%.
- Transplacental infection can occur (~ 2%), although this is less of a risk than for hepatitis B (5–10%).

70–80% of patients infected with HCV develop chronic hepatitis, and about 25% of these get end-stage cirrhosis after 20–25 years! And 1–4% of patients with cirrhosis develop hepatocellular cancer (HCC) each year (similar to chronic active HBV).

Screen for HCC every 6 months with abdominal ultrasound (as with hepatitis B and alcoholic cirrhosis). Helical CT or MRI can also be used (more sensitive but much more expensive).

Note again: Previously, alpha-fetoprotein test was also included, but the 2010 AASLD HCC guideline notes that alpha-fetoprotein does not have adequate sensitivity or specificity to support its use for every-6-months HCC surveillance. This new guideline supports an ultrasound-alone strategy.

Chronic HCV infection has become the #1 reason for liver transplantation in the U.S.

Vaccinate all patients with chronic hepatitis C against hepatitis A and B. Giving the combination HAV+HBV vaccine is the simplest method, and either the routine or accelerated immunization schedule is reasonable.

Mixed cryoglobulinemia is strongly associated with chronic HCV infection (55% of those with chronic HCV). It presents as a small vessel (leukocytoclastic) vasculitis with a rash consisting of "palpable purpura" or "crops of purple papules." Mixed cryoglobulinemia is far less common in patients with chronic hepatitis B (15%), other chronic liver diseases (30%), HIV, and connective tissue diseases.

Treatment of Chronic Hepatitis C

If the patient has chronic hepatitis C and elevated liver enzymes, the current standard treatment is the combination of the following:

- Pegylated INF-α (weekly injections—see hepatitis B), which also decreases risk of HCC
- Oral ribavirin
- Protease inhibitors telaprevir/boceprevir (genotype 1)

Prior to the use of protease inhibitors, 40–50% of patients with hepatitis C cleared the virus after 6–12 months of dual therapy. With the addition of a protease inhibitor to interferon and ribavirin, 65–75% of patients with hepatitis C cleared the virus after 6–12 months of therapy. The newer direct antivirals have been shown to result in viral clearance in over 90% of hepatitis C patients.

Measure response to treatment by following HCV RNA; if no response is noted at 12 weeks—seen as a decrease in HCV RNA by 2 log units—discontinue therapy. For those who respond, if the HCV is genotype 1, treat for 1 year; if it is genotype 2 or 3, treat for 6 months.

Notes on treatment:

Medications have no role in end-stage cirrhosis.

Ribavirin therapy can cause hemolytic anemia, but if mild, this is not an indication to stop treatment; rather, give epoetin (erythropoietin, recombinant).

However, ribavirin is relatively contraindicated in cardiac patients with borderline hematocrit levels.

Caution when using INF-α in patients with a history of depression, as depression can worsen while on treatment.

A number of newer agents for hepatitis C are under development, so the area of hepatitis C therapy is evolving rapidly.

HEPATITIS D

Hepatitis D is an RNA virus that requires a coexistent hepatitis B virus infection for the hepatitis D to become pathogenic. It is typically found in IV drug abusers and high-risk HBsAg carriers (HBV DNA levels > 10 million).

Quick Quiz

- Know Table 1-10 through Table 1-13.
- What test confirms that a previous hepatitis C infection did not become chronic?
- With which chronic hepatitis infection is mixed cryoglobulinemia strongly associated? How does it present?
- What is the treatment of hepatitis C genotype 1? Genotype 2–3?
- Which virus does hepatitis D require to replicate?
- Hepatitis E is associated with which risk factor?
- What test has an 80% rate of specificity for autoimmune hepatitis?

Hepatitis D usually does not worsen an acute HBV infection but, if acquired as a superinfection in an HBV carrier, the infection is frequently very severe. If acquired acutely, HDV does not increase risk of chronic hepatitis B. Immunity to hepatitis B implies immunity to hepatitis D. Suspect hepatitis D if sudden decompensation in patient with chronic hepatitis B. Diagnosis: anti-HDV IgM.

HEPATITIS E

Hepatitis E: single-strand RNA virus. Fecal/oral spread (like HAV). Found in the Far East, Africa, and Central America, commonly due to contamination of water supplies after monsoon flooding. Like hepatitis A, no chronic form is known.

Unlike hepatitis A, hepatitis E carries a very high risk for fulminant hepatitis in the 3rd trimester of pregnancy—with a 20% fatality rate. Think of hepatitis E in a traveler with acute hepatitis and negative standard serology (hep A, B).

HEPATITIS G

Hepatitis G is bloodborne, like hepatitis B and C. Mode of transmission is not well defined but likely is similar to HCV. There is evidence of infection in 1.5% of blood donors. It causes < 0.5% of community-acquired hepatitis. There is no evidence that HGV causes chronic liver disease.

CHRONIC HEPATITIS

Overview

There are quite a few causes of chronic hepatitis as shown in Table 1-13. We have already discussed chronic hepatitis B and C. We'll cover the other causes here.

Autoimmune Chronic Hepatitis

Type 1 autoimmune hepatitis generally has an insidious onset and is most often found in young women. Type 2 is a childhood disease and is not discussed here. All the following concern Type 1 only.

50% of adult patients with autoimmune chronic hepatitis also have other disorders of altered immunity; e.g., thyroiditis, Coombs+ anemia, and ITP.

Autoantibodies are common; affected patients may have a positive ANA (+/– anti-dsDNA), anti-smooth muscle antibodies (anti-SMA), anti-actin antibodies (AAA), p-ANCA, and anti-soluble liver antigen (anti-SLA).

ANA is the most sensitive but the least specific serological marker.

Anti-smooth muscle antibody (anti-SMA) is more specific than ANA, and it is positive in ~ 80% of patients with Type 1 autoimmune hepatitis. It is occasionally seen as an overlap syndrome with PBC or PSC. Refer to Table 1-8.

Anti-actin antibody (AAA) test is now commonly available and has, in some labs, replaced the anti-SMA test because it is even more specific and sensitive.

Anti-SLA is the most specific but not sensitive.

You can also check for antimitochondrial antibody—it is only occasionally slightly positive, but high titer occurs in primary biliary cirrhosis (PBC) and indicates an overlap syndrome. Remember, as a rule of thumb, PBC occurs in middle-aged women, autoimmune hepatitis occurs in young women, and PSC occurs in middle-aged men.

Diagnosis: Early diagnosis is essential because this form of chronic hepatitis responds well to treatment. Other forms of hepatitis must be excluded, and the antibody tests covered above are done.

Table 1-13: DDx Chronic Hepatitis

A	Autoimmune may have – ANA +/– anti-dsDNA – Anti-SMA – Anti-SLA antibody – Anti-actin antibody – p-ANCA
B	Hepatitis B
C	Hepatitis C
D_1	Hepatitis D (only with Hep B)
D_2	Drugs (see text)
D_3	Diseases: – Wilson disease – α_1-antitrypsin – Hemochromatosis
F	NAFLD

Scoring system for autoimmune hepatitis (AIH):

• ANA or SMA	> 1:40	1 point
• ANA or SMA	> 1:80	2 points
• IgG	> Upper limit Normal	1 point
	> 1:1 Upper limit Normal	2 points
• Liver histology	Compatible with AIH	1 point
	Typical AIH	2 points

- Absence of viral hepatitis
- Diagnosis —

≥ 6 = probable AIH

≥ 7 = definite AIH

Confirm diagnosis by characteristic changes (piecemeal necrosis with plasma cell infiltrate) found on histologic examination of a liver biopsy. These changes are characteristic but not specific, so drug history and serologic tests are required to rule out other types of hepatitis.

Treatment: Unlike other types of hepatitis, patients with autoimmune chronic hepatitis typically have a rapid reversal of symptoms and increased survival with prednisone/budesonide +/– azathioprine.

Azathioprine (AZA) is used as a steroid-sparing drug. Initially, AZA has no effect as a sole agent; although, over years, some patients can be tapered off steroids and remain on AZA.

Alpha-interferon (IFN-α) exacerbates autoimmune hepatitis and is therefore contraindicated (although effective in chronic hepatitis B and C). So, it is vital to make the correct diagnosis.

Despite the usual response to treatment (above), there is no cure for autoimmune hepatitis, and it frequently progresses to cirrhosis and sometimes hepatocellular carcinoma (less often than with chronic viral hepatitis).

Liver transplant is indicated for end-stage disease, although the disease process slowly recurs.

Drug-Related Chronic Hepatitis

Overview

Drug-related chronic hepatitis is associated with methyldopa, nitrofurantoin, acetaminophen, trazodone, phenytoin, methotrexate, oral contraceptives, and isoniazid (INH) (although INH far more commonly causes acute hepatitis). Histologic changes are similar to those seen in autoimmune hepatitis, and the patients are often ANA+. Hypergammaglobulinemia is also often present. Best treatment is to stop the offending drug.

Drug-related liver disease (acute) can be caused by the direct toxic, allergic, and/or idiosyncratic effects of drugs. Acetaminophen causes a direct toxic effect. Drugs causing an idiosyncratic effect are: halothane, phenytoin, chlorpromazine, and erythromycin. Drugs causing both toxic and idiosyncratic effects: methyldopa, INH, and sodium valproate.

Birth control pills, anabolic steroids, chlorpromazine, amoxicillin-clavulanate, and erythromycin are associated with cholestasis but not hepatitis.

Now let's talk a little more about acetaminophen, alcohol, methotrexate, INH, oral contraceptives, and aspirin.

Acetaminophen

Acetaminophen poisoning is discussed under Poisoning in General Internal Medicine, Book 5. Briefly, when acetaminophen is ingested, 90% of it is processed via the glucuronidation pathway, 5% is excreted unchanged in the urine, and 5% is oxidized by the cytochrome P-450 system. The P-450 system produces a toxic, intermediate compound (N-acetyl-p-benzoquinoneimine, NAPQI), which is quickly reduced by glutathione. When there is an acetaminophen overdose, glutathione is rapidly depleted, and the resulting unreduced toxin causes direct liver damage.

Alcohol-acetaminophen syndrome: Chronic, moderate-to-heavy use of alcohol has a 2-fold effect: the cytochrome P-450 system is cranked up (i.e., more NAPQI is produced) and the amount of glutathione is decreased (so less is available for detoxifying the NAPQI). Therefore, long-term users of moderate-to-heavy amounts of alcohol who take acetaminophen in normal or higher doses are at risk for severe hepatic toxicity or liver failure.

Glutathione levels are depressed in malnutrition. Acetaminophen liver toxicity also may develop by not eating for 3–4 days (e.g., with an acute viral illness) and taking therapeutic doses of acetaminophen; i.e., < 4 g/d!

30% of healthy people taking the maximum recommended dosage (4 grams per day) for 2 weeks develop an ALT > 100 IU/L.

[Again, know:] Acetaminophen liver damage is potentiated with chronic alcohol use, one-time heavy alcohol use, malnutrition, chronic use, and even dieting.

Acetaminophen toxicity is the most common cause of fulminant hepatitis in the U.S. If suspected, draw acetaminophen blood levels; and treat early with intravenous or oral n-acetylcysteine (NAC; Mucomyst®, Mucosil®).The specifics of treatment are discussed under toxicities in General Internal Medicine, Book 5. There is also potential value to NAC treatment even with late diagnosis (more than 48 hours after ingestion and/or toxicity). Liver failure in this setting may be fatal or may require lifesaving liver transplant.

Alcohol

Alcoholic liver disease results in a macrovesicular fat accumulation. There is also PMN infiltration in the liver. Women are more susceptible than men to alcoholic liver disease.

Alcohol induces GGT, so this enzyme is disproportionately high in alcoholic liver disease. Also, there is

QuickQuiz

- What is the treatment for autoimmune hepatitis?
- What drugs are commonly associated with drug-induced hepatitis?
- How does alcohol intake affect liver toxicity from acetaminophen?
- What is nonalcoholic fatty liver disease (NAFLD), and who tends to get it?
- What are the treatment recommendations for NAFLD?

discordance between AST (SGOT) and ALT (SGPT) with an AST:ALT ratio of 2:1. The AST is virtually always < 300—even with severe alcoholic liver injury.

Direct toxic effect is modified by other factors—including nutrition. Toxic effects may be additive. Alcoholics are very susceptible to acetaminophen liver damage because alcohol induces the cytochrome P-450 system. The combination may cause fulminant hepatitis. Know that acetaminophen may not be given in the patient's history. Patients may know only that they have been taking a "non-prescription pain reliever."

Corticosteroids and pentoxifylline are of transient benefit in severe alcoholic hepatitis.

Nonalcoholic fatty liver disease (NAFLD) is very similar to alcoholic liver disease; see next column.

Methotrexate

Methotrexate (MTX) can cause an indolent, asymptomatic liver disease that progresses to cirrhosis. Liver enzyme monitoring is recommended routinely in patients taking even intermittent doses of MTX. Liver injury is believed to be related to cumulative lifetime dose.

Isoniazid (INH)

INH causes an occasional, mild, transient increase in liver enzymes. 1% of these develop a more severe hepatitis —the frequency and severity of which correlate with age.

Oral Contraceptives

Oral contraceptives (OCPs) are associated with benign, hepatic adenoma; peliosis hepatis (blood-filled sinusoids); and focal nodular hyperplasia of the liver. So, a young woman on OCPs who has a mass in her liver? Probably an adenoma. Hepatocellular cancer generally occurs in the setting of cirrhosis.

Aspirin and Reye Syndrome

Reye syndrome occurs exclusively in children < 15 years old. Although rare, it tends to occur after a recent viral illness—especially influenza A or B or varicella (chicken pox)—and especially when there has been concurrent ASA use. These patients get a fatty liver (microvesicular—as in acute fatty liver of pregnancy) and progressive encephalopathy. Elevated are ALT, AST, NH_3, and prothrombin time. Hypoglycemia, as a result of severe liver failure, is common. Mortality is 50%.

Other Diseases that Cause Chronic Hepatitis

The main diseases besides hepatitis that cause chronic hepatitis are the following hereditary liver diseases. See Hereditary Liver Disease on page 1-61.

- Wilson disease
- α_1-antitrypsin deficiency
- Hemochromatosis

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Also called nonalcoholic steatohepatitis or NASH, NAFLD is an increasingly important cause of liver disease. NAFLD looks just like alcoholic liver disease, but there is no history of alcohol abuse. NAFLD is the inclusive term, which, like alcoholic liver disease, covers the spectrum of steatosis (fatty degeneration), steatohepatitis, fibrosis, and cirrhosis. 75–80% of "cryptogenic" cirrhosis is due to NAFLD.

The pattern of liver enzyme elevation is opposite that of alcoholic liver disease, with ALT > AST.

NAFLD is associated with the following:

- Obesity
- Type 2 DM
- Protein malnutrition
- Hyperlipidemia
- Amiodarone
- Corticosteroids
- "DROP"
- Prolonged IV hyperalimentation

DROP is a metabolic syndrome with: **D**yslipidemia, insulin **R**esistance, **O**besity, and increased blood **P**ressure. These patients with NAFLD and DROP have a higher incidence of fibrosis.

Treatment of NAFLD is not standardized. In general, treat with weight loss and control of any DM or hyperlipidemia. For patients with NAFLD and none of the common signs, recommend a low-fat diet. AGA and AASLD recommend vitamin E 800 IU/day as 1st line therapy for biopsy-proven NASH in nondiabetics. All patients with NAFLD should avoid alcohol and be immunized against hepatitis A/B.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC, "hepatoma"): 75% have antecedent cirrhosis. HCC is associated with chronic liver disease of any type: chronic hepatitis B and C, hemochromatosis, α_1-antitrypsin deficiency, alcoholic liver disease, and autoimmune hepatitis. In addition, hepatocellular carcinoma is associated with aflatoxin exposure (can be found in raw peanuts or raw peanut butter, especially in Asia).

Alcoholic liver disease, frequently (75%) with concurrent hepatitis C, is the most common cause of HCC in the U.S. Chronic hepatitis B infection, acquired at birth, is the most common cause in developing countries.

HCC is associated with tender hepatomegaly, a bruit in RUQ, bloody ascites, and high alkaline phosphatase. 70–80% of patients have a very elevated alpha-fetoprotein (AFP) level.

HCC-associated paraneoplastic syndromes are common and are clues to the diagnosis:

- Hypercalcemia (due to parathyroid-like hormone produced by the tumor)
- Hypoglycemia (due to tumor's high metabolic needs or, more rarely, insulin-like growth factor II)
- Watery diarrhea
- FUO

Consider HCC in any cirrhotic patient who decompensates without an obvious reason. IFN-α treatment in chronic hepatitis C reduces the risk of HCC.

Screen all cirrhotics for HCC with abdominal ultrasound every 6 months. Alternately, some centers use helical CT or MRI, which are more expensive, but either has better sensitivity than ultrasound.

Note yet again: Previously, alpha-fetoprotein test was also included as part of HCC screening, but the 2010 AASLD HCC guideline noted that alpha-fetoprotein does not have adequate sensitivity or specificity to support its use for every-6-months HCC surveillance. This guideline supported an ultrasound-alone strategy.

Know some basics about the treatment of liver cancer:

1) Resect a solitary tumor without vascular invasion (best ≤ 5 cm in diameter).
2) If unresectable or underlying liver disease is so bad (commonly due to cirrhosis), can consider for liver transplant (single lesion < 5 cm, ≤ 3 lesions all smaller than 3 cm, no extrahepatic disease or vascular invasion).
3) Even with advanced disease, there are lots of treatment options, including radiofrequency ablation, transarterial chemoembolization, and oral-targeted therapies.

CIRRHOSIS

Causes:

- Alcohol (most common cause in the United States)
- Hepatitis (B or C)
- NAFLD
- Post-necrotic (drugs and toxins)
- Biliary disease
- α_1-antitrypsin deficiency
- Hemochromatosis
- Wilson disease
- Schistosomiasis
- Cardiac causes (primarily severe, prolonged right-sided CHF—which is rare)

Stigmata of Cirrhosis

The physical exam findings of cirrhosis may include any of the following alone or in combination:

- Hepatosplenomegaly
- Jaundice
- Ascites
- Caput medusae
- Spider angiomas (Image 1-23)
- Gynecomastia and testicular atrophy
- Palmar erythema
- Fetor hepaticus
- Asterixis (in hepatic encephalopathy)
- Clubbing (usually in biliary causes)

Complications of Cirrhosis

Esophageal Variceal Hemorrhage

Overview

One-third of patients with esophageal varices bleed, and bleeding has a 30% mortality rate. With a bleed, the ratio of wedged:free portal pressure gradient is usually > 12 mmHg (normal ≤ 6). Size of varices also correlates with risk of bleeding (Image 1-24).

Prophylaxis

Nonselective beta-blockers, such as propranolol and nadolol, decrease rebleeds and may delay or prevent the occurrence of the 1st variceal bleed. Therefore, these agents should be prescribed to all patients with medium to large varices—whether or not they have had bleeding.

Endoscopic ligation can be used for primary prophylaxis in patients with large varices or in those who cannot tolerate beta-blockers. Beta-blockers have been shown to have deleterious effects (increased mortality) in patients with refractory ascites.

Sclerotherapy does not prevent a 1st hemorrhage—it actually appears to make things worse.

What do you do for the patient with cirrhosis and small esophageal varices? Do nothing—only big varices bleed!

QuickQuiz

- What is the most likely diagnosis in a patient with tender hepatomegaly, an RUQ bruit, bloody ascites, a high alkaline phosphatase, and a very elevated alpha-fetoprotein level?
- Name the causes of cirrhosis.
- Bleeding risk of esophageal varices is best correlated with what aspects of the varices?
- What drug class is used for prophylaxis against bleeding with large esophageal varices? What do you do with small esophageal varices?
- Which drugs and which endoscopic therapies are used for active variceal hemorrhages?
- Why are antibiotics given to cirrhotics with GI bleed? Which antibiotics are used?
- What drug is given to a cirrhotic patient with a history of variceal hemorrhage to decrease the chance of rebleeds?

Active Bleeds

Primary therapy of actively bleeding varices is endoscopic banding or sclerotherapy.

Somatostatin and its analog, octreotide, are splanchnic vasoconstrictors. These are frequently given parenterally in conjunction with endoscopic therapy and have a proven benefit over endoscopic therapy alone. Endoscopic injection of sclerosants (sodium morrhuate or ethanolamine) into bleeding varices will stop bleeding but cause necrosis of the esophageal tissue, which can lead to esophageal ulcers and eventual stricture formation.

Balloon tamponade is rarely used because it has a high rate of complications.

Any cirrhotic patient with GI bleeding should be carefully managed in the ICU. Consider elective endotracheal intubation if there is active hematemesis because aspiration pneumonia is common. Always do endoscopy. Remember: Cirrhotics can bleed from sources other than varices; e.g., PUD. If the bleeding is due to varices, do endoscopic therapy with either banding or sclerotherapy.

Give all cirrhotic patients with bleeding or ascites prophylactic oral or IV antibiotics to prevent spontaneous bacterial peritonitis (SBP), AKI, and to decrease mortality. 3rd generation cephalosporin or quinolones (if PCN/cephalosporin allergic) are the preferred antibiotics.

Preventing Rebleeds

Propranolol or nadolol should be prescribed to all patients who have had bleeding varices to decrease the chance of rebleeds.

TIPS (transjugular intrahepatic portosystemic shunt) is used only for cases that rebleed. TIPS allows for decompression of the portal vein—effectively a portocaval shunt without the major surgery. The other main use for TIPS is for intractable ascites due to cirrhosis.

Summary of treatment for esophageal varices:

- Nothing for small varices
- Propranolol or nadolol for all medium-large varices or any history of bleeding varices
- Banding or sclerotherapy for active bleeds or to prevent rebleeds—preferably with somatostatin
- TIPS for rebleeds

Hepatic Encephalopathy

Hepatic encephalopathy may be precipitated by:

- GI bleed
- Hypovolemia
- Hypoxia
- Hypokalemia
- Sedatives
- Tranquilizers
- Portal venous obstruction
- Infections (pneumonia, bacteremia, urosepsis, and spontaneous bacterial peritonitis [SBP])
- Alkalosis, which increases ammonia/ammonium ratio (NH_3/NH_4^+)—because only the non-ionized form, NH_3 (ammonia), crosses the blood-brain barrier. (Acidosis has the opposite effect.)

Signs of hepatic encephalopathy include fetor hepaticus (unique musty odor to breath and urine), hyperreflexia, asterixis, and altered mental status.

Treat with lactulose with goal of ~3 bowel movements/day. This disaccharide, more commonly used as an osmotic laxative, passes through the upper GI tract and is broken down by colonic bacteria into organic acids. The excess H^+ in the proximal colon:

- inhibits coliform bacterial growth and thereby decreases NH_3 production, and
- traps NH_3 as inactive NH_4^+.

Supplemental/alternative treatments:

Oral antibiotics (also to decrease NH_3 production) may be given if the patient doesn't respond to lactulose.

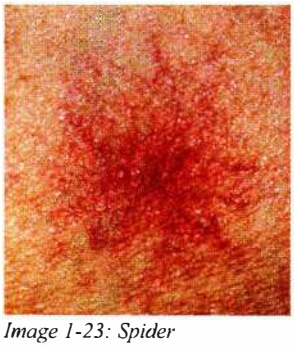


Image 1-23: Spider telangiectasia

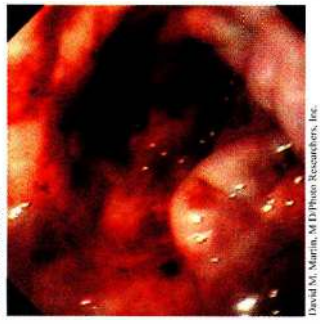


Image 1-24: Esophageal varices

Neomycin was previously used but has nephro/oto toxicity. Rifaximin, metronidazole, rifampin, and vancomycin are now used.

Acarbose (used for diabetes mellitus) inhibits breakdown of carbohydrates into monosaccharides. Monosaccharides promote the growth of bacteria that produce ammonia. Probiotics alter gut flora and similarly decrease ammonia levels.

Hepatorenal Syndrome

Hepatorenal syndrome is also called "oliguric hepatic failure." It is a diagnosis of exclusion so other causes of renal failure such as prerenal azotemia, obstruction, and drugs must be excluded before a diagnosis of hepatorenal syndrome can be made.

[Know:] Urine sodium is very low (commonly < 10) in hepatorenal syndrome.

Current treatment: Careful volume management (IV albumin infusions) and midodrine (an α_1 agonist) + octreotide (stimulates fluid absorption from GI tract).

PT in an Alcoholic

Again note: Alcohol causes malabsorption of some vitamins, including vitamin K. If the prothrombin time (PT) in an alcoholic is prolonged, it is often easily corrected by IM vitamin K. Also, if a 1:1 mix corrects the PT, the disorder is due to decreased coagulation factors; if it does not correct, there is likely a circulating inhibitor.

ASCITES

Ascites is defined as the accumulation of fluid in the peritoneal cavity.

Causes

Causes of ascites:

- Cirrhosis
- Alcoholic hepatitis
- CHF
- Constrictive pericarditis
- Peritoneal diseases
- Myxedema
- Nephrogenic ascites
- Chylous ascites
- Malignancy
- Pseudochylous ascites
- Fulminant and subfulminant hepatitis
- Hepatic veno-occlusive disease (including Budd-Chiari)
- Hypoalbuminemia (nephritic syndrome, protein-losing enteropathy, severe malnutrition)
- Pancreatogenous (pseudocyst, disrupted duct)

Table 1-14: Causes of Ascites and Associated Findings

Protein and Albumin in Ascites		
Causes	SAAG	Ascites T. protein
Cirrhosis, liver failure, Budd-Chiari syndrome, myxedema, and SBP	> 1.1	< 2.5
Right heart failure	> 1.1	> 2.5
TB peritonitis, bacterial/fungal peritonitis, nephrotic syndrome, pancreatitis, and peritoneal carcinomatosis	< 1.1	> 2.5

Cirrhosis-induced ascites: Ascitic fluid is resorbed via the peritoneal surface. Maximum capacity is ~ 900 cc/d. So, if you try to diurese off > 1 liter/day, it is at the expense of intravascular volume. This disease causes the most avid sodium retention state known.

Note: A chylous ascites is due to lymphatic blockage (trauma, tumors—especially 1° lymphoma, TB, and filariasis), not cirrhosis or CHF.

Diagnosis of Ascites

Determining the cause of ascites often requires analysis of a peritoneal fluid specimen for appearance, cell count with differential, cytology, total protein, and albumin.

Know all of the following:

Appearance: Bloody fluid suggests a tumor; cloudy, an infection; milky, lymphatic obstruction.

Cell count: If the cell count is elevated (> 250 PMNs), do a C&S and start antibiotics.

Chemistry: Portal hypertension is indicated by a serum-to-ascites albumin gradient (SAAG) > 1.1 g/dL. This occurs in ascites due to any of the following conditions (where the albumin level in the ascites is low, generally < 1.0 g/dL):

- Cirrhosis (most common)
- RHF
- Fulminant liver failure
- Budd-Chiari syndrome
- Myxedema

SAAG < 1.1 g/dL (i.e., high level of albumin in the ascites and no portal HTN) is seen with ascites due to tuberculosis peritonitis, nephrotic syndrome, pancreatitis, and peritoneal carcinomatosis. Note: SAAG is a difference, not a ratio! It is defined by:

$$\text{SAAG} = \text{Albumin}_{\text{Serum}} - \text{Albumin}_{\text{Ascites}}$$

An elevated ascites protein level (≥ 2.5 g/dL) is seen in all cases that cause increased levels of albumin. It is also seen in cardiac ascites! See Table 1-14.

TIPS (transjugular intrahepatic portosystemic shunt) is used to treat refractory ascites caused by cirrhosis. As

Quick Quiz

- If the PT is prolonged in an alcoholic and is easily corrected with vitamin K, what does this indicate?
- What is chylous ascites due to?
- How does SBP differ from neutrocytic ascites?
- How does SBP differ from PBP?
- Why is albumin given in the treatment of SBP?
- What hereditary liver disease has increased unconjugated bilirubin?
- When does jaundice in Gilbert syndrome typically occur?

stated before, TIPS allows for decompression of the portal vein. Effectively, it is a portocaval shunt without the major surgery. A common complication of TIPS is encephalopathy; therefore, it is generally not recommended for elderly patients—who are most susceptible. As previously discussed, TIPS is also used in the treatment of rebleeding esophageal and gastric varices.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is indicated by a peritoneal fluid with > 250 PMN/mL in a patient with ascites. Usual causes are *E. coli*, then *S. pneumoniae*, then *Klebsiella*.

Because SBP patients may not have abdominal pain or tenderness, you must consider SBP if there is deterioration in the status of any patient with ascites; e.g., new-onset confusion, fever, signs of hepatic encephalopathy, or renal failure.

Risk factors for SBP:

- Ascites protein < 1 g/dL
- History of variceal bleed
- Prior episode of SBP

Patients with these risk factors should receive either intermittent (preferred) or continuous prophylactic oral antibiotic therapy. Typically, use oral therapy with a quinolone (norfloxacin 400 mg daily).

You must rule out 2 other possible causes of high WBC in ascitic fluid before you can assume it is SBP:

1) Neutrocytic ascites: Basically, this is PMNs > 250/mL with no evidence of SBP and negative cultures.
2) Primary bacterial peritonitis (PBP) is due to perforated viscus. In cirrhotics, it can be confused with SBP.

Note that PBP has markedly different ascitic fluid lab findings than SBP:

- Protein > 1 g/dL, frequently > 3 g/dL
- Glucose < 50 g/dL
- WBC very elevated, often > 5,000
- Ascites fluid LDH > serum LDH

Treatment: Active SBP is typically treated with cefotaxime (Claforan®) or similar spectrum 3rd generation cephalosporin. Milder cases can be treated with oral antibiotics.

IV albumin is also given in the treatment of SBP (1.5 g/kg on day 1 and 1 g/kg on day 3). Albumin maintains blood volume and thereby decreases the incidence of irreversible renal impairment and mortality.

Treatment of Ascites

Treatment: mainly dietary sodium and water restriction (needed only if the Na^+ < 125). Then, if needed, start spironolactone, then a loop diuretic. Stop all anti-prostaglandin medications (e.g., ASA) because these decrease urinary Na^+ excretion! Also, do not give aminoglycosides in this setting because they may precipitate renal failure.

Again, do not diurese > 1 L/d. It is okay to do daily paracenteses during the initial treatment of recent-onset ascites or with severe refractory ascites if the patient's renal function is normal and there is:

- No GI bleeding
- No sepsis
- No portosystemic encephalopathy (PSE)

With large-volume paracentesis (≥ 5 L), replace 6–8 grams albumin for each liter of fluid removed. Also, give albumin IV in life-threatening ascites, although it has only a short-term effect.

HEREDITARY LIVER DISEASE

Review of Bilirubin

Hyperbilirubinemia is the main finding in hereditary liver diseases.

In general, only conjugated bilirubin passes the glomeruli and is excreted in the urine. The unconjugated bilirubin is tightly bound to albumin, and this complex is too large to pass through the glomerulus. Conjugated bilirubin is less tightly bound to albumin, and the 5% unbound portion easily passes into the urine.

So, bilirubinuria results only from conjugated hyperbilirubinemia. Because bilirubin is conjugated in the liver, bilirubinuria is an indication of cholestasis.

Unconjugated Bilirubin

Gilbert syndrome is a very common, benign, chronic disorder resulting in a mild, unconjugated hyperbilirubinemia. Remember: unconjugated = indirect = without bilirubinuria. Jaundice may come and go and is typically brought on by physical stress (especially surgery, exertion, and infection), fasting, and alcohol ingestion. Around 7% of the population has Gilbert syndrome. It appears to be an autosomal dominant syndrome with variable penetrance.

Gilbert syndrome is due to decreased or absent glucuronyl transferase in the liver cells or decreased liver cell uptake of unconjugated bilirubin. 1/2 of patients have a very low-grade, chronic hemolysis. This probably reflects 2 separate syndromes, but, for now, they are still grouped together. Phenobarbital stimulates glucuronyl transferase and decreases the bilirubin level.

Diagnosis: Increased unconjugated bilirubin after prolonged fasting. No treatment is needed.

Conjugated Bilirubin

If a patient is noted to have increased conjugated bilirubin after a major surgery, it is not Gilbert syndrome (which is unconjugated). It is most likely an entity called benign postoperative cholestasis. This is most often seen if the patient became hypotensive or required many transfusions during the operation.

α_1-Antitrypsin Deficiency

α_1-antitrypsin deficiency (autosomal recessive) mainly affects the liver and lungs and causes a chronic hepatitis and eventually leads to cirrhosis and emphysema. For diagnosis, check a serum α_1-antitrypsin level. Liver disease is caused by accumulation of intrahepatocytic AAT molecules.

Treatment: Other than liver transplant or liver + lung transplant, the only other minimally effective treatment is augmentation therapy with weekly infusions of pooled human AAT (α_1-antiprotease). Augmentation therapy has no effect on liver disease associated with α_1-antitrypsin deficiency.

Hemochromatosis

Know this topic very well. Consider all the following highlighted!

Two types of hemochromatosis: genetic and acquired.

The **genetic** form involves the *HFE* gene and is autosomal recessive (AR).

The **acquired** form is generally secondary to blood transfusions used to treat underlying anemia, such as sickle cell disease. Less frequently acquired hemochromatosis can occur secondary to an iron-related chronic anemia with secondary erythropoiesis, such as sideroblastic anemia or thalassemia. This form usually develops in men between ages 40 and 60 years.

In **both** genetic and acquired types, there is abnormally increased intestinal iron absorption, which leads to iron deposition in the tissues. This iron deposition causes fibrosis and damage to organs—especially the liver, heart, pancreas, and pituitary gland.

Note: Symptomatic hemochromatosis is 10x more frequent in men—this is probably because of the effect menses has on iron stores in women.

Clinical findings:

- Hepatomegaly (95%)
- Gray hyperpigmentation (90%)
- Secondary diabetes, "bronze diabetes" (65%), so suspect this in a thin 50-year-old with new onset DM
- Arthropathy (40%---especially 2nd and 3rd MCP joints of the wrist!)
- Cardiac involvement (15%)

Secondary hypogonadism also occurs and is caused by depression of the hypothalamic-pituitary axis. There is a 25–30% risk for hepatocellular carcinoma in patients with cirrhosis caused by hemochromatosis—higher than any other cause!

Diagnosis of hemochromatosis is suggested by high levels of serum Fe, ferritin, and transferrin levels. The most helpful screening test is transferrin saturation > 45%. (You can read up on these lab tests at the beginning of Hematology, Book 4.) Liver biopsy confirms the diagnosis and allows for staging of fibrosis.

Liver biopsy is indicated when serum ferritin is > 1,000 ng/mL.

Confirm the diagnosis for the hereditary type with an assay for the *HFE* gene.

If this disease is successfully treated early enough—especially if prior to development of cirrhosis—patients have a normal life span with negligible risk of cancer. Initial treatment is weekly phlebotomy. Ultimately, the patient has phlebotomy 4x/year with the goal of a ferritin level between 50 and 100 ng/mL. This treatment results in decreased skin pigmentation, improved cardiac function, and prolonged life expectancy. But, if already lost, the secondary sex characteristics do not return; the damage is done!

Wilson Disease

Wilson disease is an AR genetic disorder that typically presents as liver disease or neurologic/psychiatric dysfunction in adolescents. It usually presents between ages 15 and 25. Other symptoms include arthritis from chondrocalcinosis. Wilson disease is caused by impaired excretion of copper into bile, which results in an excess copper in body tissues—especially the liver.

Hemolysis is common. Serum ceruloplasmin is low (in most liver diseases, it is high) and urinary copper level is high. Kayser-Fleischer rings are pathognomonic; if suspected, a slit-lamp exam is required: Look for a single brownish corneal ring in each eye, formed by copper deposition along the outer edge of the cornea (Image 1-25). Liver biopsy confirms the diagnosis; it shows a high liver copper level—but remember, so do PBC and PSC!

Quick Quiz

- What is the risk of hepatocellular cancer in a patient with cirrhosis caused by hemochromatosis?
- What lab findings are common in Wilson disease?
- What is a pathognomonic finding in Wilson disease?
- Which patients should be considered for a liver transplant?

Screen with the following tests for Wilson disease in all adults with chronic liver disease without obvious cause, especially if younger than 40 years of age:

1) Serum ceruloplasmin
2) Slit-lamp exam
3) Urine copper

All 3 of the above are positive in < 50% of patients with Wilson disease.

Treatment of Wilson disease is a 2-phase process. First, decrease copper levels, generally with chelation. Then, order maintenance therapy to prevent reaccumulation of copper.

Phase 1: Chelation with penicillamine (must give supplemental pyridoxine with this drug). If the patient cannot tolerate penicillamine or has progressive neurologic manifestations, use trientine. Zinc is a 3rd option.

Phase 2: Maintenance therapy with low-dose penicillamine or trientine, or with zinc. Oral zinc blocks the absorption of copper. Low-copper diet is required (avoid nuts, peas, chocolate, mushrooms, shellfish, liver).

A liver transplant cures Wilson disease!

In fulminant Wilson disease, there is severe hemolytic anemia and a high serum copper level due to the release of copper from the liver. Penicillamine therapy is not effective; the only treatment is liver transplant.

LIVER DISEASE DURING PREGNANCY

1st Trimester

Hyperemesis gravidarum can cause N/V, volume depletion, and mild increase in AST and ALT.

2nd Trimester

2nd trimester is the best time for surgery for severely symptomatic gallstone patients.

Image 1-25: Kayser-Fleischer ring on rim of iris of the eye

3rd Trimester

Remember that hepatitis E can cause fulminant hepatitis in the 3rd trimester of pregnancy—with a 20% fatality rate.

Fatty liver of pregnancy is a very serious condition in which there is microvesicular fat deposition in the liver (as in Reye syndrome), with only modest elevation of AST/ALT/Bili. It occurs in the 3rd trimester and is associated with encephalopathy, hypoglycemia (again like Reye syndrome), preeclampsia, pancreatitis, DIC, and renal failure. Early delivery is required.

HELLP syndrome: Hemolysis, Elevated Liver Enzymes, Low Platelets. Most patients also have hypertension and proteinuria. This is thought by most to be a severe variant of preeclampsia. It tends to occur before 36 weeks of pregnancy. Delivery of the infant is the only consistently beneficial treatment.

Intrahepatic cholestasis of pregnancy causes itching and increased alkaline phosphatase, bili, AST, and ALT. The condition tends to recur in subsequent pregnancies.

LIVER TRANSPLANT

[Know!] Consider liver transplant for almost all patients with irreversible end-stage acute and chronic liver disease. The selection process excludes many of these patients. The selection is commonly made by a liver transplant committee at the liver transplant center. The process is inexact, and the waiting period for a liver is often more than a year. Evaluate patients with chronic, progressive liver disease early in the course of the disease.

The Model for End-stage Liver Disease (MELD) scale gives a fairly accurate short-term (3–6 month) prediction of mortality risk, and it is used to determine organ allocation for liver transplant. It uses bilirubin, creatinine levels, and INR (normalized prothrombin time). The MELD score:

$$3.78 \log_e(\text{bilirubin [mg/dL]}) + 11.2 \log_e(\text{INR}) + 9.57 \log_e(\text{creatinine) [mg/dL]}) + 6.43$$

Be sure and know this formula for the exam! And know the quick way to do logs without a calculator.

(Just kidding … on both counts.) Actually, all you might need to know about the MELD score is:

- < 10 = won't be on the transplant list unless patient has a liver tumor
- > 20 = candidate for transplant

Common indications for liver transplant: Most types of chronic end-stage liver disease, metabolic liver disease, primary and secondary biliary cirrhosis, primary sclerosing cholangitis, and fulminant hepatitis. Cirrhosis with a small, early-stage hepatocellular cancer (HCC) is another indication.

Associated biochemical indications seen in end-stage chronic liver disease: bilirubin 10–15 mg/dL, albumin < 2.5, and a PT > 3–5 sec above normal (10–12 sec). Other signs/symptoms suggesting it is time to transplant: intractable pruritus, hepatic encephalopathy, bacterial peritonitis, intractable ascites, and the development of hepatocellular carcinoma.

Controversial: liver transplant to treat alcoholic cirrhosis.

Absolute contraindications: preexisting advanced or uncontrolled nonhepatic disease, active alcohol or drug abuse, life-threatening systemic disease, and metastatic cancer. There are many relative contraindications, including advanced age.

A prior TIPS (see page 1-58 under Complications of Cirrhosis) is not a contraindication to transplant. In fact, it is often a lifesaving "bridge" to transplantation.

Table 1-15: Workup of Jaundice

	Acute Viral Hepatitis	Chronic Cirrhosis	Obstructive: CD Stone or Pancreatic Cancer
Bilirubin	< 20	< 20 unless impaired renal function	< 20
ALT/AST	> 400	< 400	< 400 usually
Alk Phos	NL–2xULN	NL–4xULN	4–10xULN
A/G	NL/NL	Low/High	Usually NL/NL
PT/PTT	NL/NL usu	High/High	Usually NL/NL
Cholesterol	NL	NL to Low	NL to High
Serologies A, B, C EBV CMV	May be helpful	Excludes acute viral etio if needed	Excludes acute viral etio if needed
Abd U/S	NL	May be helpful	93/95 sens&spec if bili > 10 x 10 d

JAUNDICE

We've discussed many of the causes of jaundice in this section, and now we'll summarize these with a quick review of the workup of a patient with jaundice.

Jaundice (also known as icterus) is a yellowish pigmentation of the skin, the conjunctival membranes over the sclerae (whites of the eyes), and other mucous membranes caused by hyperbilirubinemia (increased levels of bilirubin in the blood).

The differential diagnosis of jaundice includes:

- Viral hepatitis
- Drug-induced jaundice
- Alcoholic liver disease
- Chronic hepatitis
- Gallstones and complications
- Pancreatic cancer
- Sickle cell disease
- Gilbert syndrome
- Primary biliary cirrhosis (PBC)
- Ascariasis
- Primary sclerosing cholangitis

but the majority falls into the following 3 causes:

1) Acute viral hepatitis
2) Chronic cirrhosis
3) Obstructive problem (common duct stone or pancreatic cancer)

And these 3 causes are strongly associated with certain age groups:

1) Acute viral hepatitis is the most common cause (85–90%) in those < 30 years old.
2) Chronic cirrhosis is the usual cause (50–70%) in those 40–60 years old.
3) Obstructive jaundice (common duct stone or pancreatic cancer) is the usual cause (80%) in those 60–80 years old without other risk factors.

If the patient recently arrived from outside the United States, consider ascariasis—especially in a patient with eosinophilia.

Jaundice workup consists of:

- a careful history,
- ultrasound, and
- LFTs (Table 1-15).

Ultrasound results determine the next test to be done:

- Dilated common bile duct and stones: ERCP
- Dilated common bile duct and no stones: CT (think pancreatic cancer) or EUS
- Dilated intrahepatic ducts: CT
- Dilated ducts and testing to exclude PSC: MRCP
- If no dilated ducts: liver biopsy

QuickQuiz

- What is the usual cause of jaundice in persons < 30 years old? 40–60? 60–80?
- What is the timeframe for development of vitamin deficiency for each of these: a) water-soluble vitamins, b) vitamin A and D, c) iron and cobalt, d) B_{12}?
- What are the symptoms of wet beriberi? Dry beriberi?
- What is the classic presentation of a patient with Wernicke encephalopathy?

NUTRITION

VITAMIN DEFICIENCIES

Time Until Onset of Symptoms

[Know!] The time until onset of symptoms of vitamin or mineral deficiency—as when on TPN without vitamin supplementation (and barring other problems):

- **Weeks**: water-soluble vitamins, magnesium (muscle stiffness and cramps—often causes tetany in patients with Crohn disease), zinc (acrodermatitis and poor wound healing), and essential fatty acids
- **Months**: copper (hypochromic, microcytic anemia) and vitamin K (bleeding, high PT/INR)
- **Year**: vitamins A and D, selenium (myalgias, cardiomyopathy, and hemolytic anemia), and chromium (glucose intolerance and peripheral neuropathy)
- **Several years**: iron, cobalt (anemia)
- **Many years**: B_{12}

These deficiencies are important. [Know them cold!] A good way to review this section is to fill in the following sentence, using the appropriate times, symptoms, and mineral deficiencies from above.

If, after 1–2 (____), a patient on TPN develops (____), you would suspect (____).

More on vitamin deficiencies: Vitamins B and C are water-soluble, while vitamins A, D, E, and K are lipid-soluble. We'll discuss these in this order.

[Know all this info about vitamins and minerals!]

Vitamin A Deficiency

Vitamin A deficiency is a major cause of blindness in developing countries; night blindness is the earliest symptom.

Vitamin B_1 Deficiency

Vitamin B_1 is thiamine. Thiamine deficiency causes beriberi. It commonly develops in alcoholics or in patients on chronic hemodialysis. There are 2 major manifestations of thiamine deficiency: wet beriberi and dry beriberi.

- **Wet beriberi**: Symptoms of wet beriberi are heart failure, ascites, and often an accompanying peripheral edema.
- **Dry beriberi** is confined to the nervous system:
  - peripheral neuropathy (symmetrical sensory, motor, and reflex loss);
  - Wernicke encephalopathy (vomiting and nystagmus, ophthalmoplegia, ataxia, and mental deterioration); and
  - Korsakoff syndrome (confabulation, poor recent memory and learning).

Thiamine replacement usually cures Wernicke encephalopathy, but it reverses symptoms in only 1/2 of patients with Korsakoff syndrome—and fully cures only 25%.

Glucose infusions may precipitate Wernicke encephalopathy, so a classic presentation is a closet drinker who develops ophthalmoplegia or nystagmus post-surgery. Always give thiamine to an alcoholic before starting an IV dextrose solution.

Wernicke encephalopathy is a medical emergency. Immediately give thiamine 500 mg IM or IV. Repeat daily for 3–5 days, then transition to oral dosing.

Vitamin B_2 Deficiency

Vitamin B_2 is riboflavin. B_2 deficiency almost invariably occurs in association with other vitamin deficiencies. Phenothiazines and tricyclic antidepressants increase the tendency to develop riboflavin deficiency. Patients present with a normochromic normocytic anemia, sore throat with hyperemic mucosa and glossitis, cheilosis, angular stomatitis, and a seborrheic dermatitis, especially involving the perineal/scrotal area. Symptoms are reversed with riboflavin.

Vitamin B_6 Deficiency

Vitamin B_6 is pyridoxine. Deficiency is rare and frequently caused by drugs but may also be seen with general malabsorption syndromes and chronic alcoholism. The main drug culprits are isoniazid (INH), cycloserine, and penicillamine. Presenting symptoms include glossitis, cheilosis, vomiting, and seizures.

Vitamin B_{12} Deficiency

Vitamin B_{12} deficiency is discussed in Hematology, Book 4, under Nuclear Maturation Defects, and in Neurology, Book 5, under Myelopathies. It results in macrocytic anemia, smooth tongue, and peripheral neuropathy. Subacute combined degeneration of the spinal cord is rather specific for B_{12} deficiency; patients initially experience pins-and-needles sensation, followed by loss vibration and proprioception (position). Dementia is a rare symptom of B_{12} deficiency.

Niacin Deficiency

Niacin deficiency causes pellagra. Niacin (nicotinic acid) is made from tryptophan in the body (so it is not actually a "vitamin"). Niacin deficiency is rare in the U.S. because niacin is now added to grains. It is still seen in carcinoid syndrome, in which tryptophan is depleted, and when isoniazid (INH) is used in treating TB. Presenting signs of niacin deficiency are a dermatitis—especially on sun-exposed surfaces, glossitis ("bald tongue"), stomatitis, proctitis, diarrhea, and changing mental status—ranging from depression to dementia to psychosis. (Remember these by the 3 Ds: mucosal Dermatitis, Diarrhea, and Dementia.) Patients may be hyperpigmented.

Vitamin C Deficiency

Vitamin C (ascorbic acid) deficiency causes scurvy. Ascorbic acid is vital in connective tissue formation. Scurvy generally occurs in poverty-stricken urban areas. First symptoms are petechial hemorrhages and ecchymoses; then the patient develops hyperkeratotic papules around hair follicles, hemorrhage into muscles and joints, purpura, and splinter hemorrhages in the nail beds. Perifollicular hemorrhage is a rather specific finding. In children, it affects bone formation and can cause intracerebral hemorrhage. Symptoms improve only when the normal pool is replenished (1.5–3 grams).

Vitamin D Deficiency

Vitamin D deficiency causes rickets in children and osteomalacia in adults. Most vitamin D is synthesized in the skin (from a protovitamin D + sunlight), but some is absorbed from the gut. This vitamin D is then converted to 25-OH-D in the liver and further to 1,25-$(OH)_2$-D, the active form of vitamin D in the kidney.

25-(OH)-D is what is typically measured on blood tests. 1,25-$(OH)_2$-D levels are quite labile and are not routinely measured due to poor reproducibility.

Vitamin D deficiency causes decreased absorption of calcium from the gut and decreased calcium resorption from the kidney. Vitamin D deficiency also stimulates the release of PTH. Early in the course of the disease, the hypocalcemia is blunted by the increase in PTH, which increases absorption of calcium from the gut and also leaches calcium from the bones. Therefore, despite a normal or slightly low serum calcium level, patients still develop bone problems!

Symptoms in adults are often solely musculoskeletal pain and weakness.

Main causes of decreased 1,25-$(OH)_2$-D:

- Decreased production in skin
- Elderly: decreased skin synthesis at age > 70
- Winter: decreased sun exposure (Roughly 40% in northern climes are deficient by end of winter.)
- Decreased intestinal absorption: steatorrhea, insufficient dietary intake
- Kidney disease

Consider vitamin D deficiency especially in any older patient who has musculoskeletal pain/weakness and especially if there is a history of fat malabsorption or vegetarianism. If osteopenia is diagnosed, check 25-(OH)-D levels.

Vitamin E Deficiency

Vitamin E is an antioxidant. Deficiency is rare and is usually seen in the setting of concomitant malabsorption and codeficiency of the other fat-soluble vitamins. Vitamin E deficient patients can have areflexia and decreased vibration and position sense.

VITAMIN OVERDOSE

Vitamin A

Hypervitaminosis A can be caused by eating polar bear liver, but it is more commonly a result of over-ingestion of vitamin supplements. Symptoms include headache and flaky skin. A single massive overdose causes abdominal pain, sluggishness, papilledema, and a bulging fontanel in infants. This is followed in a few days with desquamation of the skin and recovery. Chronic over-ingestion (25,000 IU/d) is associated with arthralgias, anorexia, dry skin, hair loss, low-grade fever, and hepatosplenomegaly.

Vitamin B_6

Vitamin B_6 excess can cause a peripheral neuropathy with normal motor and sensory function, but absent positional and vibratory sensation.

Vitamin D

Hypervitaminosis D results in increased calcium absorption from the bowel, hypercalcemia, and hypercalciuria. It probably increases the tendency for calcium renal stones. The hypercalcemia and hypercalciuria seen in chronic granulomatous diseases (such as sarcoidosis and lymphomas) are due to an equivalent hypervitaminosis D state, in which there is increased 1,25-$(OH)_2$-D.

Vitamin E

Vitamin E is relatively nontoxic acutely. The main trouble with vitamin E is that large doses can cause a marked potentiation of oral anticoagulants. Long-term vitamin E supplementation has been associated with increased all-cause mortality.

Vitamin C

Vitamin C megadoses increase the incidence of oxalate renal stones and can interfere with the absorption of vitamin B_{12}.

QuickQuiz

- Petechiae are associated with which vitamin deficiency?
- Explain how vitamin D is produced and altered in the body.
- What does vitamin D deficiency cause in the adult?
- What are the findings associated with excessive continuous ingestion of vitamin B_6?

Niacin

High doses of niacin can cause acanthosis nigricans and cholestatic jaundice. The flushing and pruritus often occurring at the start of treatment can be prevented by taking aspirin 30 minutes before the niacin and/or by taking niacin in divided doses or after meals.

ENTERIC FEEDING vs. TPN

If the choice is between enteric feeding and TPN, enteric feeding is the better option. The short-chained fatty acid substrates (fatty acids are synthesized in the small intestine) in the enteric feedings help maintain the integrity of the small intestinal wall—the loss of which is associated with the onset of multisystem failure. Percutaneous endoscopic gastrostomy is often used in patients who cannot swallow. It is a better alternative to the NG tube, and general anesthesia is not required. Contraindications to percutaneous endoscopic gastrostomy are delayed gastric emptying and gastric outlet obstruction. In these instances, various types of jejunostomy tubes can be used.

MALNUTRITION

Simple clues to malnutrition:

- Weight/ideal weight < 70%
- Lymphocyte count < 1,000/mm^3
- Low albumin or prealbumin
- Low triceps skin-fold thickness
- Low urine creatinine-to-height ratio = (24-hr urine excretion of creatinine in µg) ÷ (height in centimeters); < 10 in men; < 6 in women.

Greater than 10% weight loss over 6 months indicates a possibility of malnutrition. Albumin is an indicator of nutritional status, but it may also be lower after major trauma or during an infection (due to vascular leakage) or secondary to liver disease (low production) or the nephrotic syndrome (secondary to "spillage" into the urine). Malnourished patients may be anergic. Triceps skin-fold measurement is good only for long-term assessment of nutritional status. Short-term changes may not be meaningful because of fluctuations in hydration and edema.

Indirect calorimetry units that measure oxygen consumption and CO_2 production are more precise and usually better for determining needed calories for in-hospital, critically ill patients.

Refeeding syndrome: Chronically malnourished patients (e.g., anorexia nervosa, cancer, short gut)—especially those with resting bradycardia, hypotension, or body weight < 80% ideal weight—are at risk for cardiac failure with rapid refeeding. Phosphate and potassium replacement, frequent monitoring of electrolytes, and telemetry should be used during the initial days of refeeding to minimize the risk for cardiac failure.

FOR FURTHER READING

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Infectious Disease

HOST DEFENSE

CYTOKINES

See Allergy & Immunology, Book 4, for a description of the basic functions of the immune system.

Cytokines are signaling molecules produced by immune system cells. These molecules help different branches of the immune system talk to each other and respond to threats. After cells release them, they bind target receptors on other cells to alter cell function. The molecules can ramp up the immune system or tone it down.

Examples of cytokine types include colony-stimulating factors (CSFs), interferons (IFNs), interleukins (ILs), and growth factors (Table 2-1).

Covered here are the most clinically relevant cytokines and their functions.

Cytokines are released in response to an interaction between T cells, an antigen-presenting cell (e.g., a macrophage or dendritic cell), and an antigen that stimulates an immune response. The cytokines produced depend on the type of T cell involved (termed a "T-cell subset") and the cytokine profile of that subset.

Major subsets include T-helper Th0, Th1, Th2, and Th17:

- **Th0** cells are unrestricted. They are naïve T cells that can respond to novel antigens that the immune system has not yet encountered.
- **Th1** cells produce IFN-gamma, IL-2; are important in cell-mediated immune response (e.g., delayed-type hypersensitivity reaction); and are stimulated by the IL-12 superfamily.
- **Th2** cells produce IL-4, IL-10; are important in humoral immune response (antibody development and allergic responses); and are stimulated by IL-4, IL-18, and IL-33, working together.
- **Th17** cells produce IL-17A, IL-17F, IL-22; are important in antifungal immunity and also autoimmune-related chronic inflammatory diseases (e.g., rheumatoid arthritis, inflammatory myopathies); and are stimulated by IL-1, -6, -21, -23.

Cytokines that mediate cellular migration into tissue are called chemokines. IL-8 is an example.

Some cytokines that inhibit the immune system are prostaglandins, transforming growth factor (TGF)-beta, and IL-10.

Unregulated cytokine activation contributes to the systemic inflammatory response syndrome (SIRS), which is a severe condition with systemic inflammation and organ dysfunction and failure. SIRS is diagnosed if any 2 of the following parameters are present: temperature > 38 or < 36; heart rate > 90; respiratory rate > 20; WBC > 12.0 or > 10% bands on peripheral smear. SIRS may have an infectious or a noninfectious etiology. When infection is suspected or demonstrated, the condition is called sepsis. Tumor necrosis factor (TNF)-α may be the most important mediator. TNF-α is a cytokine released by neutrophils, monocytes, and macrophages in response to endotoxin (lipopolysaccharide; LPS). Once released, TNF-α amplifies the signal LPS and transmits it to other cells.

Table 2-1: Cytokines

Type	Functions
Interleukins	
IL-1	Fever, stimulates T cells
IL-2	Proliferates T cells, activates B cells
IL-4	Immunoglobulin switch signal, suppresses Th1
IL-6	Cell proliferator, acute-phase reactant
IL-12	Increases IFN-gamma, induces Th1 differentiation
IL-15	Induces TNF-alpha release
IL-17	Important in autoimmune chronic inflammatory reactions and anti-fungal immunity.
TNF-alpha	Cachexia, stimulates T cell
IFN-gamma	Activates T cells, NK cells, macrophages
TGF-beta	Inhibits T-cell proliferation and pro-inflammatory cytokines
Platelet-derived growth factor	Proliferates fibroblasts

NEUTROPENIA

Epidemiology and Risk Factors

Neutrophils help to fight disease by disrupting or consuming disease-producing cells and microorganisms. Neutropenia (granulocytopenia) occurs in leukemia, bone marrow transplant, ablative chemotherapy, exposure to drugs or toxins, bone marrow metastases, and overwhelming sepsis. Most often, sepsis is caused by flora that are colonizing the patient and that enter the bloodstream across disrupted gut mucosa, via an intravenous catheter, or through the oropharynx into the lungs and/or sinuses. Neutropenic infections can be caused by both gram-negative and gram-positive bacteria.

Of the gram positives, the most common are *Staphylococcus aureus*, *S. epidermidis*, and streptococcal species. But we are also seeing more infections associated with the less common gram-positive organisms such as *Corynebacterium* species, *Propionibacterium acnes*, *Bacillus* species, and *Leuconostoc*. These are important to remember because some are not effectively treated with vancomycin.

Common gram-negative infections include *Pseudomonas* species and *Enterobacteriaceae* including *E. coli*, *Klebsiella* species, and *Enterobacter*.

Anaerobic infections are not seen commonly in neutropenia.

Fungi, including yeasts such as *Candida* and molds such as *Aspergillus* species, are important pathogens in patients with prolonged neutropenia. Infections with *Fusarium* species and agents of mucormycosis are especially deadly and are being seen more frequently. Not all fungi are equally susceptible to all antifungal drugs. When a patient with neutropenia develops fever and/or an infection while receiving an empiric antifungal drug, it is very important to know which organisms are resistant to that antifungal. (See discussion of antifungal drugs on page 2-14).

The risk for infection in the patient with neutropenia is directly proportional to the degree and duration of neutropenia.

Other factors that increase risk are:

- Comorbid diseases
- Presence of catheters
- Concomitant use of immunosuppressive drugs such as monoclonal antibodies and corticosteroids (risk of *Pneumocystis* and tuberculosis)

The absolute number of granulocytes is definitely important. A patient with < 500 neutrophils (severe neutropenia) is at much higher risk than a patient with just < 1,500 (mild neutropenia); however, patients can actually have an adequate number of cells yet still get infected if the present granulocytes do not function properly. Suspect granulocyte dysfunction (e.g., chronic granulomatous disease) if the patient has an adequate absolute neutrophil count (ANC) but has a history of recurrent staphylococcal skin infections, lung infections, and/or lymphadenitis. The duration of neutropenia is also key: An ANC < 500 for > 7 days greatly increases the risk of infection.

Febrile Neutropenia

Evaluation

It is important to recognize febrile neutropenia and begin emergent evaluation and empiric antibiotics. The definition of febrile neutropenia is a temperature of > 101° F (38.3° C) x 1 or 100.4° F (38.2° C) on 2 occasions > 1 hour apart and severe neutropenia (defined as an ANC < 500 or expected to be < 500 in the next 48 hours).

An important part of the evaluation is the physical exam with concentration on the upper airway mucosa (look for mucositis), teeth and periodontal tissues, eyes, and rectum. Neutropenic patients, however, may lack localizing signs of inflammation. Any rash or skin ulceration/swelling is potentially significant. Portals that allow infections to enter may include catheters and implants.

A thorough physical exam must be repeated every day. If you are giving treatment to increase the ANC, you may see localizing signs of infection become apparent as the ANC rises.

Initial lab evaluations of febrile neutropenia include:

- Complete blood count with differential
- Basic chemistries
- Liver transaminases and bilirubin
- ≥ 2 blood cultures, including a set from each lumen of central venous catheters
- Urine cultures if symptomatic and/or catheter in place and/or abnormal UA
- Cultures from other sites if symptoms (e.g., sputum)
- Chest x-ray (CXR) if there are respiratory signs or symptoms

Consider these tests in the appropriate circumstances:

- If diarrhea present, stool for *C. difficile* toxin
- Lumbar puncture if the patient is confused without identifiable cause or has other signs of meningitis
- Fungal markers such as galactomannan (*Aspergillus*) and beta-D-glucan (*Candida* and other fungi)
- CT chest if respiratory symptoms and unrevealing CXR
- Bronchoscopy or open lung biopsy for pathology, Gram stains, and bacterial/viral/fungal cultures in patients with pulmonary infiltrates
- Skin biopsies for pathology and bacterial + fungal smears and cultures

Empiric Treatment

When a neutropenic patient presents with fever, you must initially cover for gram-negative aerobic bacilli and streptococci. Oral empiric treatment in less severely ill patients includes the combination of ampicillin/sulbactam with ciprofloxacin or moxifloxacin. Treat patients with signs and symptoms of sepsis with intravenous drugs such as:

- Piperacillin-tazobactam
- Carbapenem (imipenem or meropenem)
- Cefepime

Vancomycin is added to the above empiric regimens if any of the following are present:

- Hypotension or other evidence of severe sepsis
- Positive blood culture for gram-positive bacteria (before organism/susceptibility is discerned)
- Pneumonia documented radiographically
- Persistent fever while on empiric antibiotics
- Obvious skin infection or erythema at the site of an indwelling catheter
- History of MRSA infection or known colonization
- Severe mucositis if quinolone prophylaxis has been given or ceftazidime is employed as empiric therapy

Quick Quiz

- What are some differences between Th1, Th2, and Th0 T-cell subsets?
- Name some factors that affect whether a patient with neutropenia develops an infection.
- What are your options for empiric treatment of the febrile neutropenic? When is vancomycin included?
- What fungi are not covered by echinocandins?
- In the empiric treatment of febrile neutropenia, when would you want to choose voriconazole or liposomal ampho B over an echinocandin?
- What is the most common inherited immunodeficiency?

Know which gram-positive organisms are not covered by vancomycin:

- Vancomycin-resistant *Enterococcus* (VRE)
- *Leuconostoc*
- *Lactobacillus*
- *Pediococcus*

Worry about these organisms if the patient has persistent fever and neutropenia while on empiric vancomycin; however, the last 3 are fairly uncommon. VRE is much more relevant clinically.

If vancomycin is included in the initial regimen, discontinue after 2 days if there is no evidence of a gram-positive infection.

If the fever and neutropenia persists after 4–7 days on empiric antibiotics (including vancomycin), empirically treat for a fungal infection by adding:

- an echinocandin (caspofungin is the only one FDA-approved for this indication but other echinocandins are equally effective),
- liposomal amphotericin B, or
- voriconazole.

Fluconazole is less effective as an empiric antifungal and should not be used.

Know the organisms that are not covered (or probably not covered) by the echinocandins:

- *Cryptococcus*
- *Fusarium*
- Filamentous molds (*Mucor*)
- Endemic fungi (histo, blasto, cocci)

Relative resistance to echinocandins occurs in:

- *Aspergillus* species (Echinocandins can be used for salvage and/or combination therapy.)
- Some unusual *Candida* species (*C. parapsilosis*, *C. guilliermondii*. Usually these have higher MICs with unclear clinical significance.)

Worry about these organisms if the patient has persistent fever and neutropenia while on an empiric echinocandin.

Know that fluconazole should not be used as an empiric antifungal because:

- clinical trials show it doesn't work, and
- it is ineffective against *Aspergillus* and some resistant yeasts (*C. glabrata*, *C. krusei*).

Regarding which specific antifungal to choose, usually it doesn't matter, except in the following circumstance: Definitely choose voriconazole or liposomal amphotericin B in the patient with a pulmonary presentation consistent with invasive pulmonary aspergillosis.

Empiric antifungal coverage resolves the fever in about 1/2 of patients. It is problematic, however, because resolution of fever on an antifungal drug does not necessarily mean the patient has a fungal infection. Duration of treatment is often a problem. Note: Patients with acute myeloid leukemia (AML) have a markedly increased risk of developing *Aspergillus* infection.

Prophylaxis and Adjuvant Treatment

According to the 2010 IDSA guidelines, prophylactic antibiotics (e.g., ciprofloxacin and levofloxacin) should be considered for those at high risk of infection, particularly those with expected neutropenia duration > 7 days and an ANC ≤ 100 during this time period.

In these same guidelines, colony-stimulating factors that stimulate the bone marrow to produce more neutrophils (e.g., G-CSF) are recommended in patients who are at risk (≥ 20% chance) of developing fever (e.g., expected long duration of neutropenia with low ANCs). However, these agents are not recommended in treatment of established fever and neutropenia.

HUMORAL DEFICIENCIES

Humoral deficiencies can be inherited (e.g., X-linked agammaglobulinemia, common variable immunodeficiency, IgA deficiency) or acquired (multiple myeloma [MM], acute lymphocytic leukemia [ALL], chronic lymphocytic leukemia [CLL], HIV/AIDS, asplenia).

Inherited Deficiencies

The inherited disorders usually present in childhood and are typically cared for by pediatricians. Diseases are diagnosed by measuring total levels of immunoglobulins A, G, and M. (IgA is typically low; IgG and IgM should be normal.)

Know that selective IgA deficiency is the most common inherited immunologic defect. Most patients have no symptoms. Symptomatic patients present with recurrent sinopulmonary disease from encapsulated organisms,

recurrent giardiasis, and food/respiratory allergies. These patients often form autoantibodies and may have autoimmune diseases such as chronic autoimmune thyroiditis (previously Hashimoto's), celiac disease (gluten-sensitive enteropathy), pernicious anemia, systemic lupus erythematosus (SLE), and rheumatoid arthritis.

Know these 3 important facts about selective IgA deficiency:

1) Women can have false-positive serum pregnancy tests. (Urine pregnancy test is normal.)
2) Blood transfusion is associated with a higher-than-normal risk of anaphylaxis and should be avoided if possible. These patients have anti-IgA antibodies, and transfused blood contains small amounts of IgA.
3) IVIG and plasma infusions are contraindicated for the same reason as blood transfusion.

Acquired Deficiencies

Acquired deficiencies are common clinical scenarios for the general internist. Infections arise because either effective antibodies are not produced or B and T lymphocytes are not communicating effectively with one another. Most of these diseases are associated with hypogammaglobulinemia (reduction in levels of specific IgA, M, and G) but with a relative polyclonal increase in the gamma globulin fraction (i.e., patients produce an excess of fairly useless antibodies that are not specific for an antigen, are usually ineffective, and may cross-react with normal body components such as red cells and platelet surface receptors).

Patients with acquired humoral deficiencies are predisposed to infections with encapsulated organisms, gram-negative rods (GNRs), and giardiasis. Recurrent giardiasis should trigger a workup for this.

The spleen clears out bacteria and is the site for formation of opsonizing antibodies. Opsonizing antibodies are important in defending the host from infection with encapsulated organisms, especially pneumococcus. Splenectomy and functional asplenia increase the risk of overwhelming pneumococcal, malarial, and babesial infections. The latter 2 are intra-RBC protozoan parasites.

IgA blocks viral attachment to mucosal surfaces, and IgG blocks viral attachment to host cells.

COMPLEMENT DEFICIENCY

The complement cascade and complement deficiencies are discussed in Allergy & Immunology, Book 4. Deficiencies result in an increased risk of infection and autoimmune disease.

Let's review a summary of the complement deficiencies and the types of infections that tend to occur in each.

Classical Pathway Deficiencies

C1, C2, and C4 deficiencies: recurrent sinopulmonary infections +/– otitis media with encapsulated bacteria, specifically pneumococcus, *H. influenzae*, and *N. meningitidis*. These deficiencies are associated with development of systemic lupus at an early age.

C3 deficiency: severe infections with pneumococcus and *H. influenzae* from infancy.

C5–C9 deficiencies ("terminal complement deficiency"): recurrent *Neisseria* infections (meningococcus and gonococcus). Thus, these patients often have recurrent meningo- and gonococcemia. Usually the presentation is mild or moderate—mortality from these infections in this group of patients is low.

Screen patients for classical complement deficiencies if they have had recurrent bacterial infections and normal CBC and immunoglobulins or if they have repeat neisserial infections (or a family history). The screening test of choice is the CH50, sometimes also called "total hemolytic complement" or THC. Deficiency causes an undetectable CH50 titer. Once the CH50 is established as abnormal, measure each individual complement component to determine the specific deficiency. C2 deficiency is the most common, and terminal deficiencies are least common; so start with measurement of C2.

Acquired Classical Deficiencies

Certain systemic diseases that activate complement are associated with an increased risk for infection as a result:

- Systemic lupus erythematosus
- Mixed cryoglobulinemia due to chronic hepatitis B (HBV) or hepatitis C (HCV)
- Some vasculitic diseases (polyarteritis nodosa)
- Some primary renal glomerulonephritides, even when systemic complement levels are not that low

End-stage liver disease is also associated with clinically significant hypocomplementemia because the liver cannot synthesize these proteins.

T-CELL DEFICIENCY

Overview

T-cell–deficient patients are said to have decreased "cellular" immunity. T-cell defects occur in the following:

- HIV/AIDS
- Hodgkin lymphoma if T-cell–derived
- T-cell variant of ALL
- Prolonged corticosteroid use
- Solid organ transplantation (because of immunosuppressant Rx)

Patients with T-cell defects are more susceptible to routine community-acquired bacteria and viruses (pneumococcus, *Mycoplasma*, *Legionella*, *Listeria*, *Salmonella*,

QuickQuiz

- Splenectomy predisposes a patient to worse infection from what organisms?
- Patients with which complement deficiencies are at risk for *Neisseria* infections?
- What test is used to screen for complement deficiencies?
- Review the infections associated with solid organ transplants and when each is likely to occur.

influenza, respiratory syncytial virus [RSV]), and opportunistic infection (OI) with the following pathogens:

- Bacteria (*Nocardia*, *Rhodococcus equi*, mycobacteria)
- Viruses (especially new infections with cytomegalovirus [CMV], herpes simplex [HSV], varicella zoster [VZV])
- Fungi (*Pneumocystis*, *Cryptococcus*, *Aspergillus*, endemic fungi)
- Parasites (*Strongyloides*)

Patients also frequently reactivate protozoal and viral diseases that they have previously held in check:

- *Toxoplasma gondii*
- CMV, HBV, HCV, VZV, HSV, papillomavirus, and BK polyomavirus

Solid Organ Transplantation

Patients who have received a solid organ transplant are also at risk for infections carried by the donor organ as well as nosocomial infections. Additionally, they can reactivate infections that had been previously controlled by their immune system. Some of these infections are mentioned above but also include endemic fungi and mycobacteria.

Infections caused by immunosuppressive drugs tend to arise predictably, based on the length of treatment.

Know the following classic 3 post-transplantation time periods and their associated infection risks:

1) Month 1: infections from the donor; nosocomial infection (specific to the type of surgery performed).
2) Months 2–6: Immunosuppressant medication is starting to take effect, and patients are at risk for the OIs described above. CMV can occur in a donor+/recipient– situation.
3) > 6 months: community-acquired infections.

However, the use of routine prophylaxis with TMP/SMX and valganciclovir has shifted the time of onset of some OIs. For instance, CMV may not occur until after valganciclovir is stopped in these patients.

HIGHLIGHTS

[Know.]

Inherited humoral deficiency of IgA:

- Sinopulmonary infections with encapsulated organisms
- Giardiasis
- Food and inhalant allergies
- False-positive serum pregnancy tests
- Anaphylaxis with blood transfusion and IVIG
- Association with autoimmune diseases

Acquired humoral deficiencies: splenectomy, leukemias, lymphomas, myeloma, HIV/AIDS, encapsulated organisms.

Classical complement deficiencies: sinopulmonary infections with encapsulated organisms, C2 deficiency that is associated with SLE.

Terminal complement deficiencies: encapsulated organisms, meningococcemia.

T-cell defects: HIV/AIDS, post-transplant, corticosteroids, fungi, acid-fast bacteria, viruses, parasites.

ANTIBIOTIC THERAPY

HOW ANTIBIOTICS WORK

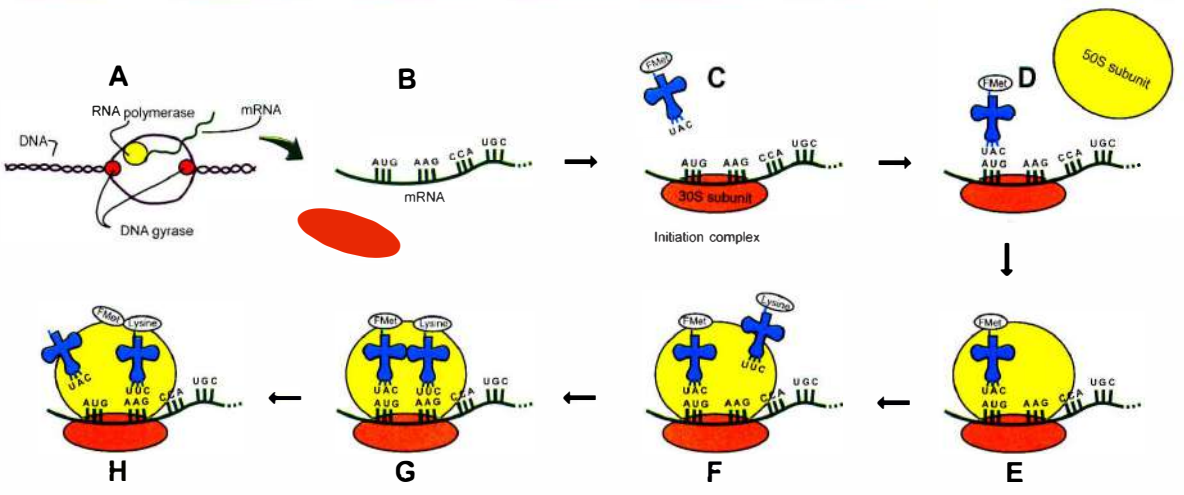
Most antibiotics work by subverting bacterial protein synthesis (Figure 2-1), folate metabolism, or the bacterial cell wall or cell membrane. First, let's review protein synthesis; then we'll tackle how specific antibiotics block it.

Review: Protein Synthesis

Transcription: The DNA molecule must be unwound from its supercoiled arrangement before it can be "read" by RNA polymerase. This involves cutting the strand, holding onto the cut ends to prevent them from being damaged, allowing the double helix to uncoil and the DNA to be copied, and then precisely gluing the cut ends back together again. The key enzyme that carries out this process in bacteria is DNA gyrase.

RNA polymerase moves along a section of DNA (a gene), uncoiled by the DNA gyrase and, following the coded messages on the deoxyribonucleotides, forms a string of complementary-paired ribonucleotides; i.e., a piece of RNA—more specifically, pre-mRNA. With the removal of an intron, the pre-mRNA becomes mRNA (messenger RNA). This is called transcription because the DNA code is transcribed into a complementary RNA code.

Translation: Ribosomes are the translation units that convert the coded message in the mRNA to a specific sequence of amino acids. A 30S ribosomal subunit attaches to the mRNA at the "ribosome binding site," then moves along the RNA until the RNA reaches the start codon (AUG). Here, a tRNA (with anticodon



A represents transcription. DNA gyrase is targeted by **quinolones** and **metronidazole**. **Rifampin** binds to RNA polymerase.
B to **C** shows attachment of the 30S subunit to the mRNA. **Tetracyclines** bind reversibly and **aminoglycosides** bind irreversibly to the 30S subunit.
C to **D** shows attachment of the 50S subunit to form the 70S ribosome. **Oxazolidinones** and **macrolides** bind to the 50S subunit.

Figure 2-1: Antibiotic Effects on Protein Synthesis

UAC), carrying an altered methionine (f-Met), binds with this subunit and mRNA to form the "initiation complex." A 50S ribosomal subunit then comes along and binds to this complex to form the 70S ribosome.

Amino acid-specific transfer RNAs (tRNA) attach to the 20 amino acids used in making protein. The bottom loop of these "inverted cloverleaf-shaped" tRNAs has 3 unpaired bases called anticodons.

As the 70S ribosome moves along the mRNA, tRNAs attach one at a time, bringing these amino acids with them. These amino acids are bound together, forming a gradually lengthening protein chain.

When the ribosome reaches the end of the coded message, translation stops. The ribosomal subunits then separate and detach from the mRNA, and the completed protein is released.

Antibiotics that Block Protein Synthesis

Rifampin binds to RNA polymerase and blocks initiation of the transcription of DNA to mRNA.

Quinolone antibiotics (e.g., ciprofloxacin, levofloxacin, moxifloxacin) specifically target the DNA gyrase of bacteria. This allows the DNA gyrase to cut the double helix but then prevents the cut ends from being rejoined.

Metronidazole, a very important antianaerobic and antiprotozoal agent, probably has a primary mode of action similar to the quinolones, although it also affects cell membrane function.

Aminoglycosides (e.g., gentamicin, amikacin) bind irreversibly to the 30S ribosomal subunit and prevent the 50S subunit from attaching.

Tetracyclines (e.g., doxycycline) bind reversibly to the 30S subunit, distorting it so that the anticodons of the tRNAs cannot align properly with the codons on the mRNA.

Macrolides (erythromycin, clarithromycin, azithromycin) bind reversibly to the 50S subunit. They prevent peptide bond formation between the amino acids and, hence, keep the 70S ribosome from translocating down the mRNA.

Clindamycin works very similarly to macrolides.

Oxazolidinones (e.g., linezolid) and streptogramins bind to the 50S ribosomal subunit, thereby preventing attachment to the initiation complex.

Trimethoprim and the **sulfonamides** block the production of folic acid from para-aminobenzoic acid (PABA). Folic acid is required to replicate DNA.

Review: Cell Wall Synthesis

Peptidoglycan is a component of bacterial cell walls. It is composed of alternating polysaccharides: N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM). Cross-links form between the alternating strands that make the wall solid. NAG and NAM (and their cross-links) vary slightly between gram-positive and gram-negative organisms.

Gram-negative organisms have an outer membrane (OM) outside of the cell wall.

Antibiotics that Affect the Cell Wall

A variety of antibiotics act at one or more stages of peptidoglycan synthesis. In order for an antibiotic to affect the cell wall of gram-negative organisms, the drug has to pass through the OM—passage is affected by

QuickQuiz

- Which antibiotics target DNA gyrase to interrupt protein synthesis?
- Which antibiotics antagonize folic acid?
- How are gram-negative organisms inherently more resistant to antibiotics, compared to gram positives?
- Which class of antibiotics affects the developing bacterial cell wall?
- What information does the disk diffusion test give you?
- What is the specific definition of MIC and MBC?

drug size and charge. Thus, some gram-negative organisms have inherent resistance to certain cell wall agents that are less able to pass through the OM.

Beta-lactams are a class of antibiotics that interrupt formation of the bacterial cell wall. Because there is no analogous structure in human cells, relatively high doses can be administered. However, idiosyncratic reactions may occur with beta-lactams. Especially remember penicillin allergy, anaphylaxis, and acute interstitial nephritis.

Vancomycin works by inhibiting cell wall synthesis of gram-positive organisms. **Telavancin** (a synthetic derivative of vancomycin) works on inhibiting cell wall synthesis and also disrupting the cell membrane.

Antibiotic that Affects the Cell Membrane

Daptomycin inserts into the cell membrane of gram-positive bacteria, creating a channel that allows for efflux of ions and disruption of membrane polarization.

IMPORTANT PHARMACODYNAMICS

Overview

What happens to those blood, urine, and goop samples in the lab?

Important Basic Microbiology

Bacteria can be directly visualized with a Gram stain and then grown in media. Some specimens are placed directly in liquid (without a Gram stain first) if they are not known to be certainly infected (e.g., blood). The liquid medium is incubated for 24 hours and observed for development of turbidity, which would indicate bacterial growth.

Once bacterial growth is established, identification and sensitivity testing are done. Traditionally, the culture would then be plated on various agar plates to identify the bacteria, and disk diffusion susceptibility would be done to determine the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the drug for those bacteria (see next).

Most hospitals currently use an automated system that performs identification and sensitivity simultaneously, usually by a microtiter method.

Disk diffusion (Kirby-Bauer) testing is now used for specific, difficult-to-treat bacteria that do not grow well in the automated media or for testing with antibiotics that are not included in the standard panels.

MIC and MBC

[Know.] The MIC is the concentration of antibiotic that inhibits visible growth (visible turbidity) *in vitro* after 24 hours of incubation. At the 24-hour assessment, some of the broth dilutions that have a higher concentration of drug than the MIC still have organisms growing in them—just not in sufficient numbers to cause turbidity. But, if you subculture the non-turbid cultures that contain higher concentrations of drug for another 48 hours and then reassess growth, you can determine the minimum bactericidal concentration (MBC). The MBC is the concentration of drug that kills $\geq$ 99.9% of the initial inoculum.

An alternative way of testing MIC is with the Epsilometer test (Etest) strip, which uses a gradient of multiple concentrations of an antibiotic on a strip placed on the lawn of the bacteria growing on the agar.

If your patient has a critical bacterial infection, which concentration of antibiotic do you aim to deliver to the site of infection—the MIC or the MBC? Of course, you would prefer the MBC—because you want 99.9% of the infection eradicated. The problem is that the MBC is costly, time-consuming, and less standardized so most microbiology labs do not perform them. However, as a general guideline, the MBC is ~ 8–10x the MIC.

Usually-prescribed drug dosages typically achieve therapeutic blood and tissue levels resulting in a concentration that is around 8–10x the MIC (i.e., the probable MBC) at the patient's site of infection. This dose may not be achievable because of toxicity, and of course you almost never know the concentration of an antibiotic at the actual site of infection.

General Rules of Antibiotic Use

Know these important points:

- Source control is key to treating serious infections. If pus can be drained, do it. Lines, catheters, and devices may need to be removed.
- Pick the drug with the proper spectrum for the suspected or proven pathogen(s) and the site of infection.
- Adjust dosage for body size and clearance when appropriate.

- If the patient does not respond, consider 3 things:
  - Is the patient getting/taking the drug? Is there resistance?
  - Is there an undrained focus of infection?
  - Know the difference between concentration-dependent killing and time-dependent killing.

Concentration-Dependent Killing

Concentration-dependent killing means that killing increases as you increase the concentration of drug above the MIC for the bugs you are treating. This is sometimes referred to as "dose-dependent" killing because killing is based on concentration above MIC, not on time. Aminoglycosides and quinolones are drugs that exhibit concentration-dependent killing.

Quinolones and aminoglycosides also exhibit a post-antibiotic effect (PAE). A PAE is persistent killing of bacteria even after the concentration of drug has fallen below the MIC at the site of infection. The dose-dependent killing and PAE allow these drugs to be dosed once daily, achieving a high peak concentration.

Time-Dependent Killing

In time-dependent killing, the concentration of drug above the MIC does not really matter. Instead, killing is related to how long the concentration of antibiotic remains greater than the organism's MIC at the site of infection (termed "time over MIC"). Beta-lactams, macrolides, and glycopeptides (vancomycin) are such drugs. Aim for serum concentrations above the MIC for > 50% of the dosing interval.

Because beta-lactams are time-dependent, it is not as important to aim for 8–10x the MIC with each dose. Instead, patients need repeated, reliable dosing intervals so they don't have prolonged periods during the dosing interval when their serum levels fall below the MIC. The clinical relevance is that, with time-dependent killing, patients who miss doses risk treatment failure.

BETA-LACTAM ANTIBIOTICS

Overview of the Penicillins

The first of the beta-lactam antibiotics was penicillin (PCN). Its derivatives were created either to increase its spectrum of activity or to address developing bacterial resistance.

The development timeline of these drugs is:

PCN → semisynthetic PCNs → aminoPCNs → extended-spectrum PCNs → aminoPCN/extended-spectrum PCNs + beta-lactamase inhibitors (BLIs).

Development of PCNs

This topic area covers the penicillin-based antibiotics using the above development timeline.

Penicillin

The drug was first mass-produced and used effectively during World War II to treat war wounds. Today, PCN is appropriate mainly for streptococci, sensitive enterococci, *Listeria*, *Pasteurella*, and syphilis. It has decent activity against gram-positive skin flora and some mouth anaerobes, but poor activity against gram negatives and gut anaerobes.

Staphylococci rapidly developed resistance by producing penicillinase, a beta-lactamase enzyme that destroys the drug. These resistant staphylococci are referred to as "methicillin-sensitive" because they were sensitive to the next major drug class to come along which was …

Semisynthetic (Penicillinase-Resistant) Penicillins

Methicillin (and later, **oxacillin**, **nafcillin**, and **dicloxacillin**): These drugs are called "semisynthetic penicillins" and are stable against penicillinase. Semisynthetic penicillins, like nafcillin, are the drugs of choice for *S. aureus* (MSSA), *S. epidermidis* (MSSE), and other coagulase-negative staphylococci.

Today you only rarely encounter a penicillin-sensitive *Staphylococcus*, but if you do, penicillin remains the drug of choice.

The semisynthetic penicillins are good for skin flora but still lack activity against gram negatives. So, the next major drug class to be developed was the …

Aminopenicillins

Ampicillin (and its oral formulation, **amoxicillin**): These drugs are called "aminopenicillins." They retain the efficacy of prior penicillins but also kill some susceptible gram-negative organisms, such as *E. coli* and *Proteus mirabilis*. Therefore, this new class added activity against urogenital and colonic bacteria.

Unfortunately, resistance developed quickly; bacteria started producing other beta-lactamases. Another standing issue was that the aminopenicillins did not kill the more resistant gram-negative rods (GNRs) such as *Klebsiella* and *Pseudomonas*. So, the next major drug class to be developed was the …

Extended-spectrum Penicillins

Piperacillin and **ticarcillin**: These drugs are called "extended-spectrum PCNs" (ES-PCNs) because they take the spectrum of ampicillin and extend it to cover the more resistant GNRs, including *Pseudomonas*. The only problem with these PCNs was the rapid development of resistance via more beta-lactamases. So, the next addition to come along was the …

QuickQuiz

- What is the difference between concentration-dependent and time-dependent killing?
- What is a post-antibiotic effect?
- In time-dependent killing, how long should a patient's serum concentration of a drug be higher than the infecting organism's MIC?
- What is the spectrum of activity of penicillin?
- Nafcillin is the drug of choice for which organisms?
- What coverage does ampicillin add over penicillin? Which important organisms does ampicillin not cover?
- Which organisms do extended-spectrum penicillins cover?
- BLIs are combined with which drugs?
- What is meant by "extended-spectrum penicillins"? Which bacteria do they cover?
- What is a potential complication of nafcillin?

Addition of Beta-lactamase Inhibitors

Addition of a beta-lactamase inhibitor (BLI): Sulbactam, tazobactam, or clavulanic acid—in combination with an aminoPCN or an ES-PCN—protects the PCN from beta-lactamase hydrolysis.

PCN + BLI combinations:

- IV ampicillin + sulbactam = Unasyn®
- Oral amoxicillin + clavulanic acid = Augmentin®
- IV ticarcillin + clavulanic acid = Timentin®
- IV piperacillin + tazobactam = Zosyn®

The drugs retain the activity of the parent PCN, but they are also effective against bacteria that make beta-lactamase. For example, Augmentin does not treat *Pseudomonas* because ampicillin is intrinsically resistant but can treat MSSA.

Extended-spectrum PCNs + BLIs (Aka Anti-Pseudomonal PCNs)

The ES-PCNs with BLIs (Timentin and Zosyn) can be used to treat gram-negative rods (including *Pseudomonas*), gram-positive cocci (including enterococci and MSSA), and both mouth and gut anaerobes. Organisms that are resistant to these drugs can be very difficult to treat.

Evolution of MRSA

Staphylococci eventually acquired the *mecA* gene, which encodes a change in the penicillin-binding proteins that the beta-lactams use to bind the bacteria. *MecA* transcription results in reduced affinity of all beta-lactams for the organisms' cell walls—except for the newest cephalosporin, ceftaroline. The staph that express this gene are called methicillin-resistant staphylococci (methicillin-resistant *S. aureus* [MRSA], methicillin-resistant *S. epidermidis* [MRSE], and other methicillin-resistant coagulase-negative staph).

Vancomycin, daptomycin, and linezolid effectively treat serious MRSA infections. Newer drugs with anti-MRSA activity include ceftaroline, telavancin, and tigecycline. Their exact clinical roles remain to be determined. Mild skin and soft tissue MRSA infections often retain susceptibility to clindamycin, trimethoprim/sulfamethoxazole, or doxycycline.

Next, we will discuss each type of PCN again, but in slightly more detail.

Penicillin Again

Penicillin (PCN), as noted above, has the beta-lactam ring. It is very active against most streptococci (groups A and B, viridans group, and *S. pneumoniae*), *Pasteurella* (animal bites), *Listeria*, and many *Neisseria* species. It is also active against some anaerobes usually found above the diaphragm (e.g., in the mouth; *Prevotella*) but not those found below (e.g., *B. fragilis*). Even though PCN is indicated for meningococcal infections, rifampin or quinolones are better for eradication of the carrier state. Rifampin concentrates in the upper respiratory mucosa.

PCN is still the drug of choice for many infections, including:

- Erysipelas due to *Streptococcus pyogenes* (group A)
- *Streptococcus agalactiae* (group B)
- Viridans streptococci (some are now resistant to PCN and ampicillin)
- PCN-sensitive *S. pneumoniae*
- *Treponema pallidum* (syphilis)
- Leptospirosis
- Actinomycosis
- *Neisseria meningitidis* (bacteremia and meningitis)

Nafcillin and Dicloxacillin Again

Penicillinase-resistant, semisynthetic penicillins (nafcillin, oxacillin, and dicloxacillin) are used to treat methicillin-sensitive *S. aureus* because 85% of the *S. aureus* have this penicillinase. Clinically, nafcillin and oral dicloxacillin are used only to treat MSSA and MSSE.

An important potential complication of these drugs is an immediate (on exposure) IgE-driven anaphylaxis. A less serious complication is a drug rash (which usually occurs several days after exposure). Serious late drug reactions include acute interstitial nephritis. Remember that manifestations of interstitial nephritis are fever, eosinophilia, and rash. Eosinophils may also be found in the urine. Allergic drug reactions are much less common with nafcillin or oxacillin than with methicillin.

Ampicillin Again

Ampicillin has a spectrum similar to PCN, but its spectrum extends to include certain gram-negative rods—especially some *E. coli*, *H. influenzae*, *Salmonella*, *Shigella*, and *Proteus mirabilis*. However, it does not cover *Klebsiella* and resistant isolates of *H. influenzae*, *E. coli*, and *P. mirabilis*.

Ampicillin is the drug of choice for:

- *Listeria monocytogenes*
- Salmonellosis—if sensitive
- UTIs due to susceptible organisms
- Susceptible enterococcal infections

Ticarcillin and Piperacillin Again

Piperacillin (the most commonly used extended-spectrum PCN) is more effective against the gram-negative organisms (including *Pseudomonas*) and anaerobes (including *B. fragilis*). Similar to ampicillin—only more "extended." Remember: A beta-lactamase inhibitor can be added to ticarcillin (Timentin) and piperacillin (Zosyn) to protect the beta-lactam from beta-lactamase hydrolysis. They are the only PCN drugs effective against *P. aeruginosa* and *Acinetobacter*.

Penicillin Allergy Again

Penicillin allergy is often claimed by patients. Know that you can test for this by performing skin testing; a negative skin test has a negative predictive value of > 95% and thus makes a future anaphylactic reaction to penicillin very unlikely. As an alternative, patients can also be desensitized.

Desensitization

Desensitization is a procedure that can be done for any patient with an IgE-mediated immediate hypersensitivity reaction to a medication. Common antibiotics that can cause this reaction are the beta-lactams, quinolones, and clindamycin.

Vancomycin can also cause an IgE-mediated immediate hypersensitivity reaction. However, the "red man syndrome" that may occur with vancomycin is a distinctly separate reaction that is approached differently (page 2-12).

A typical desensitization procedure starts with very tiny oral or IV doses (1/1,000 to 1/10,000 x normal) with increased dosage every 15 minutes. After 4–8 hours, a full dose is reached, and a temporary tolerance to the drug is achieved. The patient can then be given the full course of the antibiotic. This tolerance is lost rapidly once the drug is stopped, so the procedure has to be repeated if the drug is ever given again.

Note: Generally, oral doses are the preferred method, but even with oral doses, the patient must be in a monitored setting where treatment for anaphylaxis (injectable epinephrine and other drugs) is available at the bedside.

Overview of Cephalosporins

Cephalosporins also contain the beta-lactam ring but are inherently penicillinase-resistant because of their structure. They are slightly more difficult to remember than the PCNs—probably the easiest way is to consider them based on their generation category. It is useful to remember that the spectrum of these drugs generally tends to widen and include more GNRs as the generations increase in number. Cephalosporins have no activity against enterococci and *Listeria*. With the exception of ceftaroline, all methicillin-resistant staphylococci are resistant to all cephalosporins.

1st Generation Cephalosporins

1st generation cephalosporins (e.g., IV **cefazolin** and PO **cephalexin**) are active against MSSA and most strep.

Cefazolin and cephalexin are unlike PCN in that they have some coverage against community-acquired GNRs such as *E. coli*, *Klebsiella*, and *Proteus*. (In fact, the GNR coverage is superior to ampicillin.)

1st generation cephalosporins are commonly given for:

- Skin and soft tissue infections from sensitive organisms
- Some surgical prophylaxis
- Oral treatment of mild urinary tract infections

2nd Generation Cephalosporins

Gram-negative coverage increases for most of these drugs with coverage of *H. influenzae* (cefuroxime), *Enterobacter* and *Neisseria gonorrhoeae*. Pneumococcal coverage is retained. Two drugs in this group, **cefoxitin** and **cefotetan**, are noteworthy for their anaerobic coverage. These drugs are used to treat:

- Pelvic inflammatory disease (PID)
- Postoperative abdominal infections

The 3rd generation cephalosporins have largely replaced the 2nd generation except for anaerobic infections (usually due to gut flora).

3rd Generation Cephalosporins

3rd generation cephalosporins are generally stable against most beta-lactamases and have enhanced activity against pneumococci, *H. influenzae*, and *N. gonorrhoeae*. The GNR coverage is also enhanced over previous generations, so these drugs are better for the *Enterobacteriaceae* (*E. coli*, *Klebsiella*, *Proteus*, *Enterobacter*, and *Serratia*).

Remember the following facts about 3rd generation cephalosporins:

- They are great pneumococcus drugs, so they are recommended as 1st line agents for community-acquired pneumonia and PCN-resistant pneumococcal meningitis in combination with vancomycin for empiric treatment.

Quick Quiz

- Which cephalosporins have anaerobic activity?
- 3rd generation cephalosporins are known for their activity against which organisms?
- Which beta-lactam drug can be given to patients with a penicillin allergy?

- None of the drugs are 1st line agents for MSSA; 1st generation cephalosporins or nafcillin/oxacillin are preferred for MSSA.
- None of the drugs cover anaerobes. 2nd generation cephalosporins or PCNs are better.
- **Ceftazidime** is the only 3rd generation drug that has antipseudomonal activity.
- Three of the 3rd generation cephalosporins can cross an inflamed blood-brain barrier; therefore, they are indicated as the primary therapy for meningitis caused by *Enterobacteriaceae*. These are **ceftriaxone** (Rocephin®), **cefotaxime** (Claforan®), and **ceftazidime**.
- Their use has been associated with more *Clostridium difficile* diarrhea than early generations.

4th Generation Cephalosporins

The 4th generation drugs could be considered the broadest in spectrum and the most stable against resistance. **Cefepime** has the gram-negative activity of 3rd generations and gram-positive activity of 1st generations, with enhanced stability against cephalosporinases. It has limited anaerobic coverage.

Be aware of the highly resistant organisms that produce extended-spectrum beta-lactamases (ESBLs) and cause significant infections in hospitalized patients and patients who have been repeatedly exposed to beta-lactams. ESBL production is not always present when a patient first gets the infection. It is often induced by empiric antibiotic treatment with a beta-lactam. These patients may get better initially and then get worse again as their isolate begins to turn on the resistance genes and make ESBLs. However, a clue to the presence of an ESBL isolate is the selective *in vitro* susceptibility to cefepime, when the isolate is resistant to all other beta-lactams. Currently, a carbapenem (imipenem or meropenem) is the drug of choice for empiric ESBL therapy.

5th Generation Cephalosporins

The only 5th generation cephalosporin currently FDA-approved is **ceftaroline**. Its main advantage is that it is the only cephalosporin that covers MRSA skin infections. It cannot be used to treat *Pseudomonas* infections.

Monobactams

Aztreonam is the only monobactam beta-lactam. It covers only gram-negative bacteria, including *Pseudomonas*. Its spectrum is similar to aminoglycosides and 3rd generation cephalosporins. It is not active against gram-positive cocci or anaerobes. This drug can be used in patients with beta-lactam allergy, which is its niche. It is available for intravenous or inhaled use only.

Carbapenems

Overview

Imipenem, **meropenem**, **ertapenem**, and **doripenem** are broad-spectrum beta-lactams recommended only for use in complicated infections involving multiple organisms (such as in the abdomen or the diabetic extremity with possible bacteremia) and for empiric treatment of the very sick.

Carbapenemases

Carbapenemases are carbapenem-hydrolyzing beta-lactamases that confer carbapenem resistance. Various forms of these have been identified over the last several years.

Be aware that very resistant GNR isolates with carbapenemases are emerging—with resistance to all beta-lactams, including the carbapenems. These very resistant organisms sometimes colonize the GI tract. Generally, we rely on the carbapenems to provide coverage for the most resistant organisms, so this discovery is very discouraging.

The most critical characteristic of these very resistant organisms is their predilection for spreading—causing community-acquired infections (especially *E. coli*) and nosocomial infections (especially *K. pneumoniae*).

Individual Carbapenems

Imipenem covers most bacterial classes: gram-positive cocci (GPC); GNRs, including *Pseudomonas* and other resistant GNRs; mouth and gut anaerobes (*B. fragilis*). It also is effective against ESBL-producing organisms.

The few organisms resistant to it include:

- *Enterococcus faecium*
- *Burkholderia cepacia*
- *Corynebacterium jeikeium* (JK)
- *Stenotrophomonas maltophilia*
- *Acinetobacter species*
- MRSA

Also, remember that although *E. coli* and *K. pneumoniae* are typically sensitive to imipenem; the carbapenemase-producing variety can spread easily and cause major problems.

Resistance is increasingly common in *Pseudomonas* isolates especially in those patients with recurrent infections such as patients with cystic fibrosis.

[Know:] Imipenem can lower the seizure threshold, so it should not be used in patients with seizures and advanced-stage chronic kidney disease.

Imipenem is always formulated with equal amounts of cilastatin (combo = Primaxin®). Cilastatin is an enzyme inhibitor that impairs the metabolism of imipenem in the renal tubule, thereby increasing its half-life to 1 hour. Cilastatin is not a beta-lactamase inhibitor.

Meropenem is a similar carbapenem with a longer half-life, so there is no need for an enzyme inhibitor.

Doripenem is the newest carbapenem and has similar activity and pharmacokinetics to meropenem.

Ertapenem is a carbapenem with once-daily dosing but no activity against *Pseudomonas*. Otherwise its spectrum is similar to the other carbapenems.

Because it is available as once-daily dosing, it is useful for outpatient parenteral treatment, especially of diabetic feet, and for abdominal, pelvic, and skin and soft tissue infections.

Understand that once-daily dosing is a big deal for a beta-lactam because these drugs usually exhibit time-dependent killing; hence, most have frequent-dosing schedules.

OTHER ANTIBIOTICS

Vancomycin

Vancomycin is a glycopeptide antibiotic that is effective against most gram-positive organisms, including MRSA, MRSE, *Clostridium*, and *Corynebacterium*. It is a large molecule that diffuses poorly into most tissues with only about 1/8 of the blood concentration reaching the site of infection. It exhibits time-dependent killing, so pre-dose ("trough") levels are measured to assure that they are about 8 times the usual cutoff for susceptibility (2 μg/mL), as well as to limit toxicity. For most serious infections, pre-dose levels between 15 and 20 μg/mL are recommended.

Clearance of vancomycin in patients undergoing hemodialysis may vary widely depending on the membranes used, so levels are needed to guide dosing.

Some strains of enterococci are vancomycin-resistant. MICs are increasing in staphylococci but vancomycin-resistant staphylococci (MIC ≥ 16 μg/mL) are exceedingly rare. However, increases in the MIC that are still within the susceptible range (1–2 μg/mL) are associated with vancomycin treatment failure. Some experts suggest using an alternative drug to treat the infection; e.g., linezolid or daptomycin. (Remember that daptomycin is inactive in the lungs, so linezolid should be used for vancomycin-resistant staph pneumonia.) It remains controversial whether to start an alternative agent as soon as the MIC is available or wait for clinical outcome. Staphylococci with an MIC between 2 and 8 μg/mL for vancomycin are considered to have intermediate susceptibility, and alternative drugs should be used if possible.

Vancomycin sometimes (when it is rapidly infused) causes the "red man syndrome," consisting of tachycardia, flushing, occasional angioedema, and generalized pruritus. It is an infusion-rate–related phenomenon that is usually associated with mast cell degranulation and release of histamine. The red man syndrome is not a true allergy. Patients who experience this reaction can be retreated with the drug if it is infused more slowly. Pretreat these patients with H1 blockers. Previous formulations of vancomycin had significant renal and ototoxicity; current formulations rarely cause toxicity at normal doses (< 4 g/day).

The sole indication for oral vancomycin is *C. difficile* (pseudomembranous) colitis. IV vancomycin is not effective for *C. difficile*.

Oxazolidinones

Linezolid is the only oxazolidinone on the U.S. market.

Linezolid is a bacteriostatic agent active against gram-positive organisms, including MRSA, MRSE, and VRE (vancomycin-resistant enterococci). Linezolid has no indication for bacteremia. Linezolid is available in oral (with 100% bioavailability) and IV preparations.

The oral form of linezolid makes it a desirable alternative to vancomycin for MRSA; however, due to concerns about cost and developing resistance, as well as an unfavorable side-effect profile (below), this drug is a 2nd line agent for MRSA. Vancomycin remains the current drug of choice for MRSA treatment when the MIC is < 1 μg/mL. For staphylococcal isolates with a vancomycin MIC ≥ 1 μg/mL, the antibiotic is usually switched to linezolid or daptomycin. For a MIC ≥ 2 μg/mL, the antibiotic is always switched to linezolid or daptomycin.

Linezolid can cause reversible thrombocytopenia, anemia, and leukopenia, especially if the patient has been taking it > 2 weeks. It is also associated with development of a sensory neuropathy.

Know that linezolid can cause very serious CNS effects (serotonin syndrome) when used concurrently with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Daptomycin

Daptomycin is a cyclic lipopeptide active against gram-positive organisms. It is indicated for treatment of skin and soft tissue infections, bacteremia, and right-sided endocarditis caused by MSSA or MRSA (see above).

It is a parenteral drug with a long half-life that allows once-daily dosing. Generally, it is reserved for resistant organisms such as MRSA and VRE. Know that daptomycin is inactivated by pulmonary surfactant and thus is not effective in treating pneumonia. A potential complication of use is myopathy, so be careful with patients who are also taking a statin drug. Monitor CK levels at least weekly during use.

QuickQuiz

- Which carbapenem should be avoided in those with seizures?
- Ertapenem is useful for treating diabetic infections in what type of setting?
- What are the drugs of choice for staph pneumonia with a vancomycin MIC > 2 µg/mL?
- What are potential complications of linezolid use?
- Aminoglycosides exhibit what type of killing?
- What can happen to a ciprofloxacin if it is dosed with a multivitamin?
- The use of which class of antibiotics is associated with tendon rupture?
- What happens to the concentration of theophylline if a patient is also prescribed erythromycin?

Tigecycline

Tigecycline is the first of the new class of antibiotics called glycylcyclines, which are derivatives of tetracycline. It is broad-spectrum with activity against gram-positive organisms (including VRE, MRSA), anaerobes, and gram-negative rods. It has some coverage against ESBL-producing GNRs; however, it is not active against *Pseudomonas* and has reduced activity against *Proteus* and *Providencia*.

Tigecycline is indicated for complicated skin and soft tissue infections and intraabdominal infections. Give IV. Nausea and vomiting are its main side effects, occurring in > 20% of patients.

Aminoglycosides

Aminoglycosides (AGs; **gentamicin, tobramycin, amikacin, streptomycin)** are effective against the following:

- Aerobic GNRs (but not anaerobic GNRs such as *B. fragilis*)
- *Yersinia pestis* (plague)
- *Francisella tularensis* (tularemia)
- *Brucella species* (brucellosis)
- *M. tuberculosis*
- *M. avium-intracellulare*

AGs are also used to treat patients with febrile neutropenia, in combination with a 3rd generation cephalosporin or an ES-PCN + BLI when local beta-lactam resistance rates are too high to trust beta-lactam monotherapy.

These drugs exhibit concentration-dependent killing and a considerable post-antibiotic effect. Hence, they are best dosed once daily after a loading dose. Potential complications of use include oto- and nephrotoxicity—more likely if amphotericin B is also used.

Fluoroquinolones

Ciprofloxacin, levofloxacin, moxifloxacin, and **gemifloxacin** are the FDA-approved fluoroquinolones. Gemifloxacin is available only in oral form; the other 3 have both IV and oral forms. The oral bioavailability is ~ 100%.

Think of ciprofloxacin as a gram-negative only agent, with fairly good *Pseudomonas* activity. Ciprofloxacin should not be used for empiric *S. pneumoniae* coverage. On the other hand, levofloxacin and moxifloxacin are approved for *S. pneumoniae*; i.e., respiratory infections.

Moxifloxacin is less active than the others against GNRs, but it is the most active quinolone for *M. tuberculosis* and is active against most anaerobes.

Know the following side effects, complications, and contraindications of fluoroquinolones:

- They are chelated by cations (Mg^{+2}, Ca^{+2}), so certain vitamins and laxatives may reduce their absorption.
- They can increase theophylline levels.
- Do not give to pregnant/lactating patients or children. (FDA says no one < 18 years of age; except ciprofloxacin is now approved for 2nd line therapy in children with UTIs and patients with cystic fibrosis.)
- Do not use them to treat MRSA, even if susceptibility testing shows that the isolate is sensitive—because of the possibility of development of resistance.
- Quinolones predispose to tendonitis and tendon rupture (especially the Achilles tendon in older adults).
- Peripheral neuropathy that may be irreversible has been reported.

Macrolides

Three macrolides are currently available: **erythromycin, clarithromycin,** and **azithromycin**.

Erythromycin is effective against:

- *Mycoplasma pneumoniae*
- *Chlamydophila pneumoniae*
- *Campylobacter*
- Diphtheria
- Pertussis

It is less effective against *H. influenzae* and is not effective against Q fever (*Coxiella burnetii*), which you would treat with tetracycline. It increases intestinal motility; GI side effects may be poorly tolerated by patients.

Erythromycin increases the concentrations of theophylline, cyclosporine, and warfarin.

Clarithromycin and azithromycin have better *S. pneumoniae* and *H. influenzae* coverage than erythromycin and have better GI tolerance. Clarithromycin is available only orally, but azithromycin comes in both IV and oral formulations and has a very long half-life that allows for once-daily dosing.

ANTIVIRAL AGENTS

Acyclovir is a nucleoside analog used for the treatment of herpes simplex and varicella-zoster viruses. Treatment of zoster infections requires higher doses. High doses can cause renal failure.

Valacyclovir and **famciclovir** are oral antivirals that also treat herpes simplex and varicella-zoster infections. Only acyclovir is available intravenously and is used to treat severe infections. Valacyclovir and famciclovir drugs are used primarily for less-frequent dosing of outpatients. They are considerably more expensive than acyclovir.

Ganciclovir is used to treat cytomegalovirus (CMV) infections in post-transplant patients and those with HIV/AIDS. Typical CMV infections are retinitis, encephalitis, pneumonitis, colitis, and, occasionally, severe bone marrow suppression (neutropenia and thrombocytopenia). This drug is preferred over foscarnet and cidofovir.

Valganciclovir is an oral preparation similar to ganciclovir but with better absorption, leading to blood levels comparable to IV ganciclovir.

Foscarnet is used in patients with ganciclovir-resistant herpes infection or as an alternative to ganciclovir for CMV. Foscarnet toxicity includes decreases in serum potassium, calcium, magnesium, and phosphorus along with renal failure.

Ribavirin is used as part of combination therapy for hepatitis C. It may cause significant hemolytic anemias, requiring downward dose adjustments.

Amantadine and **rimantadine** ("adamantanes") were used to treat influenza A in the past but are no longer recommended because of resistance (unless you are certain your strain is susceptible). They are ineffective against influenza B. Occasionally, these drugs are useful against oseltamivir-resistant influenza A. One side effect is CNS/psychiatric toxicity, especially with amantadine.

Oseltamivir and **zanamivir** are neuraminidase inhibitors that treat both influenza A and B. Resistance to oseltamivir is more common than resistance to zanamivir; however, overall, these drugs are preferred to the adamantanes---depending on local resistance patterns.

See page 2-47 for the antiretroviral medications.

ANTIFUNGAL AGENTS

There are 4 major classes of antifungal medicines: polyenes, imidazoles, triazoles, and echinocandins.

Polyenes (Amphotericin and Nystatin)

Amphotericin B deoxycholate used to be the standard treatment for most systemic mycoses. Currently, it has been mostly replaced by lipid polyene formulations, echinocandins, and azoles. It is given IV only and has many side effects: fever, renal failure, anemia, phlebitis, renal tubular acidosis, and low K^+ and Mg^{2+}. Infusion-related chills and fevers ("shake and bake") may be severe. Some recommend giving a test dose first. Hypotension with the 1st dose may occur (decrease in peripheral vascular tone).

Liposomal amphotericin B preparations are less nephrotoxic and have less infusion-related side effects, but are much more expensive. They are used primarily when toxicity has become a problem with the amphotericin deoxycholate preparation. However, lipid preparations may be better for some fungal infections, especially those that enter the reticuloendothelial system, such as cryptococcal meningitis and disseminated histoplasmosis. Lipid ampho B is also used to treat zygomycosis (*Mucor* and *Rhizopus*) because you can give higher doses of the preparation without nephrotoxicity.

Topical polyene macrolides are **nystatin** and **amphotericin B**. These are effective only against mucocutaneous candidiasis (not ringworm). Both are also available in liquid form for oral and esophageal candidiasis.

Imidazoles

Ketoconazole is an oral and topical preparation that is rarely used because there are better drugs now. Increased gastric pH (low acid) decreases oral absorption, so do not prescribe to patients taking H_2 blockers or proton pump inhibitors (PPIs). Ketoconazole does not penetrate CSF well and increases levels of indinavir and digoxin, with potentiation of benzodiazepines. Side effects of oral medication include nausea and hepatitis. It also causes a decrease in androgen production; hence, patients may have decreased libido, and males may get gynecomastia.

Ketoconazole has many, sometimes dangerous, interactions with common drugs. For serious fungal infections, it has largely been replaced by fluconazole or itraconazole. It is used rarely to treat refractory tinea infections.

Clotrimazole and **miconazole** are available in both cutaneous and vaginal preparations (e.g., for vaginal candidiasis). Many other preparations are also available. They are used to treat cutaneous candidiasis, tinea versicolor, and ringworm.

Triazoles

Itraconazole is a triazole analog of ketoconazole and is generally more effective and safer. Capsules should be taken with food; a cola drink (acidity) helps with absorption. Always check levels when using itraconazole. The liquid formulation has much better bioavailability; but food decreases absorption, so take liquid on an empty stomach. Indications include endemic fungi (histoplasmosis [including chronic suppressive therapy for disseminated disease], blastomycosis, coccidioidomycosis, and cryptococcosis), oral and esophageal candidiasis (especially if fluconazole-resistant), and sporotrichosis.

Fluconazole is indicated for oral and esophageal candidiasis, candidemia (for susceptible isolates), disseminated candidiasis, cryptococcosis, and vulvovaginal candidiasis.

QuickQuiz

- What class of drugs should no longer be used to treat influenza A?
- Liposomal amphotericin B preparations are used in what circumstances? Against which fungi?
- Which candidal species are resistant to fluconazole?
- What are the indications for voriconazole?
- What are the indications for caspofungin?

It has excellent penetration into the CSF. It should never be used as empiric antifungal treatment in febrile neutropenic patients. Know the candidal species that are either entirely resistant (*C. krusei*) or have some degree of resistance (*C. glabrata*).

Be aware that fluconazole has many interactions.

Voriconazole is a triazole with an extended antifungal spectrum, including *C. glabrata* and *C. krusei*, *Aspergillus*, *Fusarium*, and *Scedosporium* (*Pseudallescheria*). The drug can be given orally or IV. Voriconazole is 1st line therapy for invasive aspergillosis. Major toxicity is transient, reversible alterations in visual acuity and color vision. It happens in about 30% of patients 30 minutes after administration and lasts 30 minutes (30-30-30 rule). Check voriconazole serum levels whenever you are treating a serious infection because significant variations in levels occur from person to person.

Posaconazole is the newest triazole with the extended antifungal spectrum of voriconazole, and it has additional activity against the zygomycetes (e.g., *Rhizopus*, *Mucor*). It is FDA-approved for prophylaxis of *Aspergillus* and *Candida* infections in those with severe immunocompromised states, including prolonged neutropenia or stem cell transplant recipients with graft-versus-host disease. It may be used for treatment of oropharyngeal candidiasis (particularly organisms refractory to itraconazole or fluconazole), invasive *Aspergillus*, and zygomycetes. It is an oral agent that requires tid or qid dosing. Check posaconazole levels, and make sure that patients take it consistently with a high-fat meal.

Terconazole is the only vaginal triazole formulation for vulvovaginal candidiasis. Oral **fluconazole** is very effective as a single dose and is usually used instead of topical agents.

Echinocandins

Echinocandins inhibit beta-1,3-glucan, an essential component of the cell walls of several fungi, including *Aspergillus*.

Caspofungin acetate is approved for:

- Candidemia and *Candida* infections of the abdomen, peritoneum, pleural space, and fluconazole-resistant esophagitis
- Invasive aspergillosis in severely immunocompromised patients who are intolerant of lipid amphotericin B or voriconazole

Micafungin (Mycamine®) is similar to caspofungin but does not require a loading dose and seems to have fewer drug interactions.

Anidulafungin (Eraxis™), the newest echinocandin, has similar activity to the other agents.

Most experts use an echinocandin as their drug of choice for empiric antifungal therapy in febrile neutropenic patients.

Other Antifungals

Flucytosine (5-fluorocytosine; 5-FC) is highly soluble and penetrates well into the CSF. Upon entering a fungal cell, it is metabolized to the antimetabolite 5-fluorouracil. If used alone, drug resistance develops quickly.

Amphotericin B used in combination with 5-FC both decreases drug resistance development and has a synergistic antifungal effect. This combination is used to treat cryptococcosis and serious forms of candidiasis.

Note that 5-FC can cause serious GI, hepatic, renal, and bone marrow toxicities—the latter usually presents as neutropenia and thrombocytopenia. Slight decreases in renal function can increase 5-FC to toxic levels.

ANTIPARASITIC DRUGS

Praziquantel (Biltricide®) is the only drug effective against all species of *Schistosoma*. It is effective against flukes and tapeworms. It is a 2nd line drug to treat neurocysticercosis (brain cysts) caused by the pork tapeworm, *T. solium*.

Albendazole is used for intestinal round worms (*Ascaris*), cysticercosis, and schistosomiasis. It should be used only in non-pregnant patients.

Niclosamide is a 2nd line drug used for the treatment of tapeworm.

Pentamidine is effective against trypanosomiasis (e.g., African sleeping sickness). For *Pneumocystis jiroveci,* which is a fungus and not a parasite, it is given via IV for treatment or via inhalation for prophylaxis. It is not recommended as a 1st line drug for treatment because of the many side effects, including azotemia, leukopenia, pancreatitis, and hypo- or hyperglycemia.

Nitazoxanide is approved for treatment of *Giardia lamblia* and *Cryptosporidium parvum*. Other antifungals for giardiasis include tinidazole, albendazole, and metronidazole with paromomycin.

Antimalarial drugs: See Malaria, page 2-33.

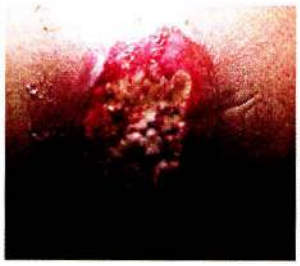
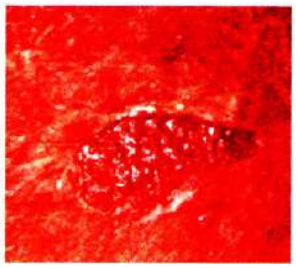


Image 2-1: Carbuncle on buttock



Courtesy of Vgaliswad, MD

Image 2-2: Staphylococcal scalded skin synd.

BACTERIA

GRAM-POSITIVE ORGANISMS

Staphylococci

Overview

S. aureus is the most common cause of soft tissue infections. *Staphylococcus* is the usual cause of folliculitis, furuncles, and carbuncles (aka skin abscesses or boils; Image 2-1), and impetigo. Patients often inaccurately report a "spider bite" when in fact they have a staphylococcal boil. The primary treatment for boils is to incise and drain the infection. Purulent drainage associated with surrounding cellulitis may also need to be treated with trimethoprim/sulfamethoxazole, a tetracycline, linezolid, or clindamycin, given orally.

S. aureus is also an important cause of bacteremia, especially among those exposed to needles such as IV drug abusers, insulin-using diabetics, hospitalized patients, and dialysis patients. In addition, it is a leading cause of hospital-acquired (line-related) bacteremia. Infection with *S. aureus* may also result in toxic shock syndrome (TSS) and scalded skin syndrome (SSS; Image 2-2). The latter does not occur in adults unless they have chronic kidney disease, because the toxin is otherwise easily renally excreted.

Pathogenicity is associated with production of entero- and exotoxins, coagulase, and leukocidin. In chronic carriers, *S. aureus* resides on the nasal mucosa.

The percentage of MRSA infections has grown substantially due to indiscriminate beta-lactam use. In almost all hospitals, the majority of *S. aureus* isolates are MRSA. Unfortunately, MRSA is now the most common community-acquired *S. aureus* as well, presenting primarily as skin and soft tissue infections, but occasionally pneumonia.

Nasal mucosal colonization is difficult to eradicate; eliminating nasal carriage is of uncertain benefit in non-outbreak situations. The typical regimen is intranasal topical mupirocin and washing with chlorhexidine scrub.

Toxic Shock

An important complication of *S. aureus* infection is staphylococcal toxic shock syndrome (TSS). TSS presents with red skin (sunburn-like rash), hypotension, and fever along with 3 or more signs of organ system involvement: GI (vomiting, diarrhea), muscle (myalgia or elevated CPK), acute kidney injury, liver (transaminase or bilirubin elevation), thrombocytopenia, or altered consciousness. Hypocalcemia may also occur. The classic association is with tampon use during menses; however, currently about half of staphylococcal TSS cases are not menstrual. Supportive care; source control, including removal of infected devices; and antibiotics are indicated.

Streptococcal TSS is the other classic form of TSS. It is a complication seen in about 1/3 of invasive infections with *Streptococcus pyogenes* (group A strep). Risk factors include trauma, surgery, and viral infections.

Note: In staph TSS, blood cultures are usually negative, whereas in strep TSS, blood cultures are usually positive.

MRSA Treatment

MRSA bacteremia and other serious MRSA infections are initially treated with vancomycin. Vancomycin remains the drug of choice for skin and moderate-to-severe soft tissue infections and invasive MRSA. Organisms with an MIC ≤ 2 μg/mL are considered "susceptible," but treatment failures are more common as the MIC climbs over 1 μg/mL. Because of this, many ID experts now recommend alternative drugs (linezolid or daptomycin) to treat isolates with MIC > 1 μg/mL in invasive disease. Tigecycline and linezolid are not indicated in MRSA bacteremia; so, for now, do not use them to treat endocarditis/bacteremia.

Linezolid and daptomycin are very expensive, and in general are not considered except as 2nd line agents and in vancomycin-resistant isolates.

Treatment for Other *Staphylococcus aureus* Infections

In nonbacteremic, mild-to-moderate MRSA skin and soft tissue infections, other antibiotics are effective, including TMP/SMX, clindamycin, or doxycycline. There is increasing resistance to quinolones.

Staphylococcus epidermidis and *Staphylococcus saprophyticus*

S. epidermidis and *S. saprophyticus* are examples of coagulase-negative staph. *S. epidermidis* is almost always methicillin-resistant. It is the most common cause of both catheter-related bacteremia and bacteremia occurring post-op when a foreign body (e.g., prosthetics, including heart valves and joints, pacemakers, shunts) is placed. Treatment is with vancomycin. Add rifampin and gentamicin for prosthetic valve endocarditis. *S. saprophyticus* causes cystitis in young women and, unlike other coagulase-negative staph, is usually susceptible to anti-staphylococcal penicillins and ampicillin.

Quick Quiz

- What is the clinical presentation of toxic shock syndrome?
- How do blood culture results differ between staphylococcal and streptococcal toxic shock?
- What is the drug of choice for initial treatment of MRSA bacteremia (until MIC results are available)?
- MRSA treatment failure is associated with organisms with what MIC?
- What antibiotics are useful to treat skin and soft tissue staph infections?
- What are the drugs of choice for treatment of PCN-susceptible pneumococci?
- What are the treatments of choice for empiric treatment of bacterial meningitis in adults?
- What clinical findings are associated with group A beta-hemolytic streptococcal pharyngitis?

Streptococcus pneumoniae

Pneumococcal Pneumonia

S. pneumoniae remains the most common cause of community-acquired pneumonia. Resistance to penicillin (PCN MIC ≥ 8 µg/mL [≤ 2 = susceptible]) occurs in 5% of *S. pneumoniae* isolates.

Penicillin-susceptible (or intermediately susceptible) strains are treated with penicillins or a 3rd generation cephalosporin.

PCN-resistant pneumonia can be treated with a 3rd generation cephalosporin, respiratory quinolone (levo-, or moxifloxacin), vancomycin, or linezolid. See specifics under Community-Acquired Pneumonia in Pulmonary Medicine, Book 2.

Pneumococcal Meningitis

S. pneumoniae is also the most common cause of bacterial meningitis in adults. Empiric treatment for community-acquired meningitis should include a 3rd generation cephalosporin (generally ceftriaxone) and vancomycin in case there is any beta-lactam resistance.

Focused treatment for susceptible pneumococcal isolates should be with high doses of ceftriaxone or cefotaxime. Cephalosporin-resistant isolates should be treated with vancomycin.

Splenectomy and *S. pneumoniae*

Remember: You need a functioning spleen and an ability to make antibodies to defend against encapsulated *S. pneumoniae* and *H. influenzae*—so both infections are seen more often in asplenic patients (including those with sickle cell [SS] disease), very young and old patients, and in CLL, MM, and agammaglobulinemia. Alcoholics also are more susceptible, but not because of antibody problems.

Post-splenectomy pneumococcal sepsis presents as nonspecific sepsis, purpura, and DIC. It can be rapidly fatal. Howell-Jolly bodies, indicative of the asplenic state, are often seen on peripheral smear.

Streptococcus pyogenes (Group A)

S. pyogenes is the only group A beta-hemolytic strep species. It causes pharyngitis (Image 2-3), TSS, and rapidly progressive cellulitis that spreads through lymphatics (erysipelas; Image 2-4) or along fascial planes (necrotizing fasciitis), or scarlet fever. Immune reaction to a cell surface protein, called the "M protein," can lead to rheumatic fever or post-streptococcal glomerulonephritis.

Strep pharyngitis (usually *S. pyogenes*) is cumulatively more likely with each of these 4 findings (the Centor criteria):

1) Temp > 100° F
2) Tender anterior cervical lymphadenopathy
3) Exudative tonsils
4) Absence of cough

If none of these is present, the chance that pharyngitis is due to *S. pyogenes* is <3%; 1 = 7%; 2 = 21%; 3 = 38%; and 4 = 57%. Adults with 3 or 4 of the Centor criteria should have rapid antigen testing and, if negative, should not receive antibiotics and should not be cultured. The rapid antigen testing is very specific for *S. pyogenes* (≥ 95%), so all patients with positive results should be treated. In adults, if you suspect streptococcal pharyngitis just do a rapid strep test; do not do a strep culture.

According to the IDSA 2012 recommendations, findings suggestive of viral pharyngitis include: rhinorrhea, cough, hoarseness, and oral ulcers. Adults with more than 1 of these should not be tested or treated for *S. pyogenes* pharyngitis. Viral causes of acute pharyngitis (other than acute HIV infection) rarely have effective treatment and rarely warrant treatment. Suspect acute HIV infection as a cause of pharyngitis in sexually active adults, men who have sex with men, sex workers, or injection drug users. More often, however, viral pharyngitis is due to a benign upper respiratory infection or EBV (see page 2-41).

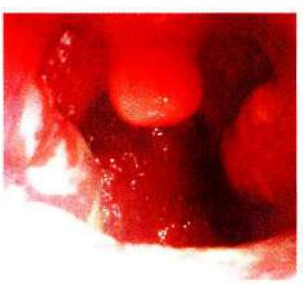


Image 2-3: Streptococcal pharyngitis

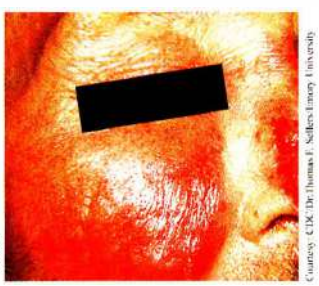


Image 2-4: Erysipelas

All patients with *S. pyogenes* pharyngitis should be treated with a penicillin; there is no resistance. Treatment shortens the duration of illness, decreases transmission, decreases suppurative complications (e.g., peritonsillar abscess), and prevents rheumatic fever (discussed later). There is no convincing evidence that treatment prevents post-streptococcal glomerulonephritis. PCN-allergic patients can be treated with clindamycin or azithromycin.

Streptococcus agalactiae (Group B)

S. agalactiae (group B) is more common in the elderly, especially if they are alcoholic or diabetic. It is a common cause of neonatal pneumonia and the most common cause of neonatal meningitis. In pregnant women, *S. agalactiae* causes UTIs and is also a cause of postpartum endometritis and bacteremia. It originates from a GU reservoir. Treat with PCN or ampicillin; in PCN-allergic patients, treat with clinda- or vancomycin.

Group D Streptococci

Group D streptococci (*S. bovis/S. equinus* complex) includes 4 species that are inhabitants of the GI tract and cause bacteremia and endocarditis. Group D streptococcus bacteremia is associated with colon cancer in 20–30% of cases, so positive blood cultures from this organism warrant a colonoscopy.

Enterococci

Enterococci are gram-positive cocci that are difficult to distinguish from streptococci under the microscope. Similar to streptococci, they occur in pairs and short chains. Two species normally inhabit the intestines with a higher amount of *Enterococcus faecalis* (95%) than *Enterococcus faecium* (5%). Similarly, *E. faecalis* causes the vast majority of enterococcal infections (e.g., UTIs, bacteremia, endocarditis, meningitis, and intra-abdominal).

All enterococci are resistant to cephalosporins and penicillinase-resistant penicillins. They are moderately resistant to the aminoglycosides such as gentamicin, but these drugs are commonly used for synergy in the treatment of endocarditis.

E. faecium is one of the few organisms resistant to imipenem and commonly exhibits high-level resistance to vancomycin (vancomycin-resistant *Enterococcus* [VRE]). The incidence of VRE is dependent on the local setting and the use of other antibiotics in the population being treated. VRE is more common in patients with liquid tumors and stem cell recipients.

Single antibiotics are used to treat mild-to-moderate infections (urinary tract infections and uncomplicated bacteremia) and include PCN G, ampicillin, or vancomycin, depending on sensitivities.

Combination treatment is used for complicated bacteremia and endocarditis because single drugs are not bactericidal. In these cases, check the isolate for gentamicin susceptibility, and if susceptible, add low-dose gentamicin.

Review treatment of enterococcal infections:

- Simple enterococcal infections = PCN G, ampicillin, or vancomycin (depending on resistance testing).
- Bacteremia (sepsis or endocarditis) = PCN G or ampicillin or vancomycin + low-dose gentamicin (if susceptible).

Listeria

Listeria monocytogenes, an anaerobic gram-positive rod, causes listeriosis, which is seen in patients with decreased cellular immunity such as AIDS, lymphoma, and leukemia. Also, these infections are associated with drugs that depress cellular immunity (glucocorticoids, transplant drugs). Listeriosis is also seen in neonates, the elderly, and pregnant women.

Listeria is one of the most virulent foodborne pathogens, and the mortality rate is ~ 15%. It may be found in deli meats, hot dogs, milk, soft cheeses, poultry, and even fruit. In 2011, an outbreak of *Listeria* in cantaloupe from a farm in Colorado resulted in 30 deaths.

Listeria can cause neonatal meningitis via transvaginal inoculation and also can affect the fetus. For this reason, pregnant women are cautioned against eating soft cheeses, unpasteurized milk, etc.

Like *Enterococcus*, *Listeria* is resistant to all cephalosporins, which is why you always include ampicillin in the empiric treatment for meningitis in the elderly, immunosuppressed, or neonates. Treat mild-to-moderate cases of listeriosis with PCN or ampicillin. PCN-allergic patients should receive TMP/SMX. Vancomycin and chloramphenicol are 3rd line drugs. Although no randomized trials have been conducted, addition of an aminoglycoside to treat meningitis is often done.

Corynebacterium diphtheriae, JK, and *Arcanobacterium haemolyticum*

Corynebacterium diphtheriae (Image 2-5) causes diphtheria. Diphtheria is an upper respiratory infection with a gray-white pharyngeal pseudomembrane (Image 2-6), hoarseness, sore throat, and a low fever (< 101° F). Toxin production causes myocarditis with heart failure and polyneuritis. Treatment is erythromycin. 2nd choice is penicillin. Diphtheria antitoxin is always given with the antibiotic.

Corynebacterium jeikeium (JK) is seen in neutropenic patients and in bone marrow transplant patients, where it causes IV catheter-related infections. It is resistant to most drugs. Vancomycin is the drug of choice.

Arcanobacterium haemolyticum causes pharyngitis in adolescents, similar to that of *S. pyogenes*, with a desquamative scarlatiniform rash and lymphadenitis. Treat with PCN, erythromycin, or tetracycline.

QuickQuiz

- When should you use 2 antibiotics to treat enterococcal infections? Which drugs would you choose?
- Which patient populations are at risk for *Listeria*?
- Treatment of serious *Listeria* infections includes which drug?
- What are the clinical manifestations of anthrax?
- Inhalation anthrax is associated with what important x-ray finding?
- What is the time of onset of vomiting due to *B. cereus* toxin ingestion?

Bacillus anthracis and *Bacillus cereus*

Bacillus anthracis is a large, gram-positive rod that causes anthrax, a potential agent of bioterrorism.

There are 3 main clinical manifestations:

1) Cutaneous (95%)
2) Inhalation ("woolsorters' disease")
3) Pharyngeal + gastrointestinal

Inoculation occurs from handling naturally contaminated hides/wool or, more recently, maliciously contaminated sources (e.g., mail or food).

Unlike plague (discussed later), anthrax is not transmitted person to person.

Cutaneous anthrax starts as a painless papule that vesiculates and forms a painless papule, then ulcer (Image 2-7), then a painless black eschar, often with nonpitting, painless induration (Image 2-8).

Inhalation anthrax presents similarly to influenza with malaise, fever, and myalgias. After 2–3 days, there is a dramatic worsening of symptoms with hypoxia, hypotension, and death. An important diagnostic finding with inhalation anthrax is mediastinal widening.

Gastrointestinal anthrax is acquired by eating undercooked, contaminated meat. Patients get pharyngeal eschars and/or gastrointestinal ulcerations.

Anthrax is usually sensitive to clindamycin, tetracycline, and quinolones (given with or without rifampin).

Bacillus cereus is a close relative of *Bacillus anthracis*. Emetic toxin (cereulide) and enterotoxin-producing strains cause gastroenteritis of 2 varieties:

1) A short incubation (1–6 hr) emetic type in which the emetic toxin is preformed in the food ingested
2) A longer incubation (8–16 hr) diarrheal type in which the enterotoxins are produced *in vivo* in the small intestine

The emetic form is associated with fried rice not cooked at a high enough temperature to kill the organism and then left too long at room temperature, which allows the organism to make the emetic toxin, which cannot be destroyed by reheating. Similar to *S. aureus*, the emetic toxin is produced outside the host, is preformed in foods, and therefore provokes a rapid onset of symptoms (1–6 hr). Vomiting is universal with diarrhea occurring in only 1/3 of cases. Symptoms generally resolve in 12–24 hours. No specific therapy is necessary.

The diarrheal form is caused by toxin produced *in vivo* after ingestion of the bacilli. It results in a profuse, watery, non-bloody diarrhea accompanied by abdominal pain and cramps, nausea, and vomiting (less common). The incubation period is 8–16 hours, and it resembles *C. perfringens* food poisoning. Symptoms usually resolve in 12–24 hours. No specific therapy is necessary.

B. cereus is rarely an invasive organism. It occasionally causes infection in contact lens wearers, after a traumatic eye injury, and in patients with IV catheters. Treatment for serious disease is vancomycin.

Clostridium

Clostridium species are anaerobic gram-positive rods that cause a wide variety of human illness:

- *C. difficile* causes antibiotic-associated colitis. (See page 2-62.)
- *C. botulinum* causes botulism—it releases a powerful paralytic toxin. The toxin blocks presynaptic acetylcholine release causing weakness and parasympathetic cranial nerve dysfunction.
- *C. perfringens* is one of the most common causes of food poisoning in the U.S. and presents as a 24-hour (or less) diarrheal illness similar to the enteric form of *B. cereus*. It is associated with contaminated meat or gravy.
- *C. septicum* is a gut organism that causes bacteremia, and the majority of patients with *C. septicum* sepsis have an associated GI malignancy.
- *C. tetani* is the cause of tetanus.

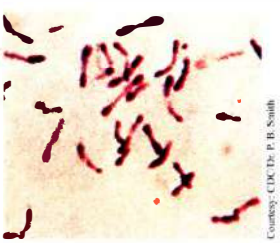


Image 2-5: C. diphtheriae

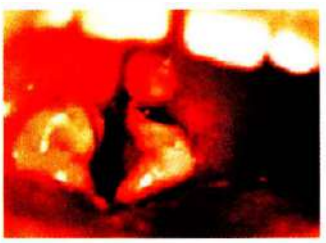


Image 2-6: Pharyngeal pseudomembrane

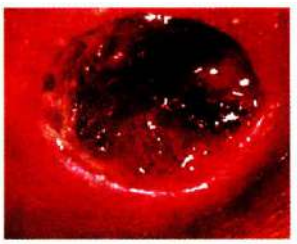


Image 2-7: Anthrax ulcer (painless)

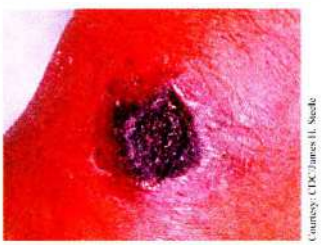


Image 2-8: Cutaneous anthrax lesion

Rapidly progressive cellulitis and gas gangrene can be caused by several species, including *C. septicum*, *perfringens*, *tetani*, or *novyi*. The main toxin in all *Clostridia* is the alpha toxin.

For acute treatment of *C. tetani* cellulitis or tetanus (page 2-71), use metronidazole (now the antibiotic of choice instead of PCN, which is still an alternative) and tetanus immune globulin.

GRAM-NEGATIVE BACTERIA

Neisseria

Neisseria meningitidis (meningococcus) is a gram-negative diplococcus that is carried in the human nasopharynx in 5–10% of healthy persons. It usually does not cause disease because specific antibodies and complement lyse the organisms as they enter the bloodstream.

Patients with complement deficiency are especially prone to meningococcemia, which presents with fever, hypotension, and skin signs that vary from petechiae (early disease) to diffuse purpuric lesions and DIC (later). Bloodstream infection may or may not be associated with meningococcal meningitis.

Treat patients with suspected infection empirically with a 3rd generation cephalosporin until susceptibilities are known. Once known, treat meningococcemia and meningitis due to PCN-susceptible isolates with penicillin or ceftriaxone. Use chloramphenicol or fluoroquinolones in patients with severe PCN allergy. With prompt treatment, the mortality rate of meningococcemia is 10%.

[Know:] Prophylaxis should be given to close contacts of patients with meningococcal bacteremia and meningitis to eradicate colonization of the nasopharynx, which has been associated with subsequent development of invasive disease.

Close contacts are defined as:

- Persons who have spent > 8 hours within 3 feet of the index case from 1 day prior to 1 day after presentation (e.g., people who live in the patient's household or contacts at day care centers)
- People exposed to the patient's oral secretions (e.g., a health care worker who has intubated the patient)

Know that the traditional clinical encounter does not merit prophylaxis for health care workers because traditional encounters usually do not involve contact with the patient's oral secretions.

To eradicate the carrier state, use:

- fluoroquinolones (non-pregnant adults), or
- rifampin (children and non-pregnant adults), or
- ceftriaxone (pregnancy and children < 15 years of age).

[Know:] Patients with meningococcal disease who are treated with penicillin still need to be given one of these "prophylaxis" drugs, because penicillin does not eradicate the carrier state.

Neisseria gonorrhoeae (NG) causes localized GU infections (gonorrhea) as well as disseminated gonococcal disease (DGI). NG is a gram-negative diplococcus. The penicillinase-producing strains of *N. gonorrhoeae* now account for the vast majority of cases in many areas in Asia and Africa and are also common in the U.S. See the discussion on STDs (page 2-62).

Moraxella

Moraxella catarrhalis is a gram-negative coccobacillus that causes respiratory infections, especially in immunodeficient patients and those with COPD. It is a common cause of sinusitis in adults and otitis media in children. Treat adults with amoxicillin-clavulanate, a 2nd or 3rd generation cephalosporin, or a quinolone. In the U.S., almost all are susceptible to erythromycin, tetracycline, and TMP/SMX.

Pseudomonas

Pseudomonas aeruginosa is a gram-negative rod that is a ubiquitous water organism and a common cause of hospital-acquired infections. There are several clinical presentations that are highly specific for infection with this organism:

- Cellulitis and/or osteomyelitis: *P. aeruginosa* survives in the moisture absorbing middle layer of tennis shoes and can be innoculated into soft tissue or bone after stepping on nails.
- Otitis externa presents as swimmers itch in nonimmunocompromised hosts and as malignant otitis externa with extensive soft tissue +/– bone destruction in patients with diabetes.
- Ecthyma gangrenosum—a round, indurated black lesion with central ulceration—may accompany *Pseudomonas* bacteremia in neutropenic patients.
- Folliculitis, which people get from improperly chlorinated hot tubs ("hot tub rash"), is usually self-limited.
- Endocarditis from *P. aeruginosa* is rarely seen on native valves, except in injection-drug users.

Treat invasive infections with 2 antipseudomonal drugs until you know the susceptibility of the isolate because these GNRs are not predictably susceptible to any single antibiotic. The most active drugs include:

- Carbapenems (except ertapenem)
- Aztreonam
- Fluoroquinolones
- Aminoglycosides
- Ceftazidime
- Cefepime
- Piperacillin/tazobactam
- Ticarcillin/clavulanate

Quick Quiz

- What is the clinical presentation of meningococcemia? Empiric treatment?
- Prophylaxis for meningococcemia should be given to which contacts?
- When should you suspect *Pseudomonas* as a cause of infection?
- *Salmonella* infection is spread by which animals?
- Which form of plague is transmitted person-to-person?
- What associated symptoms are often observed with *Legionella* pneumonia?

Enterobacteriaceae

Enterobacteriaceae is a family of aerobic GNRs that includes: *Salmonella*, *Yersinia*, *Shigella*, *Citrobacter*, *E. coli*, *Klebsiella*, *Proteus*, *Serratia*, *Enterobacter*, and *Edwardsiella*. We'll discuss *Salmonella* and *Yersinia* here. Also see Infectious Diarrhea on page 2-61.

Salmonella

Salmonella are GNBs that are usually motile.

Non-typhoidal *Salmonella* are a fairly common cause of diarrhea. Because the bacteria are not host-specific to humans, like *S. typhi*, they can be found in many different, non-human host animals. *Salmonella* may be spread by frozen foods (especially chicken), milk, and eggs. Peanut butter and alfalfa sprouts were recent sources of outbreaks. Baby chicks, iguanas, turtles, and other exotic pets also may be sources of infections.

Treatment is typically symptomatic because antibiotic therapy does not shorten the course of disease, increases the risk of developing a carrier state, and increases resistance in the organism. However, treat patients > 50 years of age with significant comorbid illness, immunosuppression, and inflammatory bowel disease with a fluoroquinolone orally or ceftriaxone intravenously.

Salmonella typhi causes typhoid fever, usually after ingestion from contaminated food, milk, or water. Adults are more likely to be carriers because *S. typhi* tends to colonize gallstones. It commonly begins with initial constipation followed by diarrhea, leukopenia, and the appearance of classic rose spots (Image 2-9) on the trunk, which begin about a week after the fever starts. These look like little 2–3-mm diameter angiomas.

Recommend typhoid vaccine to travelers (> 2 years old) who go outside of the usual tourist areas of Latin America, Asia, and Africa.

Treatment of typhoid fever is with quinolones, 3rd generation cephalosporins, ampicillin, TMP/SMX, and chloramphenicol, depending on sensitivities. Carriers without gallbladder disease or stones can usually be cleared with 6 weeks of ampicillin + probenecid. Probenecid decreases clearance and causes a higher blood level of the ampicillin.

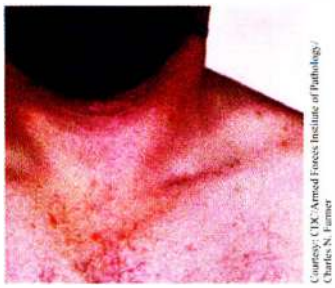


Image 2-9: Typhoid fever with classic "rose spots"

Yersinia

Yersinia pestis is a gram-negative coccobacillus that causes plague. Reservoir is wild rodents. It is transmitted by fleas or direct contact (skinning animals) and has a high mortality.

The bubonic type causes large, localized lymphadenopathy ("buboes") that suppurates. If not treated, it can lead to sepsis and death. The pneumonic form occurs after inhalation of the organism via aerosols from infected animals or from other humans with pneumonic plague. Only a small inoculum is required, making it prone to epidemics and a potential agent of bioterrorism.

Plague and tularemia present similarly (adenopathy after hunting), except that the geographic locations are different—Desert Southwest for plague vs. Arkansas, Missouri, and Oklahoma for tularemia. More on tularemia below.

Diagnose plague by aspirating lymph nodes or sputum specimens that reveal bipolar staining GNRs ("safety pin") and growth of *Yersinia pestis*.

Plague is 1 of 2 infectious diseases in which aminoglycosides (specifically streptomycin) are the drugs of choice; the other is tularemia. 2nd line choices are tetracycline or quinolones.

Other *Enterobacteriaceae* are covered under Diarrhea in Gastroenterology, Book 1.

Legionella

Legionella are aerobic GNRs that require special media for culture (charcoal yeast extract). The *Legionellaceae* family is made up of 50 species. *Legionella pneumophila* causes 80–90% of human infections. *Legionella* easily colonize standing water, and entry into the lungs is via inhalation.

Legionella pneumophila infection (legionellosis) causes legions of problems. Multisystem disease is the rule. Patients often present with diarrhea, hyponatremia, and CNS symptoms (headache, delirium, and confusion), in addition to the pneumonia.

Treatment for moderate infections is azithromycin or quinolones. Treating patients for community-acquired pneumonia using generally accepted guidelines effectively treats legionellosis.

Brucella

Brucella is an aerobic gram-negative bacillus, and *B. melitensis* causes brucellosis in goats, sheep, and camels. Other strains: *Brucella abortus* (cattle), *B. suis* (pigs), and *B. canis* (dogs). These are often transmitted to humans via unpasteurized milk or cheese or by inhalation (work-related). *Brucella* affects the:

- heart (especially suspect in culture-negative endocarditis),
- lungs (pneumonia),
- GI tract (diarrhea),
- GU area (orchitis, abortion), and
- endocrine glands (thyroiditis, adrenal insufficiency, SIADH).

Confirming the diagnosis is difficult because cultures may take up to 6 weeks to grow. Diagnosis can also be made via acute and convalescent serum titers.

Treatment requires 1 of the following regimens:

- Doxycycline + aminoglycoside (streptomycin or gentamicin) x 4 weeks.
- Doxycycline + rifampin x 6–8 weeks.
- Pregnant women should avoid doxy; treat with rifampin 900 mg daily for 8 weeks.

Francisella

Francisella tularensis is a small, gram-negative pleomorphic bacillus that causes tularemia ("rabbit fever"). It is found in many animals. *Francisella* is transmitted by ticks and bloodsucking flies, but the organism may also be ingested or inhaled. Especially seen in Arkansas, Missouri, and Oklahoma.

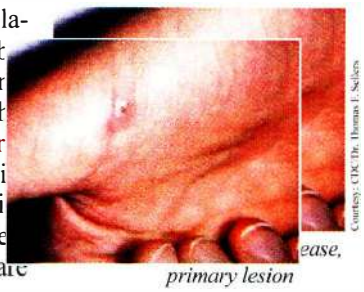
Typically, patients with tularemia present with a history of sudden onset of fever, chills, myalgias, and arthralgias, followed by an irregular ulcer at the site of inoculation that may persist for months. Regional lymphadenopathy develops, and these nodes may necrose and suppurate. If pneumonia occurs, it may have hilar adenopathy similar to plague.

The diagnosis is based on a typical clinical and epidemiological presentation. Serologic testing for *Francisella tularensis* is confirmatory as it usually takes > 2 weeks to turn positive. Cultures of apparently infected tissue have a very low yield.

Treat with streptomycin or gentamicin. Tetracycline can be used if the patient is not severely ill.

Bartonella

Bartonella henselae causes cat-scratch disease or, in the immunocompromised patient, bacillary angiomatosis. The skin lesions of bacillary angiomatosis are identical to verruga peruana (next). Cat-scratch fever has a macule → papule → pustule at the site of the infection (Image 2-10) with painful regional lymphadenopathy. Often the site of inoculation is no longer visible when the patient presents with lymphadenopathy. Treatment with azithromycin is associated with decreased duration of illness and is recommended although most cases are self-limited.



ease, primary lesion

Bartonella bacilliformis is a tiny, gram-negative pleomorphic bacterium that causes bartonellosis. *Bartonella* is transmitted by sand flies only in Peru, Columbia, and Ecuador and only in certain areas of the Andes Mountains—called the "verruga (wart) zone." Rare outbreaks where there are no sand flies indicate other vectors can exist. The only known reservoir is humans.

Bartonellosis has 2 manifestations:

1) Oroya fever ([Carrión disease]; acute/severe)
2) Verruga peruana (chronic)

Oroya fever consists of a rapid, febrile hemolytic anemia with a high mortality if untreated (~ 50%). Superinfection is a common problem—usually with *Salmonella*, staph, or *Enterobacter*. Suspect this disease in acutely ill travelers to the "verruga zone."

Verruga peruana presents 2–8 weeks after Oroya fever or inoculation. Up to 50% of patients have no memory of a febrile illness. It presents with warty growths of hemangioma-like tissue progressing from pinpoints (miliary), to nodules, to larger (mular) lesions. All stages can exist in the same person.

The drugs of choice for Oroya fever are chloramphenicol plus penicillin. Rifampin is the drug of choice for verruga peruana.

Helicobacter pylori

Helicobacter pylori is a gram-negative, spiral, flagellated bacillus. It causes gastritis and PUD and is a risk factor for adenocarcinoma of the stomach and gastrointestinal lymphoma. Further discussion about *H. pylori* is in Gastroenterology, Book 1.

RICKETTSIA

Rocky Mountain Spotted Fever

Rickettsia rickettsii is a gram-negative coccobacillus that causes Rocky Mountain spotted fever (RMSF). This disease has a 5–10% mortality rate. Classic signs and symptoms include a rash, fever, severe headache, arthralgias (but not overt arthritis), and a history of recent exposure to ticks. The rash occurs on the distal extremities (Image 2-11). It progresses from maculopapular to petechial. Patients may also present with diarrhea and abdominal pain.

Quick Quiz

- Which geographic locations have the most cases of tularemia?
- What are the manifestations of bartonellosis?
- Name the clinical signs and symptoms of RMSF. What drugs are used for treatment?
- What is Q fever? How is it treated?
- What are the forms of ehrlichiosis? How does it present?

Labs may show leukopenia or leukocytosis, thrombocytopenia, hyponatremia, and increased transaminases. PT, PTT, and fibrin split products are often increased, although the condition is not often associated with true DIC. The increase in these parameters is thought to be due to organism-induced local injury in the blood vessels.

It is important to diagnose this infection on clinical grounds to allow emergent treatment. The quickest confirmation of the diagnosis is via immunofluorescent staining of a biopsy of a petechial lesion. Serology eventually turns positive but is often negative on presentation.

Treatment is doxycycline or chloramphenicol.

Other rickettsial infections include *R. typhi* (endemic typhus), *R. prowazekii* (epidemic typhus), *R. conorii* (Mediterranean spotted fever), and *Coxiella burnetii* (Q fever).

Q Fever

Q fever (*Coxiella burnetii* infection) is a zoonosis that is transmitted mainly by inhalation of the aerosol released from the infected animal. Q fever is seen in abattoir (slaughterhouse) workers and people exposed to an infected animal's products of conception during birthing.

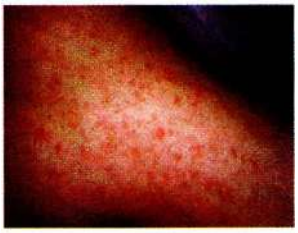


Image 2-11: Rocky Mountain spotted fever

It usually presents as a flu-like febrile illness, with or without pneumonia and/or hepatitis. 5% of infections become chronic and manifest as a fever of unknown origin or culture-negative endocarditis.

Diagnosis is made with serology. Treat symptomatic Q fever with doxycycline.

Ehrlichia and *Anaplasma*

Ehrlichia and *Anaplasma* are small, obligately intracellular gram-negative organisms that cause ehrlichiosis and anaplasmosis. Ehrlichiosis has been called "spotless" Rocky Mountain fever. Like RMSF, ticks are the transmission vectors.

There are 2 forms of ehrlichiosis:

- *Ehrlichia chaffeensis* and *E. ewingii* cause human monocytic ehrlichiosis (HME), mainly in Missouri and Arkansas.
- *Anaplasma phagocytophilum* causes human granulocytic anaplasmosis (HGA), mainly in the Northeast and upper Midwest U.S.

Rash occurs in only 1/3 of patients with HME and < 5% with HGA. The organism infects either monocytes or neutrophils, and patients typically present with the triad of fever, headache, and leukopenia—they may also have thrombocytopenia. Think of this in the patient who presents with pancytopenia and a history of tick bite.

Diagnosis is definitively made by finding intracytoplasmic inclusions in white cells. Serologies are available but require a 4-fold change in titer and thus are not useful at presentation.

Treat all patients suspected or proven to have ehrlichiosis or anaplasmosis with doxycycline just like with RMSF.

Note: There are reports of dual infection with *Ehrlichia* + *Babesia microti* (an intra RBC protozoan parasite) and *Ehrlichia* + *Borrelia burgdorferi* (Lyme) in the endemic Northeast areas.

GRAM-VARIABLE BACTERIA

Gardnerella vaginalis is a gram-variable rod. It is one of the bacteria associated with bacterial vaginosis, the most common cause of vaginal discharge in women of childbearing age (see Vaginitis on page 2-65). Treat with metronidazole or tinidazole.

ACID-FAST BACTERIA

Mycobacteria

All mycobacteria are acid-fast bacteria—they don't lose their stained color when exposed to acids (red on a green background). As a rule, the treatment of mycobacterial infections consists of a prolonged multidrug regimen.

M. tuberculosis is a prominent global cause of pulmonary infection. In addition, it can cause myriad extrapulmonary infections in any organ. More on TB in Pulmonary Medicine, Book 2.

M. avium-intracellulare (MAI) or *M. avium* complex (MAC) is a chronic pulmonary infection caused by either *M. avium* or *M. intracellulare*. Immunocompromised (especially HIV) patients are at risk for disseminated disease. Elderly, thin women and patients with severe COPD may also present with an indolent MAI pulmonary infection.

M. scrofulaceum and MAC cause lymphadenitis in children; treat by excising the nodes.

M. leprae causes leprosy. Transmission is via respiratory droplets from person-to-person, but only a very small percent of the population is genetically susceptible. Diagnose with Fite stains of skin or nerve. Armadillos may also carry *M. leprae* and are a reservoir in the southern U.S.

M. marinum is the "fish-tank bacillus." It causes nonhealing skin ulceration in people working around fish tanks (especially if any immunodeficiency is present, such as diabetes). It often causes strings of lesions along the lymphatic channels. (Similar lymphatic channel lesions occur with *Nocardia brasiliensis*, *Sporothrix schenckii*, and cat-scratch disease). Treat *M. marinum* with clarithromycin + either rifampin or ethambutol until 1–2 months after symptoms resolve.

Other non-tuberculous mycobacteria (NTM) include *M. kansasii* (lung disease clinically similar to TB), and *M. abscessus* (chronic pulmonary infections in patients with underlying lung disease).

Nocardia

Nocardia asteroides is only weakly acid fast (easily missed). It is a beaded, branching, filamentous gram-positive rod. It usually starts as a lung infection—occasionally causing a thin-walled cavitary lesion. It can cause focal brain abscesses and chronic neutrophilic meningitis—most chronic meningitides are lymphocytic. Nodular skin lesions are common. It is hard to isolate. It can spread systemically.

Usual treatment is high-dose sulfonamides or TMP/SMX. In severely ill patients, add combinations of drugs including amikacin + imipenem. Minocycline is another alternate choice for those sulfa-allergic. Treat for 3 or more months!

Nocardia brasiliensis is in the soil. Like *M. marinum* and *Sporothrix schenckii*, it can cause inflammation with associated surface lesions along lymphatic channels. Treat with sulfonamides or TMP/SMX. *Nocardia brasiliensis* is resistant to imipenem, but *N. asteroides* is usually sensitive.

OTHER ORGANISMS

Image 2-12: Actinomycosis

Actinomyces

Actinomyces is an anaerobic organism that causes an infection in which yellow "sulfur" granules can be visualized, which are actually clusters of organisms. The usual presentation of actinomycosis is cervicofacial involvement ("lumpy jaw" Image 2-12). *Actinomyces* is a cause of PID when there is an IUD in place. Also, in the abdomen, be aware of *Actinomyces* associated with appendicitis. Treatment is PCN or ampicillin; 2nd choice is tetracycline.

Chlamydia / Chlamydophila

Chlamydia and *Chlamydophila* are obligate, intracellular parasites. *C. psittaci*, *C. trachomatis*, and *C. pneumoniae* (formerly TWAR) are pathogenic in humans. Treat with doxycycline, macrolides, or quinolones.

Chlamydia psittaci is found in psittacine and other birds and causes psittacosis: pneumonia and splenomegaly. Any pneumonia associated with poultry, especially with splenomegaly, strongly suggests *C. psittaci*. (DDx: *Histoplasma* also causes pneumonia and splenomegaly; it is associated with bird and bat droppings.) Onset of psittacosis is associated with myalgias, rigors, headache, and high fever—to 105° F.

Chlamydophila pneumoniae (formerly *Chlamydia* but found to have different DNA and antigen) causes community-acquired pneumonia in adults who typically have not been exposed to birds; i.e., person-to-person spread. Bronchospasm is particularly prominent in respiratory infection caused by *C. pneumoniae*, as is an association with early pharyngitis and hoarseness.

Chlamydia trachomatis causes GU infections and trachoma (chronic, anterior eye infection causing cataracts but not glaucoma; found especially in Asia and Africa). Approximately 5% of pregnant women have *C. trachomatis* in their genital tracts. The same *C. trachomatis* is also associated with neonatal pneumonia. Lymphogranuloma venereum is an STD caused by the same *C. trachomatis*, but a different immunotype. (See STDs on page 2-62.)

SPIROCHETES

SYPHILIS

Treponema pallidum causes syphilis. Sequence of infection:

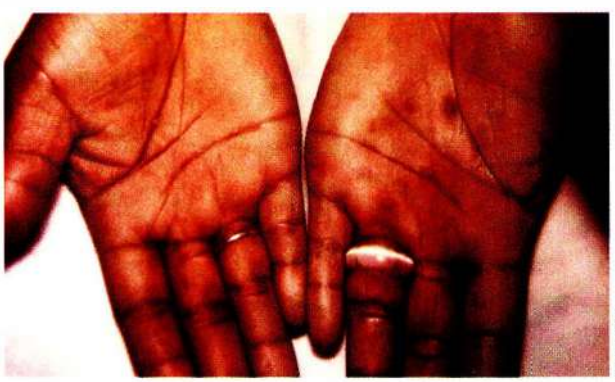
1) **Primary** syphilis presents with a painless chancre (genital, anal, or oral ulcer) within 3–40 days, depending on the number of inoculated organisms, and painless regional lymphadenopathy. In women, if the infection is cervical, it is often asymptomatic. Chancre contains flexible, mobile, worm-shaped bacteria; it lasts 2–6 weeks, then resolves.
2) **Secondary** syphilis occurs ~ 2 months later as spirochetes travel to other organs throughout the body. Symptoms include generalized lymphadenopathy, fever, malaise, and mucosal and/or cutaneous lesions that can mimic many other lesions ("the great imitator"). The skin lesions may be macular or papular but are never vesicular. They can occur on the palms and soles and are described as "nickel and dime" lesions (Image 2-13). Condyloma lata are cauliflower-like wet

Quick Quiz

- *M. marinum* causes what type of infection?
- If a pathology report describes beaded, branching, mildly acid-fast, filamentous organisms, what organism is likely?
- What organism is associated with pelvic inflammatory disease in women with an intrauterine device?
- What associated symptoms are often seen in respiratory infections due to *C. pneumoniae*?
- Stroke may occur in which stage of syphilis?
- What does PARESIS stand for, when referring to neurosyphilis?
- When will an MHA-TP revert to negative after a patient has syphilis?

lesions in genital areas or the mouth that are teeming with treponemes. Meningovascular disease also can occur in secondary syphilis and present as strokes in a young person. Non-neurologic signs and symptoms resolve in 3–12 weeks, and the disease goes into a latency period. Untreated, 1/3 of secondary syphilis cases eventually proceed to tertiary syphilis.

3) **Tertiary** syphilis occurs 1–20 years or more after the initial untreated infection. There are 3 forms:
   - **Gummatous** syphilis presents with 1 or more gummas, which are noncaseating granulomatous lesions that are locally destructive.
   - **Cardiovascular** syphilis is from obliterative endarteritis of aortic vaso vasorum resulting in ascending aortic aneurysms and aortic insufficiency.
   - **Neurosyphilis** has 3 manifestations:
     - Chronic meningovascular can present with brain and/or spinal cord strokes similar to meningovascular disease in secondary syphilis.
     - Tabes dorsalis is due to destruction of the posterior spinal cord columns leading to loss of position sense, abnormal foot-slapping gait, and Romberg sign.
     - General paresis is the name given to diffuse cortical disease seen in neurosyphilis. Its numerous manifestations can be remembered with the following mnemonic:
       P = defects in **p**ersonality
       A = reduced **a**ffect
       R = abnormal **r**eflexes
       E = **e**yes (Argyll-Robertson pupil, which is miotic and irregular; constricts normally to accommodation but not to light)
       S = defects in **s**ensorium
       I = defects in **i**ntellect
       S = defects in **s**peech



Courtesy: CDC

Image 2-13: Secondary syphilis "nickel and dime" lesions

Latent syphilis is the most commonly diagnosed stage of syphilis. It is defined as serology diagnostic of syphilis with no active manifestations of infection. It is divided into early latent and late latent depending on whether the last manifestations of syphilis or seroconversion to syphilis occurred within 1 year or after 1 year, respectively. This distinction arose from observational studies that showed that 90% of relapses occur within the 1st year of infection.

Diagnosis of syphilis is based on direct visualization of the organism via dark field microscopy of chancre exudate or cutaneous lesions of secondary syphilis; however, this is unavailable in most laboratories. Otherwise, serology is required to confirm the diagnosis of syphilis. There are 2 types of serologic tests:

1) Treponemal (MHA-TP and FTA-ABS [or simply FTA]) that detect antibodies that directly react with *T. pallidum*.
2) Nontreponemal tests (VDRL and RPR) detect antibodies directed against the cardiolipin-cholesterol-lecithin antigen (a.k.a. "reagin").

Traditionally, the diagnostic sequence has consisted of 1st an inexpensive nontreponemal test, then if that's positive, a more specific and more expensive treponemal test for confirmation. This confirmation is necessary because false-positive nontreponemal test results are common. If this sequence is followed, patients with a positive RPR and a confirmatory positive FTA are considered to have past or present syphilis.

More recently, high-volume laboratories have started to use a reversed approach: screening with a treponemal test and confirmation with a nontreponemal test. Using this sequence, if patients have a positive treponemal test, but a negative nontreponemal test, perform a 2nd treponemal test. If also positive by a 2nd treponemal test, treat the patient for late latent syphilis. If the 2nd treponemal test is negative; i.e., 1 positive and 1 negative treponemal test and a negative nontreponemal test, then no treatment is indicated.

Once positive, the specific treponemal tests (like the MHA-TP) usually stay positive for life. The nontreponemal tests become negative after treatment unless treatment has been delayed for many years, in which case they may stay positive (the "sero-fast" state). See Table 2-2.

Table 2-2: Testing Scenarios for Syphilis

Testing Sequence	Result	Interpretation	Approach
Traditional: Nontreponemal followed by treponemal	A. Negative nontreponemal	No syphilis or treated syphilis or prozone effect or very early syphilis	In most cases, no further testing or treatment is needed. If suspicion for syphilis is high, rule out prozone* effect (secondary syphilis) or perform dark field microscopy on lesion (primary syphilis) and/or repeat test in 21 days.
	B. Positive nontreponemal and positive treponemal	Active syphilis or treated syphilis	Treat, unless treatment documented.
	C. Positive nontreponemal and negative treponemal	No syphilis (false-positive nontreponemal test) or early syphilis	Treat if chancre, repeat in 6 weeks.
Reverse: Treponemal followed by nontreponemal	A. Negative treponemal	No syphilis or treated syphilis or very early syphilis	In most cases, no further testing or treatment is needed. If suspicion for syphilis is high, perform dark field microscopy on lesion (primary syphilis) and/or repeat test in 21 days.
	B. Positive treponemal and positive nontreponemal	Active syphilis or treated syphilis	Treat, unless treatment documented.
	C. Positive treponemal and negative nontreponemal	No syphilis (false-positive nontreponemal test) or late latent syphilis	Check a different type of treponemal test; if that is negative, no treatment indicated. If positive, then treat.

Note: In most treated patients, treponemal tests remain positive, but 15–25% of patients treated in primary stage will revert to seronegative in 2–3 years.
* The prozone effect is one cause of false-negative nontreponemal testing. It is caused by high levels of antibodies (mostly seen in secondary syphilis). If suspected, ask the lab to dilute the sample and test again.

According to the 2010 CDC recommendations, perform lumbar puncture in all patients who have neurologic or ophthalmic manifestations consistent with neurosyphilis, have other signs of tertiary syphilis, or have failed prior appropriate therapy for syphilis. In addition, patients with RPR titers ≥ 1:32 have a much higher risk of neurosyphilis, and this warrants a lumbar puncture as well.

RPR and VDRL titers should decrease with treatment. They should be positive only in the undiluted specimen or not at all 1 year after treatment of primary disease, 2 years after treatment of secondary disease, and 5 years after treatment of latent disease.

All pregnant women should get a nontreponemal test in the 1st trimester. If at high risk, repeat in the 3rd trimester and at delivery.

Treatment of syphilis (alternatives in parentheses):

- Primary, secondary, and early latent syphilis:
  - Benzathine PCN G 2.4 MU IM x 1 (doxycycline 100 mg bid x 14 days)
- Late latent, latent of unknown duration, and non-neurologic tertiary syphilis:
  - Benzathine PCN G 2.4 MU IM q wk x 3 (doxycycline 100 mg PO bid x 4 weeks)
- Neurosyphilis:
  - PCN G 18–24 MU IV divided q 4 hours or continuous infusion for 10–14 days. (If compliance is good: procaine PCN 2.4 MU IM qd with probenecid 500 mg qid x 10–14 days.)
  - Follow with benzathine PCN 2.4 MU IM q wk x 3. (If PCN-allergic, the best course is to desensitize the patient and give the PCN. Ceftriaxone 2 g/day x 10–14 days is an alternative for PCN-allergic patients, but cross-reactive allergies may occur. Oral doxycycline is not effective for neurosyphilis.)

Treat pregnant women and newborns for syphilis only with PCN. If the pregnant woman is PCN-allergic, desensitize her (see page 2-10); then treat with PCN. After treatment, do a quantitative nontreponemal/reagin test monthly during pregnancy.

Quick Quiz

- Can a patient have a negative RPR and have neurosyphilis?
- List the treatment regimens for the various stages of syphilis.
- What drug is used to treat syphilis in pregnancy? What if the woman has an anaphylactic PCN allergy?
- What spirochetal disease that causes jaundice and meningitis is most often found in veterinary workers and people who engage in outdoor water sports?
- What are the clinical presentations of leptospirosis?
- What symptoms are associated with the various stages of Lyme disease?

LEPTOSPIROSIS

Leptospirosis is a spirochetal disease caused by *Leptospira interrogans* and transferred by contact with infected animals or contaminated water. Leptospirosis is considered to be the most widespread zoonosis in the world. It is common in Hawaii (~ 50% of all U.S. cases) and may be seen after recreational water exposures; e.g., in cross-country runners, white water rafters, adventure racers, and triathletes—usually after contamination has been spread by heavy rains and flooding.

Leptospirosis has a wide range of signs and symptoms, from myalgias; fever; and headache, with or without aseptic meningitis, to Weil syndrome (severe hepatitis with renal failure, pneumonitis, and hemorrhagic complications). Subconjunctival suffusion is highly specific since it is only rarely seen in other illnesses like systemic lupus erythematosus and juvenile rheumatoid arthritis. The hepatitis is characterized by the bilirubin being disproportionately elevated compared to the liver transaminases. The variety of presenting symptoms makes for a high incidence of initial misdiagnoses.

Diagnose with blood and/or CSF cultures on special media within the first 10 days of illness. After that, culture the urine and send serum for anti-leptospiral IgM. Treat with PCN or doxycycline.

LYME DISEASE

Overview

Borrelia burgdorferi causes Lyme disease. It is transmitted by the *Ixodes scapularis* tick in the Mid-Atlantic, Midwest, and Northeast U.S. and the *Ixodes pacificus* tick in California. The protozoan *Babesia* is also transmitted by *Ixodes scapularis*—see page 2-35. *B. burgdorferi* crosses the placenta and may cause fetal infection and death.

Ixodes ticks have 3 stages of development: larva, nymph, and adult. Ticks transmit Lyme disease most efficiently during the nymphal stage, because nymphs are more likely to feed on a person and are rarely noticed because of their small size (< 2 mm). Ticks require at least 2 days of attachment before transmission of infection occurs. A tick found walking on the skin is not transmitting infection.

Clinical Manifestations of Lyme Disease

Stages of Lyme disease:

- Stage 1; **early localized**: Erythema migrans (EM) is the pathognomonic skin lesion of stage 1 disease; it starts at the site of the bite and is a slowly spreading, irregular erythematous lesion usually with a clear center (Image 2-14). Other stage 1 symptoms include myalgias, arthralgias, fever, headache, and lymphadenopathy. About 50% of patients have secondary skin lesions.
- Stage 2; **early disseminated**: Weeks to months later, stage 2 disease occurs with neurologic symptoms (lymphocytic meningitis, cranial or peripheral neuritis), and/or heart problems (myocarditis, with transient 1st, 2nd, or 3rd degree heart block). A peripheral 7th nerve palsy (Bell's palsy) is not uncommon. Bilateral Bell's palsy, which is essentially unheard of in Bell's palsy that is idiopathic or due to herpes simplex, can occur with Lyme disease (or occasionally sarcoid).
- Stage 3; **late**: Months to years later, stage 3 occurs, most commonly, with arthritis (oligo- or migratory—usually large joints), but there can also be chronic neurologic syndromes.

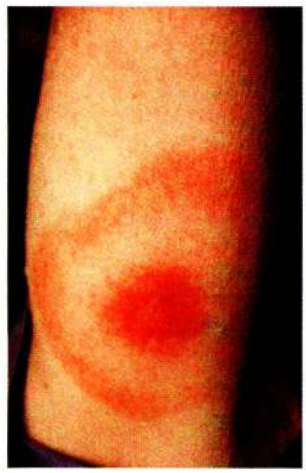
Diagnosis of Lyme Disease

According to the latest diagnostic criteria from the CDC in 2011, a diagnosis can be made in 2 ways:

1) Presence of erythema migrans, or
2) One or more stage 2 or 3 manifestations and positive serology (an EIA test, followed by a Western blot only if the EIA is positive).

There are a few important caveats about testing for Lyme disease:

Do not perform serology if there are no Lyme symptoms. Patients with seropositivity and no symptoms have had prior asymptomatic exposure; they do not warrant and would not benefit from treatment.



Courtesy: CDC/James Gathany

Image 2-14: Erythema migrans

Do not perform serology in patients with erythema migrans. Nothing else looks like it, and most patients are seronegative in stage 1. Just treat.

Reserve serology for persons from endemic areas with symptoms consistent with Lyme disease and no other obvious explanation.

Treatment of Lyme Disease

Treatment depends on the stage and type of manifestation.

- Treat stage 1, Bell's palsy, and asymptomatic 1st or 2nd degree heart block with oral doxycycline or amoxicillin x 10–21 days.
- Treat symptomatic heart block and neurologic disease with ceftriaxone 2 gm or PCN G 20 MU IV in divided doses x 14–21 days.
- Treat arthritis with oral doxycycline or amoxicillin x 30–60 days.

Although patients previously treated for Lyme disease may more commonly have chronic neuromuscular symptoms (such as muscle and joint pain, fatigue, trouble with memory and formulating ideas) than patients never infected with *B. burgdorferi*, several studies have confirmed that there is no benefit in giving additional courses of antibiotics to these individuals.

Prevention of Lyme Disease

Because transmission does not occur until at least 2 days of attachment, the best prevention is to keep ticks off the body with clothing treated with insect repellents or to find and remove the *Ixodes* tick from the skin. When ticks are embedded in the skin, remove them by grasping them with tweezers placed on their mouthparts and pulling them straight up from the skin.

Post-exposure prophylaxis: Give a single dose of doxycycline 200 mg PO if an embedded tick is found on the skin and any of the following are true:

- Tick is found and it is in the nymph or adult stage
- Tick was attached at least 36 hours and is engorged
- Patient presents within 72 hours of tick removal
- Local rate of tick infection with *B. burgdorferi* is ≥ 20% (New England, mid-Atlantic, parts of MN and WI)

There is no contraindication to doxycycline.

FUNGI

OVERVIEW

Fungi are roughly divided into 2 morphologic types: yeasts and molds. There is also a dimorphic type that changes from a yeast to a mold, and vice versa, depending on temperature. The dimorphs are the type most likely to cause systemic disease in the nonhospitalized, immunocompetent host. The dimorphic fungi are transmitted by a spore that converts to yeast at body temperature.

Some of the clinically relevant fungi include:

- *Candida* species
- *Cryptococcus* species
- *Aspergillus* species
- Endemic fungi (*Histoplasma*, *Blastomyces*, and *Coccidioides*: These are each found in specific regions of the U.S.)
- Dermatophytes (cause tinea capitis, tinea corporis, tinea pedis, and tinea cruris)
- *Sporothrix schenckii*
- Zygomycetes (*Mucor*, *Rhizopus*, and *Cunninghamella*)

CANDIDA

Candida infections are usually caused by *Candida albicans*. Infections with this organism are more likely to occur in patients who:

- are immunosuppressed,
- are on antibacterials,
- have indwelling catheters,
- are receiving intravenous hyperalimentation, or
- have uncontrolled diabetes.

Mucocutaneous candidiasis is occasionally the presenting symptom of diabetes or HIV infection.

Presentations vary. Disease can be localized to:

- Mucosa (thrush [oropharyngeal], esophagitis, or genitourinary infection)
- Bloodstream (candidemia)

However, *Candida* can also cause invasive disease such as endocarditis, ocular disease, hepatosplenic infection, and renal fungus ball. Usually, candidemia, either from an infected vascular catheter or from overgrowth of *Candida* in the gut, is the source of dissemination to these other organ systems.

Physical exam findings: Limited mucosal *Candida*, such as thrush, is visible as whitish plaques with an underlying erythematous base. Patients who have esophageal symptoms and thrush can be assumed to have esophageal candidiasis—endoscopy is not required to make the diagnosis. Vulvovaginal candidiasis presents as a thick, whitish discharge in the setting of intense vaginal itching (see Vaginal Candidiasis on page 2-66).

Candidemia

Fever; rash or painless, erythematous papules/pustules; visual complaints; and multiorgan involvement are signs and symptoms of disseminated disease. *Candida* species grow readily in routine blood culture bottles. *Candida* in a blood culture is never a contaminant; it represents real

Quick Quiz

- What is the treatment for Lyme disease with symptomatic heart block?
- In a febrile patient who is receiving intravenous hyperalimentation, what blood stream infections might you suspect?
- When can you disregard *Candida* as a blood culture contaminant?
- What is the treatment of candidemia when a line is present?
- What patient population develops hepatosplenic candidiasis?
- Patients with candidemia should have what kind of referral?
- Why are lipid amphotericin preparations not recommended in patients with funguria?

disease, even if the patient is relatively asymptomatic. Consider any localizing signs, such as rash, for biopsy—sometimes a skin biopsy is the only way to make the diagnosis of disseminated *Candida*. It may take days to grow the organisms out of the blood. If your patient is ill, it is sometimes appropriate to initiate empiric antifungal treatment; e.g., in a neutropenic patient with a prolonged fever.

Treatment of candidemia includes removal of any infected catheters and giving a systemic antifungal. Fluconazole or an echinocandin (caspofungin, micafungin, anidulafungin) are the 1st line agents in non-neutropenics.

Echinocandins are the 1st line for candidemia in the following settings:

- Neutropenia
- Moderate-to-severe disease
- Recent azole exposure
- Azole-resistant species

Chronic Disseminated Candidiasis

Also called hepatosplenic candidiasis, this entity is virtually always seen in leukemic patients as they recover from a period of neutropenia. Symptoms include fever and pain in the right upper quadrant.

Labs show increased alkaline phosphatase +/– increased transaminases and bilirubin. A contrast CT of the abdomen will show multiple small abscesses in the liver and spleen.

Severely ill patients require amphotericin induction therapy followed by fluconazole for maintenance. Clinically stable patients do not require induction. Use echinocandins if infection with azole-resistant *Candida* is suspected or proven.

Ocular Candidiasis

Ocular candidiasis can be either endophthalmitis or chorioretinitis. Disease can occur as a result of fungemia and seeding of the eye, or post-cataract surgery. Early disease (especially with chorioretinitis) may be relatively asymptomatic. Any patient who develops candidemia should have a dilated eye exam by an ophthalmologist. Postoperative patients with eye pain should have cultures of the vitreous fluid that includes evaluation for fungus.

Treatment of chorioretinitis is with systemic antifungals, but endophthalmitis necessitates antifungals plus intravitreal amphotericin B +/– vitrectomy. Fluconazole is usually the initial treatment of choice because it achieves therapeutic concentrations in the vitreous humor. Voriconazole or amphotericin B + flucytosine is used for resistant species of *Candida*.

Genitourinary Candidiasis

Candida in the urine is fairly common, especially in the hospital, and it often represents colonization—especially if the patient has had a urinary catheter.

Be concerned about repeatedly positive urine cultures for *Candida* in diabetics, in patients with recent urinary manipulation, and in patients with systemic signs of infection. Urinalysis showing pyuria is not very sensitive or specific for true infection. Evaluation should include renal imaging with either ultasound or CT of both the bladder and the kidneys.

Asymptomatic candiduria with negative imaging studies can be managed with a catheter change. If the patient is undergoing genitourinary procedures, give ampho B deoxycholate or fluconazole for a few days pre- and post-procedure.

Treat symptomatic candiduria with a systemic antifungal based on culture results. Fluconazole is preferred if the isolate is susceptible.

Know that lipid amphotericins are not excreted in high enough concentrations in the urine to be useful in treating *Candida* urinary tract infections. Echinocandins are also not recommended for the same reason. Bladder irrigation also is not recommended for cystitis, although it has some use in treating upper tract disease complicated by fungus balls.

Any fungus ball should be surgically removed if it is not improved after ampho B upper tract irrigation.

CRYPTOCOCCUS

In immunocompetent patients, *Cryptococcus neoformans* usually causes minimally symptomatic, self-limited infection after entering via the respiratory route. Patients may have a low-grade fever, cough, and a pulmonary infiltrate—all of which resolve. Although it is found in pigeon droppings, most patients have no recollection of being in contact with birds. Cryptococcal pneumonia may form cavitary lesions and peripheral "cannon ball" lesions.

Dissemination is more likely with *Cryptococcus gattii*, a related species, or in immunodeficient patients (AIDS, corticosteroid therapy, Hodgkin disease, ALL, diabetes, and those who are post-organ transplant). These patients are especially likely to get cryptococcal meningitis—the most common presentation of severe cryptococcal infection.

Suspect cryptococcal meningitis in any immunosuppressed patient who has headache +/– skin lesions and/or pulmonary lesions +/– fever. Lumbar puncture (LP) commonly shows increased CSF opening pressure, usually > 200 mmH_2O. The rest of the spinal fluid analysis may be remarkably benign with minimal leukocytosis and protein elevation, although an India ink test may reveal the organisms surrounded by haloes. Patients with very high opening pressures are at risk for blindness if the pressure is not handled properly (repeat LP to drain CSF).

Confirm presence of the organism with a serum and/or CSF cryptococcal antigen test.

Initially treat cryptococcal meningitis with amphotericin B and flucytosine. Once the patient is clinically improved, these 2 agents can be stopped and the patient can be switched to fluconazole. Additionally, daily repeated lumbar punctures are recommended in those with increased intracranial pressure (> 200 mmH_2O) or with associated headache, clouded sensorium, visual/hearing loss, or cranial nerve palsies. Sometimes shunts are required.

Patients with AIDS require secondary prophylaxis with chronic fluconazole.

ASPERGILLOSIS

Aspergillus species are ubiquitous in the environment. *A. fumigatus* is the most commonly isolated as a pathogen, and can cause severe infections, mostly in immunocompromised hosts.

Aspergillosis can present with a spectrum of disorders ranging from:

- allergic bronchopulmonary aspergillosis (ABPA), an allergic reaction to colonization with *Aspergillus* (clinical presentation similar to asthma), to
- aspergilloma (a fungus ball in a previously formed cavity), to
- invasive aspergillosis, which may be an acute destructive pulmonary process in immunocompromised patients (acute invasive pulmonary aspergillosis), or chronic in those who are immunocompromised (chronic necrotizing aspergillosis) or immunocompetent (chronic cavitary aspergillosis leading to chronic fibrosing aspergillosis).

Invasive aspergillosis can be rapidly fatal and requires prompt diagnosis and treatment. The diagnosis can be made by lung biopsy and demonstration of the organism invading the lung and on culture. Use caution in interpreting expectorated sputum and BAL specimens since the organism is so common in the environment. Alternatively, *Aspergillus* galactomannan antigen can be measured in the blood or the BAL fluid. This test is most useful in immunocompromised hosts.

Treatment of ABPA consists of itraconazole and steroids. Aspergillomas can be observed, but if symptomatic, (hemoptysis) should be resected. 1st line treatment for the invasive forms of aspergillosis is voriconazole.

ENDEMIC FUNGI

Overview

The American endemic fungi are *Coccidioides*, *Histoplasma*, *Cryptococcus gattii*, and *Blastomyces*. They have the following characteristics in common:

- They are found in specific areas of the U.S., and a patient becomes infected only after visiting or living in the area where the organism is endemic and participating in activities that encounter the organism.
- They are acquired by inhalation.
- They most commonly cause asymptomatic or mild, self-limited pulmonary disease.
- Less commonly, they cause significant pulmonary disease requiring medical treatment.
- Even less commonly, they cause disseminated disease.
- Significant pulmonary disease and dissemination are much more common in immunodeficient patients.
- Mild disease is treated with azoles. Severe or CNS disease is treated with amphotericin B.

Cryptococcus gattii is found in Northern California, Oregon, and Washington. The other endemic fungi are also discussed in Pulmonary Medicine, Book 2.

Coccidioidomycosis

Organism: *Coccidioides immitis* and *Coccidioides posadasii* cause coccidioidomycosis. The spores (arthroconidia) are highly infectious at a very low inoculum.

Geography: *C. immitis* is found in the soil of the arid Southwest U.S. and northern Mexico. This disease is often called "valley fever" because it is often identified in the San Joaquin Valley and Death Valley.

Presentation: When inhaled, the arthroconidia convert to their yeast form that, days to weeks later, causes a self-limited, flu-like illness with arthralgias, erythema multiforme, and/or erythema nodosum. Disease may result in a pulmonary "coin lesion." People at highest risk for severe infection include Filipino- and African-Americans, pregnant women, and the immunesuppressed.

Extrapulmonary coccidioidomycosis can involve bone, skin, or the CNS. Coccidioidomycosis and ABPA are the only 2 fungal diseases that cause peripheral eosinophilia.

Diagnosis: Demonstration of spherules in body fluids or tissue is diagnostic. Culture is also diagnostic and

QuickQuiz

- Cryptococcal meningitis is associated with what LP abnormality?
- Empiric treatment for cryptococcal meningitis includes what drugs?
- Where is *Coccidioides immitis* found?
- What are the clinical presentations of histoplasmosis?
- What tests are best for diagnosing various presentations of histoplasmosis?
- Severe histoplasmosis is treated with what antifungal?
- Think about blastomycosis in which patient populations?
- Which patient groups are at risk for zygomycosis?

the organism grows well on almost all media in about 1 week. IgM serology is available but takes 1–3 weeks to turn positive.

Treatment: Most patients have self-limited disease and do not require treatment. If needed, nonmeningeal, less severe infections can be treated with either itraconazole or fluconazole. Treat severe cases with amphotericin B. When treatment is indicated, continue for a prolonged duration (6–12 months).

Histoplasmosis

Organism: *Histoplasma capsulatum* causes histoplasmosis. Conidia or mycelial fragments are the infectious form.

Geography: *H. capsulatum* is found predominantly in the Mississippi and Ohio River valleys and is especially prevalent in bat and bird droppings.

Presentation: Immunocompetent patients typically have a self-limited, flu-like illness with or without mild pulmonary infiltrates. It may present with interstitial pneumonia, palate ulcers, and splenomegaly. *Histoplasma* occasionally causes upper-lobe cavitary pneumonia similar to that seen in TB.

In immunocompromised patients (especially HIV/AIDS), *H. capsulatum* can disseminate, causing a rapidly progressive sepsis picture and/or multisystem involvement.

Diagnosis: Demonstration of characteristic yeast forms with narrow-based budding is diagnostic. Culture yields are the highest in patients with chronic pulmonary disease. Serum and urine antigen detection is diagnostic and has the highest yield in immunocompromised hosts and/or disseminated disease. These tests cross-react with *Blastomyces dermatitidis*.

Treatment: Acute pulmonary disease generally requires no therapy. More severe but localized disease can be treated with itraconazole. Disseminated disease requires amphotericin B (either deoxycholate or liposomal formulations), followed by itraconazole.

Blastomycosis

Organism: *Blastomyces dermatitidis* causes blastomycosis, a flu-like illness similar to that caused by *Coccidioides* and *Histoplasma* above. It may also cause an acute illness that looks like bacterial pneumonia.

Geography: Blastomycosis is seen in states bordering the Mississippi and Ohio River basins and those near the Great Lakes and along the St. Lawrence River.

Presentation: If it disseminates, it commonly does so to the skin, usually causing verrucous (warty) lesions with central ulceration. Bone lesions are common and may cause bone and joint pain.

Diagnosis: Demonstration of the yeast form with its broad-based buds in secretions or tissue is diagnostic. Cultures require fungal media and turn positive in 1–4 weeks. Urinary antigen and serum antigen are usually positive in disseminated disease with the urine being a more sensitive test.

Treatment: Mild-to-moderate disease should be treated with itraconazole. Severe or CNS disease requires amphotericin B.

SPOROTRICHOSIS

Sporotrichosis is caused by *Sporothrix schenckii*—a dimorphic fungus associated with soil and plants. Gardeners tend to get it, often after being pricked by a thorn. Of the 4 clinical presentations, the cutaneous and the lymphangitic (nodules form on the skin over lymph channels) types are treated with itraconazole, while the severe pulmonary and disseminated types are treated initially with lipid amphotericin B. Sporotrichosis can be a chronic problem. The disseminated type is more common in immunodeficient gardeners. *Mycobacterium marinum*, *Nocardia brasiliensis*, and cat-scratch disease cause similar lesions over lymphatic channels.

MUCORMYCOSIS

Mucormycosis (also known as zygomycosis) is caused by fungi in the order Mucorales. *Mucor*, *Rhizopus*, or *Rhizomucor* are the most common causes of human disease.

Rhizopus has special physiology that allows it to live in acidic and high-glucose conditions. It has also adapted to grow well in patients with iron overload on deferoxamine chelation. So, *Rhizopus* is especially adapted to thrive in the diabetic and in those with primary or secondary hemochromatosis. The severely immunosuppressed are also at risk.

Table 2-3: Classification of Parasites

Group	Subgroup	Organism
PROTOZOA (Do replicate within the body) (no eosinophilia, except with *Cystoisospora*)	Sporozoa	*Toxoplasma*, *Cryptosporidium*, *Cystoisospora belli* (formerly *Isopora belli*), *Plasmodium*, *Babesia*
	Ameba	*Entamoeba histolytica*
	Flagellates	*Giardia*—GI; *Trichomonas*—GU; *Leishmania*, *Trypanosoma* - blood
HELMINTHS (Do not replicate within the body) (+ eosinophilia)	Nemathelminthes (= nematodes) (= roundworms)	Pinworms, Hookworms, Whipworms (*Trichuris trichiura*), *Trichinella*, *Strongyloides*, *Ascaris*
	Platyhelminthes	Cestodes (tapeworms); Trematodes (flukes)

Disease can present as invasive pulmonary or rhinocerebral infection. Rhinocerebral mucormycosis starts as a black necrotic spot on the nasal mucosa or paranasal sinuses, and extends intracranially. It has a poor prognosis.

Mucormycosis may also cause a necrotizing, cavitating pneumonia similar to aspergillosis. Rule out mucormycosis in a patient on voriconazole treatment or prophylaxis with new or worsening pulmonary disease.

Diagnosis is made by biopsy showing broad non-septate hyphae. The organism is quite fragile and may not grow in culture.

Treat with correction of predisposing factors (e.g., diabetic ketoacidosis), aggressive surgical management, and lipid amphotericin B. Posaconazole can be used as an option in those who cannot tolerate amphotericin B or for salvage therapy.

DERMATOPHYTES

Dermatophytes are the skin and hair fungi. These organisms are found in the soil, and they infect keratinized material (e.g., human nails and hair).

The names of the diseases caused by dermatophytes begin with "tinea" (e.g., tinea capitis, tinea corporis, tinea pedis, and tinea cruris).

Treat ringworm (tinea corporis) with topical clotrimazole or undecylenic acid. Then, if no success, itraconazole or terbinafine are the preferred oral agents. Infection of hair follicles (tinea capitis) requires treatment with an oral agent, usually griseofulvin.

PARASITES

PROTOZOA

Overview

There are 2 main types of parasites: protozoa and helminthic organisms. See Table 2-3.

The protozoa are single-celled and can replicate within the body, so it takes only a small number of organisms to cause infection. With the exception of *Cystoisospora*, protozoa do not cause eosinophilia.

The 3 types of protozoa are:

1) Sporozoa (*Toxoplasma*, *Cryptosporidia*, *Cystoisospora* [the new name for *Isospora*], *Plasmodium*, *Babesia*)
2) Ameba (*Entamoeba histolytica*)
3) Flagellates (*Giardia*, *Trichomonas*, *Trypanosoma*, *Leishmania*)

Sporozoa

Toxoplasma gondii

Toxoplasma gondii is the protozoan that causes toxoplasmosis. Cats are the definitive host and excrete oocysts, which are consumed by other animals in which the organism encysts in their muscles. When undercooked meat from these animals (pigs, lambs, and cattle) is ingested by humans, the organism excysts and tachyzoites are released that circulate through the blood stream and infect any nucleated cells, with a predilection for neural tissue. Approximately 20% of pork and lamb, and 10% of beef contain *T. gondii* cysts. Thus, consumption of undercooked meat, as well as cat contact or ownership, are the modes of acquisition, and infection is common in the U.S. with 1/3 of adults demonstrating seropositivity to the organism.

There are 4 clinical presentations of toxoplasmosis:

1) Toxoplasmosis in the immunocompetent host is most often **asymptomatic**, but may cause fever, lymphadenopathy, and atypical lymphocytosis similar to mononucleosis; yet pharyngitis is conspicuously absent. Diagnosis is made by demonstrating the presence of IgM antibody. It is self-limited and requires no treatment.
2) **Congenital toxoplasmosis**: The only time *Toxoplasma* is of real concern in immunocompetent people is if it is acquired during pregnancy, when it can infect the fetus and cause congenital toxoplasmosis—causing intellectual disabilities and necrotizing chorioretinitis. The fetus is more likely to have a congenital infection if the disease is acquired later in pregnancy (15% risk

QuickQuiz

- Tinea capitis requires treatment with what drug?
- How is serology useful in making a diagnosis of CNS toxoplasmosis?
- In a patient with diarrhea who has recently ingested imported fruits or vegetables, are protozoan parasites a likely cause of infection?

in 1st trimester; 70% risk in 3rd trimester), but those infected later in pregnancy are usually asymptomatic. Diagnosis is made by demonstrating the presence of IgM antibody in blood.

3) **CNS** toxoplasmosis occurs in immunocompromised patients from reactivation of previous infection. These patients present with new onset of seizures, neurologic deficit, and/or altered consciousness. Diagnosis is made by head imaging revealing multiple bilateral lesions with a predilection for the basal ganglia. Because this is reactivation disease, IgM antibody will not be present but IgG will be. A negative IgG also does not necessarily exclude infection because sometimes AIDS patients have difficulty making antibodies. Treatment is with pyrimethamine, sulfadiazine, and leucovorin. AIDS patients remain on therapy for life unless CD4 counts climb above 200 for several months.

4) **Ocular** toxoplasmosis causes retinal lesions that look like yellow-white cotton patches and also irregular scarring and pigmentation. (Disseminated candidiasis produces white cotton wool patches.) Treatment consists of pyrimethamine and a sulfonamide (sulfadiazine or trisulfapyrimidine) for 3 weeks.

Cryptosporidium

Cryptosporidium parvum and *C. hominis* are protozoa that cause infection, especially in the immunocompromised but also in the immunocompetent, and are second only to *Giardia* as the most common human GI parasite. The oocytes are passed in animal (including human) feces. In the immunocompetent it causes a secretory diarrhea, which is self-limited, lasting 1–2 weeks. In the immunosuppressed, it is chronic and requires immune reconstitution and/or specific therapy to resolve. Diagnosis is by acid-fast stains of stools and can be enhanced via monoclonal antibody staining. Immunocompromised patients improve if antiretroviral therapy can raise the CD4 count. Nitazoxanide has variable efficacy.

Cystoisospora (*I. belli*)

Cystoisospora belli (previously *Isospora belli*) is another acid-fast protozoan that causes a secretory diarrhea in patients with AIDS, similar to *Cryptosporidium*. It may also cause acalculous cholecystitis and is the only protozoan that causes eosinophilia. Diagnosis is by wet mount or acid-fast staining with or without monoclonal antibody staining. On the acid-fast stain, it is large and oval, whereas *Cryptosporidium* is small and round. Treat with TMP/SMX and quinolones in the sulfa-allergic patient.

Cyclospora

Cyclospora cayetanensis is an acid-fast intestinal protozoan parasite that causes diarrhea in both immunocompromised and immunocompetent patients similar to *Cryptosporidium* and *Cystoisospora*. It is often the cause of outbreaks related to imported fruits or vegetables. Systemic symptoms such as malaise, myalgia, low-grade fever, and fatigue are commonly seen with *Cyclospora* infection. It is diagnosed by acid-fast staining of the stool. Treat with TMP/SMX and quinolones in the sulfa-allergic patient.

Malaria

Overview

Plasmodium is the protozoan that causes malaria. There are 5 disease-causing *Plasmodium* species:

1) *P. falciparum*
2) *P. vivax*
3) *P. ovale*
4) *P. malariae*
5) *P. knowlesi*

Plasmodium is transmitted via the *Anopheles* mosquito and infects RBCs. Asplenic patients have more severe infections. Any type of malaria can cause nephritis from immune complex deposition, but *P. malariae* is most commonly associated with nephrotic syndrome.

Malaria should be considered in any fever in the returning traveler, especially if it is cyclical. The incubation period is < 30 days. Geographic hot spots include sub-Saharan Africa and tropical regions of South America, Asia, and Indonesia.

As we go through the following, see Table 2-4: Treatment and Prophylaxis of Malaria.

P. falciparum

P. falciparum causes the most severe malaria; it is the cause of virtually all fatal infections. It also has widespread chloroquine resistance. Most cases of *P. falciparum* are acquired in central Africa.

Differentiating this species from the others is critical because of its capacity to be resistant to chloroquine, its ability to infect RBCs of all ages (thus causing overwhelming parasitemia with end-organ damage), and the need to hospitalize infected patients and document a decline in parasitemia with therapy. Fortunately, *P falciparum* has several unique findings on blood

Table 2-4: Treatment and Prophylaxis of Malaria

Type of Malaria	Treatment	Prophylaxis
Non-*falciparum* malaria	Chloroquine, and primaquine	Chloroquine 500 mg (300 mg base) weekly. Give daily in endemic areas.
P. falciparum Chloroquine sensitive	Chloroquine Atovaquone/proguanil	Choose any one of the following: Chloroquine Atovaquone/proguanil Mefloquine Doxycycline
P. falciparum Chloroquine resistant Not very ill	Atovaquone/proguanil or Mefloquine	Atovaquone/proguanil: one dose daily, including 1–2 days before and 7 days after or Mefloquine: one dose weekly, including 1 week before and 4 weeks after or Doxycycline: 100 mg 1–2 days before travel and continued 4 weeks after return
P. falciparum Chloroquine resistant Very ill	IV quinidine gluconate with either doxycycline, or tetracycline, or clindamycin Alternative: Artemisinin derivative.	

smears that facilitate this speciation: banana-shaped gametocytes; double chromatin knobs (giving the parasite the appearance of headphones); > 1 parasite per cell; and the number of infected RBCs being > 5% (Image 2-15).

This contrasts with the other forms of malaria in which the parasitized RBCs are often hard to find. Even though *P. falciparum* causes the highest levels of parasitemia, the schizonts are not seen on peripheral smear. If you see schizonts, the patient has one of the other types.

Treatment of *P. falciparum* malaria depends on the likelihood of chloroquine sensitivity, which depends on the country of acquisition. As of 2012, chloroquine-susceptible regions remain in 4 parts of the world. Malaria acquired from these areas can safely be treated with chloroquine:

1) Central America west of Panama
2) Haiti
3) Dominican Republic
4) Middle East

P. falciparum from other areas must be assumed to be chloroquine-resistant. Non-severe disease (i.e., no end-organ damage) should receive atovaquone/proguanil or mefloquine.

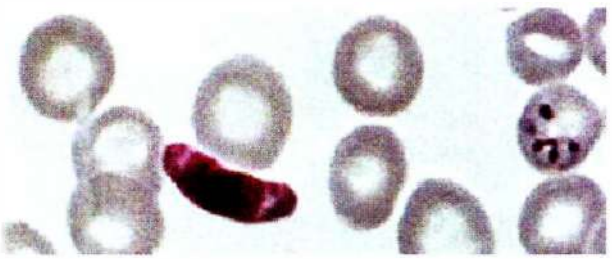


Image 2-15: P. falciparum, "banana-shaped gametocytes"

Patients with severe disease should receive IV quinidine gluconate with either doxycycline or tetracycline or clindamycin. Artesunate may be used as an alternative.

Non-*falciparum* Malaria

P. vivax from Papua New Guinea and Indonesia should be assumed to be chloroquine-resistant; otherwise all non-*falciparum* species are chloroquine-sensitive and should receive chloroquine.

Primaquine is adjunctive medication for infections with *P. vivax* and *P. ovale* to eradicate hypnozoites in the liver. Hypnozoites are the malarial forms responsible for relapse. Some *P. vivax* isolates in Southeast Asia are resistant to chloroquine and can be treated with mefloquine, atovaquone-proguanil, or quinine + doxycycline.

Remember that primaquine induces hemolytic anemia in G6PD-deficient persons, so you must screen for G6PD deficiency before prescribing it.

Prophylaxis in chloroquine-sensitive areas: Use chloroquine. Start it 1–2 weeks before patient departs to the endemic area and continue 4–6 weeks after leaving the area.

Prophylaxis in chloroquine-resistant areas: Use mefloquine or atovaquone/proguanil. Primaquine should be given the last 2 weeks of a prophylaxis period after travel to areas where there is *P. vivax* or *P. ovale* to eradicate the liver stage. Know that the main causes of malaria in the U.S. are either not taking prophylaxis or stopping prophylaxis too soon after returning from travel to endemic areas!

Atovaquone/proguanil is considered the drug of choice for prophylaxis. Specifically, the main advantage is that it can be started just prior to leaving and stopped soon

QuickQuiz

- Which form of malaria is associated with the banana-shaped gametocyte?
- Chloroquine is useful against which species of malaria?
- For travel to chloroquine-resistant areas, what drugs are used for malaria prophylaxis?
- What is the presentation of *Babesia* infection?
- How do you diagnose and treat extraintestinal amebiasis?
- How is a *Giardia* infection diagnosed?

after return—and has fewer side effects. The disadvantage is that it must be taken daily.

Doxycycline has activity against chloroquine-sensitive and chloroquine-resistant malaria, and it can be used for prophylaxis at a dose of 100 mg daily. The advantage is that it is very inexpensive. The disadvantages are that it can cause photosensitivity, has to be taken daily, and has to be taken for 4 weeks after leaving the endemic area.

Babesia

Babesia microti is an intra-RBC protozoan parasite that causes babesiosis. This disease causes a febrile, hemolytic anemia. Asplenic patients are at increased risk for severe babesiosis.

The organism is naturally transmitted via the *Ixodes* tick from rodents, as is the spirochete *B. burgdorferi*, which causes Lyme disease. It is most prevalent in the Northeast U.S. and upper Midwest—usually in summer or early autumn. Rare cases result from blood transfusion.

Symptoms, which may persist for months, include fever, profuse sweats, myalgias, and shaking chills. Severe cases cause liver, renal, and neurological failure, and death. Hemoglobinuria is a predominant sign. Because of the symptoms and the parasitized RBCs, it may be misdiagnosed as malaria.

B. microti is distinguished from *Plasmodium* by the classic intra-RBC pear shapes, which occasionally form a tetrad appearing as a "Maltese cross." (See Image 2-16; the malarial parasites have a ring form.) PCR assays are available and more sensitive than peripheral smears.

Image 2-16: Maltese cross—Babesia microti

Mild babesiosis infections are usually self-limited. Treat moderate infections with atovaquone + azithromycin. If severe, treat with clindamycin + quinine and consider an exchange transfusion.

Ameba

Human amebiasis is caused by the protozoan *Entamoeba histolytica*. Transmission is fecal-oral and can be food- or waterborne. In the U.S., the usual population groups in which it is found are the institutionalized, immigrants, and men who have sex with men. It can be asymptomatic or cause dysentery: profuse diarrhea, abdominal pain, fever, and bloody stools. The organism sometimes invades the portal circulation and can cause usually solitary liver abscesses. Diagnosis of intestinal disease is by stool for ova and parasites. Amebic liver abscesses often show no ameba or PMNs. These cases can be diagnosed by serology.

Treatment is with metronidazole (or tinidazole) for both forms of the disease. Although metronidazole treats ameba that have invaded, it does not kill intraluminal cysts. This must be accomplished with the administration of paromomycin, diiodohydroxyquin, or diloxanide furoate.

Flagellates

The flagellates: *Giardia lamblia*, *Trichomonas vaginalis*, *Trypanosoma*, *Leishmania*.

Giardia lamblia (a.k.a. *G. duodenalis*)

Giardia infections are found in campers, travelers, children in day care, HIV-infected persons, men who have sex with men, and in patients with IgA deficiency and/or hypogammaglobulinemia. It infects the duodenum and proximal jejunum by adhering to the mucosa and causing a malabsorption syndrome, yet 75% of infected persons are asymptomatic. If they occur, symptoms include a watery, smelly diarrhea and flatulence. Diagnosis is made by microscopic examination of fresh stool samples. Antigen excretion is intermittent, and up to 3 specimens may need to be obtained. Detection assays have a similar yield with a single stool.

Treatment is available with many agents: tinidazole, nitazoxanide (both FDA approved); non–FDA approved alternatives include metronidazole, albendazole, and paromomycin (which is approved in pregnancy).

Trichomonas vaginalis

Trichomonas vaginalis causes an STD. Treat with metronidazole. More under Vaginitis, page 2-65.

Trypanosomiasis

Trypanosoma species causes trypanosomiasis. There are 2 main types. The African disease is **sleeping sickness**, which is caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. These are transmitted via the tsetse fly. The American illness, **Chagas disease**, is caused by *T. cruzi* and is found in South America and Mexico. You can impress your friends by knowing that it's transmitted by bites of the triatoma or reduviid bug.

Usually, it is self-limited, but the chronic form can cause problems with the heart (from heart block to CHF), the GI system (especially achalasia, megaesophagus, and megacolon, as discussed in Gastroenterology, Book 1), and occasionally the CNS. Treatment is species specific. *T. brucei gambiense* responds to pentamidine (for early disease) and eflornithine + nifurtimox (for late disease). *T. brucei rhodesiense* is treated the same way, but nifurtimox is not needed. *T. cruzi* is treated with benznidazole or nifurtimox.

Leishmaniasis

Another deadly tropical protozoan is *Leishmania*. Leishmaniasis is caused by any of the following 4 species of the *Leishmania* protozoa: *L. donovani*, *L. tropica*, *L. mexicana*, and *L. braziliensis*. *L. donovani* is spread by sand flies and causes visceral leishmaniasis, also called kala-azar. Infected patients may have GI symptoms, hepatomegaly, and massive splenomegaly. The other species cause cutaneous and mucocutaneous forms of the disease. Recent reports indicate there is a higher susceptibility for leishmaniasis in HIV-infected patients who travel to endemic areas.

Sodium stibogluconate (pentavalent antimony), pentamidine, or amphotericin B are the treatments of choice.

HELMINTHIC ORGANISMS

Overview

Helminthic organisms are the other major type of parasite. (Remember: 1) protozoa and 2) helminthic organisms.) Helminthic organisms are multicellular worms that cause eosinophilia. Helminthic organisms consist of nematodes (roundworms), tapeworms, and flukes.

With the exception of *Strongyloides*, helminthic organisms do not multiply in the human body.

Image 2-17: Roundworm egg

Image 2-18: Pinworm eggs

Nematodes

The following list summarizes diseases caused by roundworms:

1) ***Ascaris lumbricoides*** (roundworm; causes ascariasis) (Image 2-17):
   - Epidemiology: Worldwide, > 1 billion people are infected, and the sole host is humans. In the U.S., 2% overall infected—worse in rural South with up to 30% of young children affected in some areas.
   - Life cycle: Eggs are ingested, hatch in the small intestine, and the larvae penetrate the intestinal wall and migrate to the lungs where they mature over 10 days. Then they ascend the bronchial tree and are swallowed, mature into adult worms in the small intestine, and excrete eggs in the stool. Eggs can live for up to 10 years in dark, moist conditions. Worms may migrate into the biliary tree and the appendix.
   - Presentation if symptomatic: pulmonary eosinophilic syndrome, acute appendicitis, ascending cholangitis.
   - Diagnosis: eggs (and rarely worms) in stool.
   - Treatment: albendazole or mebendazole.
2) ***Enterobius vermicularis*** (pinworm) (Image 2-18):
   - Epidemiology: Most common helminthic infection in the U.S.; humans are the only host.
   - Life cycle: Eggs are ingested and hatch in the small intestine. Gravid females migrate to the rectum and, at night, lay eggs in the perianal area.
   - Clinical presentation if symptomatic: perianal itching.
   - Diagnosis: microscopic exam of transparent tape that was touched upon the perianal area demonstrating eggs and sometimes female worms.
   - Treatment: single dose of albendazole, followed by repeat dose in 2 weeks to kill worms from hatched eggs.
3) ***Necator americanus*** (hookworm):
   - Epidemiology: requires coming into contact with larva in the soil that have hatched from eggs excreted by humans. Especially at risk are people walking barefoot or with open sandals in contaminated areas.
   - Life cycle: Larvae penetrate the skin and migrate to the lungs, up the bronchial tree, and are swallowed. Once in the small intestine, they mature and attach to the intestinal wall where they feed. Eggs are excreted in stool.
   - Presentation if symptomatic: cutaneous: itching at the site of larval entry ("ground itch"); serpiginous eruption along the course of the larva's migration ("cutaneous larval migrans"). Chronic infection leads to iron deficiency anemia from chronic GI blood loss and hypoalbuminemia in persons already malnourished.
   - Diagnosis: eggs in stool.
   - Treatment: single dose of albendazole.

Quick Quiz

- What is kala-azar?
- Disseminated strongyloidiasis can be seen in which patient population?

4) ***Trichiura*** (whipworm):
- Epidemiology: affects over 1.5 billion people worldwide. Found in warm moist places with poor sanitation, similar to *Ascaris;* coinfection is not uncommon.
- Life cycle: eggs ingested, hatch in small intestine, mature in caecum and ascending colon; excrete eggs in stool.
- Presentation if symptomatic: diarrhea, abdominal pain, blood in stool, rectal prolapse.
- Diagnosis: eggs in stool.
- Treatment: albendazole for 3 days; repeat Rx prn.

5) ***Trichinella*** (trichinosis):
- Epidemiology: *T. spiralis* is the most common *Trichinella* species in the U.S. The main sources of the disease are from undercooked wild game (e.g., bear, wild boar) and domesticated pigs. In the U.S., about 20 cases are reported each year, although there is a much higher incidence on autopsy.
- Life cycle: Eggs are ingested, and larvae attach to the small intestine wall. Larvae are released, and these larvae spread via the blood vessels to the muscle, where they burrow and encyst in a muscle cell.
- Presentations if symptomatic: muscle pain, tenderness, and weakness. High worm burdens can affect the CNS, lungs, heart, and k dneys.
- Diagnosis: Serology is available and turns positive after several weeks. Muscle biopsy may be performed to look for organisms.
- Treatment: for mild cases is supportive. For systemic infections, treat with albendazole for 10–14 days. Glucocorticoids should be given to suppress the inflammatory consequences of worm death.

6) ***Wuchereria bancrofti***, ***Brugia malayi***, and ***Brugia timori*** (filariasis):
- Epidemiology: More than 100 million people worldwide are infected, and 1/3 of those are symptomatic. These worms are transmitted via mosquito bites.
- Life cycle: Mosquito introduces larvae into skin during feeding. Larvae enter the lymphatics and mature over 9 months. Adult worms then produce microfilariae that migrate into the bloodstream (usually at night) where they are ingested by feeding mosquitos.
- Presentation if symptomatic:
  - Acute infection causes a nonspecific febrile illness in a traveller that may be similar to malaria (filarial fever). There may be associated tender lymphadenopathy (acute adenolymphangitis).
  - Tropical pulmonary eosinophilia is due to microfilariae trapped in the lungs and causes nocturnal wheezing.
  - Chronic infection leads to lymphatic obstruction, scarring, and severe lymphedema (elephantiasis).
- Diagnosis: Blood smears best demonstrate microfilariae between 10 p.m. and 2 a.m.
- Treatment: Diethylcarbamazine kills the larvae and adult worms. It must be obtained from the CDC.

7) ***Strongyloides stercoralis*** (strongyloidiasis):
- Epidemiology: endemic throughout tropical regions of the world and in parts of the southeastern U.S. It is the only helminthic organism that can complete its life cycle within the human body, resulting in autoinfection and persistence of infection. This also permits overwhelming infection in immunocompromised patients.
- Life cycle: Like hookworm, the *Strongyloides* larvae penetrate the skin and migrate to the lungs. They then migrate up the tracheobronchial tree and are swallowed. Once in the small intestine, they attach to the mucosa and mature. Adult female worms produce eggs that hatch into noninfectious rhabditiform larvae that are mostly excreted in the stool. However, some of these noninfectious larvae convert to infectious filariform larvae while still within the small intestine. These larvae penetrate the wall of the colon or perianal skin to hematogenously travel to the lung, just like exogenously introduced larvae do.
- Presentat ons if symptomatic:
  - Like hookworm, itching at the site of larval entry ("ground itch") and a serpiginous eruption along the course of the larva's migration ("cutaneous larval migrans") may occur.
  - GI symptoms include abdominal pain, nausea, vomiting, and diarrhea.
  - Pulmonary eosinophilic syndrome may occur.
  - Immunosuppression may lead to strongyloides hyperinfection syndrome. This represents an augmented and accelerated autoinfection cycle. Patients generally present in shock resulting from gram-negative sepsis. (Bacteria are carried from the intestine into the bloodstream.) Gram-negative meningitis may also occur.
- Diagnosis: Larvae in the stool are diagnostic but are seen in < 50% of those infected. Yield is increased by inoculating the stool in agar and looking for the trail left by migrating larvae. Serology is useful in immunocompetent patients. In hyper nfection syndrome, many larvae are usually seen in respiratory samples.
- Treatment: Ivermectin is the drug of choice; albendazole is a less effective alternative. Repeat treatment after 2 weeks for eradication.

8) ***Toxocara canis*** and ***T. cati*** (toxocariasis, visceral larva migrans):
- Epidemiology: *T. canis* (the dog ascarid) is more common than *T. cati* (the cat ascarid). It occurs worldwide with a 14% prevalence in the U.S. Humans are not normal hosts for these helminths and are not a required part of their life cycle.
- Life cycle: The adult tapeworm sheds eggs in the stool of its animal host. If humans ingest these eggs, they hatch into larvae that travel through tissue, elicit an immune response, and subsequently die.
- Presentation if symptomatic: Migrating larvae may cause injury to liver, heart, lungs, brain, muscle, and eyes. Fleeting migratory pulmonary infiltrates that self-resolve are typical.
- Treatment: If systemic symptoms, give albendazole for 5 days.

9) ***Angiostrongylus cantonensis*** and ***A. costaricensis*** (angiostrongyliasis):
- Epidemiology: *A. cantonensis* (the rat lungworm) is endemic in Southeast Asia and tropical Pacific islands and is the most common parasitic cause of eosinophilic meningitis. *A. costaricensis* is endemic in Latin America and the Caribbean. Both parasites have rats as their definitive hosts.
- Life cycle: *A. cantonensis* adult worms live in the pulmonary arteries of rats, and eggs laid there hatch into larvae that migrate to the pharynx, are swallowed, and are passed in the rats stool. These larvae infect snails that, if eaten by humans, migrate to the central nervous system.
  A. costaricensis lives in the mesenteric arterioles of rats. They shed eggs that hatch into larvae that are passed in the rat's feces, which hatch into larvae when ingested by snails. If these infected snails are ingested by humans, the larvae migrate to mesenteric arteries and shed eggs that cause severe endothelial damage and enteric tissue necrosis. Humans do not shed the eggs.
- Manifestations if symptomatic: *A. cantonensis* causes symptoms typical of meningitis that may be self-limiting or neuroinvasive. Headache is the most prominent symptom, and lumbar puncture yields an eosinophilic inflammatory response.
  A. costaricensis causes abdominal pain, fever, vomiting, and may progress to GI bleeding and perforation.
- Diagnosis: *A. cantonensis* is rarely visualized in the CSF, so the diagnosis is based on the presence of eosinophilic meningitis in the appropriate epidemiologic setting.
  A. costaricensis: Tissue specimens revealing the organism is the only way to make a diagnosis because the worms and eggs are not shed in the stool.
- Treatment: *A. cantonensis*: The disease is self-limited, and no antiparasitic drugs have been shown to be effective. *A. costaricensis*: Antiparasitic drugs are not effective and may cause worm migration and worsening symptoms. Perform surgery for complications.

Tapeworms

Clinically important tapeworms include *Taenia solium* (pork tapeworm) and *Echinococcus*.

T. solium is endemic in many regions of Central and South America, sub-Saharan Africa, India, and Asia. It is important to recall the life cycle of *T. solium* in order to understand the 2 manifestations of human disease it may cause. Although it is called the pork tapeworm, humans are the definitive host (the host in which the adult worm lives). If eggs are ingested, these hatch into oncospheres that travel through the blood to encyst in tissues (most commonly the central nervous system) as cysticerci causing neurocysticercosis. CNS cysticerci can be in the parenchyma or be extraparenchymal in the CSF where they usually lodge in the aqueduct of Sylvius. Cysticerci are able to suppress the human host response and thus remain asymptomatic until the organism dies, when an inflammatory response ensues. If the cysticerci are intraparenchymal, they cause seizures; if in the CSF, they cause hydrocephalus. If cysts are ingested from undercooked pork, the organism excysts and grows into the adult tapeworm in the gut (taeniasis). A person carrying a tapeworm will then start shedding eggs. Most people with tapeworm disease limited to the gut have no symptoms.

Niclosamide is the usual treatment for all intestinal tapeworms. Albendazole (1st choice) or praziquantel are the antiparasitic drugs used to treat neurocysticercosis. Anticpileptic treatment is important in patients with inflamed brain lesions or with a history of seizures and calcified lesions. These patients (and those with disease of the extraocular muscles or optic nerve) should be treated with an antiparasitic plus corticosteroids. If cerebral edema or lots of inflammation is present, hold off on treating with antiparasitics and give corticosteroids first. No treatment is necessary for patients with only calcified lesions and no history of clinical disease. Cutaneous and intramuscular disease can be treated with analgesics.

Another tapeworm to be aware of is the *Echinococcus*. It causes a condition known as "hydatid disease" in which hydatid cysts proliferate throughout the body. It is acquired after ingesting food contaminated with feces from the definitive hosts, which are other mammals (sheep, dogs, rodents, foxes, etc.) Most cases are diagnosed in immigrants from China, South and Central America, the former Soviet Union, and the Middle East. Hunters and veterinarians are also susceptible. Initial phase of infection is typically asymptomatic, and most people are infected as children. The liver is the most common organ affected (especially with *E. granulosus*), followed by the lungs (especially with *E. multilocularis*). The right lobe of the liver is most commonly affected and generally presents as a single large cyst. Complications can occur if the cyst ruptures into the biliary tree or peritoneum. Ultrasound or other imaging is diagnostic and can be confirmed with a serologic test (ELISA usually). Treatment with newer surgical techniques is

QuickQuiz

- What is visceral larval migrans?
- When do you not treat patients with neurocysticercosis with an antiparasitic drug?
- Multinucleated giant cells can be seen associated with which infections?
- When are most cases of neonatal HSV infection acquired?

evolving; but open surgery is recommended for large cysts (> 10 cm), and chemotherapy with albendazole before and after surgery is useful.

Tapeworm infections are zoonoses. Common vectors of tapeworm disease are listed below:

- *Diphyllobothrium latum*: from eating undercooked fish
- *Hymenolepis nana*: rodent exposures
- Sparganosis: frogs/snakes

Flukes ("Flatworms")

Clonorchis sinensis is the Chinese liver fluke, which is endemic in the Far East. Infection is caused by eating raw fish, and it is often associated with biliary obstruction. It increases the risk of cholangiocarcinoma. Other flukes in the liver? *Opisthorchis* or *Metorchis*. Flukes in the lung? *Paragonimus* species.

Schistosoma haematobium is found in North Africa, sub-Saharan Africa, the Middle East, Turkey, and India. *Schistosoma mansoni* is a fluke found in Africa, the Middle East, and South America; *Schistosoma japonicum* is found in Asia. The flukes themselves do not cause symptoms, but the eggs they shed do. *S. hematobium* eggs cause inflammation and fibrosis of the bladder wall, with symptoms of urinary tract infection, and predispose to bladder cancer. *S. mansoni* and *S. japonicum* shed eggs into the portal venous system, leading to portal hypertension, cirrhosis, and esophageal varices.

Schistosoma species are acquired by contact with freshwater containing cercarial larva. Initial manifestation of schistosomiasis (Katayama fever) occurs ~ 2 months after inoculation. This presents with fever, lymphadenopathy, hepatosplenomegaly, and marked eosinophilia.

Diagnosis is made by finding the eggs in the stool or urine, depending on the species.

Treatment is a 1-day course of praziquantel.

VIRUSES

HERPES SIMPLEX VIRUS (HSV)

Herpes simplex virus (HSV): a DNA virus. Many HSV infections are spread by asymptomatic shedding of virus.

HSV-1 causes orofacial infections in ~ 40% of the population. In the primary infection, the vesicular lesions and ulcers are usually localized to the oral mucosa, lips, and surrounding skin and may have constitutional symptoms. Recurrent infection ulcers are typically just on the outer lip. It is possible to autoinoculate the virus, so the infection can spread from the lips (or other areas) to the eyes of a patient.

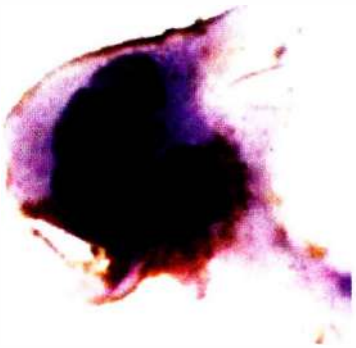


Image 2-19: Multinucleated giant cell

Recurrent HSV-1 eye infection resulting in keratitis is the most common infectious cause of blindness in industrialized nations.

Tzanck smears are performed by scraping down to the bottom of a vesicle, placing the material on a slide, then staining with either Giemsa or Wright. In herpes simplex and varicella zoster virus infections, it shows multinucleated giant cells (Image 2-19). However, in current clinical practice, PCR, and DFA (direct fluorescent antibody) are the most commonly used diagnostic tests.

HSV-2 causes "genital herpes." It causes about 75% of HSV genital infections—the rest are due to HSV-1. Note that the prevalence of HSV-2 is 25%, and of those, only 25% have symptoms. In 10% of patients, the initial occurrence of HSV-2 is associated with only a herpetic exudative pharyngitis. Most cases of neonatal HSV are from intrapartum contact, so a C-section is recommended if the mother has symptoms or signs of genital herpes, or its prodrome, at the time of delivery. The risk for transmission to the neonate is high (30–50%) among women who get their 1st episode of genital herpes near the time of delivery and is low (< 1%) among women with a history of recurrent herpes. HSV reactivates in 2/3 of seropositive transplant patients within 6 weeks of transplant, but this rate is drastically lower in patients receiving antiviral prophylaxis.

HSV encephalitis is the most common cause of sporadic viral encephalitis and causes the highest number of deaths due to viral encephalitis in adults. Patients with herpes encephalitis usually present with altered mental status, seizures and/or focal neurologic deficits. The virus has a predilection for the temporal lobes. Prognosis is poor, and more than 60% have neurologic sequelae.

MR imaging is often abnormal on presentation, but LP and empiric treatment should not be delayed to obtain an MRI. CSF usually shows increased protein, lymphocytic pleocytosis, and increased red cells, but it can be normal in early infection. Diagnosis of HSV DNA by PCR in CSF is the most sensitive (98%) and specific (97%) test, not brain biopsy.

HSV is one of the many causes of erythema multiforme. (See Dermatology, Book 5.)

Treatment of HSV: Initial or recurrent mucocutaneous HSV can be treated with acyclovir PO but is of benefit only if treatment is given within the first 72 hours. Famciclovir and valacyclovir are similarly effective but more expensive. Give acyclovir after 72 hours if the patient is immunocompromised. For HSV, give encephalitis IV acyclovir for 14–21 days. IV acyclovir should also be given if there is disseminated HSV (e.g., lung, skin, liver). Acyclovir (or famciclovir or valacyclovir) can also be given chronically to suppress infection in those with frequent recurrences, especially if they are complicated by erythema multiforme. Use foscarnet to treat those with HSV resistant to acyclovir; ganciclovir is not used because cross-resistance is common in acyclovir-resistant strains.

VARICELLA-ZOSTER VIRUS

Overview

Varicella-zoster virus (VZV; DNA) causes chicken pox (Image 2-20) and herpes zoster (shingles).

Chicken Pox

Chicken pox is an airborne, highly contagious disease that causes a characteristic pruritic vesicular eruption that comes in successive crops. On exam, these skin lesions are typically found in various stages, from new erythematous papules, to vesicles, to crusted-over lesions.

Patients are contagious for 1–2 days before eruption and stay contagious until the last lesion has crusted over. These pox marks do not leave scars unless superinfected.

Adolescent and adult patients also have a characteristic prodromal phase with fever, malaise, pharyngitis, myalgias, nausea, and headache. Children have a short prodromal phase (< 24 hours), or a papular rash may be the 1st symptom.

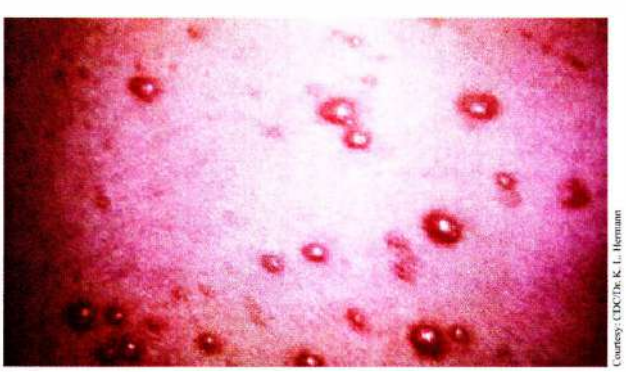


Image 2-20: VZV: Chicken pox

Chicken pox symptoms are typically mild in children but may be severe in adolescents and adults, and especially pregnant women in whom pneumonia is more likely to occur. In pregnancy, besides increased disease severity and pneumonia, birth defects are more likely if the mother is infected between 8- and 20-weeks gestation.

Diagnosis is usually made clinically based on the classic appearance of the rash. DFA or PCR can be used for atypical appearing rashes.

Treatment: All adult patients should be treated with PO acyclovir if they present within 24 hours of rash onset. This treatment decreases the number of lesions and the duration of disease. Give IV acyclovir for non-skin organ involvement and to patients who are immunocompromised.

Prophylaxis: Development of chicken pox in persons who have come in contact with a case of chicken pox and are at risk for developing chicken pox can be prevented in 2 ways. Persons at risk are those who are not currently immune (because they have never had chicken pox or the chicken pox vaccine) or are currently immunocompromised or pregnant. Immunocompetent persons should receive the varicella vaccine. Immunocompromised or pregnant patients should not receive this vaccine because it is a live vaccine. These people should receive varicella zoster immune globulin (VZIG) as soon as possible after exposure. In 2012, the FDA approved its use up to 10 days after exposure.

Herpes Zoster (Shingles)

Overview

Herpes zoster is caused by reactivation of the varicella-zoster virus after the initial infection. After the initial infection, virus becomes dormant and asymptomatic in sensory ganglia neurons until it is reactivated and spreads down the nerve, causing a painful rash.

Reactivation causes a prodromal phase with constitutional symptoms followed by hyperesthesia and a burning, frequently lancinating pain over the dermatome. This is followed by the characteristic vesicular skin rash.

In about 10–20% of patients, the ophthalmic branch of the trigeminal cranial nerve is involved, which can be sight-threatening if zoster keratitis results. The most common dermatomes involved are the thoracic dermatomes. Usually one thoracic dermatome is involved, but occasionally it may involve 1–2 more. If there are more than 3 dermatomes involved, or more than 30 lesions outside of the primary dermatomes, it is considered disseminated zoster.

Just as with chicken pox, the zoster lesions are contagious until crusted over—and can give a nonimmune person chicken pox.

QuickQuiz

- What is the most sensitive and specific method for diagnosing HSV encephalitis?
- In what situation should a pregnant woman be given varicella vaccine?
- Which patients should receive the zoster vaccine?
- How is CMV diagnosed?
- What is the clinical presentation of EBV mononucleosis?

Disease duration is about 2–4 weeks. If there are any new lesions after 7–10 days, consider underlying cell-mediated immunodeficiency. Immunocompromised patients are at increased risk for dissemination, which may include organ involvement (CNS, lung, liver). Shingles recurs in < 5% of immunocompetent patients.

Postherpetic Neuralgia

Postherpetic neuralgia is the most common complication (~ 12% overall) of zoster, and it is more likely to occur with increasing age (20% in those > 80 years of age). It can cause a lancinating, sometimes debilitating pain for many months to years.

Vaccination for Herpes Zoster

The zoster vaccine decreases the incidence of zoster by 1/2 and the incidence of postherpetic neuralgia by 2/3. It is currently FDA approved for those 50 years of age or older, but the Advisory Committee on Immunization Practices (ACIP) recommends the vaccine for those 60 years of age or older.

Treatment

Oral acyclovir, famciclovir and valacyclovir are shown to decrease the incidence of postherpetic neuralgia. They also shorten the duration and severity of the initial pain.

Adding prednisone provides no additional benefit and even prolongs the course of herpes zoster in immunosuppressed patients.

For pain control, tricyclic antidepressants, gabapentin, and lidocaine patches have some efficacy. Narcotics are effective and underused in this instance. Capsaicin cream is useful after the lesions have healed.

CYTOMEGALOVIRUS (CMV)

Cytomegalovirus (CMV) is a DNA virus in the herpes virus family. CMV infection in the normal population is fairly common; 1/2 of the population has anti-CMV antibodies by the age of 35.

CMV infection in the normal population is typically asymptomatic, but ~ 10% have a mononucleosis-type illness with fever, sore throat, adenopathy, fatigue, and hepatitis. Exudative pharyngitis is rare though. Think of this in a monospot-negative adult with these symptoms (especially if younger-to-middle-aged because EBV mono usually occurs more in adolescents). Also, consider acute HIV with this presentation.

CMV is a very common infection in patients with decreased cellular immunity (post-transplant and AIDS). 75% of seronegative transplant recipients get CMV if the donor is seropositive. With a post-transplant systemic CMV infection, the patient can have concurrent "-itises," which may include encephalitis, hepatitis, retinitis, colitis, and adrenalitis (causing adrenal insufficiency); these are especially common and more severe if the recipient is seronegative prior to the transplant.

HIV/AIDS: When the CD4 count gets < 50, CMV can cause chorioretinitis, pneumonitis, esophagitis, and colitis. This CMV retinitis is distinctive; it has both retinal blanching and hemorrhage and follows along the path of the retinal arteries.

Diagnose acute CMV infection by demonstrating DNA in peripheral blood. Immunohistochemical stains can be used to stain CMV-infected cells in tissue-invasive disease. Occasionally, tissue-invasive disease presents without viremia.

Treat susceptible CMV infection with valganciclovir or ganciclovir. For resistant virus, foscarnet or cidofovir may be used.

EBV

Epstein-Barr virus (EBV) causes infectious mononucleosis. Incubation period is 1–2 months. Most (> 90%) patients have pharyngitis (which is commonly exudative) or tonsillitis, fever, lymphadenopathy, and abnormal liver function. Splenomegaly may be seen.

Lymphocytosis is commonly found in acute EBV infection usually with > 10% "atypical lymphocytes." Atypical lymphs are enlarged with abundant cytoplasm, vacuoles, and indentations of the cell membrane. These are T cells that are actively trying to fight the EBV-infected B cells. 90% of patients with acute EBV develop a macular rash if given ampicillin, which can occur if the exudative pharyngitis is mistaken for *S. pyogenes* infection.

Diagnosis of infectious mononucleosis may be made clinically and confirmed by serology. Heterophile antibody titers (monospot) are nonspecific antibodies that cross-react with RBCs of other mammals. They are absent ~ 25% of the time in the 1st week of illness ("heterophile-negative mononucleosis"). Thus, the most common cause of heterophile-negative mononucleosis of 1-week duration is still EBV. The diagnosis can be made by testing for IgM capsid antibody in these patients. Other causes of heterophile-negative

mononucleosis are CMV toxoplasmosis, acute HIV, and HHV-6 infection.

Treatment of acute EBV infection remains supportive because of its excellent prognosis and unavailability of any antivirals active against EBV.

EBV causes oral hairy leukoplakia, which may be seen as an early manifestation of HIV disease. Chronic fatigue has no proven association with EBV. EBV is oncogenic and is associated with nasopharyngeal carcinoma and non-Hodgkin lymphoma, specifically Burkitt lymphoma. Other cancer-causing viruses include hepatitis B and C.

RUBELLA (GERMAN MEASLES)

Rubella (ssRNA virus) is "German measles" (Image 2-21). If it is acquired by a pregnant patient in the 1st trimester, there is a 50% chance that the baby will have congenital defects. It is diagnosed by the hemagglutination inhibition test or by ELISA. If this test is negative in a newly exposed pregnant patient, repeat it in 3 weeks (after incubation period) before any decisions are made. If it is then positive, offer the patient the option of a therapeutic abortion. Immune globulin does not prevent the infection, but it may give some fetal protection in the patient who refuses therapeutic abortion.

RUBEOLA (MEASLES)

Rubeola is "measles" caused by an ssRNA virus. Symptoms start ~ 10 days after the initial exposure. Symptoms at the onset are the "3 Cs": cough, coryza, and conjunctivitis (with photophobia). Patients also have malaise and fever. Koplik spots (whitish spots on an erythematous base) appear on the buccal mucosa before the onset of the skin rash (Image 2-22). The skin rash starts at the hairline and spreads downward. It lasts ~ 5 days and then resolves, also from the hairline downward. Outbreaks continue to occur in at-risk persons who have not been vaccinated.

RETROVIRUS

Retroviruses are RNA viruses.

- HTLV-1 causes T-cell leukemia and a neurologic syndrome, spastic tropical paraparesis, seen in Japan and the Caribbean.
- HTLV-2 causes a rare T-cell variant of hairy cell leukemia.
- HIV-1 causes AIDS (much more on page 2-52).
- HIV-2, found in West Africa and parts of the U.S., is a virus that causes an illness indistinguishable from AIDS. (Both HIV-1 and -2 are now picked up by EIA/ELISA.) More on HIV on page 2-46.

RESPIRATORY VIRUSES

Rhinoviruses

Rhinoviruses are a common cause of URI in adults.

Respiratory Syncytial Virus

RSV infections occur year round, usually during the autumn and winter. RSV infections are more severe in the infant, occasionally resulting in pneumonia. Only 1% of infected infants are hospitalized. RSV infection has similar morbidity as influenza and especially affects the elderly and those with immunodeficiency. It is now thought to be responsible for up to 25% of excess winter season mortality that was previously attributed solely to influenza.

RSV is also an important pathogen in hematopoietic stem cell transplant recipients and lung transplant recipients. Diagnosis can be made by detecting RSV antigen or with PCR of nasal secretions. Ribavirin (oral or inhaled) is used as an antiviral therapy in immunocompromised hosts, but the efficacy is limited.

Influenza

Influenza is still a major cause of death, especially if the patient is > 55 years of age with COPD. Vaccination decreases mortality.

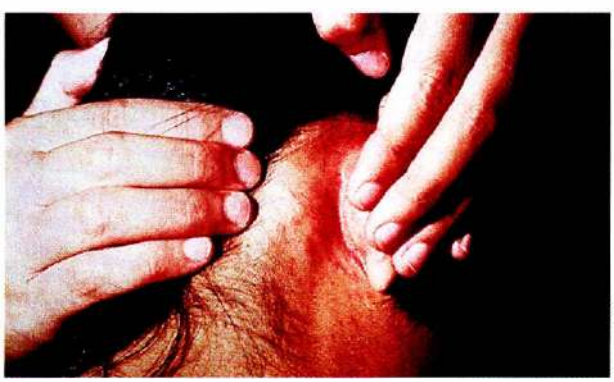


Image 2-21: Rubella infection with postauricular adenopathy

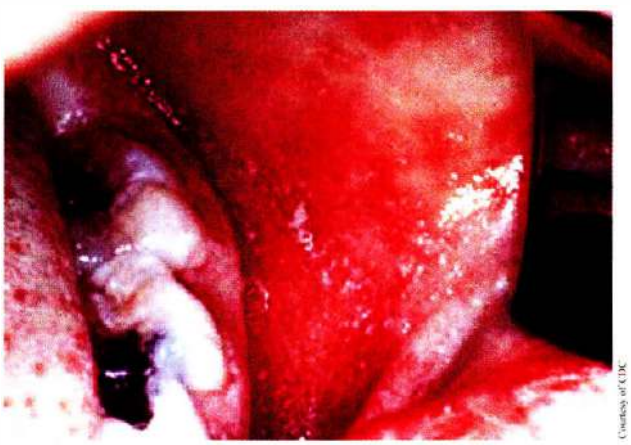


Image 2-22: Measles; Koplik spots, small white spots that occur before the rash

QuickQuiz

- What are the clinical symptoms of measles?
- How do you diagnose influenza A?
- What drugs are recommended for empiric treatment of probable influenza?
- Which patient groups can receive the intranasal influenza vaccine?
- Name some animals that are high-risk for transmission of rabies.

There are 3 types of influenza viruses: influenza A, B, and C. Subtypes of influenza A exist based on their specific neuraminidase (N1 and 2) and hemagglutinin (H1–3) antigens. A and B cause the yearly epidemics of respiratory illnesses. Influenza C causes very mild, if any, symptoms.

Example: The major circulating influenza A subtypes in 2009–2010 were seasonal H3N2, seasonal H1N1, and novel H1N1 (swine flu). The novel H1N1 subtype was especially virulent in the following situations: pregnancy, children < 24 years of age, adults > 65 years of age, and immunodeficient states.

Influenza presents as an acute febrile respiratory illness with fever and cough. Serious complications include viral pneumonia, secondary bacterial pneumonia, rhabdomyolysis, and encephalitis.

Diagnosis: A positive antigen test or PCR for influenza A and B on nasopharyngeal swab or respiratory secretions is diagnostic. While a positive test does not always have to result in antiviral treatment, it is quite useful to rule out bacterial infection (antibiotic stewardship) and has a role in infection control.

Treatment should be given in 3 settings:

1) Those at high risk of complications (immunocompromised, pregnancy; underlying heart, lung, liver, kidney disease; > age 65; residents of chronic care facilities; active malignancy, diabetes, hemoglobinopathies, neurologic conditions causing compromise of handling respiratory secretions; Native Americans; Alaska Natives; and morbid obesity)
2) Hospitalized patients
3) Severe, progressive, or complicated illness

In addition, anyone outside of these high-risk groups who presents with influenza within 48 hours of onset may be treated based on clinical judgment.

Two classes of drugs have been used to treat influenza. The newer neuraminidase inhibitors (oseltamivir, zanamivir) have replaced the older M2 ion channel inhibitors (amantadine, rimantadine). Oseltamivir and zanamivir decrease duration of illness and spread of disease and are most effective if given within 48 hours of onset of symptoms. The prevalence of antiviral resistance to any specific agent is dependent on the circulating strains and is steadily increasing.

Prevention: All individuals > 6 months old should receive annual influenza vaccination. Influenza vaccines are targeted at the serotypes that are most likely to be present when the influenza season occurs. The better the antigenic match between this year's strains and next year's, the better the vaccine works. There are 2 types of influenza vaccines in the US: inactivated and intranasal live-attenuated. The live-attenuated (intranasal) vaccine is available for healthy, non-pregnant patients ages 2–49 years. All others should receive the inactivated vaccine. Vaccines should be administered when they become available each year, which is usually in October.

Coronavirus

Usual Coronavirus Infection

Coronavirus is an enveloped RNA virus. In its usual form, it is responsible for 3–5% of "common colds." Coronavirus "colds" are more likely to occur in winter and early spring.

Severe Acute Respiratory Syndrome (SARS)

Severe acute respiratory syndrome (SARS) is due to SARS-associated coronavirus (SARS-CoV). From November 2002 to July 2003, there were > 8,000 cases worldwide and 916 deaths according to the World Health Organization. Patients typically had early "flu-like" symptoms that quickly progressed to severe respiratory distress. The elderly were far more likely to be severely affected. Novel SARS-like coronaviruses continue to emerge, posing an ongoing threat; e.g., Middle East respiratory syndrome MRES-CoV in 2013.

POLIO

90% of polio is self-limited. Its onset is characterized by aseptic meningitis and an asymmetric flaccid paralysis with loss of reflexes. It is essentially eliminated in the western hemisphere and developed countries worldwide secondary to vaccination, but it is still a problem in the developing world, especially India. Spinal cord infection with enterovirus 68 mimics polio, and should also be considered in children with flaccid paralysis. More in Neurology, Book 5.

RABIES

Rabies is especially found in bats, raccoons, skunks, foxes, dogs, cats, and ferrets; but not in squirrels, rats, or any other rodents. Worldwide, the vast majority of rabies is transmitted to humans by dogs. By contrast, in the U.S., 24 of the 25 cases of human rabies that occurred between 1995 and 2006 were from bats. Rabies usually presents within 1–3 months after exposure with a viral prodrome followed by encephalitis, a Guillain-Barré mimic, or neuropathic pain +/– sensorimotor deficits.

The encephalitis is commonly associated with the classic rabies symptoms of hydrophobia, choking, and delirium.

Preexposure prophylaxis is recommended for cave explorers, veterinarians, animal control workers in endemic areas, and anybody who handles bats—but not for hunters, mail carriers, or the average person.

Diagnosis: evaluation of several specimens, including saliva, skin, and brain biopsy, and CSF. Serology is not useful.

Post-exposure prophylaxis: The need for prophylaxis is based on the suspected animal source. Bites from bats, raccoons, foxes, and skunks are considered high-risk, and prophylaxis should be given. Pet dogs, cats, and ferrets should be observed for 10 days, and if no signs of rabies, prophylaxis is not needed. Small rodent bites never need prophylaxis. Prophylaxis consists of human rabies immune globulin (HRIG) injected in the tissue around the wound with the remainder administered IM, and vaccination with human diploid cell vaccine may be indicated. Each should be given in a separate site. If a person has been vaccinated previously, they need only a booster vaccine after a bite, not HRIG.

Remember: "Woke up with bat in room" means that the patient should receive prophylaxis regardless of documented bite.

MUMPS

Mumps (RNA virus) occurs most commonly in winter and early spring. Although it often is asymptomatic, it can present with uni- or bilateral parotitis, aseptic meningitis, and/or encephalitis. 15–20% of post-pubertal males with mumps get an epididymo-orchitis, which is usually unilateral. Postinfection sterility is a rare occurrence. To differentiate mumps from bacterial parotitis, check a Gram stain of the parotid secretions. There are many WBCs and organisms in bacterial parotitis and none in mumps. Other causes of enlarged parotid glands are frequent vomiting or parotid duct stones. Always consider bulimia in an adolescent or adult with parotid gland enlargement.

PARVOVIRUS

Parvovirus is a small DNA virus. One parvovirus, B19, causes human disease. It is spread by respiratory secretions and is usually acquired early in life, commonly manifesting as erythema infectiosum (Fifth disease) with a high fever and a "slapped cheek" appearance.

Clinical manifestations: Adult-acquired illness is typically a self-limited fever, symmetric small joint arthritis, and a lacy rash on the extremities. Immunocompromised hosts and patients with chronic anemias (e.g., sickle cell) are at risk of chronic severe "aplastic" anemia secondary to parvo B19. In aplastic anemia, the bone marrow stops producing blood-forming cells, and fat replaces hematopoietic cells.

Diagnosis: Testing for IgM antibody can be used in immunocompetent patients. Diagnosis in immunocompromised patients (who may not mount an antibody response) is made with a serum PCR assay for parvovirus DNA.

Therapy: No specific antiviral therapy for parvo is available. IVIG may be used in immunocompromised hosts, and antiretroviral therapy for patients with HIV/AIDS may be helpful.

ARBOVIRUSES

Arboviruses (short for "arthropod-borne" viruses) are transmitted by mosquitoes or ticks. Various arboviruses occur in the U.S., typically in the late spring and summer. Until recently, most cases occurred along the Gulf Coast in Louisiana and Florida. Now, with West Nile virus, the arboviruses are seen from coast to coast. West Nile virus (WNV) is the most commonly identified arbovirus.

Besides WNV, La Crosse, St. Louis, Eastern and Western equine, Venezuelan equine, Powassan, and Colorado tick fever viruses occur on occasion in the U.S.

Clinical manifestations: Almost all symptomatic arboviral infections have similar symptoms: fever, headache, chills, and varied severity of encephalitis or aseptic meningitis. Symptomatic cases of WNV usually present as a nonspecific viral illness, but most cases (80%) are asymptomatic. Neuroinvasive disease (encephalitis, meningitis, or an asymmetric flaccid paralysis similar to polio) occurs in about 1/150 patients. Since polio is no longer present in the U.S., a person with this presentation should be tested for WNV. Less common presentations are tremor, myoclonus, parkinsonism, and cranial neuropathies.

Diagnosis: virus-specific IgM antibody in the CSF or serum.

Treatment: supportive; no specific antiviral therapy available.

Control: mosquito netting, mosquito repellents, insect control.

HANTAVIRUS

Hantavirus pulmonary syndrome (HPS) starts as a nondescript viral syndrome, often with GI symptoms; patients then develop muscle pain, fever, headache and cough, which quickly progresses to hypoxia, hemorrhagic pneumonia, ARDS, and death in more than 50% of cases. Laboratory findings include hemoconcentration and thrombocytopenia.

The primary reservoir in the U.S. is the deer mouse. On the East Coast and in the Southeast, the cotton rat is the main reservoir. The infection occurs when the excreta or saliva are inhaled. Transfer of the virus can also occur through broken skin, possibly by insect bites. No person-to-person transfer is known to have occurred.

No specific antiviral therapy is available.

Quick Quiz

- What are complications of mumps in the male?
- Which virus is associated with the "slapped cheek" rash?
- What does the bone marrow show in patients with pure red cell aplasia from parvo B19?
- Are arboviruses spread by a) biting insects, or b) person-to-person contact?
- How is West Nile virus encephalitis diagnosed? What other viral infection does it mimic in the peripheral nervous system?
- Characterize a patient with hantavirus pulmonary syndrome.
- How does dengue hemorrhagic fever present? Where is it most often contracted?
- What virus causes PML, and how does it present?

DENGUE

The dengue virus causes a spectrum of disease ranging from asymptomatic infection to dengue fever or, most ominously, to dengue hemorrhagic fever. It is the most common mosquito-borne viral disease and is seen throughout the tropics. Virus is transmitted to humans via the day-biting *Aedes* mosquitoes. (*Anopheles* mosquitoes carry malaria.)

Dengue fever symptoms are rapid onset of high fever, markedly severe myalgias, arthralgias, and headache ("breakbone fever"). This may be followed by a macular red rash that covers most of the body.

Dengue hemorrhagic fever is due to a diffuse capillary leak syndrome that results in hemoconcentration, anasarca, thrombocytopenia, and spontaneous bleeding. Death due to circulatory collapse may occur. It is more common in people who have had a prior infection with dengue.

Diagnosis is via a serum IgM antibody assay. Treatment is supportive with IV fluids. No specific antiviral therapy is available, and there is no vaccine.

SLOW VIRUSES

Overview

There are 2 classes of slow viruses:

1) Normal viruses, such as papillomavirus (warts) and polyomavirus (progressive multifocal leukoencephalopathy [PML])
2) Defective viruses, such as the defective measles virus (subacute sclerosing panencephalitis)

Papillomavirus

Papillomavirus is transmitted by direct contact and causes warts.

Genital warts are associated with an increased risk of cervical, vaginal, vulvar, penile, and anal cancer. There are many variants, and 15 of these variants found worldwide are designated high-risk for cancer. HPV 16 and 18 are the most common causes of cervical cancer (60% and 10%, respectively). The strains that cause cervical cancer are usually subclinical. Much more on cervical cancer in Oncology, Book 4.

HPV 6 and 11 are the most common causes of the exophytic, grossly visible genital warts. HPV 6 and 11 carry little risk for cervical cancer.

HPV 1, 2, and 5 are common causes of plantar warts.

HPV vaccines contain the most oncogenic serotypes and are recommended for all men and women ages 9–26.

Polyomavirus JC

Reactivation of the JC virus in the immunosuppressed host, generally HIV/AIDS and CD4 < 200, results in progressive multifocal leukoencephalopathy (PML), which is due to progressive demyelination of the white matter. PML, because it is multifocal, has varied presentations. Usually, the patient suffers altered mental status, followed by various focal motor/sensory deficits.

Diagnosis is suggested by an MRI showing multifocal demyelinating lesions in the white matter and can be confirmed by CSF PCR, which has a sensitivity of 70–90%.

No specific antiviral therapy is available, but some patients may have improvement if immunosuppression can be reversed.

PRION DISEASE

Prions are proteinaceous infectious particles that lack nucleic acid and constitute a previously unknown means of transmitting disease.

The most important prion diseases are Creutzfeldt-Jakob disease (CJD), and variant of CJD (vCJD). In animals, prions cause mad cow disease (= bovine spongiform encephalopathy = vCJD when transmitted to humans).

CJD is almost always sporadic but ~ 5% are infectious (e.g., corneal transplants, cadaveric human growth hormone), and very few are genetic. Its incubation period is ~ 18 months. Patients with CJD get myoclonus and severe dementia. MRIs show diffuse cerebral disease, and EEGs classically show periodic synchronous bi- or triphasic sharp wave complexes. An abnormal protein, 14-3-3, may be present in the CSF. Course is one of progressive deterioration with the majority of patients dead within 6 months of diagnosis. There is no effective therapy for CJD.

vCJD, probably transmitted from beef with bovine spongiform encephalopathy (BSE, mad cow disease),

has been contracted worldwide, with most cases in the United Kingdom. No endemic U.S. human cases of vCJD have been reported, although some veterinary cases have been reported.

vCJD patients have early-on psychiatric symptoms, late-appearing neurologic symptoms (typically ataxia), and rapidly developing dementia—occurring over months rather than years. Once neurologic symptoms appear, progression to death is rapid.

Related illnesses include kuru and fatal familial insomnia.

HIV AND AIDS

OVERVIEW

Changes in the treatment and management of HIV infection are evolving rapidly. The following covers the basics. Antiretroviral drugs are listed in the content specifications for the exams, so this information is presented here. However, realize that exam questions are more likely to focus on diagnosis and complications of disease and side effects of medications than on having you start or change antiretroviral treatment (ART) regimens.

HIV STRUCTURE

The HIV particle is composed of a dense, single-strand RNA core surrounded by a lipoprotein envelope. The RNA contains reverse transcriptase, which allows the RNA to be transcribed into DNA, which is then integrated into the host's genome. The cell then becomes an HIV-producing machine.

The receptor in the lipoprotein envelope that allows the HIV to attach to the CD4+ T cell is named gp120. As opposed to influenza, the envelope on HIV is highly variable; therefore, it is much more difficult to make a vaccine against it.

HOW HIV INFECTS

HIV gp120 envelope glycoprotein binds to the CD4 receptors and coreceptors (such as CCR5) on the helper T cells, macrophages, and monocytes. The virus must bind to both the CD4 and CCR5 molecule to fuse with the cell. After fusion, the viral core material enters the cell and is reverse transcribed into DNA that integrates into the human genome and codes for the production of more virion RNA and structural proteins. These proteins, after being cleaved by a protease, then combine with the viral RNA and bud off of the cell using the CD4 cell membrane as a new envelope. This eventually causes destruction of the CD4 cells. The CD4 cells are the major regulator cells in the body; they suppress B lymphocytes and regulate the CD8 suppressor cells.

With the decrease in CD4+ counts, B cells become deregulated and are no longer suppressed, causing a polyclonal increase in total serum immunoglobulins, even though overall antibody function is decreased. For this reason, infectious diseases in AIDS patients include not only the cell-mediated infections (PCP, viruses, mycobacteria, and fungi), but also those seen with humoral deficiency (pneumococcus, meningococcus, *Giardia*).

EPIDEMIOLOGY

The latest U.S. statistics are representative of 2008–2011. The numbers given are estimates made by the CDC, based on a statistical analysis that corrects for reporting delays and missing risk factor information.

Relevant epidemiology:

- New diagnoses of HIV in 2011 = 49,273.
- Age group with the highest rate of infection = 40–44 years (27.4/100,000).
- Race/ethnicity with the highest rate of infection = African-Americans (60/100,000) compared with Caucasians (7.0/100,000).
- The transmission category with the greatest number of new diagnoses was male-to-male sexual contact = 62% of all new diagnoses.
- Heterosexual transmission represented 9% of all new diagnoses.
- Injection drug use accounted for 5% of cases.

DIAGNOSIS

HIV infection is diagnosed by demonstrating the presence of the virus or antibody to the virus.

The standard screening test for HIV is an enzyme immunoassay (EIA). This test detects antibody to the virus and is 99% sensitive and 90–99% specific. Positive responders are confirmed by the Western blot. Antibody to HIV is usually detectable 3–7 weeks after inoculation.

The presence of HIV can be assessed with tests that measure the actual levels of HIV RNA (viral load) by amplifying the RNA. The main use for determining the level of HIV RNA (viral load) is to assess prognosis and monitor response to ART (antiretroviral therapy). Disadvantages of its use as a tool to diagnose HIV include cost and time. However, it may have a role in some clinical situations such as acute infection, indeterminate results of serologic testing, and neonatal infection.

A number of rapid tests are available which assay blood, serum, plasma, or saliva; many are able to provide results in less than 30 minutes. Positive tests must be confirmed with EIA and Western blot tests.

Again:

1) EIA for HIV antibody is the usual means of determining HIV infection. A positive test is confirmed by Western blot.
2) HIV RNA test determines actual RNA levels or "viral load," which may be undetectable in a person under treatment for HIV infection.

Quick Quiz

- Patients with HIV/AIDS are at risk for developing infections with what organisms?
- How is HIV infection diagnosed in the acute and chronic stages? What is the utility of measuring HIV RNA?
- What is the viral set point, and what is its significance?
- What are side effects of ZDV? ddI? d4T?
- What is the serious side effect of abacavir?

After initial infection, the virus replicates quickly and robustly, until the body controls the infection with cell-mediated immunity. The body establishes a kind of homeostasis with the virus, where the virus is contained to some degree; however, the body does not contain the virus entirely (e.g., viral load of zero). Some people contain their virus better than others.

The **viral set point** is that viral load which is established after a patient's immune system controls primary infection, and it varies from person to person. When a patient stops ART (antiretroviral treatment), their virus typically rebounds to a level that is at least as high as their set point.

TREATMENT OF HIV INFECTION

Combination drug ART is the standard of care.

When to start treatment is easy: Start ART on all treatment-naïve HIV patients (discussed more under When to Initiate Antiretroviral Therapy on page 2-50).

Adherence to the ART regimen is a key determinant in the degree and duration of viral suppression. It is extremely important to actively involve the patient in the treatment decision-making process. Guide decisions regarding initiation or changes in ART by monitoring plasma HIV RNA (viral load) and CD4 T-cell counts, in addition to the patient's clinical condition. The effectiveness of all drugs decreases if drugs are used in regimens that are not fully suppressive due to development of resistant mutations. All treatment decisions should be based on treatment guidelines that are released yearly and are posted on the Internet (http://www.aidsinfo.nih.gov/guidelines). Know that treatment options are always evolving in HIV disease.

First, we will review the major classes of anti-HIV drugs, then the treatment protocols. To get a good understanding of how these drugs work, refer frequently to the earlier paragraphs on HIV Structure and How HIV Infects as you go through the different classes of anti-HIV drugs.

For exam questions regarding HIV treatment, you mainly need to know:

- when to initiate treatment (page 2-50)
- the main treatment protocols (page 2-50), and
- the main side effects and Quick Quiz (page 2-49).

Antiretroviral Drugs

Drug acronyms for the major classes of anti-HIV drugs:

- NRTIs = nucleoside reverse transcriptase inhibitors and nucleotide reverse transcriptase inhibitors
- NNRTIs = nonnucleoside reverse transcriptase inhibitors
- PIs = protease inhibitors
- FI = entry/fusion inhibitor
- Integrase inhibitors

NRTIs

Nucleoside Reverse Transcriptase Inhibitors

These drugs are analogs of the deoxynucleotides needed to synthesize viral DNA. They inhibit the replication of HIV by competing with the normal deoxynucleotides. When a NRTI is incorporated into the growing viral DNA, the growing chain terminates and that DNA cannot then be incorporated into the cell's DNA and produce more HIV. Note that nucleotide RTIs work the same way (see page 2-48) and the term "NRTI" covers both.

Zidovudine (ZDV) = azidothymidine (AZT). This is the oldest of the antiretroviral drugs but still remains very useful, especially in the settings of resistant virus or pregnancy. ZDV is well tolerated at currently used doses, but may cause bone marrow suppression (anemia, granulocytopenia) and myopathy. A macrocytosis (elevated MCV) always occurs but has no clinical consequence. ZDV does not usually cause problems for the kidneys or lungs and does not cause pancreatitis. ZDV is associated with lipoatrophy when taken chronically.

Currently, ZDV is only rarely used as initial therapy. Some patients, who have been on treatment for a long period of time, remain on ZDV, typically in combination with 3TC.

Lamivudine (3TC) is a very effective drug, and it is well tolerated. 3TC has been the most commonly prescribed antiretroviral agent. Side effects are rare.

Emtricitabine (FTC) is a drug that is not only extremely effective, but it has minimal toxicity. FTC is an analog of 3TC and exhibits complete cross-resistance (i.e., if patients have resistance to 3TC, they have resistance to FTC). It is used in all the recommended combinations for ART-naïve patients.

Abacavir (ABC) is very effective. The most serious reaction is a hypersensitivity reaction, which usually occurs within 4 weeks. The reaction consists of a generalized rash and/or a flu-like illness with fever, chills, N/V, myalgias, cough, and shortness of breath. In

patients with this hypersensitivity reaction, a rechallenge with abacavir (after discontinuation of the drug) causes an accelerated hypersensitivity reaction that causes multiple organ failure, which can be rapidly fatal.

Abacavir hypersensitivity is linked to the *HLA B-57:01* gene, and now it is recommended that all patients be tested for this gene before beginning abacavir therapy. If negative, the hypersensitivity rate decreases to < 2%.

The following NRTIs are rarely used:

Didanosine (ddI): This is now less commonly used due to toxicity. The most severe side effects are pancreatitis (which can be life-threatening) and peripheral neuropathy. ddI is also associated with lipoatrophy and mitochondrial toxicity, and low CD4 counts (even with a suppressed viral load). Fatal lactic acidosis can occur with concomitant use of d4T.

Stavudine (d4T): d4T is now used only in salvage therapy because of toxicity. d4T can cause lipoatrophy and mitochondrial toxicity syndromes. Side effects include pancreatitis and peripheral neuropathy. Also, d4T in combination with ddI can cause a fatal lactic acidosis—especially in pregnant women. This combination of d4T and ddI is basically used only for salvage regimens in the U.S.

Nucleotide Reverse Transcriptase Inhibitors

Tenofovir (TDF; Viread®) is a nucleotide-RTI very similar to the above nucleoside analogs, except that nucleotide RTIs are chemically pre-activated and, therefore, require less biochemical processing than the nucleoside RTIs.

Tenofovir has once-daily dosing and a good side-effect profile—mainly asthenia/headache/N/V/D/flatulence. Azotemia and a Fanconi-like syndrome have been seen with tenofovir, particularly in patients predisposed to renal disease.

NRTI Combinations

NRTI combinations:

- Combivir® (3TC/ZDV)
- Trizivir® (3TC/ZDV/abacavir)
- Epzicom® (3TC/abacavir)
- Truvada® (TDF/FTC)
- Atripla® (TDF/FTC/efavirenz)
- Complera® (TDF/FTC/rilpivirine)
- Stribild® (TDF/FTC/elvitegravir/cobicistat)

Know that the 2 drugs, TDF and FTC, are included in all recommended combinations for initial treatment of ART-naïve patients.

Do not use ZDV and d4T together due to antagonism. Avoid the combination of tenofovir and ddI because of drug interactions and intracellular accumulation of metabolites that can actually cause T-lymphocyte levels to drop.

NNRTIs

Nonnucleoside RTIs work very differently from the NRTIs. These make the reverse transcriptase ineffective by binding to a different site on the enzyme.

Nevirapine is the 1st of this class of drugs. Rash, which can be severe, is the primary toxicity. Fatal hepatic toxicity, especially in women with CD4 count > 250 and in patients coinfected with hepatitis, has been reported.

Efavirenz (EFV) is effective and commonly used. However, it is associated with teratogenicity, absolutely contraindicated in pregnancy, and discouraged from use in women of childbearing potential. Other side effects include rash, vivid dreams, insomnia, fuzzy thinking, and mood swings. A fixed-dose coformulation with TDF/FTC is available (Atripla).

Etravirine was approved in 2008. It may cause a serious skin rash. It is useful in HIV infection that has been previously resistant to the other NNRTIs.

Rilpivirine (Edurant®) is a new NNRTI just released for use in naïve patients. A fixed combination with TDF/FTC is available (Complera).

PIs

HIV protease inhibitors—PIs (ataza-, daru-, rito-, lopi-, fosampre-, saqui-, indi-, nelfi-, tipranavir) inhibit the HIV protease enzyme that is involved with processing the final assembly of the virion. Except for nelfinavir, all PIs are given with low-dose ritonavir (another PI) because ritonavir interferes with the catabolism of the drug and thus boosts the drug levels of the coadministered PI (termed "ritonavir boosting").

Atazanavir and darunavir are the most commonly used protease inhibitors. Lopinavir is less commonly used due to side effects, but remains useful in pregnancy and for those patients who tolerate it well. Tipranavir is used only very rarely for highly resistant virus not sensitive to other PIs. Fosamprenavir is sometimes used because of its flexibility of dosing and lack of drug interactions.

Fat redistribution, lipid abnormalities (increased triglycerides and cholesterol), new-onset Type 2 diabetes, and osteoporosis have been recognized with the use of PIs. When treating lipid abnormalities in HIV-infected persons, it is important to note that PIs inhibit the P450-mediated metabolism of simvastatin and lovastatin, and coadministration may cause high drug levels of the statins and precipitate rhabdomyolysis. These drugs are contraindicated in patients on PIs. Also avoid other drugs that cause interactions: rifampin, astemizole, cisapride, and St. John's wort.

Atazanavir is a once-daily PI that doesn't have adverse lipid effects. For maximum potency, the drug needs to be boosted with ritonavir. It is associated with unconjugated (indirect) hyperbilirubinemia of no clinical consequence.

Darunavir was approved in 2006. Monitor use closely in patients with underlying hepatitis virus coinfection.

Quick Quiz

- Which NRTI can be associated with development of kidney disease?
- What is the primary toxicity of nevirapine?
- Which antiretroviral is teratogenic?
- Which PI is used to boost the drug concentrations of other PIs?
- What metabolic defects have been associated with use of protease inhibitors?
- Which antiretroviral drug is associated with indirect hyperbilirubinemia?

Currently, darunavir is used in all lines of therapy from naïve to salvage. It can be used qd or bid and is better tolerated than lopinavir/ritonavir (Kaletra®).

Ritonavir (usually shown as "/r" in its low-dose boosting role) is now mainly used in low doses to boost the levels of most other PIs. It is a potent drug, but patient tolerability is poor due to side effects. The main side effects are N/V, flushing, distorted taste, and paresthesias. There are many drug interactions because of interference with the p450 enzyme system.

Lopinavir/ritonavir (LPV/r) is a coformulation of lopinavir and low-dose ritonavir. Lopinavir is available only in this coformulation. It is very potent and well tolerated. Currently, it is not generally used for initial therapy because it is less well tolerated than atazanavir or darunavir and causes more lipid abnormalities.

Fosamprenavir is the prodrug of amprenavir. It requires fewer pills and eliminates the major side effects of amprenavir. Primarily used because of lack of drug interactions and flexibility of qd or bid dosing.

These PIs are rarely used:

Saquinavir is not used much, having been replaced by newer, simpler PIs. In 2010, the FDA added a warning that ritonavir-boosted saquinavir has been associated with prolongation of the QT interval and development of *torsade de pointes*. Do an ECG before prescribing, and do not give the regimen to any patient with a QT interval > 450 ms. Also, recheck the ECG after 2 weeks for new prescriptions.

Indinavir has side effects that include an asymptomatic hyperbilirubinemia and a high incidence of nephrolithiasis. Indinavir is rarely used because of the development of PIs that are less toxic and have more convenient dosing.

Nelfinavir side effects include diarrhea and rash. It is less commonly used because of the GI intolerance and the better efficacy of the newer PIs. Nelfinavir is the only PI that is not boosted with ritonavir.

Tipranavir was approved in late 2005. It has adverse lipid effects, and its main side effects are GI related and rash. Used only rarely for extremely resistant virus.

Entry / Fusion Inhibitors

Maraviroc (Selzentry®) is the first drug approved for treatment of CCR5-tropic HIV—which are the strains of HIV that appear early in the disease and require binding to this coreceptor to allow cell entry. A coreceptor tropism assay to confirm the presence of the CCR5 coreceptor should be performed prior to use of maraviroc. It is an oral agent and carries an FDA boxed warning for drug-induced hepatitis. Maraviroc is approved for use in combination therapy in all lines of therapy, including naïve patients. It is generally well tolerated.

Enfuvirtide (Fuzeon®) is the only fusion inhibitor available. It binds to and alters the structure a glycoprotein on the HIV envelope, gp41, which is required for fusion of the virus with the CD4+ cell. Given by subcutaneous injection, its main side effects are local reactions at the injection site and increased risk of bacterial pneumonia. It is not part of most regimens because it requires injection and is used only for salvage treatment.

Integrase Inhibitors

Raltegravir was the 1st integrase strand transfer inhibitor (INSTI) available. It prevents the HIV integrase enzyme from inserting HIV's reverse transcribed DNA into an infected cell's own DNA, halting this critical step in the life cycle of HIV. It is an oral agent. Raltegravir is now indicated for all lines of therapy, including naïve patients. Its twice-daily dosing is well tolerated with few drug interactions and no effect on lipids. Integrase inhibitors decrease viral load more rapidly than any other class of antiretroviral.

Elvitegravir is an integrase inhibitor that is given with cobicistat to boost its levels. It is available as a 4-drug fixed combination with FTC and tenofovir to allow once-daily dosing. It is indicated for treatment in naïve patients only. Renal function needs to be monitored closely because of the interaction between tenofovir and cobicistat.

Key Words and Side Effects

Key words/phrases to remember for side effects:

- NRTIs
  - ZDV: bone marrow suppression and myopathy
  - Abacavir: potentially fatal hypersensitivity reaction
  - The "Ds" (ddI and d4T): pancreatitis, peripheral neuropathy, mitochondrial toxicity (lipoatrophy)
  - Tenofovir: acute kidney injury with possible renal failure
- NNRTIs
  - Nevirapine: rash
  - Efavirenz: teratogenic; CNS side effects (bad dreams)

- PIs:
  - All PIs: lipodystrophy, hyperlipidemia (except atazanavir), Type 2 diabetes, osteoporosis
  - Atazanavir: indirect hyperbilirubinemia
  - Indinavir: kidney stones
  - Boosted saquinavir: prolonged QT
  - Nelfinavir: diarrhea

State of Current Treatment

Overview

Again, combination ART is the standard of care. Many factors go into the choice of when to start ART and which regimen to choose. Patients should understand the risks and benefits of therapy, that treatment regimens are currently lifelong, and the importance of adherence. Base selection of an ART regimen for an individual patient on many factors including efficacy, side effects, dosing frequency, pill burden, comorbidities, and drug interactions. The goal of ART is undetectable HIV-1 RNA.

HIV RNA assays are available for accurately determining viral load. Prior to the availability of these assays, most believed the HIV virus entered a prolonged latency period until the onset of symptoms. It turns out that there is continuous replication from the onset of infection to death. HIV is not ever eradicated, even in people with undetectable viral loads on ART. The virus remains in "reservoirs," although we do not fully understand where all the reservoirs are.

Long-lived memory T cells seem to be an important site of reservoir virus.

The CD4 T helper lymphocytes are the principal cells targeted by reproducing HIV virions. Tremendous and continuous CD4 lymphocyte destruction—eventually causing decreased levels—occurs after HIV infection. CD4 levels are a good indicator of disease severity and level of immunity.

Know the following regarding HIV treatment:

- Remember that CD4 count is no longer used to determine when to start ART therapy. ART therapy is now recommended for all patients with HIV infection.
- Always use combination therapy for HIV. Combination therapy decreases serum viral load—sometimes tremendously—for prolonged periods. Combination therapy prolongs survival and decreases AIDS-associated opportunistic infections.
- The degree of decrease in viral load induced by combination ART is of good prognostic value.

Indications for Using Drug-Resistance Assays

Resistance testing is now a standard of care and recommended for those:

- initially presenting for HIV care, or
- who may be developing drug resistance, or
- who are pregnant.

It is indicated for treatment-naïve patients immediately before initiating treatment; e.g., if ART is deferred, resistance testing should also be deferred and done just before initiation of ART.

Currently, 2 types of resistance testing are available—genotypic and phenotypic. Either or both can be used in the setting of increased viral load with presumed HIV-resistance to help determine change in therapy. If resistance is determined, then you can switch from ineffective drugs to ones that are theoretically effective.

The genotype test detects specific genes in the individual patient's HIV virus known to confer resistance toward a specific antiretroviral drug. It is a cheaper and faster test; it also gives more information. As such, it is recommended over the phenotype.

The phenotype test determines if the gene is operating and resistance is being expressed. This is sort of like a crude antibiogram for the HIV virus. This phenotype test becomes more useful as the number of mutations increases and as the interpretation of genotypes becomes more difficult and less reliable.

When to Initiate Antiretroviral Therapy (ART)

The following is the newer (and much more simplified) guideline regarding when to initiate therapy for treatment-naïve patients based on the Panel on Antiretroviral Guidelines for Adults and Adolescents (2012).

Consider initiating treatment without delay for all HIV-infected patients.

Which Combination of Drugs to Use

The following recommendations come from the DHHS 2012 treatment guidelines. They consist of a "backbone" of 2 NRTIs (tenofovir + emtricitabine) with a "base" of either an NNRTI (efavirenz), a ritonavir-boosted PI (atazanavir or darunavir), or an integrase inhibitor (raltegravir).

Preferred initial regimens for antiretroviral-naïve patients (after resistance testing):

- Tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV)
- Tenofovir/emtricitabine/ritonavir-boosted atazanavir (TDF/FTC/ATV/r)
- Tenofovir/emtricitabine/ritonavir-boosted darunavir (TDF/FTC/DRV/r)
- Tenofovir/emtricitabine/raltegravir (TDF/FTC/RAL)

Remember: EFV (efavirenz) is absolutely contraindicated in pregnancy.

When to Change HIV Therapy

Consider changing therapy when there is failure to completely suppress viral load to an undetectable level based on > 1 viral load or when the patient becomes

QuickQuiz

- Which PI is associated with kidney stones?
- What is the best predictor of long-term outcome in the patient infected with HIV?
- Below what CD4 count is initiation of ART recommended?
- Which new HIV+ patients should receive resistance testing?
- Which exposures should not receive PEP for HIV?
- Which pregnant women should be treated for HIV? With what? What is the treatment goal?
- What are the symptoms of primary HIV infection?

intolerant to 1 or more of the drugs. What therapy to change to is based on resistance testing, which should be done while the patient is still taking the current regimen. Place the patient on a regimen of 3 drugs to which the virus is susceptible and that will not cross-react with side effects of prior medications.

Pre-Exposure Prophylaxis (PREP) to Prevent Sexual Acquisition of HIV

Several studies have shown that administration of tenofovir-emtricitabine (Truvada) significantly decreases rates of HIV transmission in high-risk populations such as men who have sex with men, promiscuous heterosexuals, and HIV-discordant heterosexual couples. In July 2012, the FDA approved Truvada for HIV-negative persons in such risk groups. It is administered once daily.

Post-Exposure Prophylaxis (PEP) for Health Care Workers

First, recommend cleaning the site of exposure with water and soap, if applicable. Then, determine the exposure risk: Was the source material blood or bloody fluid? If so, then determine if it was a percutaneous exposure (PEP recommended), or mucous membrane or skin with compromised integrity (PEP probably recommended). It is easier to remember to whom not to give PEP: Do not give PEP for intact skin exposures and urine-source exposures.

When PEP is indicated, use potent combination therapy. Start treatment ASAP—within hours of exposure—and continue for 4 weeks. HIV testing is recommended at 0, 6, and 12 weeks, and 6 months after the exposure.

Pregnancy and ART Therapy

Lowering viral loads in pregnant women decreases the risk of vertical transmission to the child.

Treat all HIV-infected pregnant women with ART regardless of CD4 level or viral load. The goal is to make their viral load undetectable. Always do initial resistance testing.

Commonly used ART drugs to avoid in pregnant women:

- Efavirenz (EFV) due to association with teratogenicity.
- Nevirapine (NVP) is not recommended for women with CD4 counts > 250, and caution is advised for use in any pregnant woman.

Preferred therapy for ART-naïve pregnant women is ZDV/lamivudine + lopinavir boosted with ritonavir (ZDV/3TC + LPV/r).

Two scenarios in pregnancy:

1) If the patient is already on ART and has undetectable virus, continue her current regimen except avoid EFV, NVP, and d4T/ddI as discussed above.
2) If the patient is not on ART at time of pregnancy, initiate therapy immediately if indicated for her health (high viral load/low CD4, etc.). If she is ART-naïve, give the same ART therapy as above: ZDV/3TC + LPV/r. Therapy should be started before resistance testing results are back—especially if she is in the 3rd trimester.

So, notice that the same therapy is recommended to ART-naïve pregnant women whether they need it for their health or solely to prevent transmission to the child.

If she is not ART-naïve, use past ART history and do resistance testing to determine the best course.

Labor and Delivery

All HIV-infected pregnant women should be given ZDV as a continuous infusion during labor in addition to their current ART therapy.

C-section is recommended if viral load > 1,000 copies at 38-weeks gestation.

Infants born to HIV-infected mothers should receive ZDV for 6 weeks starting within 6–12 hours of birth.

PRIMARY HIV INFECTION

Primary HIV infection was previously termed acute retroviral syndrome. This is a flu- or mononucleosis-like syndrome that occurs 2–4 weeks after initial infection and lasts 1–2 weeks.

Patients with primary HIV infection may present with:

- Fever
- Lymphadenopathy
- Pharyngitis
- Rash (usually erythematous maculopapular with lesions on face, trunk, or extremities; can include palms and soles)
- Mucocutaneous ulcerations involving the mouth, esophagus or genitals

- Myalgias/arthralgias
- Aseptic meningitis

Consider primary HIV infection in any person at risk for HIV who presents with signs/symptoms of mononucleosis, scarlet fever, or aseptic meningitis.

Diagnosis is made by assaying plasma for RNA viral load or the p24 antigen. Low viral loads (< 10,000 copies) may be false-negative tests and should be repeated with referral to a provider experienced with HIV. HIV EIA antibody test becomes positive at 3–7 weeks after exposure, so it is usually not positive during primary HIV infection.

Current treatment guidelines recommend that ART should be considered for patients with primary HIV infection.

HIV / AIDS OPPORTUNISTIC INFECTIONS

Introduction

Opportunistic infections (OIs) are caused by microorganisms that do not usually cause disease unless the host is immunocompromised. However, in the setting of immunosuppression such as HIV/AIDS, these microorganisms are able to take advantage of the weakened host. The opportunistic infections a patient is at risk for depend on the patient's CD4+ cell count.

Opportunistic infections in HIV-infected persons often present in 1 of 4 ways:

1) **Pulmonary**: shortness of breath, cough, fever
   - Think of:
     - *Pneumocystis*
     - Tuberculosis
     - "Routine" causes of pneumonia, *S. pneumoniae*, endemic fungi, etc.
2) **Systemic**: fever and wasting
   - Think of:
     - MAI/MAC
3) **CNS**: altered mental status, focal defect, seizure
   - Think of:
     - *Cryptococcus*
     - Toxoplasmosis
     - PML
     - Neurosyphilis
4) **Gastrointestinal**:
   - Esophagitis—Think of:
     - *Candida* infection
     - Viral (CMV, HSV)
   - Chronic diarrhea—Think of:
     - Parasitic infections (*Cystoisospora*, *Cyclospora*, *Cryptosporidium*)
     - Bacteria (*Shigella*, *Salmonella*, *Campylobacter*)

Common infections and skin findings in HIV disease include:

- Persistent or recurrent seborrheic dermatitis
- Tinea infections
- Psoriasis
- Molluscum contagiosum
- Folliculitis
- Recurrent HSV, varicella-zoster virus
- Recurrent vaginal and oral candidiasis
- Oral hairy leukoplakia

PULMONARY INFECTIONS

Pneumocystis Pneumonia

Epidemiology: *Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia is acquired via the respiratory route. This pneumonia is the most common opportunistic infection in patients with HIV and is the presenting illness in 50% of AIDS patients. 90% of patients with PJP have CD4 counts < 200.

Presentation: Unlike bacterial pneumonia, *Pneumocystis jiroveci* pneumonia (PJP) has an insidious onset of fever, shortness of breath, and dry cough that usually worsens over weeks, not days. There is minimal inflammatory response, which accounts for the lack of sputum production and rarity of pleuritic pain.

Lab: ABGs typically show a pH > 7.40. Hypoxia is common. A-a gradient is commonly increased. pCO_2 is commonly low (from respiratory alkalosis). LDH is elevated (> 400), and liver enzymes are normal. The chest x-ray usually shows a diffuse "batwing" infiltrate, although it may also be lobar or unilateral. In 10–15%, the chest x-ray is normal.

Diagnosis: The best method of diagnosis is by methenamine silver stain of pulmonary secretions either from induced sputum or bronchoalveolar lavage (BAL). Because of the high inoculum of the organism present during active disease, BAL is highly sensitive.

Treatment: Treatment is based on disease severity. Moderate-to-severe infection is defined as a $P_aO_2 < 70$ or A-a gradient > 35. All other cases are considered mild.

Treat PJP with TMP/SMX. Use oral regimens for mild disease. Give the drug intravenously for severe disease, e.g., in the patient with significant dyspnea or hypoxemia. AIDS patients have a high incidence of sulfa allergy, so 2nd line drugs are often used. Mild disease 2nd line drugs are dapsone + trimethoprim and primaquine + clindamycin. Moderate-to-severe 2nd line drugs are clindamycin + primaquine or pentamidine.

All drug regimens are for a 21-day course.

All patients with moderate-to-severe hypoxemia should receive glucocorticoids within 72 hours of receiving antibiotics.

QuickQuiz

- What illnesses does primary HIV infection sometimes resemble?
- What is the most common OI in the patient with HIV/AIDS?
- What is the usual CD4 count in the patient with HIV/AIDS who develops PJP?
- How is PJP best diagnosed?
- What ancillary treatment should be given to patients who develop moderate-to-severe hypoxemia due to PJP?
- When should patients be given primary prophylaxis for PJP?
- What is the treatment duration for latent TB in patients with HIV/AIDS?
- When should patients be given primary prophylaxis for MAC?

Side effects: TMP/SMX side effects include neutropenia/leukopenia, skin rash, nausea/vomiting, and, occasionally, fever.

Pentamidine may cause neutropenia/leukopenia, fever, nausea, vomiting, renal failure, and diarrhea. Long courses of pentamidine may destroy the beta cells of the pancreas, causing initial release of insulin and hypoglycemia and then eventual diabetes.

Prophylaxis: Primary prophylaxis is the term used when prophylaxis is given to a patient with no prior history of the OI. Secondary prophylaxis is what is given when the patient has a history of previous treatment for that OI.

TMP/SMX DS 1/day or 3/week is the drug of choice. Start primary prophylaxis when the CD4 count is < 200 or if the patient has *Candida* esophagitis. Secondary prophylaxis should occur after a full course of treatment for PJP.

Stop PJP prophylaxis if and when CD4 is > 200 for ≥ 3 months in response to ART.

If the patient cannot tolerate TMP/SMX, dapsone or atovaquone are alternative therapies. Atovaquone is more efficacious than dapsone and has a lower incidence of side effects than TMP/SMX but is much more expensive than either. TMP/SMX also provides prophylaxis against toxoplasmosis (page 2-54).

Tuberculosis

Epidemiology: Most tuberculosis in HIV is reactivation of prior asymptomatic infection and thus occurs in those with the usual risk factors for TB (e.g., homeless, institutionalized, IV drug abuse, born in an endemic country). Reactivation occurs at the rate of 3–16% per year in patients coinfected with HIV and TB.

Presentation: TB typically presents as a chronic pneumonia but with a presentation different from patients without HIV in that infiltrates may be absent or diffuse and cavitation is uncommon. Patients may also present with a more acute pneumonia, clinically similar to bacterial community-acquired pneumonia. Disseminated disease is more common in HIV-infected persons.

Diagnosis: Diagnosis is made in the usual fashion by demonstrating AFB on sputum, BAL, or bronchial biopsy.

Treatment: Patients commonly respond very well to the usual treatment regimens: isoniazid, rifampin (or rifabutin), ethambutol, and pyrazinamide x 2 months; then narrow to isoniazid + rifampin (rifabutin) x 4 months. Rifampin may have to be replaced by rifabutin or other drugs in patients with HIV and TB coinfection because of extensive drug interactions. Rifabutin also needs adjustments because of drug interactions.

See Pulmonary Medicine, Book 2, for more on treatment.

Prophylaxis: Prevention of active TB in HIV-infected persons is facilitated by annual screening for latent infection with either a TB skin test or interferon-gamma–releasing assay (IGRA).

All patients with a positive PPD (> 5 mm) or +IGRA without signs of active disease should receive INH for 9 months.

SYSTEMIC INFECTIONS

Mycobacterium Avium Complex / *Mycobacterium Avium-intracellulare*

Epidemiology: *Mycobacterium avium* complex (MAC) is ubiquitous in the environment. The MAC consists of 2 species, *M. avium* and *M. avium-intracellulare* (MAI); 95% of isolated strains are the former. It is acquired by the respiratory or gastrointestinal route without clear association with any activity and reactivates when CD4 counts drop to < 50.

Presentation: It usually presents as disseminated infection in patients with AIDS and causes a wasting syndrome with fever, weight loss, night sweats, lymphadenopathy, hepatosplenomegaly, diarrhea, and abdominal pain.

Diagnosis: Diagnosis is confirmed by growing MAC from otherwise sterile body fluids or from biopsies.

Treatment: Treat with clarithromycin and ethambutol +/– rifampin.

Prophylaxis: Start primary prophylaxis for MAC with clarithromycin or azithromycin when CD4 is < 50. Azithromycin has the advantage of once-weekly dosing. Stop primary prophylaxis when CD4 is > 100 for ≥ 3 months in response to ART. Secondary prophylaxis is the same as the treatment regimen. Secondary prophylaxis may be stopped if CD4 is > 100 for 6 months.

CNS INFECTIONS

Cryptococcus

Epidemiology: *C. neoformans* is endemic worldwide. Although it causes disease in both immunocompetent and immunosuppressed individuals, most HIV-infected patients have CD4 counts of < 100 at the time of diagnosis, and the fungus commonly presents as disseminated disease with CNS involvement.

Presentation: The most common presentation is a subacute meningitis or meningoencephalitis that is very different than bacterial meningitis. Subtle signs of decreased mental status, personality changes, and memory loss may be the only manifestations and are due to increased intracranial pressure, not invasion of the organism.

Diagnosis: Detection of cryptococcal antigen in the CSF or serum is diagnostic and is seen in the vast majority of patients.

Treatment: Meningitis is treated in 3 stages: induction with amphotericin B deoxycholate + flucytosine x 2 weeks; consolidation with fluconazole 400 mg/d for ≥ 8 weeks; maintenance with fluconazole 200 mg/d for ≥ 1 year.

Repeat LPs should be done, and CSF removed, to obtain normal CSF pressures. If this is not possible, CSF shunts should be inserted.

Prophylaxis: Do not give primary prophylaxis for *Cryptococcus*. Secondary prophylaxis is given with daily fluconazole and usually continued irrespective of the CD4 count.

Toxoplasma

Presentation: *Toxoplasma gondii* is the most common cause of focal lesions in the CNS in HIV-infected persons. Typical symptoms: headache, new onset of seizures, neurologic deficit and/or altered consciousness, and multiple lesions on MRI or CT. The main differential diagnoses are primary B cell lymphoma, and infections that may produce focal lesions (TB, fungal, bacterial, nocardial). CT scan shows CNS abscesses due to toxo as ring-enhancing lesions.

Diagnosis: Diagnosis is made by imaging consistent with toxoplasmosis in a seropositive patient and confirmed by a response to empiric treatment.

Treatment: Pyrimethamine + sulfadiazine (and folinic acid). Clindamycin should be used in sulfa-allergic patients. Failure to respond warrants other testing, including brain biopsy.

Prophylaxis: Primary prophylaxis is indicated in patients with CD4 count < 100/mm^3 with a positive *Toxoplasma gondii* IgG. It is accomplished with the same regimen used for PJP prophylaxis (e.g., TMP/SMX DS 1/day or 3/week). Primary prophylaxis for *Toxoplasma* encephalitis can be stopped when the CD4+ cell is > 200 cell/mm^3 for 3 months, similar to PJP primary prophylaxis. It gets more complex in patients who cannot tolerate sulfa. Most would not give primary prophylaxis, but alternative regimens include a combination of dapsone + pyrimethamine + leucovorin.

Secondary prophylaxis includes slightly lower doses of pyrimethamine + sulfadiazine + leucovorin.

Syphilis

Syphilis, even if previously treated, may reactivate in AIDS patients and cause neurosyphilis. Syphilis is treated the same in AIDS as in non-AIDS. Some experts recommend that you should have a low threshold for evaluating a patient for neurosyphilis with lumbar puncture; however, controversy remains on this issue. CDC guidelines recommend evaluation of CSF if neurological symptoms are present.

GI INFECTIONS

Esophagitis

Candida infection is the most common cause of infectious esophagitis in patients with HIV. Common viral causes include CMV and HSV. Note that these can occur at the same time. Consider coexistent viral infection if symptoms don't improve after treating the *Candida*.

Diarrhea

Chronic diarrhea in AIDS patients is commonly caused by *Cryptosporidium*, microsporidia (includes *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*), *Cyclospora cayetanensis*, *Cystoisospora* (previously *Isospora) belli*, or bacterial pathogens (*Salmonella*, *Shigella*, *Campylobacter*). Special stains on stool specimens are needed to diagnose *Cryptosporidium* (modified acid-fast), microsporidia (modified trichrome), and *Cystoisospora* (modified acid-fast).

There is no reliable treatment of cryptosporidiosis except to start ART and increase the CD4 count. Nitazoxanide is an option for patients with substantial symptoms, but may not be effective without concurrent CD4 increases. Treat *Cyclospora* and *Cystoisospora* with TMP/SMX. Treat *Salmonella*, *Shigella*, and *Campylobacter* with ciprofloxacin.

MISCELLANEOUS INFECTIONS

HCV

Test all HIV-infected patents for HCV. Treat those with combined disease the same as those without. Treatment for both is generally initiated simultaneously but, because of pill burden, overlapping toxicities, and drug interactions, if the CD4 count is > 500, some hold ART therapy until the completion of the HCV treatment. Conversely, in patients with very low CD4 counts, most generally treat HIV first and hold HCV treatment until the HIV is stable.

Quick Quiz

- How is cryptococcal meningitis diagnosed?
- Name some of the organisms that can cause chronic diarrhea in a patient with HIV/AIDS?
- What is the typical presentation of CNS toxoplasmosis?
- Which side of the heart is more prone to developing native valve endocarditis?
- What is the usual cause of prosthetic valve endocarditis in the 1st year after surgery?
- What are some specific physical exam signs of endocarditis?

CMV

Eye problems are commonly due to CMV retinitis. (See page 2-41.) CMV retinitis is treated with ganciclovir or valganciclovir. Primary prophylaxis is not given. Secondary prophylaxis is with valganciclovir.

Kaposi Sarcoma

Kaposi lesions are a neoplasia of blood vessels and are due to human herpesvirus 8. Lesions are nodular and well localized, often with some surrounding bruising. Treat with chemotherapy, surgery, or radiotherapy.

And Again: PJP and MAC Prophylaxis

For both primary and secondary prophylaxis:

- Start PJP prophylaxis when CD4 is < 200 or oropharyngeal candidiasis occurs.
- Start MAC prophylaxis when CD4 is < 50.
- Stop PJP prophylaxis when CD4 is > 200 for ≥ 3 months in response to ART.
- Stop MAC prophylaxis when CD4 is > 100 for ≥ 3 months in response to ART.

COMMON ID SYNDROMES

INFECTIVE ENDOCARDITIS (IE)

Overview

The current approach to endocarditis is based on the 2008 update to the 2005 guidelines published by the American Heart Association and endorsed by IDSA.

For treatment purposes, endocarditis is typed as follows: native valve, prosthetic valve, culture-negative, and injection drug user. The previous designations of "acute" and "subacute" are no longer used.

Native Valve Endocarditis

Native valve endocarditis is more common on the left side of the heart and usually occurs on regurgitant AV valves (although it can also occur with VSDs and PDAs). According to the International Collaboration on Endocarditis (ICE), which is a prospective study of over 2,700 patients with definite infective endocarditis, the median age of endocarditis is 58 years old.

The most common organism infecting native valves is *S. aureus*, followed by viridans streptococci and then enterococci. Patients with *S. aureus* endocarditis are more likely to die and develop emboli. Enterococci seem to be the least virulent cause of IE. **HACEK** organisms (***H****aemophilus* species, ***A****ggregatibacter actinomycetemcomitans* [previously *Actinobacillus actinomycetemcomitans*], ***C****ardiobacterium hominis*, ***E****ikenella* species, and ***K****ingella kingae*) also cause endocarditis.

Prosthetic Valve Endocarditis

Early prosethtic valve endocarditis ([PVE]; within 2 months of valve insertion) is usually due to seeding during surgery. Acute cardiac decompensation means emergent surgery on the valve or neighboring tissue is necessary. Even with surgery, PVE still has a 40% mortality.

Late PVE (> 2 months after valve insertion) invades the annulus, and surgery is commonly required. *S. epidermidis* is seen in 55–60% of the cases in the 1st year after surgery. If the infecting organism is a viridans streptococcus, streptococci, or enterococci, the likelihood of cure with antibiotics is higher than it is with staphylococci. Better antibiotic treatment success is seen with porcine bioprosthesis, as opposed to metal valves.

History and Physical Exam

History should focus on potential exposures to typical organisms:

- Skin infections
- Dental work
- Genitourinary manipulation or obstruction
- IV catheters
- Injection drug use

Also look for uncommon organisms, especially if blood cultures are negative. (Animal exposures predispose to *Coxiella*, *Bartonella*, and *Tropheryma whipplei*.)

Physical exam may show the following classic stigmata:

- Fever
- Conjunctival hemorrhages
- Petechiae (most common skin finding)
- Splinter hemorrhages (of the fingernails)
- Janeway lesions (nonblanching, painless, reddish lesions on hands/feet)
- Osler nodes (painful, purplish lesions on fingers/toes)
- Roth spots (retinal hemorrhage)

Since IE is usually diagnosed earlier in the course than previously, these classic signs are less common now.

Systemic involvement commonly includes neurologic deficits (most common cause of death), infarctions of spleen and kidneys, immune-complex glomerulonephritis, and septic pulmonary infarction in right-sided disease. Some of the above clinical characteristics are included in the modified Duke Criteria for diagnosis (discussed under Diagnosis, below).

Laboratory Evaluation

Blood cultures are vital in diagnosing endocarditis of any type, and 3 sets should be drawn before starting empiric antibiotics.

Blood cultures in IE patients are positive in over 95% of cases due to the constant level of bacteremia. However, bacterial concentration in the blood is low in IE, so a proper amount of blood should be inoculated into each culture bottle.

Ideally, 3 sets separated by at least 8 hours are drawn from peripheral sites, prior to starting antibiotics. If a patient is unstable, get 3 sets up front from various sites and repeat blood cultures later, after antibiotics are started.

Laboratory abnormalities commonly seen in endocarditis include:

- Increased ESR and CRP
- Anemia of chronic disease
- Leukocytosis or leukopenia
- Thrombocytopenia
- Active urine sediment (proteinuria and red cell casts)
- Immune activation evidence (low complement levels, cryoglobulinemia, rheumatoid factor, and RPR+)

Culture-Negative Endocarditis

If blood cultures are negative, there is no history of pre-culture antibiotic treatment, and the patient has clinical criteria for endocarditis, consider the following:

- Fungi
- Q fever (*Coxiella burnetii*)
- *Bartonella* species
- *Tropheryma whipplei*
- *Legionella*
- *Chlamydia psittaci*
- Nutritionally deficient streptococci

If you alert the microbiology lab, it will hold blood cultures longer when endocarditis is clinically likely. Still, HACEK organisms are only rarely found this way. The other organisms are diagnosed with serology or pathology and culture of the valve. *Coxiella* is diagnosed by serology.

Echocardiography

The 2005 AHA guidelines were reevaluated in 2006 for the use of echo to diagnose valvular heart disease. IDSA has endorsed the 2006 ACC/AHA recommendations, which include:

- Only patients with moderate-to-high clinical probability of endocarditis should get echocardiography.
- Transthoracic echo (TTE) has a low sensitivity (but high specificity), so a negative test does not exclude a valvular lesion. If clinical suspicion is moderate to high, these patients should progress to transesophageal echo (TEE).
- TEE, as a 1st test, is recommended for patients with prosthetic valves and for patients in whom you suspect a perivalvular abscess. Even though it's the best test, be aware that TEE can miss an abscess in a significant number of patients.
- A negative TEE in a patient with native valves has a negative predictive value of almost 100%.
- If a patient does not have a high clinical probability or a technically limited TTE, then a negative TTE is a definitive study (meaning no further workup with TEE is necessary). To be diagnosed with endocarditis, the patient would have to fulfill the Duke criteria without the echocardiographic findings (rare).

Diagnosis

Diagnosis is based on fulfillment of the modified Duke criteria, which includes clinical, laboratory, and echocardiographic characteristics, regardless of whether a patient has native or prosthetic valve. A structured approach is useful because not all patients have positive blood cultures or obvious murmur. Using these criteria also makes it unlikely that a case of endocarditis is missed, which is important because it is universally fatal if untreated.

Definite endocarditis is diagnosed when the patient has any of the following:

- Pathologic evidence of disease
- 2 major criteria (see below)
- 1 major criterion + 3 minor criteria
- 5 minor criteria

Pathologic evidence would be visible organisms from a vegetation or valve lesion or a positive culture from the same tissue.

Possible endocarditis is diagnosed with 1 major + 3 minor criteria.

The 2 major criteria are:

1) Positive blood cultures. There are 3 ways that the blood culture major criteria can be met:
   - If the organism is one that typically causes endocarditis and is found in at least 2 blood cultures 12 hours apart, the criteria are met. These organisms are *S. aureus*, viridans streptococci, *S. bovis*, enterococci, or HACEK.

Quick Quiz

- How many sets of blood cultures should be drawn on the patient with suspected endocarditis?
- What organisms should be considered as a cause of culture-negative endocarditis?
- What 2 types of tests make up the major criteria for the diagnosis of endocarditis?
- If a patient has a high clinical probability of endocarditis, should a negative TTE dissuade you from the diagnosis?
- Which patients should definitely receive a TEE in the evaluation of possible endocarditis?
- What is the negative predictive value of a TEE in a patient with native heart valves?
- Review and commit to memory the modified Duke criteria. What is required for the definite diagnosis of endocarditis?
- Study and know the various regimens to treat endocarditis based on resistance patterns and type of valve (native vs. prosthetic).

  - If the organism is not one that typically causes endocarditis, there must be at least 3 cultures (+) or the majority of ≥ 4 cultures drawn at least an hour apart from first to last.
  - A single blood culture (+) for *Coxiella burnetii* meets the criteria. This is the only organism that meets the criteria with a single positive blood culture.

2) Abnormal echocardiogram. Significant echo findings include any of the following:
   - An oscillating mass on a valve, or supporting structures
   - An oscillating mass in the path of a regurgitant jet
   - An oscillating mass on an implanted device.
   - An abscess
   - Prosthetic valve dehiscence
   - A new regurgitant valve

The 5 minor criteria are:

1) Predisposing condition (valve disease or injection drug use)
2) Fever > 38.0° C (100.4° F)
3) Vascular phenomena (arterial emboli, pulmonary infarcts, mycotic aneurysms, stroke, conjunctival hemorrhages, Janeway lesions)
4) Immunologic phenomena (acute glomerulonephritis, Osler nodes, Roth spots, +RF)
5) Positive blood culture that does not meet a major criterion

Preferred Treatment of Bacterial Endocarditis

We outline the recommendations from the 2005 AHA guidelines (Table 2-5).

Viridans Streptococci and *S. bovis*

Sensitive to PCN: 4 weeks of PCN G or ceftriaxone (2 g/d). Adding gentamicin can reduce duration to 2 weeks; keep at 4 weeks if there is an abscess. Gentamicin is not recommended for patients with renal insufficiency. Vancomycin can be used x 4 weeks in patients unable to tolerate the beta-lactam, but it is not preferred for initial treatment.

If there is intermediate resistance to PCN, the regimen is the same but the dose of PCN G is increased.

Prosthetic valve treatment is generally the same regimen, but the duration of treatment is lengthened.

Endocarditis caused by either *S. bovis* bacteremia (or *Clostridium septicum*) should lead to a colonoscopy, given the high prevalence of colon cancer in these patients.

Staphylococcus aureus without Prosthetics

MSSA left-sided or right-sided disease with emboli requires nafcillin x 6 weeks +/– gentamicin for 3–5 days (if isolate is susceptible). This recommendation was included because of data showing that aminoglycoside synergy sterilized the blood more quickly. However, this recommendation became controversial in 2010 because of data showing that inclusion of the aminoglycoside is associated with an increase in nephrotoxicity but no other difference in outcome (despite the more rapid blood sterilization). Most experts are not including the aminoglycoside to treat staph endocarditis now.

MRSA isolates are treated with vancomycin x 6 weeks. Alternatively, daptomycin may be used, especially if the vancomycin MIC is > 1.

MSSA uncomplicated right-sided disease: nafcillin + gentamicin x 2 weeks; or daptomycin. If the isolate is not gentamicin-susceptible, then the 2-week regimen cannot be used. MRSA isolates are treated x 6 weeks with vancomycin only.

Surgery may be required for *S. aureus* endocarditis, even with native valves. Exact optimal timing and indication for surgery remain controversial.

Staphylococcus aureus with Prosthetic Valves

MSSA/MRSA prosthetic valve disease: nafcillin (or vancomycin) + rifampin + gentamicin x 6 weeks or longer. Surgery is almost always indicated.

Enterococci

Sensitive to PCN: ampicillin or PCN G or vancomycin, depending on susceptibility, + gentamicin x 4–6 weeks.

Table 2-5: Treatment of Bacterial Endocarditis

Organisms	Susceptibility Testing	Drug Regimen	Duration
Viridans streptococci, *S. bovis*	PCN-sensitive	PCN G or ceftriaxone	4 weeks Prosthetic valve = > 4 weeks
		(PCN G or ceftriaxone) + gentamicin	2 weeks
		Vancomycin (alternative)	4 weeks
	PCN-intermediate	Increased dose PCN G or ceftriaxone	4 weeks
S. aureus or coagulase-negative	Methicillin-susceptible	Nafcillin	6 weeks Prosthetic valve = add rifampin and gentamicin
	Methicillin-resistant	Vancomycin	6 weeks Prosthetic valve = add rifampin and gentamicin
Staph, uncomplicated right-sided	Methicillin-susceptible	Nafcillin + gentamicin or daptomycin	2 weeks
Enterococci	PCN-sensitive (depending on amp and vanc susceptibilities)	(PCN G or ampicillin or vancomycin) + gentamicin	4–6 weeks Prosthetic valve = 6 weeks
	Ampicillin + PCN G + Vancomycin-resistant	Very specialized	Very specialized
HACEK		Ceftriaxone	4 weeks Prosthetic valve = 6 weeks

Prosthetic valve treatment is generally the same regimen, but the duration of treatment is lengthened.

For enterococcal species resistant to ampicillin, PCN G, and vancomycin, treatment is difficult and specialized, utilizing variations of linezolid or daptomycin (if sensitive) +/– imipenem/cilastatin with either ampicillin or ceftriaxone.

HACEK Organisms

Treat HACEK organisms with ceftriaxone x 4 weeks. Alternatives include ampicillin-sulbactam or ciprofloxacin. If a prosthetic valve is involved, duration is 6 weeks.

Complications of Endocarditis

Surgery is often required for endocarditis with:

- Vegetations
  - Persistent vegetation after one has already embolized
  - Vegetation > 10 mm
  - Vegetation on the anterior mitral leaflet
  - An increasing vegetation size while on antibiotics
  - Persistent emboli while on antibiotics
- Valve dysfunction
  - Heart failure
  - Valve perforation
  - Rupture
- Perivalvular extension
  - Fistula
  - Valve dehiscence
  - Heart block
  - Large abscess
  - Persistent bacteremia on appropriate antibiotic therapy

MENINGITIS

Bacterial Meningitis

Overview

S. pneumoniae is the most common cause of meningitis. Next is *N. meningitidis* (meningococcus). See Table 2-6. Older data show that *Listeria* meningitis became more prevalent again in those > 50 years old, but data published in 2011 show that *Listeria* has actually decreased in incidence (from 20% to 4%).

Quick Quiz

- List some complications of endocarditis.
- What organism is the most common cause of bacterial meningitis in adults?
- What is standard empiric treatment for bacterial meningitis? For elderly and neonates?

The main culprit in the meningococcal group is B (B for Bad). There are effective vaccines against A, C, Y, and W-135, but not type B. (See page 2-20 for a discussion of meningococcemia.)

Approach to the Patient with Suspected Bacterial Meningitis

Time is of the essence in this disease, and an organized approach to diagnosis and treatment is essential. Bacterial meningitis should be suspected in anyone with fever, headache, and stiff neck. Kernig and Brudzinski signs are very insensitive but highly specific (> 95%). Lumbar puncture (LP) should be performed as soon as possible, but caution must be taken to avoid precipitating herniation in patients who may have focal CNS lesions. Two studies have shown that the following parameters are predictive of finding such lesions on CT scan: immunocompromised, prior CNS disease, seizures in the last week, altered consciousness, papilledema, focal neurologic deficit, age ≥ 60 years. These people need a CT prior to LP yet should not have a delay in the administration of antibiotics. Stat blood cultures should be obtained, followed by empiric antibiotics and dexamethasone (see next), and then they should be sent for CT scan. LP is then performed if the CT shows no contraindication. In patients who do not warrant a stat CT, stat blood cultures and LP should be done, immediately followed by empiric antibiotics and dexamethasone (see next).

If CSF is obtained, it should undergo testing via Gram stain, culture and sensitivity, cell count with differential, protein, and glucose. Rapid antigen testing is no longer recommended because it uncommonly alters treatment.

Culture results are the gold standard but can be negated by prior antibiotic therapy.

Antibiotics in Bacterial Meningitis

Bacterial meningitis is routinely fatal without treatment. The major caveats related to treatment: Start treatment as soon as possible; use bactericidal drugs that cross the blood brain barrier; and treat based on the epidemiologic setting, which is highly predictive of causative organisms.

Drugs that are or can be bactericidal and easily cross into the CSF:

- Quinolones
- Chloramphenicol
- TMP/SMX
- Metronidazole

Antibiotics that are or can be bactericidal and cross into the CSF only with inflamed meninges:

- PCN
- Vancomycin
- 3rd generation cephalosporins
- Aztreonam
- Imipenem

Antibiotics that are or can be bactericidal and poorly cross the blood-brain barrier:

- Tetracycline
- Aminoglycosides
- Cefoxitin
- 1st generation cephalosporins

Table 2-6: Etiology of Meningitis in the United States

0–2 months	%	3 mo to 15 years	%	Adult	%	Notes on > 60 years
Gram-neg *(E. coli & Klebsiella)*	20–30	***S. pneumoniae***	30–50	***S. pneumoniae***	30–50	*S. pneumoniae* *N. meningitidis*
Strep (Group B) *(S. agalactiae)*	40–50	***N. meningitidis***	10–35	***N. meningitidis***	10–35	See more often: *E. coli* *H. influenzae* *Pseudomonas*
Listeria	2–10	***H. influenzae***	0–7	***Listeria***	2–11	
Staphylococci	2–5	Streptococci	2–4	Gram-negative	1–10	
S. pneumoniae	0–5	Gram-negative	1–2	Streptococci	5	
H. influenzae	0–3	Staphylococci	1–2	Staphylococci	5	
N. meningitidis	0–1	*Listeria*	1–2	*H. influenzae*	1–3	

Remember: For the newborn and adults > 50 yrs, empiric therapy now includes ceftriaxone, ampicillin (for *Listeria*), and vancomycin (for resistant *S. pneumoniae*). Although *Listeria* is now decreasing in > 50, guidelines still have ampicillin.

Selecting Empiric Therapy

Decades of microbiologic data have shown us which organisms are typical in various epidemiologic settings. Age is the most useful predictor. In adolescents and adults < 50 years of age, *S. pneumoniae* and *N. meningitidis* are the predominant organisms. Empiric therapy for this age group is ceftriaxone (which covers > 90% of *S. pneumoniae* and 100% of *N. meningitides*) and vancomycin (which covers 100% of *S. pneumoniae*).

In adults > 50 years of age, *L. monocytogenes* becomes more common and should be empirically treated with ampicillin until culture results are known.

Immunocompromised patients are at risk for *L. monocytogenes* and gram-negative aerobes, so empiric therapy consists of ampicillin and ceftazidime.

Patients with bacterial meningitis after neurosurgical procedures are at risk of staphylococcal and gram-negative aerobic infection and should be treated with vancomycin and ceftazidime.

Again, empiric treatment of meningitis: 3rd generation cephalosporin + vancomycin +/– ampicillin (if elderly or neonate).

Selecting Definitive Therapy

Cultures grow organisms from the CSF in the majority of patients with bacterial meningitis and should be used to narrow or change empiric therapy.

Use of Dexamethasone

Dexamethasone has been shown to decrease morbidity and mortality in adults with pneumococcal meningitis. Dexamethasone should be started 15–20 minutes prior to antibiotic administration and continued for 4 days if pneumococci are cultured, and discontinued if another causative agent is found.

Settings to Consider Non-bacterial Meningitis

In AIDS, ALL, or Hodgkin disease, think *Cryptococcus* and do a cryptococcal antigen. Amebic meningitis should be the primary consideration when the meningitis patient has been swimming in brackish water (e.g., cow ponds).

Aseptic Meningitis

In aseptic meningitis, CSF contains inflammatory cells, but Gram stain and culture are negative. Patients present with similar complaints as with bacterial meningitis, although generally, symptoms are less acute and severe.

Viruses are the most common cause of aseptic meningitis—these include:

- Enteroviruses
- Mosquito-borne arboviruses (West Nile virus) in the summer/early fall
- Mumps in the spring (very rare in U.S. today, although sporadic outbreaks may occur)
- HSV-2
- Acute HIV infection (remember!)

Fungal and bacterial causes of an aseptic meningitis picture include:

- *Coccidioides* and *Histoplasma* (suspect in endemic areas—arid Southwest and Mississippi/Ohio River valleys, respectively)
- Cryptococcal meningitis (common in AIDS, Hodgkin disease, and ALL)
- Chronic neutrophilic meningitis—unusual (think of *Nocardia* or fungus as possible causes)

In AIDS patients, the CSF may have no WBCs with cryptococcal meningitis.

TB Meningitis

Tuberculous meningitis is sometimes manifested by cranial nerve palsies, especially of the 6th cranial nerve. It has a thick basilar enhancement on CT scan. CSF glucose is extremely low.

Lyme Meningitis

Lyme meningitis can cause peripheral and cranial nerve palsies, especially of the 7th cranial nerve; so think of Lyme disease or herpes simplex virus infection when a patient presents with Bell's palsy. (See Treatment of Lyme Disease on page 2-28.)

Spinal Epidural Abscess

Spinal epidural abscesses may be caused by either hematogenous spread or local extension (i.e., from osteomyelitis). *S. aureus* is the most common cause. Patients can present with the classic triad of fever, spinal pain, and nerve compression problems. Rule out spinal epidural abscess anytime any 2 of these 3 symptoms occur.

CSF analysis may resemble aseptic meningitis.

Do an MRI. CT is not as good as MRI because it is susceptible to bony artifacts. Drainage is required. Empiric coverage should include drugs effective against staphylococci.

Neurosyphilis

See prior discussion on page 2-25.

Brain Abscess

Location of the abscess is often related to the source. Frontal lobe—paranasal sinus: pneumococcus, *H. influenzae*, and anaerobes. Temporal or cerebellum—middle ear: pneumococcus, *H. influenzae*, *S. aureus*, and gram

Quick Quiz

- What lab results are consistent with viral meningitis?
- Name 2 infectious diseases that can cause Bell's palsy.
- You should assume that a patient with fever and back pain has what illness until proven otherwise?
- Empiric coverage for a patient with a spinal epidural abscess should cover what organism, specifically?
- What are acceptable empiric regimens for a brain abscess?
- What finding on stool evaluation suggests invasive diarrhea?
- What is a possible adverse consequence of treating infectious diarrhea due to *E. coli* O157:H7 with antibiotics?

negatives. Both frontal and parietal abscesses can be due to hematogenous spread from lung infections and endocarditis.

Diagnosis is by CT scan with contrast (> 95% sensitivity). If accessible, aspirate the abscess and give antibiotic treatment based on results. Occasionally, you need to surgically excise the lesion. Lumbar puncture is absolutely contraindicated if signs of increased intracranial pressure are present—such as focal neurologic signs. LP rarely helps with diagnosis anyway because the infection is not in the meningeal space. Overall, the risk of herniation is as high as 20%.

Treatment of brain abscesses is initially empiric. Pick 1 of the following for 4–8 weeks:

- (PCN or ceftriaxone or cefotaxime) + metronidazole to cover aerobes and anaerobes.
- PCN-allergic: Give metronidazole + a 3rd generation cephalosporin.
- If you suspect *Enterobacteriaceae* (e.g., if ear focus), give a 3rd generation cephalosporin + metronidazole.
- If there was a history of bacteremia/endocarditis or a neurosurgical procedure, or penetrating head trauma, think *S. aureus* and add vancomycin (high incidence of MRSA). For neurosurgical patients, use ceftazidime/cefepime to cover hospital-related gram negatives including *Pseudomonas*.

Nocardia pulmonary disease can spread and cause focal lesions in the brain. It is also a rare cause of neutrophilic aseptic meningitis.

INFECTIOUS DIARRHEA

Overview

Fecal WBCs suggest an invasive bacterial etiology and are evident in *Shigella*, *Salmonella*, *Campylobacter jejuni*, *Yersinia enterocolitica*, *C. difficile*, and amebic GI infections. They are also seen in inflammatory bowel disease. All of these organisms can be found on C&S. Stool for ova and parasites should be reserved for patients with diarrhea for > 10 days. The yield of stool for O&P in nosocomial diarrhea is essentially zero. See Gastroenterology, Book 1, for more on diarrhea.

Diarrhea due to *Shigella*, *Salmonella*, or *Campylobacter*

Also see previous discussions of specific organisms.

Salmonella is discussed on page 2-21.

Note: Start cultures for *Shigella* (usually *Shigella sonnei*) as soon as possible after the bowel movement because *Shigella* dies soon after exposure to air.

Treatment: If there are fecal WBCs, do a stool C&S. However, fluoroquinolones or TMP/SMX are typically given empirically, although antibiotics may prolong *Salmonella* infection. Do not give antimotility agents for any infectious diarrhea. *Campylobacter* is resistant to TMP/SMX, so give erythromycin or quinolones instead if treatment is indicated. Like *Salmonella*, *Campylobacter* does not usually need to be treated. *Shigella* should always be treated. Prolonged, intermittent diarrhea with malaise and flatus suggests *Giardia* or *Cyclospora*.

Diarrhea due to *E. coli*

E. coli is the most common cause of bacterial diarrhea (generally without blood or WBCs) worldwide, affecting both the resident children and travelers in developing countries.

Hemorrhagic *E. coli* (serotype O157:H7) causes localized outbreaks of hemorrhagic colitis, thrombocytopenic thrombotic purpura (TTP), and hemolytic uremic syndrome (HUS), usually after eating undercooked beef or unpasteurized milk. Fever is conspicuously absent. Do not treat diarrhea caused by *E. coli* O157:H7 with antibiotics because you increase the risk of HUS by killing the organism and releasing more toxin.

Enterotoxigenic *E. coli* is the usual cause of travelers' diarrhea. Prophylaxis and treatment are discussed on page 2-72.

Diarrhea due to *Vibrio*

Vibrios grow in salt water and are transmitted via seafood and shellfish. *V. cholerae* serogroup O1 (causes cholera) is occasionally associated with Gulf Coast crabs. The non-O1 *V. cholerae*, *V. parahaemolyticus*, and other vibrios are even more frequent causes of

shellfish-associated diarrhea. These are usually self-limited. *Vibrio vulnificus* causes skin infections and sepsis, especially in the setting of immunocompromise or chronic liver disease (see page 2-68).

Diarrhea due to *C. difficile*

Antibiotic-associated diarrhea is typically caused by alteration of fecal flora resulting in an osmotic diarrhea, or the promotility action of some antibiotics (e.g., macrolides). Antibiotic-associated colitis is caused by *Clostridium difficile*.

Clindamycin, cephalosporins, and quinolones are especially likely to cause *C. difficile* disease, but any antibiotic may cause it. Symptoms can occur up to 8 weeks after the antibiotics are stopped. Diagnosis is made by assay for the *Clostridium difficile* cytotoxin. Do not do cultures for *C. difficile.*

IDSA released guidelines in 2010 with the following recommendations:

- Stop the current offending antibiotics, if possible.
- Treat based on disease severity.
- Severe disease has WBC > 15,000 or an increase in creatinine by 50%; treat with PO vancomycin.
- Mild-to-moderate disease has neither; treat with PO metronidazole.
- Severe disease is considered complicated in the presence of ileus, megacolon, or hypotension. Treat these patients with PO vancomycin (+ rectal, if ileus is present) +/– IV metronidazole. Colectomy should be considered for patients with very severe disease with rising lactate levels.

Relapses occur in ~ 25% of patients. Treatment is to repeat the 1st regimen---either metronidazole or vancomycin. But do not use metronidazole for more than 2 relapses. Patients with more than one relapse can be treated with tapering doses of vancomycin over several weeks. Fidaxomicin was FDA approved in 2011 and has only ~ 10% relapse rate and thus can be considered in *C. difficile* patients as well. Fecal microbiota transplantation ([FMT]; or fecal transplant, fecal bacteriotherapy) is a highly successful procedure for treating severe, recurrent *C. difficile* colitis.

Hand gels do not prevent transmission because they do not kill the spores of *C. difficile*. Only hand washing prevents spread. Patients with *C. difficile* diarrhea should be isolated to a private room and placed on contact precautions.

Diarrhea due to *Cryptosporidium*

Cryptosporidium is known to cause prolonged diarrhea in AIDS patients and a self-limited diarrhea in travelers. Animals (including humans) are the reservoirs. It is found with acid-fast stains of the stool (small, round, red organisms on a green background). HIV-infected patients should receive ART, and nitazoxanide can be added with variable results.

Viral Gastroenteritis

There are many viral causes of diarrhea. Rotavirus is frequently found in children. It is the most important cause of severe diarrhea in infants and is easily identified in their stools. Noroviruses (formerly known as Norwalk-type viruses) are associated with clams and oysters, causing "winter vomiting disease," but it can also be waterborne. Identify noroviruses with the ELISA test. Look for outbreaks on cruise ships.

SEXUALLY TRANSMITTED DISEASES

Overview and Screening

There are many causes of STDs. Most can be categorized into those that cause urethritis, cervicitis, and pelvic inflammatory disease (gonorrhea and *Chlamydia*) and those that cause genital ulcers (syphilis, chancroid, HSV, and lymphogranuloma venereum [LGV]). The latest treatment guidelines were released by the CDC in 2010. An update on the treatment of gonorrhea was circulated in 2011. The following discussion reflects these recommendations.

The U.S. Preventive Services Task Force (USPSTF) says evidence does not exist for or against screening for most STDs. CDC gives a couple of recommendations. Generally, screen populations that are "at risk." Some established risk factors:

- Age 15–24 years
- African-American
- New partner in past 2 months
- Multiple partners
- History of previous STDs
- Drug use
- Recent exposure to jail or detention facility
- Finding sex partners from the Internet
- Contact with prostitutes
- Men who have sex with men

Screen for gonorrhea by sending an intraurethral swab specimen for Gram stain and culture or DNA probe. Alternatively, DNA amplification by PCR can be done on swab or urine.

Screen for *Chlamydia* in women (per CDC and USPSTF) in the sexually active < 25 years of age and any woman > 25 years who has the above risk factors. USPSTF has no opinion on screening men (because most are symptomatic). Screen for *Chlamydia* by sending either urine or cervical swab for DNA amplification.

Screen for syphilis in the above risk factor groups, plus during pregnancy. Order a serum RPR or VDRL, followed by an FTA-ABS if (+).

Screen for hepatitis viruses in patients with risk factors (e.g., sexual contact and/or injection drug use). Screen for HBV by sending serum for HBsAg and anti-HBc. Anti-HBs are the only antibody present in patients who have been vaccinated in the absence of exposure; screen for HCV by sending serum for anti-HCV.

Quick Quiz

- *Vibrio vulnificus* can cause severe disease in which groups of patients?
- What is the current treatment of choice in patients with severe *C. difficile* diarrhea?
- What is the recommendation for treatment of first recurrence of *C. difficile*?
- What infection control precautions must be used on patients with *C. difficile* diarrhea?
- How do you screen for gonorrhea? For *Chlamydia*? For syphilis?
- Characterize the ulceration caused by syphilis. By chancroid?
- Discuss the clinical manifestations of LGV and granuloma inguinale.

Screen for HIV/AIDS in pregnancy and in groups with the above risk factors. Send serum for an HIV-1 antibody test (with reflex confirmatory Western blot in positive specimens). Do not screen for HIV using DNA tests except in very specific circumstances, when the likelihood of a false-negative serum antibody test is high (e.g., acute infection, neonatal HIV, and in patients with indeterminate test results).

No general screening is recommended for herpes simplex infections.

GU Infections with Genital Ulcerations

Genital ulcerative diseases include syphilis, chancroid, HSV, lymphogranuloma venereum (LGV), and granuloma inguinale.

With syphilis, the ulcer is usually single, clean with raised borders, and painless. Patients with syphilis also typically have large, painless lymph nodes. (See page 2-24 for more on syphilis.)

HSV presents with tender, grouped vesicles on a reddish base with or without regional adenopathy. Treat with oral acyclovir for the initial episode. You may also try this for severe, recurrent disease.

Haemophilus ducreyi causes chancroid in which there are tender genital papules, which become painful, purulent ulcers with irregular borders. There is associated, very painful lymphadenopathy, which rapidly becomes fluctuant and ruptures. Treat with:

- 1 dose of ceftriaxone (250 mg IM), or
- oral azithromycin 1 g oral single dose, or
- ciprofloxacin 500 mg bid x 3 d, or
- erythromycin 500 mg tid x 7 d.

Chancroid is caused by *Haemophilus ducreyi*, a small gram-negative coccobacillus. Although much less common than syphilis in the U.S. as a cause of ulcerative STD, it is the most common ulcerative STD in Africa. The initial lesion transforms from a papule to pustule to a ragged ulcer, all of which are painful. It can progress to secondary chancroid with tender inguinal lymphadenopathy (buboes), which may drain. Spread from there (tertiary chancroid) is rare.

LGV is due to specific serogroups of *Chlamydia trachomatis* (LGV-1, -2, -3). It is extremely rare in the U.S. (< 500 cases/year) but is endemic in many parts of Asia, Africa, and South America. It initially presents with a commonly painless papule and vesicle that eventually forms a clean, painless ulcer. This stage is present in only 1/3. Most patients present in the 2nd stage with tender inguinal masses on both sides of the inguinal ligament (groove sign).

Granuloma inguinale ("Donovanosis") is very rare. *Klebsiella granulomatis* (formerly *Calymmatobacterium granulomatis*) is the causative gram-negative organism that produces beefy red oozing and paradoxically painless genital ulcers. Spread to the inguinal area produces bilateral soft tissue granulomas that look like lymphadenopathy (pseudo-buboes).

Diagnostic tests for painless ulcers:

Syphilis: dark field exam of deep swab, RPR (+ in 70% of cases).

LGV: culture of lesions (low yield), serology by CF or micro–immunofluorescence.

Granuloma inguinale: Culture (low yield) biopsy showing intracellular dark staining organisms (Donovan bodies).

Diagnostic tests for painful ulcers:

Chancroid: culture *H. ducreyi*. Probable diagnosis can be made in the presence of a painful ulcer that has a negative RPR and no detectable HSV.

HSV: culture or antigen detection.

Treatment

Treatments of syphilis and HSV have been discussed previously.

Chancroid should be treated with directly observed single-dose therapy whenever possible with ceftriaxone (250 mg IM) or oral azithromycin 1 g. In patients who cannot take these, ciprofloxacin 500 mg bid x 3 d may be used. Erythromycin 500 mg tid x 7 d also is effective but requires a full week of treatment, has considerable GI toxicity, and patients that can take this should be able to take azithromycin.

LGV: Preferred treatment is doxycycline 100 mg bid x 21 d. Erythromycin 500 mg tid x 21 d is a 2nd line choice.

Granuloma inguinale: doxycycline 100 mg bid x minimum of 21 d or until all lesions have healed.

PID

Pelvic inflammatory disease can be caused by *N. gonorrhoeae*, *Chlamydia*, or mixed genitourinary flora (aerobes and anaerobes). Oral contraceptives reduce the risk of symptomatic PID caused by gonococci, but "silent" PID has the same incidence of sequelae (e.g., infertility) as does that associated with peritoneal signs.

Presentation is with bilateral lower quadrant pain, fever, +/– vaginal discharge. Physical exam commonly reveals bilateral adnexal tenderness, lower quadrant tenderness, and cervical motion tenderness. The clinical diagnosis has a PPV of < 90% so laparoscopy should be used when the diagnosis is uncertain.

If there is no cervical discharge and cervical swabs fail to show WBCs, PID is unlikely. All other patients should be tested for gonorrhea and chlamydia. Occasionally, PID patients get a perihepatitis (Fitz-Hugh-Curtis syndrome) with mild LFT abnormalities; this has been caused by both *N. gonorrhoeae* and *Chlamydia*.

Treatment depends on whether the patient requires admission or not. Patients should be admitted if:

- Clinical response to prior oral antimicrobial therapy is inadequate.
- The patient is unable to follow or tolerate an outpatient oral regimen.
- Severe illness, nausea and vomiting, or high fever are present.
- You suspect or find a tubo-ovarian abscess.
- The patient is pregnant.

Outpatient treatment for PID:

- ceftriaxone 250 mg IM, then doxycycline 100 mg bid x 14 d +/– metronidazole 500 mg bid x 14 d; or
- cefoxitin 2 gm IM and probenecid 1 gm x 1 plus doxycycline +/– metronidazole; or
- other parenteral cephalosporin plus doxycycline +/– metronidazole.

Because of the rate of fluoroquinolone-resistant gonorrhea, fluoroquinolones are no longer recommended.

Inpatient treatment for PID:

- cefoxitin 2 grams IV q 6 hours and doxycycline 100 mg orally or IV q 12 hours; or
- clindamycin 900 mg IV q 8 hours + gentamicin.

An alternative to these 2 is ampicillin/sulbactam and doxycycline.

When treating gonorrhea, always cover for *Chlamydia*. Tubo-ovarian abscesses require inpatient, intravenous antibiotic therapy—same as the inpatient PID choices above. Note that ampicillin/sulbactam + doxycycline is also recommended for tubo-ovarian abscesses.

Follow up with patients treated for chlamydial infections with a test for cure at 3 weeks. The PCR test can remain positive for many weeks.

Cervicitis

Cervicitis is usually caused by *Chlamydia* (especially if the discharge is mucopurulent), but also *N. gonorrhoeae*, HSV, and papillomaviruses. Because *Chlamydia* is intracellular, you must have cervical cells for a valid smear/culture (so scrape or use a brush). *Chlamydia* cervicitis commonly has a mucopurulent discharge. Gram stain of cervical secretions is not sensitive or specific in the diagnosis of gonococcal cervicitis (in contrast to male gonococcal urethritis).

Urethritis

Urethritis may be gonococcal (GC) or nongonococcal. From the 2010 CDC guidelines: Specific diagnosis of infection with *N. gonorrhoeae* can be determined by testing endocervical, vaginal, urethral (men only), or urine specimens. Culture, nucleic acid hybridization tests, and NAATs are available for the detection of genitourinary infection with *N. gonorrhoeae*. With GC urethritis, the patient virtually always has a purulent discharge. The diagnosis is confirmed from either positive culture results or the finding of gram-negative intracellular (within PMNs) diplococci on Gram stain (Image 2-23).

Otherwise, consider it non-GC urethritis, which is generally due to *Chlamydia trachomatis* and, less frequently, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, or HSV. For 35% of cases, the cause is unknown.

Patients with nongonococcal urethritis usually have a clear urethral discharge, and a Gram stain shows WBCs and no bacteria. Gonococcal urethritis has a shorter incubation period (2–6 days vs. 1–4 weeks for *Chlamydia*) and produces a more purulent and more productive discharge.

In all of these patients, check a VDRL and, if negative, repeat it in 2 months (in case the syphilis was incubating when blood for the 1st test was drawn). Offer HIV testing to all urethritis patients.

Treatment of urethritis:

Treat non-GC urethritis with a single does of directly observed azithromycin 1 g orally. Less desirable is doxycycline 100 mg bid x 7 d. Levofloxacin and ofloxacin are also effective but should be avoided in pregnancy.

GC urethritis: Resistance to penicillins, tetracyclines, and fluoroquinolones is commonly found. As a result, the CDC recommends dual therapy for gonorrhea infections of the cervix, urethra, and rectum with a cephalosporin plus azithromycin—in hopes that routine cotreatment might hinder the development of further antimicrobial-resistant *N. gonorrhoeae*.

The following is recommended for uncomplicated gonococcal infections of the cervix, urethra, and rectum:

- Ceftriaxone 250 mg IM x 1 + azithromycin 1 g PO x 1

QuickQuiz

- True or false? Pregnant women with PID rarely need hospitalization.
- Know the outpatient and inpatient regimens for treatment of PID.
- What is the typical clinical presentation of disseminated gonorrhea?
- What is the best way to diagnose disseminated gonorrhea?
- What 3 tests are useful to determine the etiology of vaginitis? In what way?

For treatment of uncomplicated gonococcal infections of the pharynx:

- Ceftriaxone 250 mg IM x 1
- Plus, if *Chlamydia* has not been ruled out:
  - Azithromycin 1 g PO x 1, or
  - Doxycycline 100 mg PO bid x 7 days

Consider gonococcal disease in acute exudative pharyngitis in a sexually active adolescent, especially if tests for *S. pyogenes* are negative.

Pregnant women: Do not use a quinolones or tetracycline. Use a cephalosporin for gonorrhea and either erythromycin or azithromycin for *C. trachomatis*. If she is allergic to cephalosporins, the 2010 CDC guideline recommends azithromycin 2 g PO x 1.

Always treat the sexual partners of patients with either type of urethritis, even if they are not symptomatic! And always treat suspected cases immediately—don't wait for C&S results.

Gonococcemia

Disseminated gonorrhea: Patients present with fever, arthralgias, and asymmetric oligoarthritis—usually of the knee or ankle. A typical rash of < 10 papules/pustules is classic. Tenosynovitis is common.

Gram stain and culture have a very low yield (15%) from the lesions, but if you swab all orifices, there is an 85% yield. Even though the lesions have a low yield, they should still be tested because similar lesions can be caused by other disseminated diseases, such as staph endocarditis (which does have a positive Gram stain and C&S).

Treat patients diagnosed with gonococcemia—including tenosynovitis—with a 3rd generation cephalosporin (ceftriaxone, ceftizoxime, or cefotaxime). Pending culture and sensitivity, single-dose azithromycin, levofloxacin, or doxycycline is included to cover for *Chlamydia*.

Epididymitis

Epididymitis is an inflammation of the epididymis. It is usually caused by *Enterobacteriaceae*, especially *E. coli*, in prepubertal boys and men > 35 years of age and STD pathogens in sexually active men < 35 years—especially *C. trachomatis*

Vaginitis

Vaginitis presents with change in or increase in vaginal discharge. There are 3 major causes. A systematic approach diagnoses the etiology in the vast majority of cases.

Approach to the Etiology of Vaginitis

3 tests on vaginal secretions/discharge almost always lead to an etiologic agent on initial exam: pH, wet prep, and KOH prep.

pH: Normal vaginal pH is < 5.0, and remains so with vaginal candidiasis. A pH > 5.0 is seen in bacterial vaginosis and trichomoniasis.

Wet prep (secretions placed in normal saline under microscopy): reveals epithelial cells studded with causative organisms in bacterial vaginosis and trichomonads in trichomoniasis. It may show fungal elements in candidiasis.

KOH prep (secretions placed in KOH under microscopy): yields a fishy odor in bacterial vaginosis and trichomoniasis. KOH dissolves epithelial cells and increases the yield of finding fungal elements in candidiasis.

Bacterial Vaginosis

Bacterial vaginosis is a clinical syndrome resulting from the replacement of the normal H_2O_2-producing *Lactobacillus* in the vagina with high concentrations of anaerobic bacteria (*Mobiluncus*, *Gardnerella vaginalis*).

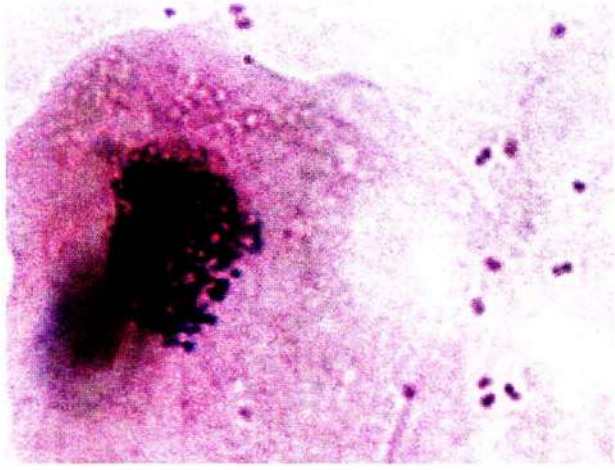


Image 2-23: Gram-negative diplococci—these are extracellular; require intracellular for Dx

There is a thin, "skim milk," scanty, foul-smelling, non-irritating discharge that has 2 identifying features:

1) Clue cells (an epithelial cell with many adherent bacteria; Image 2-24)
2) Fishy odor when mixed with KOH (+ whiff/sniff test)

There is no cervical discharge.

Treatment is metronidazole—oral (500 mg bid x 7 d) or vaginal gel (0.75% bid x 5 d)—alternately tinidazole or clindamycin orally or as a cream 2% intravaginally (at bedtime x 7 d).

Treatment guidelines for pregnant women:

- metronidazole 500 mg bid x 7 days, or
- metronidazole 250 mg tid x 7 d, or
- clindamycin 300 mg orally bid x 7 d.

Creams are not recommended in pregnancy.

The reason to treat systemically is that there is a much higher risk of preterm labor and delivery than of complications from a short course of therapy with metronidazole or clindamycin. The male sex partner does not need to be treated.

Vaginal Candidiasis

Vulvovaginal candidiasis (VVC) is almost always caused by *Candida albicans*. It presents with adherent white plaques with an erythematous base and is almost always pruritic. Remember that this may be a sign of undiagnosed diabetes or HIV, especially if recurrent. Women with recurrent vaginal candidiasis should be screened for both illnesses.

Treatment:

- Uncomplicated VVC in a non-pregnant patient: butoconazole, miconazole, or terconazole vaginal creams. Oral azoles are equally effective—especially oral fluconazole 150 mg x 1.
- Treat pregnant patients with only the azole creams for 7 days.

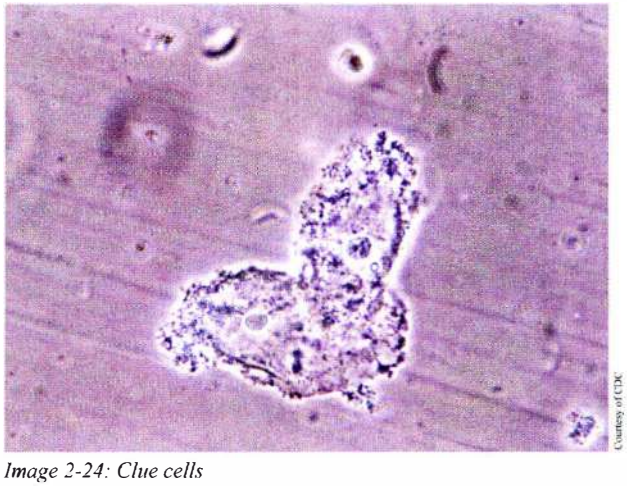


Image 2-24: Clue cells

- A subgroup of patients has recurrent VVC. Weekly topical clotrimazole and oral fluconazole 150 mg one-time doses are equally effective.

Trichomonas

Trichomonas vaginalis infection causes a vaginitis in women. Men may also be infected but are usually asymptomatic. *Trichomonas* vaginitis presents with a profuse, thin, frothy, yellow-green, foul-smelling discharge (which, like bacterial vaginosis, has a positive whiff test), vaginal erythema, and a strawberry cervix.

Treat *Trichomonas* vaginitis with metronidazole 2 grams single dose or tinidazole 2 grams single dose. Even though these are the best treatments, they are only moderately effective. If pregnant, recommendations say it is OK to give a one-time dose of 2 grams metronidazole.

URINARY TRACT INFECTION

The standard definition of a positive urine culture remains $\geq 10^5$ organisms/mL of urine. However, a positive urine culture does not equal UTI. If a person has bacteriuria without symptoms and no urinary catheter, this is considered asymptomatic bacteriuria (ASB). The diagnosis of UTI can be difficult especially in older adults. Classic symptoms include dysuria, frequency, stranguria, and urgency.

Pyuria has good negative predictive value; the absence of pyuria essentially rules out UTI. On the other hand, presence of pyuria even with bacteriuria does not make the diagnosis of UTI.

A wide variety of organisms may cause UTI, but *E. coli* and other enterics are the most common. *S. saprophyticus* is a coagulase-negative staphylococcus that may cause UTI as well.

UTIs are the most common nosocomial infections.

Risk factors for UTIs in women include diabetes mellitus, sexual activity, diaphragm use, vaginal atrophy, and genetic predisposition.

UTIs are rare in men and are not associated with male sexual activity, except in men who have sex with men. In heterosexual men, UTIs are usually a result of an abnormality in the urinary tract, such as obstruction, ureterovesical reflux, or prostatic hypertrophy.

In either gender, UTIs are increased in the presence of diabetes mellitus, sickle cell disease, hyperparathyroidism, or gout.

Proteus infections are associated with neurogenic bladder or urinary stones; therefore, when *Proteus* is indentified in the urine, order imaging tests to look for stones. Group B strep (*S. agalactiae*) infections are seen in pregnancy.

[Know!] UTI and ASB in pregnant women: Treat asymptomatic bacteriuria in pregnant women. (1/3 go on to pyelonephritis if untreated!) Also, always admit and treat pregnant patients with pyelonephritis as a

QuickQuiz

- Women with recurrent or recalcitrant candidal vulvovaginitis should be tested for what infection? For what metabolic disease?
- What is the standard treatment for uncomplicated cystitis, complicated cystitis, uncomplicated pyelonephritis, and complicated pyelonephritis?
- In what 2 settings would you treat asymptomatic bacteriuria?
- Otitis externa is usually due to what organism?

complicated pyelonephritis (below). Pregnancy-safe antibiotics to use for UTI/pyelonephritis are ampicillin, cephalosporins, and TMP/SMX—but do not give TMP/SMX in late pregnancy or to early-nursing mothers because it might cause kernicterus in the child. Avoid tetracycline, doxycycline, and quinolones in pregnancy, infancy, and early childhood because they are toxic.

The Infectious Diseases Society of America updated the approach to diagnosis and therapy of UTIs in 2010. The 1st step in treating UTIs is to determine whether they are lower tract (cystitis) vs. upper tract (pyelonephritis). Cystitis typically has no systemic signs of infection or flank tenderness. Pyelonephritis typically has fever (often > 102° F) and flank pain. Sepsis may be present, and blood cultures are positive in ~ 10%.

The next step is to determine whether it is complicated or not. Complicated UTIs are those in persons with diabetes, immunocompromise, structural anomalies, foreign bodies, prior resistant organisms, or male gender.

Uncomplicated cystitis may be treated based on symptoms alone and does not require a urine culture. All other patients should have a urine culture. Imaging of the urinary tract (ultrasound or CT) should not be performed in cystitis, and should be performed in pyelonephritis only if symptoms persist after 72 hours of culture-guided therapy.

Treatment:

- Uncomplicated cystitis: TMP/SMX x 3 days is the 1st line treatment but only if the known level of *E. coli* resistance is ≤ 20%. If it exceeds this, nitrofurantoin for 5 days or fosfomycin x 1 dose should be given. Quinolones should be reserved for complicated infections (because overuse is creating resistance), and beta-lactams should be avoided due to decreased efficacy.
- Complicated cystitis: quinolone x 7 d.
- Uncomplicated pyelonephritis: quinolone x 7 d if *E. coli* resistance is ≤ 10%. An initial dose of IV ceftriaxone may be given pending cultures.
- Complicated pyelonephritis and/or hospitalized patients: quinolone, or ceftriaxone, or beta-lactam + beta-lactamase inhibitor, or ampicillin + aminoglycoside for 10–14 d.

Asymptomatic bacteriuria should be treated in only 2 settings: pregnancy and anticipated urologic surgery (e.g., transurethral resection of the prostate).

Urinary catheters do not need to be changed unless there is a symptomatic UTI.

Recurrent UTIs are common and should be approached in a systematic way. First, define the type of recurrence. Recurrences can be relapses (same strain within 2 weeks of the end of therapy) vs. reinfection (different strain than the initial infection). Relapses are usually due to a persistent nidus of infection (stones, abscess, urethral/ureteral/bladder diverticula, obstruction) so CT of the abdomen and pelvis should be performed. Reinfection may be related to sexual activity. If so, very low dose prophylaxis (e.g., TMP/SMX 1/2 SS tablet, nitrofurantoin 50 mg) before or after sexual activity should be given. If there is no such relationship and < 3 episodes a year, treat as they occur. If ≥ 3 episodes a year, consider chronic low-dose suppression for 6 months.

OTITIS AND SINUSITIS

Otitis Media

Otitis media is very uncommon in adults, and its presence suggests structural anomalies or immunocompromise. It presents with ear pain and hearing loss +/– fever. Diagnosis is made by visualizing both inflammation of the tympanic membrane and fluid in the middle ear. *S. pneumoniae* is the most common bacterium. *H. influenzae* and *M. catarrhalis* are also common. Treat with amoxicillin alone if the patient hasn't taken antibiotics recently. Treat with amoxicillin/clavulanate, cefuroxime, ceftriaxone, or clindamycin if the patient has recently taken other antibiotics. Treatment failure: Consider tympanocentesis. In patients on mechanical ventilation: Rx for *Pseudomonas* or *Enterobacter* with ceftazidime, imipenem, piperacillin/tazobactam.

Otitis Externa

Otitis externa is also predominantly a pediatric infection. It presents with unilateral pain and itching in the external auditory canal. It is predisposed by trauma, foreign bodies, dermatitis and moisture, especially swimming ("swimmer's ear"). The causative organism is usually *P. aeruginosa*. Treat with a topical quinolone. If moderately severe, give an oral quinolone.

This should be differentiated from malignant (necrotizing) otitis externa, which initially presents the same but progresses to an invasive and destructive infection of soft tissue and bone. It is also due to *Pseudomonas* infection, and > 90% of patients are diabetic. Others at risk: AIDS and chemo patients. IV antibiotics are usually required.

Sinusitis

Sinusitis is inflammation in the paranasal sinuses. Acute sinusitis is defined as persisting up to 4 weeks. Chronic sinusitis is defined as persisting > 4–8 weeks. Recurrent sinusitis is ≥ 3 separate episodes of acute sinusitis per year.

The most important factor in the development of sinusitis is obstruction of the ostia (blocked with thickened sinus secretions, sinus congestion, nasal polyps, and trauma).

Most sinusitis is viral, and clinical criteria (see below) should be used to decide whether there is a likelihood of bacterial infection, and thus a response to antibacterials. According to IDSA guidelines, 3 clinical findings are predictive of bacterial sinusitis: duration of > 10 days, fever > 102° F with purulent drainage or facial pain, and worsening of symptoms after an initial improvement.

The most common causative bacterial organisms are *S. pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis*. Chronic sinusitis may also be caused by *S. aureus*, group A strep, *P. aeruginosa* (especially with cystic fibrosis), and anaerobes such as *Fusobacterium* and *Bacteroides*.

Fungal sinusitis is seen in patients with diabetes (especially zygomycetes), cancer, and in those receiving corticosteroid therapy. A patient with rhinocerebral zygomycosis may present with symptoms of only a sinus infection or unilateral nasal congestion. Tissue necrosis occurs as infection spreads outside of the sinuses with the resulting distinctive black eschar sometimes visible on the palate and/or nasal mucosa.

Symptoms may assist in localizing which sinus is involved. Frontal sinusitis may have headache that is worse when leaning forward ("bowler's headache"). Maxillary sinusitis may have maxillary tooth pain. Sphenoid sinusitis may have headache at the vertex of the skull.

Note: Patients with similar headache and pressure, along with rhinorrhea and sneezing, usually have allergic or viral rhinitis—not sinusitis.

Patients with chronic sinusitis present differently, often with signs/symptoms such as chronic refractory sinus congestion, bad breath, postnasal drip, cough, and headache.

Sinusitis symptoms, especially if seasonal, should be differentiated from allergic rhinitis. Nasal smears with a high number of eosinophils are seen with both allergic rhinitis and nonallergic rhinitis with eosinophils syndrome (NARES). Bacterial sinusitis shows large numbers of neutrophils and bacteria.

Bacterial sinusitis is treated empirically, but failure to respond or frequent relapses warrants sinus aspiration. Consider cystic fibrosis if *Pseudomonas* grows from a sinus culture (especially in a young adult with history of recurrent respiratory issues).

Radiography: Sinusitis is generally a clinical diagnosis and imaging is not usually required. If indicated, noncontrast CT scan is the gold standard for diagnosing sinusitis but cannot differentiate viral from bacterial. In addition to the frontal and maxillary areas, it shows the ethmoid and ostiomeatal complex. CT also shows subtle thickening. The T2-weighted MRI is useful for differentiating an inflammatory process (high-intensity bright) from a tumor (intermediate-intensity bright). X-rays showing opacification, air-fluid level (Waters view of the frontal and maxillary sinuses), and thickening indicate sinusitis.

Treatment: If acute bacterial sinusitis is suspected based on above criteria, start amoxicillin-clavulanate. 2nd line drugs are the fluoroquinolones and doxycycline. Recommended duration of therapy is 10 days. Intranasal corticosteroids and saline irrigation may be used as adjunctive treatment.

Chronic sinusitis rarely responds to antibacterial therapy. ENT consultation may prove helpful.

Use endoscopic sinus surgery when medical therapy fails.

Treatment of rhinocerebral zygomycosis is emergent and aggressive—with radical surgical debridement and lipid amphotericin B. (Lipid formulation is used so that you can give higher ampho doses with less toxicity.) Most other fungal meds are not effective. Posaconazole has been used successfully in conjunction with debridement; it is considered a good agent to use after patients stabilize and begin to improve on amphotericin.

SKIN / SOFT TISSUE, BONES, JOINTS

Classic Soft Tissue Infections

Vibrio vulnificus causes a necrotizing soft tissue infection after inoculation into non-intact skin (e.g., skin penetrated by fishing hook). It almost always only does so in patients with liver disease. Vibrios are found in warm salt water, and infection occurs mostly in the areas of Chesapeake Bay and the Gulf of Mexico. Diagnose by culture, and treat with a combination of ceftriaxone and doxycycline.

Mycobacterium marinum is also called "fish tank bacillus." It causes nonhealing skin ulceration in people who work with fish tanks. Infection may present as a single granuloma, but the organism often invades the lymphatics and can cause a series of lesions over a lymphatic drainage similar to the lesions seen in sporotrichosis. Lesions tend to localize in the distal extremities because the organism does not grow well at body temperature. Diagnosis is made by biopsy and AFB stain and culture.

Treat with clarithromycin plus either ethambutol or rifampin for at least 1-2 months after the lesions have resolved.

Erysipelothrix rhusiopathiae infects a large number of domestic and marine animals and causes skin infection after occupational exposure in fishermen and meat handlers. Lesions are usually localized nodules with lymphangitis in ~ 25%. Systemic disease is uncommon and more likely in alcoholics. Treat with PCN.

Quick Quiz

- How many days of symptoms are required to diagnose a patient with bacterial sinusitis and prescribe antibiotics? What are the usual causative organisms?
- True or false? A patient with 5 days of facial pain, fever to 100.6° F, and clogged nasal passages should be treated for bacterial sinusitis.
- What are some symptoms of rhinocerebral zygomycosis?
- How can you differentiate allergic rhinitis from bacterial?
- Treat bacterial sinusitis with which antibiotics?
- What is the clinical presentation of *M. marinum*?
- What organism is associated with osteomyelitis in a patient with sickle cell anemia (besides *S. aureus*)?
- How is osteomyelitis in a prosthetic joint diagnosed?

PCN-allergic patients should receive quinolones or 3rd generation cephalosporins.

Impetigo presents as honey-colored crusts over nodular lesions. *S. aureus* is the most common cause; occasionally *S. pyogenes* is the culprit. Lesions are often present around the nose or mouth.

Osteomyelitis

Osteomyelitis may be acute or chronic, the distinction being that the latter has necrotic bone. Acute is usually caused by *S. aureus.* Some organisms have certain epidemiologic niches. In IV drug abusers, *Pseudomonas* has a predilection for several: the sternoclavicular joint, symphysis pubis, and vertebrae. Sickle cell patients have a high incidence of *Salmonella* osteomyelitis. Prosthetic joints are infected most commonly by *S. aureus* and coagulase-negative staph (see below).

Diagnosis of diabetic foot osteomyelitis can be made with high accuracy if a solid probe is able to reach bone on exam. Otherwise, imaging is needed to demonstrate osteomyelitis prior to recommending bone biopsies for culture. Initial plain x-rays may be done with the understanding that radiolucency requires > 50% demineralization of the bone, and this takes weeks to occur. The most sensitive image is MRI, which is the study of choice. Pyrophosphate bone scans are also sensitive but are very nonspecific because they are positive whenever there is new bone formation (trauma, fracture, prosthetic joint incorporation).

Cultures of the bone are the gold standard. Evidence of osteomyelitis on imaging and a positive blood culture are presumptive evidence of microbiologic causation. Blood cultures are often (50%) positive in acute osteomyelitis.

In chronic osteomyelitis, a sinus tract may be present. A culture of the tract may be performed, but the only organism that has any predictive value as the causative organism is *S. aureus*.

Except for small bone disease and very early prosthetic joint infection, you must remove all necrotic bone and prosthetic material before a chronic osteomyelitis can be cured with antibiotics.

Prosthetic joint infection occurs in 1–5% of cases. Manifestations are wound drainage, cutaneous erythema, or prosthetic joint pain. Plain x-rays are helpful if they show a widening of the bone-cement interface, changes in the position of prosthesis, cement fractures, periosteal reaction, or motion of components on stress views. Other imaging techniques commonly are not helpful because of a high degree of false-positives. If clinical suspicion is high based on symptoms +/– x-ray, a joint aspiration should be performed to document infection and determine the infecting organism (prior to antibiotics).

If the infection occurs within 30 days of surgery, patients may be treated with antibiotics and debridement with retention of the prosthesis. All others should have removal of the prosthesis, followed by a temporary spacer implant and > 6 weeks of IV antibiotics. If this results in a sterile joint space, a new prosthetic joint can then be implanted. This is the so-called 2-stage procedure.

NOSOCOMIAL INFECTIONS

Important nosocomial infections include pneumonia (hospital-acquired and ventilator-associated), blood stream infections, urinary tract infections, surgical site infections, and *Clostridium difficile* infections.

Nosocomial pneumonia is almost always bacterial and has the highest mortality rate of all the nosocomial infections (30% if bacteremic; 50% if gram-negative bacteremic!). It is usually caused by gram-negative organisms; next most frequent is *S. aureus.* The most common risk factor is mechanical ventilation. The diagnosis of ventilator-associated pneumonia is not straightforward and depends on documenting a combination of increased secretions, positive respiratory cultures, and radiographic infiltrates.

Intravenous catheter-related infections may present as a generalized illness without symptoms localizing to the line. (This is the most common scenario.) Alternatively, a localized infection either of the subcutaneous tunnel and/or of the site of entry may be present. Finally, and least commonly, signs and symptoms of a septic clot may be present in line-related thrombophlebitis.

Secondary endocarditis is more likely to occur in patients with catheters that extend into or close to the heart. IV lines commonly become infected after ~ 3 days. Metal

needles are less likely than plastic angiocatheters to become infected. IV catheter infections are usually due to *S. epidermidis* and *S. aureus*. Some other causes are *Candida*, *Corynebacterium jeikeium* (especially in bone marrow transplant units), and gram-negative rods.

The key decision in treating catheter-related infections is whether the line should be removed. Per IDSA guidelines all catheters should be removed if associated with any of the following conditions: severe sepsis; suppurative thrombophlebitis; endocarditis; bloodstream infection that continues despite 7 days of appropriate antimicrobial therapy. In addition, all lines should be removed in infections with the following: *S. aureus*, *P. aeruginosa*, fungi, or mycobacteria. In the case of enterococcal infection, short-term catheters should be removed; for long-term catheters salvage may be attempted.

Patients should be treated with antibiotics (e.g., vanco for staph) for 14 days after line removal. In the case of *S. aureus* infection of long-term catheters, 4–6 weeks of antibiotics are needed. Lines used for hyperalimentation may cause fungal infections. Treat with vori- or an echinocandin if candidiasis is present.

If line salvage is attempted, an antibiotic lock solution should be used.

VACCINES

Adult Vaccinations

Vaccine Types

Note: Vaccines used solely in childhood are not discussed.

- Live-attenuated vaccines should not be given to the immunocompromised (including pregnancy):
  - Measles-mumps-rubella
  - Varicella
  - Zoster
  - Smallpox
  - Typhoid oral
  - BCG
  - Yellow fever
  - Intranasal influenza
- Killed (inactivated) are safe for immunocompromised:
  - Td
  - Tdap
  - HAV
  - Polio
  - Cholera
  - Rabies
  - Japanese encephalitis
  - Typhoid polysaccharide
  - HBV and HPV, which are recombinant
  - Pneumococcal vaccines (PPSV-23 and PCV-13)
  - Meningococcal polysaccharide and conjugate
  - Trivalent influenza (TIV)

Vaccine Schedules

The specific schedule for vaccinations changes very frequently. The current schedule can be found on the webpage for the Advisory Council on Immunization Practices at: http://www.cdc.gov/vaccines/schedules/index.html.

Vaccinations that are recommended for adults, according to age groups:

- Td or Tdap: 1 dose q 10 years. (DTaP and DT are for children < 7 years.) Tdap is now approved for all > 7 years of age. Tdap needs to be given only once if the usual childhood series was given; after that, Td can be given.
- HPV: 3 doses for ages 9–26 (but not older), both genders.
- Varicella (chicken pox vaccine): 2 doses, if no history of immunity or vaccination.
- Zoster (booster to prevent shingles): adults > 50 years of age.
- MMR: 2 doses if not vaccinated or 1 more if received only 1 vaccine as a child.
- Influenza: given annually to all persons > 6 months old.
- Pneumococcal vaccination: > 65 years and those at risk (see below).
- HAV: at-risk adults without evidence of immunity.
- HBV: at-risk adults without evidence of immunity and no history of childhood vaccination.
- Meningococcal polysaccharide or conjugate: everyone ages 11–18 years and at-risk adults ages 19–55 years.

Varicella virus vaccine is recommended for all individuals ≥ 12 months of age who are not immune. Note that a history of chicken pox by the patient is not sufficient for assuming immunity. If the adult patient doesn't know or believes he/she has had no previous infection, check immune status by serologic testing (IgG Ab) before giving the vaccine because most adults are immune. This vaccine is contraindicated in patients with immunodeficiency because it is live virus.

Zoster vaccine is licensed for patients ≥ 50 years of age and recommended after age 60, even if they have had a recent outbreak of shingles. Because it is live virus, this vaccine is contraindicated in patients with immunodeficiency or who are pregnant. Both the varicella and the zoster vaccine have the same virus, but the latter has a much higher dose.

MMR: It is recommended that persons born after 1956 receive 2 doses of live measles vaccine. These should be given not less than 1 month apart but can be given years apart. The present recommendations are the 1st dose at 12 months and the 2nd dose at age 4–6 years. All young adults (since they would have been born after 1956) who have had only 1 live measles vaccine should receive another.

QuickQuiz

- Which vaccines contain live virus? To which patients should they not be given?
- Which vaccines are safe to be given to immunocompromised or pregnant patients?
- Know which vaccines are recommended to adults and in what age groups.
- How many doses of MMR are considered most desirable and protective?
- Which patient groups should be given the pneumococcal polysaccharide vaccine?
- Which patient groups should receive some form of the meningococcal vaccine?
- How do you decide how to prevent tetanus in a patient presenting with a wound? Is a crush injury "tetanus-prone?"

Pneumococcal vaccines include the 23-valent polysaccharide vaccine (PPSV-23) and the 13-valent conjugate vaccine (PCV-13). The rules for giving these vaccines are a little complicated:

1) Timing:
   - After PCV-13, you need to wait 8 weeks before you give PPSV-23.
   - After PPSV-23, you need to wait a year before giving PCV-13.
   - A booster dose of PPSV-23 should be given 5 years after the 1st dose of PPSV-23.
2) Indications:
   - All patients ≥ 65 years of age should receive PPSV-23.
   - Patients19–64 years of age with the following conditions should also receive PPSV-23:
     - Chronic heart disease
     - Chronic lung disease
     - DM
     - Alcoholism
     - Chronic liver disease
     - Cigarette smoking
3) Patients 19–64 years of age with the following conditions should receive PCV-13 followed by PPSV-23 8 weeks later:
   - Cerebrospinal fluid leak
   - Cochlear implant
   - Sickle cell disease/other hemoglobinopathy
   - Congenital or acquired asplenia
   - Congenital or acquired immunodeficiency
   - HIV
   - Chronic renal failure
   - Nephrotic syndrome
   - Leukemia
   - Lymphoma
   - Hodgkin disease
   - Generalized malignancy
   - Iatrogenic immunosuppression
   - Solid organ transplant
   - Multiple myeloma

HAV: Unless otherwise contraindicated, inactivated hepatitis A vaccine is universally recommended at or after age 1 year.

HBV is universally recommended at birth and for all of those who were not immunized in childhood, particularly adolescents.

Serologic testing for immunity is recommended only for specific groups:

- Health care and public safety workers
- Chronic hemodialysis patients
- HIV-infected persons
- Immunocompromised persons
- Sexual partners of HBsAg-positive persons

Persons who do not develop a protective response (anti-HBs concentration of < 10 mIU/mL) should receive another full vaccine series.

Meningococcal vaccines include conjugate and polysaccharide vaccines. If exposure is ongoing, a booster should be given every 5 years.

- All persons 11–18 years of age should be vaccinated with 2 doses of the conjugate vaccine.
- Previously unvaccinated at-risk patients (see list below) between 18 and 55 years should receive conjugate vaccine.
- Previously unvaccinated at-risk patients (see list below) > 55 years of age should receive polysaccharide vaccine.

At-risk patients for meningococcal disease:

- Asplenia or complement deficiencies
- 1st year college students who live in dorms; military recruits
- People who are traveling to the meningitis belt of sub-Saharan Africa, Saudi Arabia (e.g., for the Hajj), or Nepal
- Lab workers who work with *Neisseria*

Approach to Tetanus Prevention

Tetanus can be prevented with the appropriate use of tetanus toxoid (Td) and tetanus immune globulin (TIG). The use of these depends on the type of wound and the vaccination status of the patient.

Tetanus-prone wound: At-risk wounds include crush injury, bite injuries, dirt or fecally contaminated wounds, puncture or missile wounds, deep penetrating wounds, compound fractures, wounds containing foreign bodies (e.g., wood splinters), and re-implantation of an avulsed tooth. Tetanus can be prevented based on whether it is

certain patients have had the primary series of 3 injections of Td or not. Those who have had a primary series should receive a booster dose of Td if they have not received Td in the last 5 years. This allows production of antitoxin antibodies prior to the ability of the tetanus toxin to travel from the wound site to the central nervous system. Patients who have not received the primary series (or of uncertain immunization history) should be considered at high risk of tetanus. The patients should receive Td to begin or attempt to complete the primary series. However, since they did not have adequate prior immunization, boosting of their immune response cannot be relied upon. Therefore, these are the only patients for whom TIG is indicated.

Non–tetanus-prone wound: Persons who do not have tetanus prone wounds (often called "clean wounds") are not at risk for tetanus. However, the patient encounter provides an opportunity to begin immunization in the previously unvaccinated or to boost immunity in people who haven't received a booster in the last 10 years. Thus, those who have not received all 3 primary series injections of Td (or are uncertain) should receive as many Td injections needed to complete the 3-shot primary immunization sequence. Those who have completed the primary series but have not been boosted in the last 10 years should receive a Td booster. TIG is never indicated in the management of non–tetanus-prone wounds.

Unusual Vaccines for Special Situations

Anthrax: AVA is the only licensed human anthrax vaccine in the U.S. It contains proteins only, no dead or live bacteria. The vaccine is recommended for people who work with anthrax cultures or who are exposed to activities with high potential for aerosolization of *B. anthracis*. In addition, a course should be given after potential exposure in previously unvaccinated persons.

BCG is not recommended in the U.S. but is commonly given to children in other countries where TB is common. BCG immunization may cause a positive tuberculin skin test, complicating later evaluation of tuberculosis. Having received the BCG vaccine does not change the interpretation of the TB skin test in the U.S. (An indurated test should still be subjected to the same cut-offs for significance as in any other patient. See Pulmonary Medicine, Book 2, for discussion of TB skin testing.) Interferon-gamma–releasing assays (IGRAs) are not affected by BCG.

Japanese encephalitis vaccine is recommended for travelers who plan to stay a long time in rural Asia.

Rabies vaccine is discussed in the section on rabies disease (page 2-43). Preexposure vaccination is recommended for those at occupational risk and for travelers (and especially their children) planning extended stays in areas where dog rabies is enzootic.

Typhoid vaccine is recommended for travelers (> 2 years old) who go outside of the usual tourist areas within Latin America, Asia, and Africa. An oral live-attenuated vaccine is recommended for those > 2 years of age. It has a protection rate of 70–90% and is recommended every 5 years.

Smallpox vaccine is available on demand. Military personnel and select health care workers have been vaccinated in the past. In the event of a bioterrorist attack with smallpox, large numbers of people will be vaccinated to prevent epidemic spreading of the disease. Contraindications to smallpox vaccine include pregnancy, age < 12 months, and immunosuppression.

Polio vaccine is not routinely recommended to persons > 18 years of age. Polio vaccine is recommended for previously unimmunized travelers to endemic areas. A booster is indicated for travelers who have had only the primary vaccination and who travel to areas where exposure to the wild-type virus is likely. Only the inactivated vaccine is recommended in the U.S.

Yellow fever vaccine is recommended for travel in equatorial Africa and much of tropical South America. It is a live vaccine and should not be given to immunosuppressed patients.

Cholera vaccine is not very effective and is rarely required.

PROPHYLAXIS

Meningococcemia

Meningococcemia chemoprophylaxis may be done with rifampin, ciprofloxacin, or ceftriaxone. Each is 90–95% effective in reducing nasopharyngeal carriage of *N. meningitidis*. Remember that ciprofloxacin is not routinely given to children or pregnant women (possible cartilage damage). Ceftriaxone is usually reserved for pregnant women. Health care workers do not receive chemoprophylaxis unless they had direct contact with the index patient's secretions (e.g., mouth-to-mouth resuscitation, airway suctioning, or intubation).

Travelers' Diarrhea

Travelers' diarrhea (TD): Educate patients on what to avoid so they do not contract travelers' diarrhea in the first place. When traveling in a country where it may occur, they should:

- Not drink the local untreated water or eat ice, including mixed alcoholic drinks with ice
- Ensure the water or ice is either boiled or filtered first
- Remember that dishes are washed in local water, so drink from the can with a straw, instead of from a glass
- Avoid fresh fruits (but peeled ones are safe, like apples), vegetables, and meat salads, like tuna, as well as condiments, such as salsas

QuickQuiz

- BCG vaccine is used to prevent which illness? Is it used for this purpose in the U.S.?
- Can IGRA tests distinguish patients with BCG vaccination vs. those with active tuberculosis?
- What are the contraindications to receiving the smallpox vaccine?
- Know the recommendations for prophylaxis and treatment of travelers' diarrhea.
- In whom should a post-vaccine hepatitis B titer be checked?

Fancy hotels do not guarantee healthy food and water. Carbonated drinks and hot tea or coffee are usually safe.

A good general rule: Boil it, peel it, cook it, or forget it.

Typically, prophylactic antibiotics are not indicated. Prophylactic antibiotics are justified for patients with immunodeficiencies, severe manifestations, or history of cardiac, kidney, or inflammatory bowel disease.

Prophylactic regimens include:

- Norfloxacin 400 mg qd
- Ciprofloxacin 500 mg qd
- Rifaximin 200 mg qd or bid
- Bismuth subsalicylate 2 tablets chewed qid

For self-treatment once travelers' diarrhea is acquired, have the patient determine the severity of diarrhea and treat accordingly. Patients with > 4 unformed stools a day, bloody or mucopurulent stools, or fever should be treated with 1 of the following:

- Ciprofloxacin 500 mg bid x 1–2 days
- Norfloxacin 400 mg bid x 3 days
- Azithromycin 1,000 mg x 1 dose
- Rifaximin 200 mg tid x 3 days

The 3-day regimens can be abbreviated to 1 day if the diarrhea has completely ceased after a day of treatment. Loperamide can be used cautiously with the antibiotics but should not be used alone as a form of treatment in severe disease.

Malaria

Malaria prophylaxis is discussed in the section on the organisms involved (page 2-33).

FOR FURTHER READING

[Guidelines in blue]

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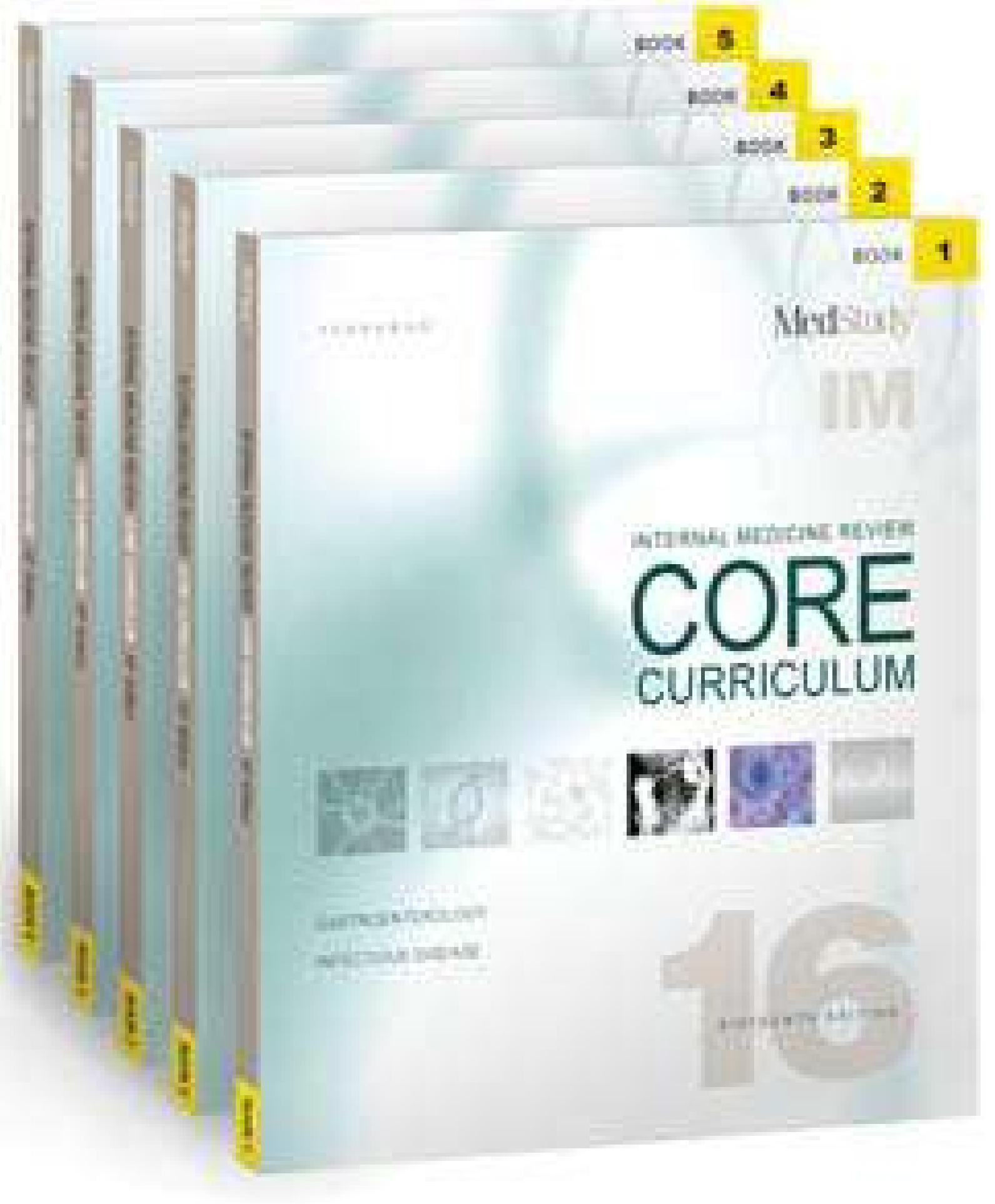
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Pulmonary Medicine

DIAGNOSTIC TESTS

CT

You need to understand a little about types of CT scans to order the proper tests, so let's dive into CT scans as they relate to pulmonary parenchymal and vascular diseases. These are pretty complicated in their techniques, but you don't need to understand much about how they work. Focus on knowing the limitations/benefits of the different types and which to order when.

There are basically 4 types of CT scans, and within the helical CT type, there are 2 subtypes:

1) "Conventional" CT (cCT)
2) High-resolution CT (HRCT)
3) Helical CT (hCT):
   - Single-section hCT
   - Multidetector hCT (MDCT)
4) Electron beam CT

cCT ("step and shoot") works by shooting x-rays in an incremental axial or helical rotation. cCT scans require cables to wind and unwind, so they're slow and have a few subsequent disadvantages (e.g., respiratory misregistration and unreliable imaging of vascular structures due to timing issues). cCT is still used to look at anatomy but is not used much to evaluate lungs.

HRCT is similar to cCT, but the x-rays are thinly collimated (restricting the beam to a given area), so we can see the lung parenchyma at high resolution (down to about 5 acini surrounded by interlobular septa). HRCT is used when disease is suspected by history and physical exam, but the chest x-ray is either normal or only slightly abnormal (interstitial lung diseases [ILD], emphysema from α_1-antitrypsin deficiency, bronchiectasis, lymphangitic spread of malignancy). Certain patterns and distributions of CT abnormalities are associated with histopathology in ILD, so sometimes a diagnosis can be made using HRCT without a lung biopsy. HRCT is always the first place to start when you suspect ILD or bronchiectasis! HRCT is sometimes used for focal diseases (solitary pulmonary nodules or pulmonary-renal vasculitides) to guide biopsies. HRCT does not require contrast because the lung inherently has significant contrast (soft tissue, air, etc.), and the technique of HRCT is not typically used to evaluate vasculature.

hCT (helical CT; previously called "spiral" or "volumetric") works by shooting x-rays in a continuous helical rotation using slip rings instead of cables (no need for all that winding and unwinding, and scans much faster). The first kind of hCT was called "single-section." Be aware that unless a contraindication exists, IV contrast dye is used with hCT.

Single-section hCT is being replaced by multidetector (or "multislice") hCT. **MDCT** is now the best method for performing CT-pulmonary angiography (**CTPA**) because it sees subsegmental emboli better than single-section. MDCT is also replacing single HRCT at some hospitals because MDCT inherently provides higher-resolution images of the pulmonary parenchyma.

MDCT has these 3 distinct advantages:

1) Scanning large sections on a single breath (such as the pelvis and the lungs)
2) Collecting images precisely when the flow of contrast is in the system you're concerned about (i.e., specific blood vessels)
3) Narrowing of the collimation through the chest so the lung and hilar images are "high resolution"

Electron beam CT (a.k.a. ultrafast CT) was initially developed for imaging of the heart. It is very fast because the x-ray source is swept electronically rather than mechanically. It is able to take multiple images within the time frame of a single heart beat and, therefore, is capable of evaluating congenital defects and pulmonary vasculature.

It also gives a lower radiation dose than hCT. Electron beam CT units are rare and cost double that of an hCT unit.

Following are some CT buzzwords taken from the above items:

- Diagnose ILD or bronchiectasis = HRCT.
- Work up solitary pulmonary nodule = hCT or HRCT.
- Diagnose pulmonary embolism = CTPA, which can be done by MDCT. (In testing situations, your correct choice may be only CTPA or hCT or MDCT as the option.) Do not select HRCT to diagnose a PE!

Again, most hospitals have added MDCT technology, and you use it for everything in the lungs. You don't need to differentiate HRCT from MDCT anymore. You may order a CTPA or a chest CT, and the test is performed with MDCT. Some hospitals and testing situations may still ask you to request "high-resolution" imaging for certain disease states and helical CT to diagnose pulmonary emboli.

MRI

MRI is useful only in specific situations while evaluating pulmonary disease:

- When evaluating tumors near adjacent blood vessels or nerves.
- For determining what is tumor and what is not; e.g., superior sulcus tumors, brachial plexus tumors, mediastinal tumors, tumors near the aorta or heart.
- MRI is also used at very few centers to evaluate venous thrombosis using magnetic resonance angiography (MRA) and magnetic resonance venography (MRV).

Again, HRCT and hCT are generally the best tools for assessing lung parenchyma and vessels.

BIOPSY

Use lung biopsy to assist in diagnosing interstitial lung disease in patients with atypical clinical features and non-diagnostic HRCT, especially when you need to exclude neoplastic and infectious causes of an interstitial pattern.

Collect biopsies by the transbronchial approach, the open lung approach, or by video-assisted thoracoscopic lung surgery (VATS). The technique chosen depends on where abnormalities are located—with chest x-ray and HRCT results used to plan strategy. In sarcoidosis, for example, transbronchial biopsy yield is highest when infiltrates are obvious on the chest x-ray (90%) and lowest (70%) when hilar adenopathy is the only abnormality.

Perform lung biopsy if you are entertaining the diagnosis of 1 of the following: interstitial lung disease, lymphangitic spread of cancer, eosinophilic pneumonia, vasculitis, or certain infections.

As with other ILDs, lung biopsy is no longer routinely used in evaluating possible interstitial pulmonary fibrosis (IPF)—except in atypical cases—because HRCT usually is diagnostic.

OTHER PULMONARY TESTS

Bronchoalveolar lavage (BAL) is an important pulmonary diagnostic tool. [Know Table 3-1.]

Pulmonary angiogram is still considered the gold standard for pulmonary embolism diagnosis, but this test is rarely required anymore because CTPA is very reliable.

PET scan is useful in differentiating benign vs. malignant pulmonary nodules and infectious or inflammatory conditions (most useful with > 1–2-cm nodules).

Thoracentesis, V/Q scan, and pulmonary function tests (PFTs) are covered in their respective sections.

RESPIRATORY PHYSIOLOGY

Acid-base is covered in depth in Nephrology, Book 2.

Know respiratory physiology well. The information is used extensively in clinical practice and is often tested on exams.

SHORT REVIEW

Atmospheric pressure (P_b) varies. At sea level, at 59° F, it is 29.92 inches Hg or 760 mmHg. The medical standard is to use mmHg (millimeters of mercury). Atmospheric pressure decreases as you get further away from the surface of the earth and also as temperature increases. The component gases of the atmosphere each exert a consistent partial pressure to the atmospheric pressure. For example:

Partial pressure O_2

$= F_iO_2 \times P_b$

$= 0.209 \times 760$ mmHg

F_iO_2 = fraction of inspired oxygen

P_b = atmospheric pressure

Table 3-1: Findings in Bronchoalveolar Lavage

Results	Cause
< 1% neutrophils; < 16% lymphocytes; no eosinophils	Normal findings
Increased neutrophils	Idiopathic pulmonary fibrosis (IPF), collagen vascular disease, asbestosis, suppurative infections, granulomatosis with polyangiitis, ARDS
Increased lymphocytes	Hypersensitivity pneumonitis and sarcoidosis
Increased eosinophils	Acute and chronic eosinophilic pneumonia, some ARDS, Churg-Strauss, Löffler syndrome, tropical eosinophilia, parasite infection (esp. ascariasis), TB, collagen vascular disease, malignancy, and drug reactions
Diagnosis of specific types of pneumonias and other infectious diseases	*95% sensitive for PJP in AIDS patients *CMV pneumonia (*inclusion bodies) *Disseminated TB or fungal infection *Diagnosing pneumonia in ARDS patients
Turbid, PAS-positive material	*Alveolar proteinosis
Langerhans cells	*Langerhans cell histiocytosis
Bloody with a large amount of hemosiderin in the alveolar macrophages	*Diffuse alveolar hemorrhage
Hyperplastic and atypical type II pneumocytes	*Cytotoxic lung injury
"Foamy" changes with lamellar inclusions	*Amiodarone-induced disease
* In these, BAL results are sufficient for diagnosis.	

QuickQuiz

- High resolution CT scan is used to diagnose which conditions?
- What are the advantages of helical CT?
- What diseases are associated with a reduced DLCO?

This partial pressure O_2 = 158.84 mmHg in the air surrounding us at sea level at 59° F. This pressure is called the P_iO_2 (inspired). This fraction of 20.9% remains constant as atmospheric pressure decreases with increasing altitude.

The following is the alveolar gas equation. It calculates the partial pressure of O_2 in the alveoli.

$$P_AO_2 = [(P_b - P_{H_2O}) \times F_iO_2] - [P_aCO_2/0.8]$$

This equation looks different from the simpler P_iO_2 equation just discussed. The reason is that the partial pressure of inspired gases changes a little when it gets into the damp alveoli, where $O_2 \leftrightarrow CO_2$ exchange occurs. Here, we must account for the additional partial pressure of water vapor P_{H_2O} (= 47 mmHg at sea level) and the shifts in concentrations of O_2 and CO_2 in the alveoli. The respiratory quotient (0.8) is the minute production of CO_2/minute consumption of O_2. This quotient allows us to use the measurable P_aCO_2 (arterial) in the alveolar gas equation instead of the P_ACO_2 (alveolar), which we can't readily measure.

So, to get back to the alveolar gas equation:

$$P_AO_2 = [(P_b - P_{H_2O}) \times F_iO_2] - [P_aCO_2/0.8]$$

We see that the F_iO_2 is still multiplied by the P_b but only after its value is decreased to account for the water vapor. The second term decreases this product by an amount that takes into account the $O_2 \leftrightarrow CO_2$ exchange in the alveoli.

Other terms:

P_aO_2 = partial pressure of oxygen in the arterial blood. Commonly called the "pO_2."

P_aCO_2 = partial pressure of carbon dioxide in the arterial blood. Commonly called the "pCO_2."

S_aO_2 = oxygen saturation of hemoglobin in the arterial blood.

$S_{\bar{v}}O_2$ = mixed venous blood oxygen saturation. Mixed venous blood is in the pulmonary artery.

$S_{c\bar{v}}O_2$ = central venous blood oxygen saturation. This measurement is used in sepsis management. Central venous blood is obtained from the superior vena cava.

HYPOXEMIA

Hypoxemia (low oxygen tension) has 6 causes:

1) Ventilation/Perfusion (V/Q) mismatch: the main cause of hypoxemia in chronic lung diseases—responds well to 100% O_2. It may be due to airspace inadequately perfused or perfused areas inadequately ventilated. Examples: asthma, COPD, alveolar disease such as pneumonia, interstitial disease, and pulmonary vascular disease; e.g., pulmonary hypertension or pulmonary embolism. The hypoxemia improves after oxygen administration.
2) Right-to-left (R-to-L) shunting: seen in ARDS or pneumonia, where hypoxemia is due to perfusion of non-ventilated alveoli. ARDS does not respond well to 100% O_2; it responds better to positive end-expiratory pressure (PEEP). See Ventilator Support for ARDS on page 3-66. Other causes of R-to-L shunting, besides alveolar collapse, include intra-alveolar filling (pneumonia, pulmonary edema), intracardiac shunt, and vascular shunt. PEEP may worsen a R-to-L intracardiac shunt by increasing the shunt fraction as a result of increased right sided pressures.
3) Decreased alveolar ventilation: seen with decreased tidal volumes or low respiratory rates; e.g., stopping breathing. This always has a high P_aCO_2 associated with the hypoxemia. The A-a gradient ($D_{A\text{-}a}O_2$, discussed next) is normal. Think drug overdose, neuromuscular disease, or CNS disorder.
4) Decreased diffusion: actually has little causal effect on hypoxemia at rest, but can play a role in exercise-induced desaturations. It takes a tremendous amount of thickening of the alveolar-capillary interface to decrease diffusion of O_2. The carbon monoxide diffusing capacity (DLCO) test measures how well inspired CO diffuses from the alveoli to RBC hemoglobin and acts as a surrogate marker for CO_2 and oxygen diffusion. Low DLCO occurs with interstitial lung diseases (ILDs) and emphysema, in which symptoms improve with supplemental O_2. Hypoxemia at rest occurs when the DLCO is ≤ 30% of predicted. It may occur at higher DLCO if there is an increased cardiac output, as with a rapid heart rate. With an increased cardiac output, the time for diffusion is limited, so decreased O_2 transfer occurs. Increased DLCO is seen with alveolar hemorrhage, polycythemia, and during an acute asthma attack.
5) High altitudes (low F_iO_2): results in a reduced P_AO_2. $D_{A\text{-}a}O_2$ is normal unless lung disease is present.
6) Low mixed venous O_2 (P_VO_2): can decrease the P_aO_2 during resting conditions, secondary to the normal shunt that exists (~ 5%); it also exaggerates all other causes of low P_aO_2.

Again:

- Supplemental O_2 does not cause significant increase in P_aO_2 with R-to-L shunting or shunt physiology.
- A-a gradient is normal with hypoventilation and with high altitudes.

A-a GRADIENT

The alveolar-arterial gradient (A-a gradient), or A-a O_2 ($D_{A\text{-}a}O_2$), is the difference between the partial pressure of oxygen in alveoli (A) and that in arterial blood (a):

$$D_{A\text{-}a}O_2 = P_AO_2 - P_aO_2$$

The P_AO_2 is relatively consistent in a group of people in a room. It is the P_aO_2 that varies individually with lung problems. And it is the difference between these 2 partial pressures that is the key indicator of problems with the alveolar-capillary unit. Again, $D_{A\text{-}a}O_2$ is increased in all causes of hypoxemia except in hypoventilation and high altitude. In reality, the $D_{A\text{-}a}O_2$ is useful only when performed on room air since the gradient increases as the F_iO_2 increases; it is also hard to know the exact F_iO_2 when a patient breathes with nasal cannula or a poorly fitted face mask.

$D_{A\text{-}a}O_2$ is 5–15 mmHg in healthy young patients. It increases normally with age and abnormally in lung diseases, causing a V/Q mismatch; i.e., blood flow or diffusion abnormality. Note: A patient with a significant pulmonary embolus invariably has an increased $D_{A\text{-}a}O_2$, but, if the patient is hyperventilating (which is common), the P_aO_2 may be normal!

As mentioned, $D_{A\text{-}a}O_2$ increases with age. 2 rules-of-thumb for determining normal $D_{A\text{-}a}O_2$ are:

1) Normal $D_{A\text{-}a}O_2 \leq 0.3 \times$ age (years)
2) Normal $D_{A\text{-}a}O_2 \leq$ (age/4) + 4

To find the $D_{A\text{-}a}O_2$, first determine the partial pressure of O_2 in the alveoli (P_AO_2)––discussed earlier.

$$P_AO_2 = [(P_b - P_{H_2O}) \times F_iO_2] - [P_aCO_2/0.8]$$

And at standard temperature at sea level:

$$P_AO_2 = [(760 - 47) \times 0.209] - [P_aCO_2/0.8]$$

$$P_AO_2 = [149] - [P_aCO_2/0.8]$$

or, for an easier mental calculation,

$$P_AO_2 = 149 - 1.25(P_aCO_2)$$

So, getting back to the original formula ...

$$D_{A\text{-}a}O_2 = P_AO_2 - P_aO_2$$

... where the P_aO_2 is obtained from the arterial blood gas. Or, for an easier mental calculation, the formula is shifted around to:

$$D_{A\text{-}a}O_2 = 149 - [P_aO_2 + (1.25 \times P_aCO_2)]$$

Okay, got this? The P_aCO_2 and the P_aO_2 are read off of the ABG report. If at sea level and inspiring room air, take a quarter more than the P_aCO_2 and add it to the P_aO_2, then subtract the result from 149.

You should calculate the gradient for every arterial blood gas you get. It helps you quickly identify whether hypoxemia exists because of a problem in the alveolar-capillary unit (e.g., low: pulmonary embolism, pneumonia) or if some other cause is to blame (e.g., hypoventilation).

OXYGEN DELIVERY TO TISSUES

What is important to the tissues is how much oxygen they receive. This depends on both of the following:

- The amount of oxygen transported to the tissues
- How much of the transported oxygen is taken up and subsequently utilized by the mitochondria and/or cells

Oxygen Transport to Tissues

Oxygen transport to the tissues = DO_2. DO_2 = cardiac output × oxygen content of arterial blood (C_aO_2), where

$$C_aO_2 = (1.34 \times \text{Hgb level} \times S_aO_2) + (0.003 \times P_aO_2)$$

(In practice, we can ignore the miniscule amount of O_2 dissolved in plasma: $0.003 \times P_aO_2$.)

So essentially …

$$DO_2 = \text{cardiac output} \times (1.34 \times \text{Hgb level} \times S_aO_2)$$

Notice, from this equation, that oxygen transported to the tissues depends on 3 factors:

1) Cardiac output.
2) Hemoglobin level.
3) Hemoglobin saturation (S_aO_2). This is why the hemoglobin-oxygen (oxyhemoglobin) dissociation curve (and the use of pulse oximetry) is so important.

These are also the 3 factors you look at when a critically ill patient requires better oxygen delivery. In exam questions, you typically are given a critically ill patient with either a low cardiac output or an obvious anemia with an O_2 sat of 90% and P_aO_2 of 60 mmHg. The answer is to address the obviously low Hgb or cardiac output—the P_aO_2 is fine because the S_aO_2 is fine!

Oxyhemoglobin Dissociation Curve

The oxyhemoglobin dissociation curve (or oxygen saturation curve; Figure 3-1) typically shows the percent of O_2 saturation of hemoglobin (S_aO_2) for a certain P_aO_2. It is the amount of O_2-saturated Hgb that is important. You can see from the graph that, everything else being normal, a P_aO_2 of 60 mmHg results in an S_aO_2 of > 90%.

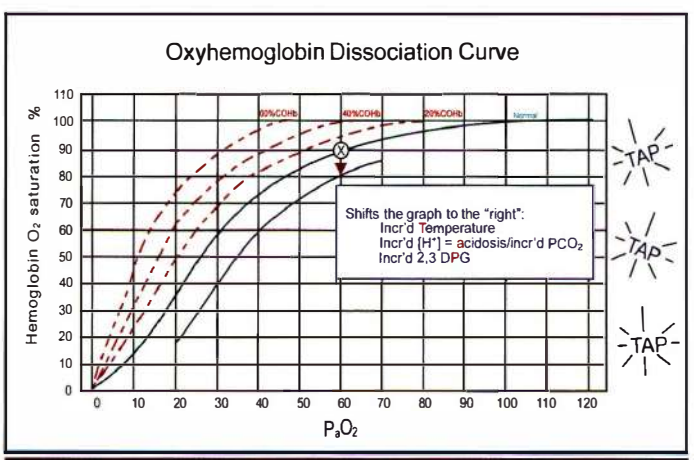


Figure 3-1: Oxyhemoglobin Dissociation Curve

Quick Quiz

- A normal A-a gradient in a hyperventilating patient should make you think of this diagnosis.
- What is a simple formula for calculating the A-a gradient?
- Name 3 factors that, for a specific P_aO_2, cause a decrease in hemoglobin O_2 saturation.
- What does CO poisoning do to the oxyhemoglobin dissociation curve?
- What are the symptoms that occur at increasing levels of methemoglobinemia? Treatment?

The actual oxygen saturation of a particular hemoglobin molecule at a particular P_aO_2 is dependent on temperature, erythrocyte 2,3-DPG (2,3-diphosphoglycerate) level, and pH status. High or low levels of serum phosphorus cause an increased or decreased 2,3-DPG. The oxyhemoglobin dissociation curve shows the S_aO_2 for a certain P_aO_2—given variations in these 3 factors: temperature, **T**; pH, **A** (for acidosis); 2,3-DPG (based on phosphorus), **P**. This gives us the mnemonic **TAP** for remembering what shifts the curve.

When the curve is shifted to the right, it reflects a decrease in Hgb affinity for O_2 (so a decreased O_2 uptake by the Hgb). Decreased affinity promotes off-loading of the O_2 to the tissues.

With a shift to the left (with decreased levels of TAP), it reflects an increased Hgb affinity for O_2 (so an increased S_aO_2 for a particular P_aO_2).

The blue line on the graph indicates what is called a "shift to the right," but it is more logical to think of it as a "shift down" in which, for a certain P_aO_2, the S_aO_2 is decreased. On the graph, at a P_aO_2 of 60, the O_2 saturation decreases from 92% to 82% with this right shift.

Note that the TAP, TAP, TAP on the right of the graph is to remind you of the factors that shift the graph to the right—increased **t**emp, **a**cidosis, and **p**hosphorus.

Carbon monoxide binds tightly to Hgb, preventing O_2 from binding. Additionally, the binding of CO causes the other oxyHgb to bind even more tightly to O_2—shifting the curve to the left. The typical noninvasive saturation tests (e.g., pulse oximeter) do not distinguish between oxyHgb and carboxyHgb, so the oxyhemoglobin curve not only shifts to the left but also appears to quickly get 100% saturated. With severe CO poisoning, the majority of Hgb is saturated with CO, leaving little room for O_2. The red tracing shows how the graph would be shifted to the left with increasing amounts of COHgb.

Methemoglobin is produced when the iron in the Hgb molecule is oxidized from the ferrous (Fe^{+2}) to the ferric (Fe^{+3}) form, and the resulting methemoglobin molecule cannot hold onto O_2 or CO_2—with disastrous results to the tissues. Methemoglobin, like carboxyhemoglobin, causes regular ferrous Hgb to hold much more tightly to O_2, thereby shifting the oxyhemoglobin dissociation curve to the left (or up for a set P_aO_2). Also, like carboxyhemoglobin, typical bedside O_2 saturation tests cannot differentiate oxyhemoglobin from methemoglobin. The net result is a left shift of the oxyhemoglobin saturation curve that climbs to 100% at lower P_aO_2 levels. Again, similar to the COHgb effect but for different reasons.

Methemoglobinemia may be acquired (drugs) or hereditary. Clinical effects of methemoglobinemia:

- > 25% = perioral and peripheral cyanosis
- 35–40% = fatigue and dyspnea begin
- > 60% = coma, death

Treat methemoglobinemia with removal of the cause, 100% O_2, and methylene blue (which causes rapid reduction of methemoglobin back to hemoglobin). Chronic, hereditary methemoglobinemia is best treated with 1–2 grams daily of ascorbic acid.

Know that the normal oximeter, which measures the absorption of 2 wavelengths of light, is inaccurate when there are significant levels of CO or methemoglobin. You should also know that the oxygen saturation reported on an arterial blood gas analysis is a calculated value, not a measured one. Measuring a true level of the different hemoglobin saturations requires inserting blood into a special CO-oximeter that uses a spectrophotometer to make the measurement of oxygen saturation, methemoglobin, carboxyhemoglobin, and sulfhemoglobin levels. (Lipemic serum results may be inaccurate since the fat potentially interferes with light absorption.)

A newer device, not yet available in most hospitals, measures 8 wavelengths and can identify both methemoglobin and carbon monoxide.

Bottom line: Realize that the standard bedside pulse oximeter is not always helpful in CO poisoning and methemoglobinemia because the value is often falsely normal—you must order measurement of the various hemoglobins on blood samples.

Oxygen Release to Tissues

Okay, we discussed oxygen transport to the tissues. What about oxygen release to the tissues? Here again, we look at the oxyhemoglobin dissociation curve as it applies to oxygenated blood in the tissues. Any factor that shifts the graph to the right/down reflects a decreased affinity between oxygen and hemoglobin and, in the local tissue environment, causes a release of oxygen to the tissues.

In the area of the capillaries of working muscles, for example, there is an increase of pCO_2 due to normal metabolism → local acidosis → decreased affinity of Hgb for O_2 → release of O_2 to the tissues (Bohr effect).

Similarly, RBCs produce 2,3-DPG as a byproduct of anaerobic metabolism. (All RBC metabolism is anaerobic.) The more 2,3-DPG there is, the more O_2 is released

from the Hgb for use by the RBCs. Similarly, patients with chronic anemia have increased 2,3-DPG.

Blood stored > 1 week has a decreased level of 2,3-DPG, and large transfusions of this blood result in a shift to the left.

When there is systemic acidosis (or high temp or high 2,3-DPG), the decrease in affinity for O_2 by Hgb results in less O_2 picked up by the Hgb in the lung, as well as more O_2 released in the tissues. So, although the Hgb O_2 saturation (S_aO_2) is lower for a certain P_aO_2, more of the oxygen carried by the hemoglobin is released to the tissue. The net result is to dampen the effect of low S_aO_2 caused by acidosis, high temp, and high 2,3-DPG. It dampens but does not negate or reverse the effect.

Conditions that shift the curve to the left (alkalosis, low temp, low 2,3-DPG) work similarly, although more O_2 is bound by the Hgb, and less is released to the tissues. Again, it dampens but does not negate the effect.

DLCO

Carbon monoxide diffusing capacity (DLCO) is decreased by anything that interrupts gas-blood O_2 exchange.

Decrease in DLCO implies a loss of effective, capillary-alveolus interface. It is usually due to loss of alveolar-capillary units, as seen in emphysema, interstitial lung disease, and pulmonary vascular diseases. Anemia also causes a decrease in DLCO.

Know that the DLCO is the 1st parameter to decrease in interstitial lung disease; thus, it should be followed when prescribing potentially dangerous medications such as amiodarone or lung-toxic chemotherapy. Also, DLCO may be the only abnormal pulmonary function parameter in pulmonary vascular disease.

Normal DLCO is usually seen in asthma and chronic bronchitis because, although there is bronchoconstriction, there is no alveolar disease. Therefore, recognize that the DLCO is the major pulmonary function parameter that helps you to distinguish emphysematous COPD (low DLCO) from chronic bronchitis and asthma (normal DLCO).

Increased DLCO is seen in problems that increase effective blood flow to the functional lung, such as heart failure, diffuse alveolar hemorrhage, pulmonary infarction, and idiopathic pulmonary hemosiderosis (IPH).

LUNG VOLUMES AND PULMONARY FUNCTION TESTS

Overview

In your office, with spirometry, you can determine most of the lung volumes and capacities, expiratory flows, and flow-volume loops and also assess bronchodilator response.

A pulmonary function lab is needed for:

- Total lung capacity determination
- DLCO determination
- Methacholine or other challenge tests

For the lung volumes discussed below, generally < 80% is abnormal, and > 120% may also be significant.

When reviewing PFTs, keep in mind the following:

- Total lung capacity (TLC) is decreased in restrictive lung disease.
- Expiratory flow rate (FEV_1/FVC) is used to assess obstructive lung disease. Airway obstruction is diagnosed when the FEV_1/FVC is < 0.7 (70%). To be very specific and to avoid overdiagnosis of obstructive lung disease, many pulmonologists use the predicted 95% confidence interval to diagnose a reduction in the FEV_1/FVC ratio. General internists just need to know the 70%.

Lung Volumes

Review the Lung Volumes diagram (Figure 3-2). There are 4 basic functional volumes of which the lung is made:

1) Residual volume (RV) = unused space
2) Expiratory reserve volume (ERV) = from full non-forced end-expiration to full forced end-expiration
3) Tidal volume (TV) = used in normal unforced ventilation
4) Inspiratory reserve volume (IRV) = from normal unforced end-inspiration to full forced end-inspiration

A "capacity" is 2 or more of these basic volumes and gives even more functional significance to them. For example, vital capacity (VC) is the volume you have available for breathing (makes sense) and is composed of the IRV + TV + ERV. The total lung capacity (TLC) is composed of the VC + RV.

In severe COPD, TLC is normal or increased (even though vital capacity is decreased) due to a greatly increased RV—seen as barrel chest.

In restrictive disease, the TLC is decreased due to both a decreased VC and RV.

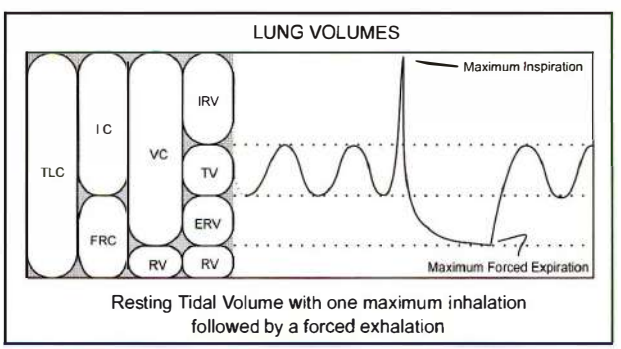


Figure 3-2: Lung Volumes

QuickQuiz

- What is vital capacity (VC), and what smaller lung volumes make up VC?
- Characterize the differences in the flow-volume loops for restrictive and obstructive (dynamic and static) airway diseases. (See Figure 3-5.)

TLC is determined in the lab by helium dilution, nitrogen wash-out, or plethysmography. Use plethysmography for patients with airflow obstruction.

The tracing in the Lung Volumes diagram shows a forced expiration from maximum inspiration. The next diagram (Figure 3-3) shows a comparison of similar expirations for patients with normal, obstructive, and restrictive airways. This is an easy and important test, but usually you will not see it diagrammed this way.

Although the TLC cannot be determined from spirometry (must know the RV), you can determine the degree of obstruction by comparing the forced expiratory volume at 1 second (FEV_1) to the forced vital capacity in the ratio FEV_1/FVC (FVC = VC during a forced expiration).

In a patient with a normal lung, the ratio is about 0.8. It is always less in a COPD patient or an asthma patient having an acute attack, but it may be normal or increased in a patient with restrictive disease—even though the VC is small—because this patient has no trouble getting air out.

A patient with asthma has reversible disease and, if not having an acute attack, may have a normal FEV_1/FVC.

Flow-Volume Loops

The diagrams of flow-volume loops shown are a more common way of expressing airflow in the different lung diseases. Again, these are derived from the spirometry data and are calculated and plotted by an attached computer, where the FEV_1/FVC is automatically determined. Note that the *y*-axis is flow rate.

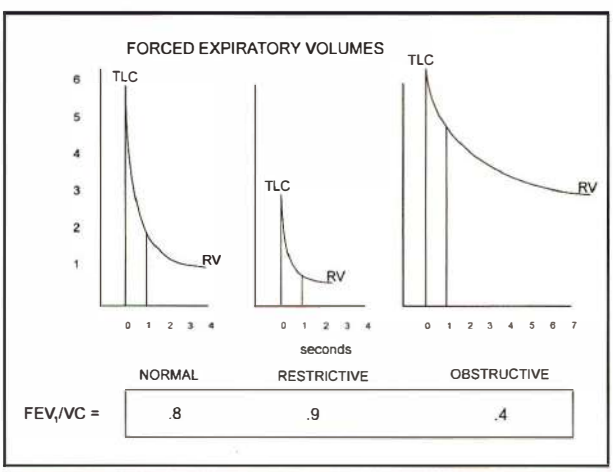


Figure 3-3: Forced Expiratory Volumes and FEV_1/FVC

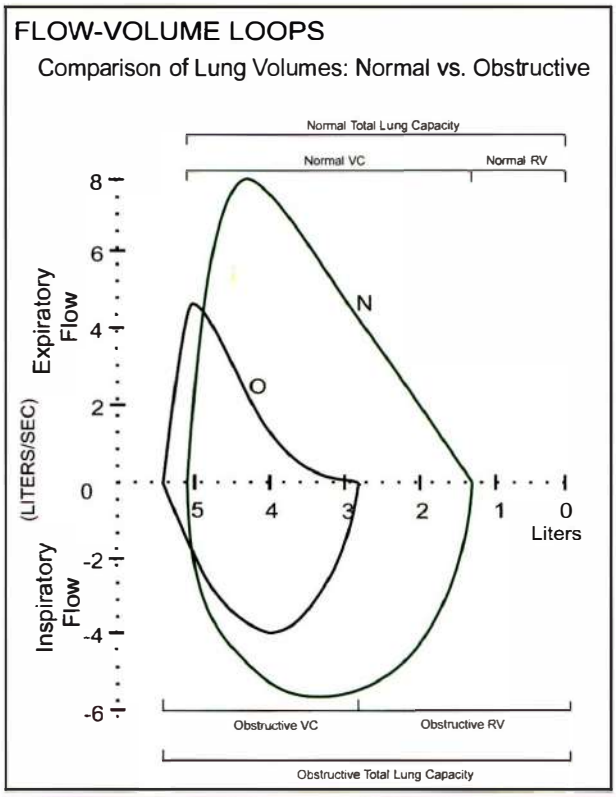


Figure 3-4: Flow-Volume Loops — Obstruction

Because we cannot determine residual volume (RV) from spirometry, we get most of our information by the shape of the loop. The exception is in restrictive disease; the shape is similar to normal, but the vital capacity (= TLC – RV; width) is much smaller than normal.

Figure 3-4 compares obstructive vs. normal lung flow loops. Figure 3-5 includes restrictive diseases. Know the shapes and sizes of these loops!

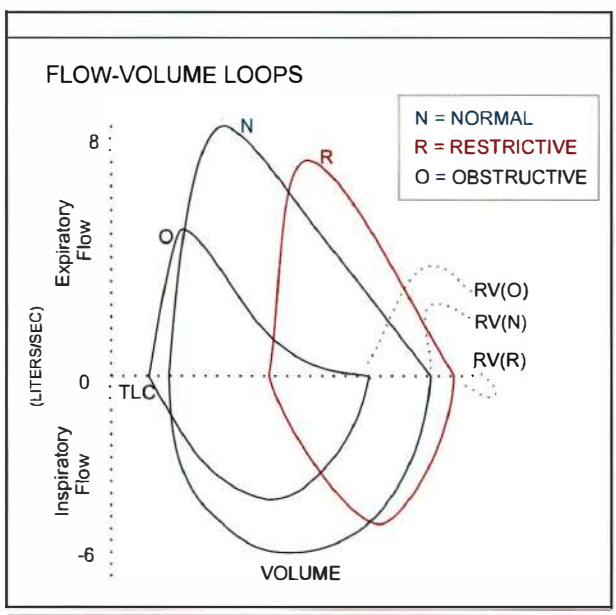


Figure 3-5: Flow-Volume Loops — All

In obstructive disease, Figure 3-4, increased expiratory airway resistance causes decreased expiratory flow rate. Again, while normal $FEV_1/FVC = 80\%$, obstruction is defined as < 70%. (In severe obstruction, it may be only 40%!) Additionally, there is a scooping of the tracing in the latter half of expiration. Causes of lower airway obstruction include asthma, COPD, bronchiectasis, and cystic fibrosis.

Restrictive disease: Notice that Figure 3-5 shows intrathoracic (parenchymal; ILD) restrictive disease in which residual volume (RV) is always decreased. Extrathoracic restrictive disease states (e.g., obesity, kyphosis) may have a normal RV, but the shape and size are similar.

Bronchodilator response during pulmonary function testing is done for 2 reasons:

1) To determine if the obstruction is responsive to beta-agonists. Before testing, withhold beta2-agonists for 8 hours and theophylline for 12–24 hours.
2) To test for efficacy of current regimen. In this case, medications are not withheld. If treated patients have a response to beta2-agonists, it suggests they are not on an optimum regimen.

Methacholine or other bronchoprovocation-challenge testing is done in people with normal spirometry and intermittent asthma-like symptoms, or other symptoms suggestive of airflow obstruction, to determine if they have bronchial hyperreactivity. This test is often done in the workup of chronic cough (see Asthma on page 3-10) and occasionally in patients with cold air-induced exercise-related bronchospasm.

Inhaled methacholine (or histamine or cold air) is given to the patient while monitoring for a drop in FEV_1. Know that asthmatics bronchoconstrict at a very low dose of the irritant, whereas non-asthmatics do not.

Also know that PFTs are always the 1st test in the evaluation of a possible asthmatic, and bronchoprovocation is done only when initial PFTs are normal.

Pre-Op

PFTs are not indicated in the routine preoperative evaluation.

PFTs + ABGs are indicated in these circumstances:

- If the surgical procedure is close to the diaphragm (gallbladder, etc.).
- If the patient has moderate or worse lung disease. In these cases, an $FEV_1 < 1$ L or an elevated pCO_2 indicates that the patient is at risk for postoperative pulmonary complications.
- For lung cancer or lung resection presurgical evaluation. Assuming a worst-case scenario (pneumonectomy), the patient must still have adequate lung function post-op. High risk of post-op morbidity is suggested by a predicted $FEV_1 \leq 0.8$ L after surgery. In a patient with a pre-op $FEV_1 \leq 1.6$ L, you can estimate the post-op FEV_1 by doing split-lung PFTs (hard to do), obtaining a quantitative ventilation, or by quantitative perfusion lung scan. Then multiply the % perfusion (or ventilation) of what is left after surgery by the FEV_1 to obtain the estimated post-op FEV_1.

Now, let's first look at what PFTs show in the major lung diseases. In subsequent discussions, we focus on the clinical aspects of the major lung diseases.

PFTs for Specific Lung Diseases

The following lists detail the PFT findings for common chronic pulmonary diseases.

1) Emphysema:
   - Decreased expiratory flow volume (shortened height of top portion of the flow-volume loop).
   - Concave expiratory flow-volume loop tracing.
   - Minimal response to beta2-agonist: < 12% improvement or < 200 mL improvement in FEV_1 or FVC.
   - Increased TLC, reduced VC = hyperinflation with trapped air.
   - DLCO is decreased (the destruction of alveolar-capillary interface—suggests emphysema).
2) Chronic bronchitis:
   - Decreased expiratory flow volume (shortened height of top portion of the flow-volume loop).
   - Concave expiratory flow-volume loop tracing.
   - Minimal response to beta2-agonist: < 12% improvement or < 200 mL improvement in FEV_1 or FVC.
   - Normal or only slight increase in TLC = normal or slightly reduced VC.
   - DLCO is normal to slightly decreased, but it is not as low as in patients with emphysema. Remember DLCO is the test that allows you to differentiate emphysema from chronic bronchitis and asthma. Understand that most cases of COPD have mixed physiology with components of both chronic bronchitis and emphysema.
3) Asthma:
   - PFTs may be normal if no active disease.
   - Decreased expiratory flow (shortened height of top portion of the flow-volume loop).
   - Concave expiratory flow-volume loop tracing.
   - Significant response to beta2-agonist.
   - Normal or increased TLC (due to hyperinflation) and normal or reduced VC.
   - DLCO is normal.
4) Interstitial lung disease:
   - Normal to increased FEV_1/FVC.
   - Straight or slightly convex expiratory flow-volume loop tracing.
   - Proportional decrease in all lung volumes.
   - DLCO is reduced (due to thickening of the alveolar-capillary interface) and is the 1st pulmonary parameter to change with disease progression.

QuickQuiz

- When is methacholine bronchoprovocation testing performed?
- What is the DLCO in emphysema? In asthma? In interstitial lung diseases?
- What are the results of these lung tests in patients with restriction: VC, TLC, FEV_1, FEV_1/FVC, RV?
- What are the results of these lung tests in patients with obstruction: VC, TLC, FEV_1, FEV_1/FVC, RV?

Now some examples. When evaluating a PFT scenario, think in terms of:

- Expiratory flow
- Lung volumes
- Diffusion capacity
- Response to bronchodilators

Also consider that anything < 80% of normal is an abnormal finding. (FEV_1/FVC is already age-adjusted, and % predicted is sex, age, and height adjusted.)

Approach to PFT results analysis: We will be using Table 3-2 during this discussion. Remember, we are basically looking for normal, restrictive, or obstructive disease. Each time you figure out a line, label it.

1) Look for all normals: Circle everything ≥ 80%— these values are "normal." If all values are ≥ 80%, the results are normal. Label it "normal." Remember that most smokers have normal values.
2) Look for restrictive disease:
   - Any TLC < 80% is, by definition, restrictive. Label these results as "restrictive." If TLC is not known, restrictive disease is reflected in a proportional decrease in FEV_1 and FVC (i.e., FEV_1/FVC = 80% but FVC is < 80%).
   - If restrictive, check the DLCO. This determines if it is extrathoracic or intrathoracic:
     - If the decrease in DLCO is proportional to the decrease in TLC, it means that the restriction is not due to parenchymal disease—rather, it is of extrathoracic origin. Label it "extrathoracic" and think of obesity and kyphosis.
     - If the decrease in DLCO is disproportionately low compared to the decrease in TLC, label it "intrathoracic" and think of interstitial lung disease.
3) Look for obstructive disease:
   - Obstruction is defined by a disproportionately low FEV_1. So both FEV_1 and FEV_1/FVC are low. Label these lines "obstructive."
   - If obstructive, check the TLC, DLCO, and reaction to beta2-agonists:
     - "Emphysema" if the TLC is high but the DLCO is low; minimal-to-no response to beta2-agonist.
     - "Asthma" if the DLCO is normal, or there typically is a reaction to beta2-agonist.
4) Others are combinations of obstructive and restrictive diseases. Especially seen in patients with combined problems (asthma + obesity) or with certain lung diseases, especially sarcoidosis, Langerhans cell histiocytosis, and lymphangioleiomyomatosis.

Okay, let's apply this to a table of PFT results. [Know!] This is not only for exam questions; it is valuable to know for clinical practice. Table 3-2 reviews some PFT results as a percentage of predicted. Remember that, in general, < 80% of predicted is abnormal.

#1 You should have all these values circled. These are, of course, normal. Remember that normal results are seen in most smokers!

#2 Extrathoracic restrictive mechanics (i.e., non-parenchymal). All restrictions, intra- and extrathoracic, are defined by a decrease in TLC. The normal FEV_1/FVC ratio proves that there is no obstructive mechanism involved: The FEV_1 is decreased in proportion to the decrease in FVC, so the FEV_1/FVC is ≥ 80%. The extrathoracic involvement is indicated by the proportional decrease in TLC and DLCO—that is, the decrease in DLCO is due to the decrease in TLC. Pure extrathoracic restriction is seen with kyphosis and obesity. Kyphoscoliosis is usually a result of compression fractures of the thoracic vertebral bodies, secondary to long-standing osteoporosis. It also occurs in a small percentage of neurofibromatosis patients (von Recklinghausen disease) and may be due to tuberculosis involving the thoracic vertebrae.

If a patient is 1–3 days post-CABG and suffering from orthopnea, check the PFTs, but also check FVC both standing and lying down. If the patient has extrathoracic restrictive mechanics and the difference in FVC is > 20% (decreases with lying down), consider bilateral diaphragmatic paralysis from the cold cardioplegia. (This is for exam questions—a chest x-ray could have told you this!)

Table 3-2: PFT Analysis

	% FEV_1	% FVC	% TLC	% DLCO
1	83	89	92	85
2	58	62	68	64
3	52	80	110	65
4	55	87	100	88
5	57	82	70	68
6	66	72	75	66

Unilateral phrenic nerve problems can be diagnosed by a "sniff test" with fluoroscopy. Also note that a decrease in FVC (from standing to lying) in the high-normal range (15–20%) is commonly seen with obesity. The DLCO could be disproportionately low (say, 54%) if this post-CABG patient also had some post-op atelectasis.

Question: Besides cold cardioplegia, what are other possible causes of bilateral elevated hemidiaphragm? Answer: poor inspiration, SLE, bilateral phrenic nerve paralysis (spine injury, tumor, neurological disorder), diaphragmatic weakness from ALS, large-volume ascites, and bilateral subpulmonic effusions. These all make sense, so just think about them, but don't memorize them!

#3 Pure obstruction with low DLCO and a high TLC. The FEV_1/FVC is < 80%. The TLC is high and the DLCO is disproportionately low, indicating a loss of alveolar-capillary units. Emphysema, either smoking or a_1-antitrypsin deficiency, is the most common cause of this finding.

#4 Pure obstruction with normal DLCO. Same as #3, except the DLCO is normal, indicating asthma. In both #3 and #4, you may find a low FVC if the obstruction is so severe the patient does not have enough time to fully expire before getting short of breath, but the FEV_1/FVC remains < 70%.

#5 Combined obstruction and extrathoracic restriction. The low FEV_1/FVC indicates obstruction. The low TLC indicates restriction, while the proportionate decrease in DLCO narrows it to an extrathoracic etiology. Possible etiologies: an obese patient with asthma or an osteoporotic, kyphotic patient with asthma.

#6 Intrathoracic restriction. As in extrathoracic restriction, the FEV_1 and FVC are proportionately low (so FEV_1/FVC > 80%). Contrary to extrathoracic restriction, in intrathoracic restriction the DLCO is disproportionately lower than the decrease in TLC. Intrathoracic restriction is seen with many interstitial lung diseases.

OBSTRUCTIVE LUNG DISEASES

ASTHMA

Overview

Asthma is an inflammatory condition of the airways with a multifactorial etiology and varying presentation. Patients can have intermittent or persistent and acute or chronic manifestations. The primary manifestations due to bronchoconstriction are recurrent episodes of wheezing, shortness of breath, and/or cough—usually reversible either spontaneously or with treatment.

Causes of Asthma

Asthma typically develops early in life. Development of asthma appears to be a complex interaction of mainly 2 factors:

1) Host factors (especially genetic susceptibility): The role of genes is complex and not well defined at this point. Some asthma cases are IgE-mediated. Atopy is the strongest identifiable predisposing factor for developing IgE-mediated asthma.
2) Environmental factors: exposure to certain environmental agents at critical points in immune development. Triggers are environmental factors that may be the cause of asthma or that induce worsening symptoms when the airways are hypersensitive. Triggers can be broadly categorized into 6 areas: allergens, irritants, chemicals, respiratory infections, physical stress, and emotional stress. Both airborne allergens and viral respiratory infections play important roles in the development of asthma in susceptible individuals. Other environmental agents associated with the development of asthma are pollution, tobacco smoke, and airborne agents prevalent in certain occupations. These have not been studied as much as allergens and viral infections.

The cause of asthma is often not discovered, especially in adult-onset asthma.

Some specifics: occupational causes (isocyanates are most common!), cotton dust (byssinosis), formaldehyde, volatile organic compounds, toluene diisocyanate, fluorocarbons, grain dust, and wood dust (especially western cedar). But not silica! Unvented gas stoves release NO_2—which worsens asthma.

Occupational asthma may be IgE-dependent, which causes an early or biphasic reaction, or IgE-independent (late reaction). Both smoking and a history of atopy are important sensitizing factors for occupational asthma.

Patients with ASA-sensitive asthma often have the asthma triad (Samter triad): ASA-sensitivity + asthma + nasal polyposis. Patients are young to middle-aged adults. Symptoms start with rhinitis or congestion and progress to asthma, then polyposis, then ASA sensitivity. ASA sensitivity can be extreme (anaphylaxis). ASA-sensitive asthmatics may also be sensitive to other NSAIDs and tartrazine dyes but not to sodium or choline salicylates.

Allergic rhinitis and asthma are both systemic inflammatory conditions that affect upper and lower airways and may reflect a spectrum of the same disease. Up to 80% of people with asthma have rhinitis. Treatment of allergic rhinitis with intranasal glucocorticoids improves asthma symptoms and decreases emergency department visits and hospitalizations.

A very interesting aspect of asthma is its relationship to GE reflux, although it is incompletely understood. A lot of asthmatics have GERD, and past data support the idea that untreated reflux leads to uncontrolled asthma. In

Quick Quiz

- What is the difference in the DLCO in intrathoracic restriction vs. extrathoracic?
- What skin finding is a predisposing factor for IgE-mediated asthma?
- What is the "asthma triad"?
- What are the comorbidities that may exacerbate asthma?
- In the management of asthma, initial treatment is based on _____. After therapy is started, focus is on _____.
- What spirometry findings are required to diagnose asthma?
- How can you diagnose exercise-induced bronchospasm?

fact, pH probe studies show that many asthmatics have esophageal reflux without having reflux-type symptoms. Smaller studies show that uncontrolled asthmatics should be treated for possible asymptomatic GERD. The National Asthma Education and Prevention Program (NAEPP) 2007 asthma guidelines recommend empiric treatment for GERD in patients with uncontrolled asthma, whether or not they are symptomatic. Later data, however, show that empiric treatment of asymptomatic GERD with a proton pump inhibitor does not affect asthma outcomes in patients with inadequately controlled asthma. So, while there is an association between GERD and asthma, the relationship has uncertain elements.

Asthma is exacerbated by comorbid conditions:

- Allergic bronchopulmonary aspergillosis (ABPA)
- Obstructive sleep apnea-hypopnea (OSA)
- Stress

Changes in the Lung with Asthma

This airway inflammation, whatever the etiology, causes a nonspecific airway hyperresponsiveness → airway edema and bronchoconstriction. Persistent airway inflammation leads to remodeling of the airways with fibrosis and muscular hypertrophy, resulting in a continuous nonresponsive airflow obstruction as a component of the clinical picture.

Acute Exacerbation of Asthma

Early in an asthmatic attack, bronchospasm is the major factor. Later on, however, increased airway inflammation, airway edema, and airway secretions with possible mucous plugging may dominate, especially in patients with status asthmaticus.

Asthmatics usually have episodes of some combination of dyspnea, cough, and wheezing. However, on the initial presentation, the patient may have complaints only of a chronic cough. (Remember: Patients with GERD may also present with cough, but a nonasthmatic cough due to GE reflux disease occurs typically when supine.)

Regarding patients with a fatal asthma attack, the predictor of mortality is the amount of auto-PEEP they experience (discussed under Intubation on page 3-17).

Diagnosis of Asthma

Severity of asthma is the basis for treatment at an untreated patient's initial evaluation.

After initial therapy is started, focus on control and response to treatment, rather than severity.

Severity of airflow obstruction is categorized as intermittent, mild persistent, moderate persistent, and severe persistent. Any severity level can have exacerbations—which in turn may be mild, moderate, or severe. See the Severity column under Initital Evaluation in Table 3-3 on page 3-14.

For diagnosis, the patient must demonstrate at least partially reversible bronchospasm and a history compatible with asthma. Consider performing a challenge test to induce bronchospasm if these are not demonstrated.

FEV in 1 second (FEV_1), FVC, and FEV_1/FVC, before and after use of a bronchodilator, should be performed in all patients > 5 years old. Response to a short-acting bronchodilator is defined as an increase in the FEV_1 of ≥ 12% and an increase of at least 200 mL.

Bronchoprovocation tests are done in a patient who has normal spirometry and 1 or more of the following:

1) Chronic cough
2) Intermittent symptoms of cough/wheeze
3) Exertional dyspnea of unknown cause

Methacholine challenge, histamine challenge, and thermal (cold air) challenge can be used to confirm the diagnosis of asthma. These work on the principle of nonspecific hyperirritability. For the diagnosis of asthma (which requires "reversible bronchoconstriction"), the patient must both tighten up with the challenge and loosen up with subsequent bronchodilators.

Exercise-induced bronchospasm (EIB) is diagnosed by a decrease in FEV_1 of ≥ 10% after graded exercise on a treadmill or a stationary bicycle. Patients who have exercise-induced bronchospasm that is exclusively elicited by cold air can have false-negative exercise tests. Bronchoprovocation using methacholine, cold air, or eucapnic voluntary hyperventilation is useful to diagnose cold air-induced EIB. It is also useful in patients who might otherwise have a false-negative exercise test.

Treatment of Asthma

Overview

Patients with persistent asthma should have their environment assessed for untreated irritants and allergens. This includes looking for seasonal variation of symptoms, home and workplace evaluation, and skin testing.

The most effective treatment for most asthma is stopping exposure to any environmental agents that act as triggers. The goal should be to remove the trigger entirely, but when unable, the patient should minimize contact. Alternatively, the patient can take extra bronchodilator inhalations before exposure—a common way to handle unavoidable triggers such as visiting a house with a pet.

Because of the association of GERD and allergic rhinitis with asthma, the 2007 guidelines recommend empiric medical management for these conditions when patients have difficult-to-control asthma.

For GERD:

- Avoid intake of foods that lessen lower esophageal sphincter tone; e.g., alcohol, caffeine, nicotine, and peppermint.
- No eating within 3 hours before bed.
- Elevate the head of the bed.
- Treat with proton pump inhibitors (PPIs).

Treat rhinitis with intranasal steroids.

Comorbid ABPA, OSA, and stress should be addressed.

Monitor peak expiratory flow (PEF; a.k.a. peak expiratory flow rate [PEFR]) in patients with moderate-to-severe asthma and/or in patients who cannot reliably describe symptoms of an exacerbation.

Note that symptom-based monitoring is as effective as PEF in all other groups.

Prescribe pharmacologic treatment when needed. We categorize these medications into "quick relief" and "long-term control" categories.

Quick relief (for acute exacerbations and mild, intermittent disease):

- Short-acting beta2-agonists (SABAs)
- Systemic corticosteroids
- Anticholinergics

Long-term control:

- Inhaled corticosteroids (ICS; most potent and most effective)
- Long-acting beta2-agonists (LABAs)
- Mast-cell stabilizers (cromolyn sodium and nedocromil)
- Leukotriene modifiers
- Methylxanthines (theophylline)
- Immunomodulators (omalizumab = anti-IgE)

The following text is a review of these drugs followed by the recommended treatment regimens (Table 3-3 through Table 3-5).

SABAs

The inhaled short-acting beta2-agonist, albuterol, is the 1st choice for "rescue" treatment of an acute exacerbation, even if the patient routinely uses them at home.

For chronic asthma treatment, albuterol is indicated for patients who have intermittent symptoms. Know that SABA use of > 2 days/week indicates "poor control" of symptoms, and treatment should be intensified.

Systemic Corticosteroids

Oral corticosteroids (OCSs) are an effective, short-term treatment for acute asthma. They potentiate the effect of beta2-agonists and have an antiinflammatory effect that has been shown to decrease the frequency of return visits to the emergency department (ED).

OCSs are indicated in the acute treatment of asthma when peak flow is < 80% after 3 treatments of rescue SABAs.

Oral steroids have near complete bioavailability and onset of action within 1 hour, so they can be used instead of IV if the patient is not vomiting. Current preparations taste awful (liquid is so bad that it sometimes causes vomiting), so know that IM injections are equivalent to an oral dose.

IV steroids should be used in respiratory failure.

Chronic administration of OCSs for asthma should be prescribed by highly-trained asthma specialists and only under strict circumstances because of side effects. The asthma algorithm does not include chronic oral steroids until Step 6 (Table 3-4) after institution of all other therapeutic options.

Anticholinergics

Ipratropium bromide is the short-acting drug, and tiotropium is the long-acting drug. Only ipratropium is used in asthma treatment. Long-acting anticholinergics are used in COPD.

Anticholinergics cause a decrease in cGMP that relaxes contractions of bronchial smooth muscle. They are usually given along with beta2-agonists for acute exacerbations of asthma/COPD.

For acute asthma, the 2007 National Asthma Education and Prevention Program (NAEPP) Expert Panel Report limits the use of ipratropium to ED management of moderate-to-severe exacerbations. In this case, ipatropium is used in combination with SABAs. Ipratropium is not recommended for use in managing hospitalized asthma exacerbations (unless the cause of the asthma attack has been due to ingestion of beta-blockers).

Quick Quiz

- Describe the relationship between symptom-based monitoring and peak expiratory flow rate.
- What is the short-acting drug of choice for asthma exacerbations?
- OCSs are recommended if peak flow is < __% after ___ treatments with rescue SABAs.
- According to the expert panel guidelines, when is ipratropium used during a hospital stay to treat an asthma exacerbation?
- What is the preferred drug for chronic treatment of persistent asthma?

Anticholinergics have not routinely been used in the chronic treatment of asthma, but recent studies suggest that long-acting anticholinergic such as tiotropium might decrease the need for systemic corticosteroids in severe persistent asthmatics.

Oxygen

Oxygen is given during an exacerbation of asthma with a goal of keeping the P_aO_2 of at least 60 mmHg or $S_aO_2 \geq 90\%$.

Inhaled Corticosteroids

An inhaled corticosteroid (ICS) is the preferred drug for chronic treatment of persistent asthma when symptoms are not controlled with SABAs. Why is this? Asthma is an inflammatory process, and inhaled corticosteroids subdue the inflammation where it occurs—with minimal side effects. Beta2-agonists are merely bronchodilators and provide only symptomatic treatment.

Twice-per-day inhalations of corticosteroids are as effective as qid. Know that the dose-response curve for inhaled steroids is flattened in patients with mild persistent asthma (more is not better), so low doses are best in this group. But, in "severe persistent" asthmatics, the dose-response curve is not flattened, and this group may benefit from increasing the steroid dose early in treatment.

A spacer greatly reduces the amount of drug deposited in the oropharynx (large particles are trapped in the spacer), thereby decreasing systemic effects from swallowed drug. A spacer also increases the amount of drug reaching the lungs.

ICSs and safety:

- There is little, if any, effect on the pituitary-adrenal axis.
- No increase in fractures.
- Cataracts and glaucoma are much less of a problem with ICS than OCS.
- Budesonide is the preferred inhaled steroid in pregnancy because it has been the most studied. However, if mom is stable on another ICS, then she should continue that agent.
- May cause easy bruising in elderly patients.
- May cause initial slowing of growth in children, but there is a catch-up period resulting in normal height.
- Higher doses cause oral thrush and dysphonia and have been implicated in recurrent pulmonary infections.

LABAs

Like SABAs, LABAs (salmeterol, formoterol) induce an increase in cAMP, which results in relaxation of the bronchial smooth muscles. Unlike SABAs, however, LABAs cause a sustained effect. Still, LABAs do not address the inflammatory component of asthma, and as such, they are added only after ICS in the treatment guidelines.

LABAs are indicated for treatment of moderate-to-severe persistent asthma after initial therapy with SABA + ICS. LABAs are not recommended for mild asthma or acute treatment.

LABAs should never be used as monotherapy in asthma, but should always be added to inhaled corticosteroids! LABA monotherapy has been associated with more frequent exacerbations and with increased mortality. The data are so concerning that many pharmaceutical companies have combined a LABA with an ICS in a single inhaler, so patients cannot inadvertently increase their use of LABAs. This question of how LABAs affect mortality and exacerbations is not settled.

Know that you should never use LABAs as the sole drug for chronic asthma management, and that LABAs are recommended as an add-on drug in an asthma regimen for patients who are uncontrolled on a SABA + an ICS.

LABAs can be used to treat exercise-induced bronchospasm (EIB), but only if the patient does not require daily treatment. If medication is needed daily, the preferred drugs are inhaled albuterol or cromolyn ~ 15 minutes prior to exercise.

Mast Cell Stabilizers

Cromolyn sodium and nedocromil (Tilade®) are mast cell stabilizers and act by inhibiting degranulation of mast cells. They have a mild antiinflammatory effect from decreasing the release of inflammatory mediators. These are mentioned here more as a historical note. Neither is in current use in the U.S.

These drugs are considered 2nd line for use after prescription of the preferred drugs (SABAs, ICSs, and LABAs). No toxicity.

Inhaled cromolyn is an alternative to inhaled albuterol for daily control of exercise-induced bronchoconstriction.

Leukotriene Modifiers

Leukotrienes are chemical mediators released from mast cells, basophils, and eosinophils. They are potent:

- Smooth muscle contractors
- Promoters of mucus production
- Causes of airway edema
- Vasoconstrictors
- Stimulators of more arachidonic acid release

Montelukast (Singulair®) and zafirlukast (Accolate®) are leukotriene-receptor antagonists, and zileuton (Zyflo®) is a 5-lipooxygenase pathway inhibitor.

Leukotriene modifiers are less potent than ICSs and are not as effective as LABAs. They are more often used in children and are never the preferred treatment in adults.

Leukotriene modifiers also have some utility in treating patients with EIB, but they are effective in only ~ 50% of patients. Patients with aspirin allergy are more likely to benefit.

Rarely, a patient treated with a leukotriene modifier may be diagnosed with eosinophilic granulomatosis with polyangiitis, termed Churg-Strauss disease. The agent does not cause Churg-Strauss disease. However, the disease may become unmasked when patients are weaned off corticosteroids and started on a leukotriene modifier. This vasculitis is discussed in greater detail on page 3-31.

Methylxanthines

Theophylline, a methylxanthine, is a less effective bronchodilator than beta2-agonists. Some mechanisms of action include bronchodilation and mild antiinflammatory activity brought about through inhibition of phosphodiesterase. Unfortunately, the dose-response curve for theophylline is log-linear, which translates into a narrow therapeutic index and an increased risk for toxicity.

Theophylline is not recommended for acute treatment of any asthma exacerbation (including in-hospital management) because the benefit does not exceed the risks of toxicity and drug interactions.

For chronic treatment, theophylline is indicated as an adjunct to ICSs for difficult-to-control asthmatics, but know that theophylline + an ICS is inferior in efficacy to the combination of a LABA + an ICS. Theophylline is also an alternative to ICSs (but is not as effective) for patients who simply cannot use inhalers or have a serious aversion to them.

Definitely know the theophylline toxicity and drug interactions. Ideally, theophylline should be given as a sustained-release preparation, and the serum concentration should be maintained in the therapeutic range of 5–15 mcg/mL. Toxicity symptoms include nausea and vomiting (first symptoms), headache, tremulousness, and palpitations. Toxic patients may die or suffer morbidity from seizures, hypotension, and cardiac arrhythmias.

Table 3-3: Initial Tx and Maintenance Tx for Patients ≥ 12 years of age

Factors used in the determination of both SEVERITY (with initial eval) and CONTROL level (when on continuing treatment)					Initial evaluation: Treatment is based on SEVERITY		Continuing therapy: Treatment is based on CONTROL	
Days with Sx	SABA use (control only)	Nighttime awakenings	FEV_1 or PEF ***	Impairment of activity	SEVERITY	Treat per Step level:	CONTROL level	Changing Tx based on CONTROL level
≤ 2 days/ week	≤ 2 days/ week	< 2/month	≥ 80%	None	Intermittent	Step 1	Well controlled	Maintain current step
> 2 days/ week but not daily	> 2 days/ week but not daily and not more that 1x on any given day	3–4/month	≥ 80%	Minor limitation	Mild Persistent	Step 2	Well controlled	Maintain current step
Daily	Daily	> 1/week but not nightly	> 60%, < 80%	Some limitation	Moderate Persistent	Step 3	Not well controlled	Step up 1 step Reevaluate in 2–6 wks
Through out the day	Several times per day	Often 7/week	≤ 60%	Extremely limited	Severe Persistent	Step 4–5	Very poorly controlled	Consider short course of oral corticosteroids Step up 1–2 steps Reevaluate in 2 weeks

***Use only FEV_1 for initial evaluation. Use either FEV_1 or PEF for determining control and continuing therapy.

QuickQuiz

- What are signs and symptoms of theophylline toxicity? What is a therapeutic level?
- What is the preferred treatment for a new patient having asthma symptoms > 2 days/week, but not daily, and not more than 1x/day?
- What is the preferred regimen for patients who are on medium-dose inhaled corticosteroids and still require albuterol daily?

The list of drug interactions with theophylline is long but important. Board-relevant interactions to remember include:

- Increases theophylline levels (causing toxicity): ciprofloxacin, clarithromycin, zileuton, allopurinol, methotrexate, estrogens, propranolol, and verapamil
- Decreases theophylline levels (possibly exacerbating asthma): various antiepileptic drugs, rifampin, St. John's wort, smoking (more of an issue when patients stop smoking and theophylline levels subsequently increase on the same dose)
- Decreases level of coadministered drug: phenytoin and lithium

See General Internal Medicine, Book 5, for an in-depth discussion on theophylline toxicity, including treatment.

Table 3-4: Treatment Steps Used in Asthma

	Preferred	Alternative
Step 1	SABA prn	N/A
Step 2	Low-dose ICS	Cromolyn, LTRA, nedocromil, or theophylline
Step 3	Low-dose ICS + LABA or medium-dose ICS	Low-dose ICS plus either LTRA, theophylline, or zileuton
Step 4	Medium-dose ICS + LABA	Medium-dose ICS plus either LTRA, theophylline, or zileuton
Step 5	High-dose ICS + LABA and consider omalizumab for patients with allergies	N/A
Step 6	High-dose ICS + LABA + oral corticosteroid and consider omalizumab for patients with allergies	N/A

ICS = Inhaled corticosteroid; SABA & LABA = short- and long-acting beta2-agonists (inhaled); LTRA = leukotriene receptor antagonists

Long-Term Control: Immunomodulators

Omalizumab (anti-IgE) is a monoclonal antibody that blocks the IgE receptors on mast cells and basophils. It is indicated in patients who have allergies and severe uncontrolled persistent asthma on high doses of an ICS + a LABA (Steps 5–6 on asthma treatment algorithm, Table 3-4.)

Long-Term Control: Bronchial Thermoplasty

This technique was approved by the FDA in 2010. The bronchoscopic procedure delivers thermal energy to the airway wall, thereby reducing excessive airway smooth muscle. Purported benefits include improved asthma-related quality of life and reduced emergency room visits and hospitalizations.

Management of Asthma

Notes on the Guidelines

Management discussion is based on the 2007 National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma.

Note the following points made by these guidelines.

For chronic asthma management, think about asthma as 2 separate types of clinical encounters: treatment initiation and continuing therapy (rather intuitive). Refer to Table 3-3 during this discussion.

Treatment initiation occurs when a patient initially presents with signs/symptoms of asthma and is not on chronic management. Assess disease "severity" based on a number of factors (including the FEV_1, but not the peak flow!), then prescribe a Step level of treatment.

If your patient's risks include more than 1 category, then classify according to the most severe category. Use the purple part of the table to classify the patient, and find the patient's initial severity level by reading over into the green section of the table in the "Severity" column. The initial meds you start are based on the initial severity classification and are designated as Steps 1–5 (see Table 3-3).

Continuing therapy. After instituting the proper initial Step level of treatment, reevaluate the patient again in 6 weeks to 2 months to assess the level of control using the same set of factors (now you can use either FEV_1 or PEF).

Table 3-5: Asthma Control Classification

	Classification of asthma severity in well-controlled patients			
	Intermittent	Persistent		
		Mild	Moderate	Severe
On Step	1	2	3 or 4	5 or 6

At this initial follow-up visit and all future visits, determine the control level of asthma using the purple part of the table and reading over into the green section in the "Control" column to determine whether the asthma is well controlled, not well controlled, or very poorly controlled. Based on the level of control, modify Step level of treatment if needed (again, per Table 3-4).

Once the patient is well controlled for 3 months, look at the regimen required to maintain control, and assign the patient a category of severity that corresponds with that Step level of treatment (Table 3-5). Note that it is only at this point, when the patient is well controlled, that we can define how severe the disease is because the severity of asthma is based on the Steps needed to control it. The control aspect of care is dynamic: Every 3 months, step up if the patient is not controlled or step down if controlled. The goal is to maintain control on the fewest medications.

So, initial assessment is based on "severity of presenting symptoms." Determination of continuing therapy is based on "control of symptoms" with treatment. And determination of the "severity of disease" is based on how much medication is required to maintain good control of it. Be careful that you do not confuse these 2 uses of severity.

The Treatment Steps

Again, refer to Table 3-4 for this discussion.

Initial treatment of mild symptoms is with a SABA used as needed. Asthma is an inflammatory condition and anything more than very mild symptoms require that inhaled corticosteroids be added in a stepwise fashion starting with the lowest dose (Step 2). Note that before you increase the ICS dose from low to medium, it is preferred that you add a LABA (Step 3).

Chronic, severe asthma may require continuous oral prednisone. Steroid-sparing drugs have been tried, including methotrexate, cyclosporine, and troleandomycin, but the guidelines specifically state not to prescribe any of these drugs for the acute or long-term treatment of asthma.

When an exacerbation occurs, chronic management can be "stepped up" one or two levels, then slowly "stepped down" until symptoms recur, and then stepped up one level. When treatment is initially started, it is usually started one or two levels above the presumed severity level and then gradually stepped down in the same way.

Give chronic oral steroids only for severe asthma (or for an acute asthma exacerbation) and, even then, repeat attempts to wean.

Use LABAs only for moderate-to-severe asthma and in addition to inhaled corticosteroids.

Treat acute exacerbations at any level the same: inhaled SABAs and oxygen as needed. Add OCS if the patient's peak flow is < 80% after 3 treatments with an inhaled SABA.

Studies show that guideline-based treatment of asthma is superior to other methods.

Management of Exercise-Induced Bronchospasm

Treat exercise-induced bronchospasm (EIB) with inhaled albuterol 15–30 minutes before exercise. A warm-up period prior to exercise is also helpful. Inhaled cromolyn is an alternative. Leukotriene modifiers are effective in ~ 50% of patients. LABAs also have some efficacy, but they should not be used unless combined with an ICS. (Avoid daily monotherapy with LABAs in asthma!)

Treat active bronchospasm with warm, moist air and inhaled short-acting beta2-agonists.

Management of Acute Exacerbations

Algorithms for managing acute asthma exist in the guidelines, and the one you should use depends on whether you are treating patients at their home or in the emergency department (ED). Important considerations include:

First, assess severity based on clinical history, exam (can be described to you over the phone), and peak expiratory flow (PEF; "peak flow"). Any PEF < 80% predicted or personal best suggests obstruction, and you should treat it with medication.

If the patient is at home and responds to the SABA with a PEF > 80%, then the patient can remain at home with increased frequency of a SABA—q 3–4 h.

If the PEF is < 80%, give systemic steroids in whatever manner you can get them in the patient (IV if in respiratory failure).

If the patient is at home and has started oral steroids, keep tabs on the response to increased frequency of the SABA. Either the patient stabilizes or does not. If a poor response is observed with PEF < 50% (either after the 1st round of SABA, or after trying an OCS + a SABA), the patient should go to the ED.

Patients with initial peak flow of < 50% should be told to get to the ED ASAP.

If the patient is presenting to the ED, and the PEF is < 40%, the exacerbation is considered "severe."

Institute 2 treatments of a SABA, 20 minutes apart. Patients with a "severe" presentation should have ipratropium added to the SABA.

In the ED, the patient is stratified into either a moderate (PEF 40–69%) or severe (PEF < 40%) exacerbation based on response to the initial set of SABAs (+/– ipratropium).

Obviously, patients with impending respiratory failure at presentation fall out of the algorithm and should be admitted to the ICU. Only patients with severe exacerbations continue to get ipratropium in the ED; moderate exacerbations can be treated with oxygen, an OCS, and a SABA q hour.

Quick Quiz

- What is the preferred treatment for patients with exercise-induced bronchospasm?
- For an acute exacerbation, what peak flow measurement requires that you intervene with some medications?
- For an acute exacerbation, what peak flow measurement requires that you tell patients to go to the ED?
- For patients being treated in the ED for asthma, at what peak flow should you consider hospitalization?
- Explain permissive hypercapnia.
- What ventilator settings are appropriate for a patient intubated for a severe exacerbation of asthma?
- What is the specific definition of COPD?

A patient who has a sustained PEF > 70% one hour after the last SABA treatment and who "looks good" can be discharged to home with a prescription for continued outpatient SABA, OCS, and a close follow-up.

A patient should be considered for hospitalization if he or she continues to maintain a PEF of 40–69% despite treatment in the ED with a SABA, oxygen prn, and an OCS.

If the patient deteriorates in the ED, dropping the PEF < 40%, admit to the ICU. Inpatient care consists of a SABA, oxygen prn, and systemic steroids. If the patient was on an ICS prior to exacerbation, continue the ICS during hospitalization.

Intubation and the Asthma Patient

During a severe asthma attack, the patient initially hyperventilates and pCO_2 is low. As chest wall and diaphragm muscles fatigue, the patient starts to breathe more and more slowly, normalizing the pCO_2 and finally becoming hypercapnic. Mild hypoxemia and hypocapnia are the norm with acute asthma attacks. Normocapnia or hypercapnia indicates impending respiratory failure and the need for intubation or noninvasive ventilatory support!

If intubation is required, first sedate and then paralyze only if needed. Try to avoid use of neuromuscular blocking drugs to avoid prolonged blockade (might be harder to wean off). Avoid morphine because it may cause histamine release.

Once intubated, do not ventilate too quickly! These patients require a prolonged expiration period, and ventilating at too high a rate causes progressive air trapping ("stacking" or "auto-PEEP"), which causes decreased venous return or barotrauma; e.g., tension pneumothorax, decreased venous return → decreased filling pressure → decreased cardiac output → hypotension and poor perfusion of vital organs.

Permissive hypercapnia is a technique of controlled hypoventilation with small tidal volumes. We no longer try to get the pCO_2 down to 40 to resolve the acute respiratory acidosis; this effort in just-intubated asthmatics has had bad outcomes (auto-PEEP)! Initially, focus on maintaining an O_2 sat of 90%, and don't worry about the pCO_2—a reasonable level is 60–70 mmHg (or even 80 mmHg) with a serum pH of 7.20–7.25.

Besides maintaining an adequate O_2 saturation, you must ensure enough time for the inspired air to get out! Listen with your stethoscope and check that the ventilator is not kicking in while the patient is still exhaling, or check the flow-over-time waveform on the graphic package of the ventilator. Some ventilators actually measure auto-PEEP during an expiratory hold maneuver.

When putting an asthmatic on a ventilator, use a low rate, a small tidal volume, and high inspiratory flows. Each of these helps provide a prolonged expiratory phase. High flow on the inspiration allows for less time devoted to inspiration and more to expiration. High flow may result in slightly higher circuit pressure, but this rarely affects our concern with end-inspiratory plateau pressure and avoidance of auto-PEEP.

COPD

Overview

Chronic obstructive pulmonary disease (COPD) is diagnosed when patients have typical symptoms indicative of disease of large airways (dyspnea, cough, and sputum production) with evidence of irreversible airflow obstruction ($FEV_1/FVC < 0.70$) without another explanation for disease.

COPD results from chronic exposure to an inflammatory stimulus; e.g., cigarette smoke, pollution, dust. The lungs respond with inflammatory cell infiltrates and eventual development of structural changes due to repeated repair attempts. These structural changes are usually permanent, even after smoking cessation. Smoking causes damage to large airways, small airways, and in the lung parenchyma. In later stages, the pulmonary vasculature becomes involved when chronic hypoxic vasoconstriction causes pulmonary hypertension.

Although smoking is definitely a cause of COPD, not all cigarette smokers develop COPD—with disease expression mediated by additional factors such as genetics and environment.

Important Pathophysiology

Cigarette smoking damages both large and small airways, as well as the alveoli.

Large airway damage causes the cough and mucus production that we clinically diagnose as "chronic bronchitis."

Small airway damage causes airflow obstruction with hyperinflation. Airflow obstruction is caused by narrowing of these small airways in response to smoke. Inflammatory cells are recruited and infiltrate the walls, secreting mucus. Fibrosis ultimately contributes to chronic airflow obstruction and intermittent bronchoconstriction.

Over time, the smallest airways and alveolar spaces increase in size to try to overcome the airway resistance instigated by the narrowing—this phenomenon is called hyperinflation. As a compensatory maneuver, it works nicely, at first, and is expressed as a spirometric increase in residual volume. But as the lungs lose elastic recoil, the stretched-out small airways and alveolar sacs trap air, instead of forcing it out against resistance. Clinically, we see this as development of the barrel chest and prolonged expiratory phase, which is expressed as an increase in total lung capacity.

Alveolar damage also leads to impaired gas exchange. Over time, the alveolar sacs become distended with perforated units full of an inflammatory "soup" of macrophages and other immune cells. Pathologically, these changes are described as emphysema.

Emphysema can occur focally in the bronchioles (termed "centriacinar," which is seen most often in smokers—affecting upper lungs usually), or it can occur evenly across the lung (termed "panacinar," and seen most often in α_1-antitrypsin deficiency—affecting lower lungs typically). Advanced COPD from cigarettes typically involves both types.

Disease of the small airways and alveoli is present in almost all people with COPD, but the damage does not universally correlate with a specific presentation—meaning, the damage to these units causes symptoms that vary from person to person.

Diagnosis and Assessment of COPD

Suspect COPD in any patient who presents with complaints of dyspnea and productive cough—whether they smoke or not. Know that bronchitis without objective airway obstruction is not COPD, by definition.

Recognize that some patients do not complain of shortness of breath. Rather, they progressively restrict their exertion in order to avoid activities that would make them short of breath. For example, they might start taking elevators instead of the staircase, or they might give up riding a bicycle.

Chronic bronchitis is defined as cough with sputum production for at least 3 consecutive months for at least 2 consecutive years. Patients may have a bronchospastic component responsive to bronchodilators.

Physical exam classically shows an obvious prolonged expiratory phase, wheezing, barrel chest, and increased lung sizes to percussion. Late-stage patients sit forward on their elbows in the "tripod" position in order to harness strength from accessory muscles. These patients are often cyanotic in nail beds and lips.

The traditional definitions of "pink puffers" and "blue bloaters" have fallen out of favor because COPD is always a mixed pathologic picture of chronic bronchitis and emphysema. Differentiation between the 2 clinical presentations is artificial because the overwhelming majority of patients do not present that way.

[Know:] COPD, as an isolated disease process, does not cause clubbing. If you see clubbing in a patient with COPD, look for other lung pathology, such as idiopathic pulmonary fibrosis or lung cancer.

The Global Initiative for Obstructive Lung Disease (GOLD) is a worldwide association that sets criteria for the diagnosis, grading of severity, and management of COPD.

The GOLD criteria categorize COPD into 4 levels of severity based on the reduction of the FEV_1 compared to the predicted value. All 4 groups require spirometric diagnosis of irreversible obstruction as defined by an $FEV_1/FVC < 0.70$. The COPD levels are:

- GOLD 1 = mild: $FEV_1 \geq 80\%$ predicted
- GOLD 2 = moderate: FEV_1 50–79% predicted
- GOLD 3 = severe: FEV_1 30–49% predicted
- GOLD 4 = very severe: $FEV_1 < 30\%$ predicted

There is some controversy involving the fact that GOLD spirometric diagnostic criteria overdiagnose COPD in the elderly and underdiagnose it in patients younger than 45 years with mild disease.

The GOLD guidelines had a major update in 2011. This update emphasizes that spirometry alone does not capture COPD's full impact on individual patients. Therefore, it is recommended to assess COPD with a combination of:

- the GOLD spirometry criteria (1–4) just discussed,
- severity of symptoms (using COPD Assessment Test [CAT] or Modified British Medical Research Council [mMRC]) breathlessness scale,
- risk of exacerbations (based on previously treated exacerbations), and
- the presence of comorbidities.

Based on this combined assessment, patients are divided into 4 groups:

- A = fewer symptoms, low risk of exacerbations
- B = more symptoms, low risk
- C = fewer symptoms, high risk
- D = more symptoms, high risk

Treatment recommendations are based on these A, B, C, and D patient groupings. The groups are associated with the GOLD spirometric classifications, such that group A and B patients tend to fall into GOLD 1–2 and groups C and D fall into GOLD 3–4. See the GOLD Guideline

QuickQuiz

- In COPD, what are the symptoms of disease in the large airways? The small airways? The alveoli?
- What is the specific definition of chronic bronchitis?
- What is the significance of clubbing in a patient with COPD?
- What is the best prognostic indicator in COPD?

referenced in For Further Reading on page 3-79 for additional information.

The treatment that we discuss below takes into account these recommendations.

The **BODE** index (**b**ody mass index, airflow **o**bstruction, **d**yspnea, **e**xercise capacity) adds a little to the GOLD severity criteria by considering how outcomes are affected by some extrapulmonary manifestations. Patients get points for FEV_1, 6-minute walk test results, dyspnea, and body mass index. The result helps prognosticate 4-year survival and assess response to treatment changes. Higher BODE scores are associated with an increased risk of death.

COPD pathology results in airflow obstruction, hyperinflation, and problems with gas exchange.

Must-know items and useful clinical pearls:

- The best prognostic indicator in COPD is FEV_1.
- The best predictor of FEV_1 is pack years of cigarette smoking. The normal age-related decrease in FEV_1 is ~ 15–30 mL/yr; COPD patients can lose 60–120 mL/yr of lung function.
- Cessation of smoking is most beneficial to the lungs when accomplished at a younger age and before any loss of pulmonary function.
- P_aO_2 does not usually fall until late in the disease, when FEV_1 is < 50% of predicted (or even lower in many patients).
- Chronic retention of CO_2 does not generally occur until very late in the disease, when FEV_1 is < 25% of predicted.
- Cor pulmonale occurs only after prolonged, marked reductions in FEV_1 (usually < 25% predicted) with severe, chronic hypoxemia.
- Hypoxemia in COPD is almost exclusively due to V/Q mismatching; therefore, COPD exacerbations are responsive to low flow oxygen (2–3 L/min). If a patient with an apparent COPD exacerbation is not responsive to moderate amounts of oxygen, consider another cause for decompensation, such as a shunt process.

One more time, review of lung mechanics in emphysema: Decreased elastic recoil means increased compliance (and increased TLC). Although there is an increase in TLC, there is an even greater increase in residual volume from air trapping, so the VC (or FVC) is decreased! This air trapping leads to the process of dynamic hyperinflation and can result in a large amount of auto-PEEP (intrinsic PEEP). DLCO is reduced in patients who have a great amount of emphysema.

Image 3-1 through Image 3-3 show classic COPD changes on CT and chest x-rays.

Treatment of COPD

General Treatment Principles

Management based on 2007, 2009, 2011, 2013, and 2014 GOLD updates:

- Educate everybody and encourage them to stop smoking. Nicotine replacement therapy in many forms (gum, nasal spray, patch, tablets, lozenges, inhaler) is effective. Other pharmaceutical options include varenicline, bupropion, and nortriptyline.
- SABAs as needed in all patients.
- LABAs in moderate-to-very severe stages when SABAs fail to control symptoms. These drugs reduce exacerbations and hospitalizations. Tiotropium improves the efficacy of pulmonary rehab, if the patient is enrolled.
- ICS is recommended in patients with GOLD 3–4 disease (FEV_1 < 50% predicted). In these groups, these drugs reduce exacerbations but also improve lung function and quality of life. However, they are associated with an increased risk for pneumonia. Do not use as long-term monotherapy. The drugs should be combined with LABAs.
- Combination LABA + ICS is more effective at reducing exacerbations than either agent alone, but it also is associated with an increased risk of pneumonia.
- GOLD 3–4 patients may benefit from roflumilast, a phosphodiesterase-4 inhibitor. Roflumilast is primarily directed at patients with predominant bronchitis, not emphysema.

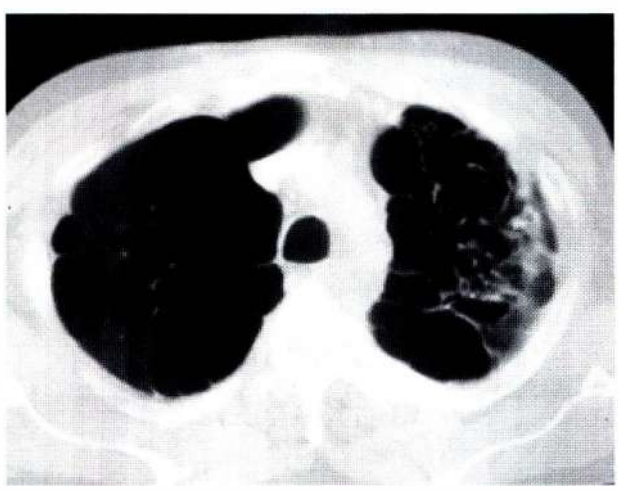


Image 3-1: CT: Bullous emphysema

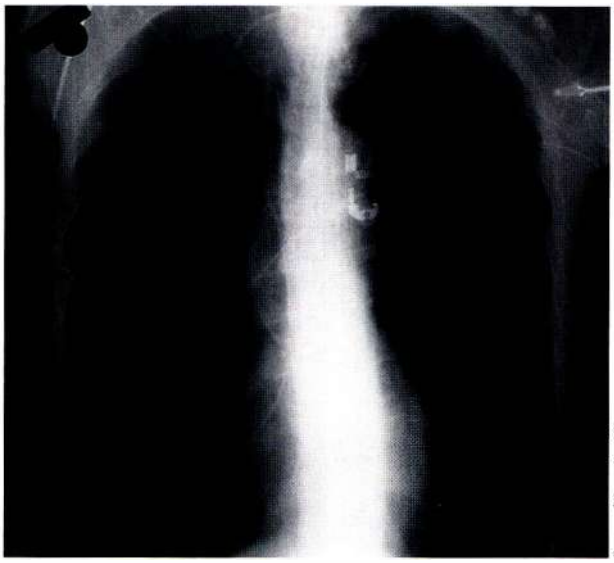


Image 3-2: Emphysematous COPD

- Reserve theophylline for those who are on maximum therapy. It adds a slight bronchodilator effect to salmeterol, which relieves breathlessness and reduces exacerbations. It may also have salutatory effects on diaphragmatic function and the hypoxic drive to breathe.
- Do not use nedocromil or leukotriene modifiers. These are ineffective in COPD.
- Give pneumococcal and influenza vaccines.
- Oxygen as needed when patients meet criteria (see next).
- Monitoring of blood gases in patients with FEV_1 < 50% predicted or clinical signs of respiratory or right heart failure.
- Screen for α_1-antitrypsin deficiency in all Caucasian patients who get COPD and are younger than 45 years and/or have a lower lobe prominence of bullae.

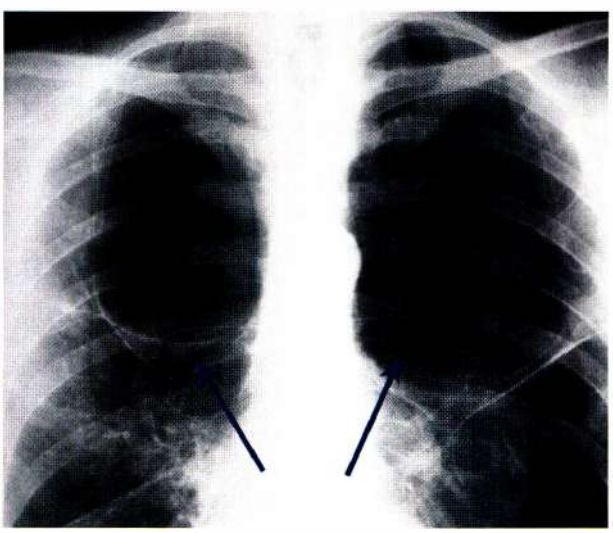


Image 3-3: Chest x-ray showing emphysema bubbles

Oxygen therapy for patients with COPD:

The focus of O_2 therapy for patients with COPD (or any patient, for that matter) in respiratory distress is to give them enough O_2 to achieve 90% O_2 saturation (S_aO_2)—or as close as possible. This is a required endpoint in initial management! Not treating hypoxia causes further end-organ damage, worsening pulmonary vasoconstriction, and a downward spiral to death.

Criteria for starting continuous O_2:

- resting $P_aO_2 \leq 55$ mmHg or $S_aO_2 \leq 88\%$,

or, with evidence of cor pulmonale:

- resting $P_aO_2 \leq 59$ mmHg or $S_aO_2 \leq 89\%$

Criteria for evidence of cor pulmonale:

- Clinical evidence of right heart failure
- P pulmonale on ECG (> 2.5 mm P wave height in II, III, and AVF)
- Hct > 55% (Cor pulmonale causes chronic hypoxia, which causes polycythemia.)

Continuous O_2 use, if needed per the above criteria, increases life span. Keep these patients on supplemental O_2 24 hr/d (if not possible, at least 15 hr/d).

Intermittent O_2 use: Some patients have similar findings of hypoxia/desaturation during low-level exercise or sleep. Giving these patients supplemental O_2 during these activities may improve exercise capacity and/or quality of life, but does not improve survival.

COPD patients placed on oxygen during an exacerbation should be re-assessed at 2 months after they are on a stable regimen of drug therapy—oxygen can be discontinued in up to 40%!

Pulmonary rehabilitation: A pulmonary rehabilitation exercise regimen results in a small but significant improvement in overall strength and endurance. Unfortunately, pulmonary rehab does not improve PFT or ABG parameters. [Know:] Pulmonary rehab improves symptoms and quality of life and reduces the number of hospitalizations and days in the hospital. The 2011 GOLD update states that survival is improved (level of evidence B). However, this is not universally accepted, and many of the immediate benefits of pulmonary rehab are lost if the rehab exercises are discontinued.

Lung volume-reduction (LVR) surgery: LVR surgery can be useful for emphysematous patients with upper lobe disease and low exercise capacity. The Center for Medicaid and Medicare Services (CMS) now pays for LVR surgery when performed by an approved center as part of the NETT trial in patients who are symptomatic despite using bronchodilators and pulmonary rehabilitation. However, the most severe group is excluded from approval due to high mortality in their subset.

[Know:] No medication prevents the decline of FEV_1 in COPD! The only interventions that affect COPD outcomes long-term are smoking cessation, oxygen in hypoxemic patients, and lung volume reduction surgery or lung transplantation in appropriately selected patients.

QuickQuiz

- A COPD patient with evidence of right heart failure has a resting P_aO_2 of 58. How many hours a day should he be on supplemental oxygen?
- What are the benefits of pulmonary rehabilitation? Does pulmonary rehab improve mortality?
- Describe the emergent workup of a patient with an apparent COPD exacerbation.
- A 30-year-old smoker presents with COPD and emphysematous bullae in the bases. What disease should you suspect?

Treatment of Stable COPD

As discussed previously, the GOLD COPD assessment classifies patients into groups A, B, C, and D (see page 3-18). Note: In the following treatment, bronchodilator means either anticholinergic or beta-agonist. Thus, short-acting bronchodilator can be either short-acting anticholinergic or SABA. Long-acting bronchodilator can be either long-acting anticholinergics or LABA.

Treatment, based on this classification:

- Group A patients: **short-acting bronchodilator** (short-acting anticholinergic or SABA) to improve breathlessness; alternative is combination of short-acting bronchodilators or use of single long-acting bronchodilator.
- Group B patients: **long-acting bronchodilator** (long-acting anticholinergic or LABA); for patients with persistent breathlessness, long-acting bronchodilators can be combined (anticholinergic + beta-agonist).
- Group C patients: First choice is combination therapy with **ICS + long-acting bronchodilator**. Alternatively, 2 long-acting bronchodilators can be combined. Short-acting bronchodilators can be combined with theophylline if long-acting bronchodilators are unaffordable; **roflumilast** can be used for patients with chronic bronchitis.
- Group D patients are initially treated same as group C with **ICS + long-acting bronchodilator**; alternatives include ICS + LABA + long-acting anticholinergic ± roflumilast if chronic bronchitis is present.

Treatment of Exacerbations of COPD

An exacerbation is a worsening of respiratory symptoms beyond the normal variation requiring a change in medication. Patients frequently present with worsening shortness of breath, cough, wheezing, sputum production, or hypoxemia.

For assessment of the exacerbation:

- Do a chest x-ray because up to 23% show new infiltrates that may change the chosen therapy.
- Do an ECG and pay attention to the history for clues suggesting pulmonary embolism such as $S_1Q_3T_3$, anterior T-wave inversions, new RBBB, or RAD. This is a hot topic now because of data showing that pulmonary emboli are often an unsuspected trigger of COPD exacerbations. Remember that the most common ECG abnormality in pulmonary embolism is sinus tachycardia.
- Assess the S_aO_2 and draw an arterial blood gas if respiratory failure is suspected. $P_aO_2 < 60$ mmHg or $S_aO_2 < 90\%$ +/– $P_aCO_2 > 50$ mmHg on room air = respiratory failure. Give low flow oxygen (1–2 L/min with close observation to keep the saturation > 90%. Note that patients with initial abnormal blood gases are at risk for hypercarbia and subsequent respiratory failure with supplemental O_2 administration.
- Do not use spirometry or peak flows to diagnose or assess the severity of a COPD exacerbation.

For treatment of COPD exacerbation:

- Start treatment with SABA and add an anticholinergic drug if the patient doesn't improve quickly.
- Begin systemic corticosteroids. These drugs shorten recovery, reduce the risk of early relapse, and decrease the length of the hospital stay. 40 mg of oral prednisone is recommended for 10–14 days.
- In moderately and severely ill patients, the presence of purulent sputum is an indication for empiric antibiotics targeted against *Moraxella*, pneumococcus, and *Haemophilus influenzae*. GOLD 3 and 4 patients also are at risk for infection with *Pseudomonas*. Recommended antibiotics are broad in spectrum: amoxicillin-clavulanate, azithromycin, and respiratory quinolones. Antipseudomonal coverage is parenteral.
- NIPPV (noninvasive positive-pressure ventilation) is the 1st choice for hypercapnic ventilator failure in selected groups; it reduces hospital stay and reduces mortality in exacerbations.

α_1-ANTITRYPSIN DEFICIENCY

Overview

α_1-antitrypsin deficiency causes 1–2% of COPD cases, so it is rather rare. Consider it in young smokers with bullous COPD in the lung bases and/or family histories of both liver and lung disease.

The alleles responsible for α_1-antitrypsin deficiency occur on a locus called *Pi*. The most common allele is *Pi M*. The *M* means it moves moderately fast on an electrophoretic strip. There are variants of *Pi M*—some move faster (*Pi F*) and some slower (*Pi Z*). Null alleles do not code for any α_1-antitrypsin. Patients homozygous for the slower allele (Pi^{ZZ}) or heterozygotes for *Z* and null alleles

(both groups referred to as Pi^Z) have severely decreased levels of α_1-antitrypsin. Levels of α_1-antitrypsin in heterozygotes (Pi^{MZ}) are about 60% of normal.

Disease is variable among all individuals with the deficiency. For example, some Pi^Z individuals do not get COPD, and airflow obstruction among Pi^{MZ} individuals is unpredictable. Contrary to previous teachings, some studies show that heterozygote (Pi^{MZ}) nonsmokers may have more airflow obstruction than patients with normal α_1-antitrypsin levels (Pi^{MM}). One unifying factor in disease progression is cigarette smoking. Smoking worsens lung disease in both groups. Genetic factors, other than *Pi* locus alleles, likely account for the variability in disease expression.

Don't forget! Patients with α_1-antitrypsin deficiency can also develop progressive liver fibrosis and cirrhosis. As with the lung disease, expression of the genetic defect in the liver is variable, but Pi^Z patients are most affected.

As with cirrhosis of any cause, there is an increased incidence of hepatocellular carcinoma.

Disease presents as airflow obstruction in a young person with unusual bullous formation in the lung bases, and/or elevated serum aminotransferase levels. In severe Pi^Z cases, liver disease can progress to cirrhosis in childhood.

Diagnose α_1-antitrypsin deficiency by measuring the serum level of α_1-antitrypsin followed by genetic testing of the *Pi* locus. 2009, 2011, and 2013 GOLD guidelines recommend screening with a serum level in any Caucasian patient who develops COPD and is < 45 years old or has a "strong" family history of COPD. The benefit in knowing phenotype and genotype is to better counsel not only the patient but also the patient's family members.

Treatment of α_1-Antitrypsin Deficiency

α_1-antiprotease (pooled human α_1-antitrypsin) can be given in weekly IV infusions in patients with severe disease. It costs approximately $40,000/year.

Selection criteria for IV augmentation: Pi^Z status and serum α_1-antitrypsin level < 11 µmol/L (equal to 50–80 mg/dL depending on the assay) with both an abnormal chest CT and spirometry. Patient must be a nonsmoker or ex-smoker.

Some experts advocate treating all deficient individuals with low levels of α_1-antitrypsin to help maintain the current lung function. However, the expense of this intervention is hard to justify in COPD patients with end stage lung damage.

In addition to the IV infusion, patients should continue to be treated with bronchodilators, antibiotics, oxygen as needed, and yearly vaccines. And don't forget the vigorous anti-smoking message.

When the emphysema is severe, the only treatment is lung transplantation. Note that IV infusion has no effect on liver disease, and the only treatment for cirrhosis is liver transplantation.

BRONCHIECTASIS

Bronchiectasis is persistent, pathologic dilatation of the bronchi caused by infection-mediated inflammation and destruction of airway walls. The bronchi fill with mucus and pus, and then become fibrotic. The infectious insult sometimes is primary (e.g., adenoviral infection), or it may be secondary, due to an underlying lung disease that prevents adequate clearance of organisms from the respiratory tree (e.g., cystic fibrosis).

Consider it in an older or middle-aged female with a chronic cough productive of purulent sputum (+/– hemoptysis) that either arose insidiously over years or followed a dramatic lung event (e.g., chemical inhalation or bad pneumonia).

Specific causes of bronchiectasis:

- Initial infections, such as severe viral pneumonia from adeno- or influenza virus; severe, untreated or poorly treated staph or gram-negative pneumonia; *Bordetella pertussis* infection; and mycobacteria (especially if focal area of involvement). It is often difficult to tell whether the organisms growing in the patient's lungs initiated the bronchiectasis or are colonizing. *M. avium* complex is sometimes just a colonizer of bronchiectatic lungs, but it can also cause bronchiectasis.
- Focal lung obstructions as with endobronchial tumors, lymph nodes, or foreign bodies.
- Systemic diseases that reduce mucociliary clearance or prevent an adequate immune response and, thus, allow for colonization of destructive bacteria (e.g., cystic fibrosis, ciliary dyskinesia, HIV/AIDS, and immunoglobulin deficiency).
- Inhalation of a toxin (e.g., chemical fumes or gastric contents).
- Allergic bronchopulmonary aspergillosis (ABPA) (a favorite test question).
- α_1-antitrypsin deficiency (rare).

Diagnose bronchiectasis with a HRCT of the chest (Image 3-4). Chest x-rays usually are nonspecific. Routine Gram stains with culture and acid-fast bacteria (AFB) smears/cultures should be done to assist treatment decisions. Based on clinical history and physical exam, you might consider testing for HIV, measuring immunoglobulins, performing the prick test for ABPA, and/or ordering a sweat chloride measurement.

Treatment is a 10–14-day course of antibiotics to reduce the burden of pathogenic organisms in the small airways. (Or, treat ABPA if that is the underlying cause.)

The antibiotic decision should be driven by microbiologic data from sputum. The big organism to worry about

Quick Quiz

- What is the single environmental agent that worsens lung disease in all types of α_1-antitrypsin deficiency?
- What disease should you suspect in a patient with a chronic cough productive of purulent sputum?
- What are the newer treatments for cystic fibrosis?

is *Pseudomonas*. In cystic fibrosis patients, it is often multi-drug resistant. Treat based on resistance testing. However, empirically, start with oral ciprofloxacin or an aminoglycoside plus a parenteral antipseudomonal penicillin. No solid data exist on benefit of chest physiotherapy and mucolytics, but they are often used. Chronic prophylaxis for bronchiectasis breeds resistant bacteria and does not prevent acute infection or deterioration of pulmonary function.

Do not treat bronchiectasis with aerosolized recombinant DNase (because it can cause harm), except in patients who have underlying cystic fibrosis.

Massive hemoptysis or unresolving focal infections usually require surgical resection.

CYSTIC FIBROSIS

Cystic fibrosis (CF) occurs as a result of a mutation in the CF transmembrane conductance regulator (CFTR) protein gene on chromosome 7. This protein normally controls Na^+/Cl^- transport on epithelial membranes in the lung, GI tract, sweat glands, and urogenital system. The gene mutation results in decreased Na^+ absorption and Cl^- secretion. Lung mucus is dehydrated, sticky, and low in oxygen, which contributes to bacterial superinfection with particularly virulent, and difficult to treat, organisms.

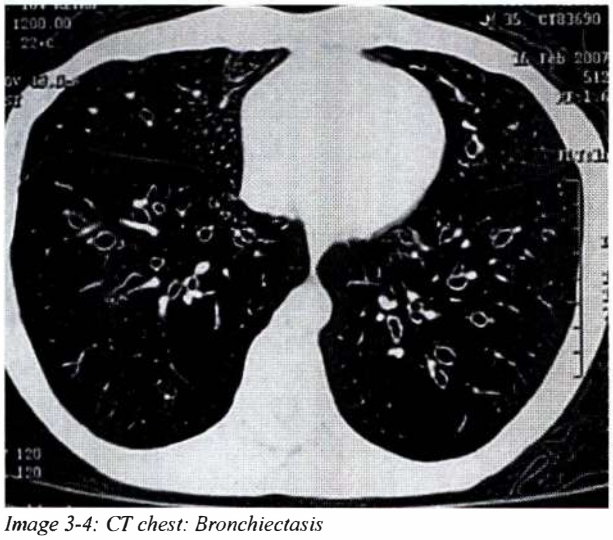


Image 3-4: CT chest: Bronchiectasis

5% of patients with CF initially present in adulthood, and median survival is 41 years.

Initial diagnosis: Consider adult CF in a patient with a history of recurrent sinusitis, nasal polyps (found in 25%), weight loss, and a chronic cough productive of thick, purulent sputum with recurrent exacerbations of febrile respiratory infections requiring antibiotics. Sputum Gram stain showing gram-negative rods (GNRs) and cultures that grow staph, *H. influenzae*, *Pseudomonas*, enteric GNRs (*Proteus*, *E. coli*, *Klebsiella*). Weird organisms that you've never heard of before (e.g., *Alcaligenes xylosoxidans* and *Burkholderia gladioli* or *B. cepacia*) should really tip you off. *Aspergillus* and non-tuberculous mycobacteria are also commonly found.

Most male patients with CF are infertile, so that may be an additional historical clue. Females may not be infertile.

Clubbing and signs/symptoms of cor pulmonale occur in late-stage disease.

Chest x-ray changes are nonspecific (hyperinflation and bronchial cuffing). Pneumothorax occurs in 10%. Spirometry shows reductions in FEV_1/FVC ratio and FEV_1, some of which are reversible until late disease.

Screen for CF by performing the sweat chloride test. 1–2% of patients with CF have normal sweat chloride tests, so continue testing if the patient has a strong clinical history but a negative sweat chloride test. The nasal potential difference (NPD) test and a genetic analysis are confirmatory tests.

Manage CF with aggressive pulmonary toilet (percussion and exercises, as these maneuvers preserve lung function); pancreatic enzymes; supplemental vitamins A, D, E, and K; and culture-guided antibiotics for exacerbations.

Recombinant human DNase and inhaled hypertonic saline are 2 recent additions to CF management. DNase degrades accumulated DNA in the airways and provides for better airflow. Hypertonic saline improves airway clearance.

IV antibiotics are used for more severe pulmonary exacerbations or resistant organisms. All gram-negative organisms get 2 antipseudomonal antibiotics until you know resistance patterns and identification of your organism.

For chronic management of CF, antibiotic prophylaxis using rotations of drugs helps prevent exacerbations by reducing microbial colonization. Inhaled aminoglycosides, or aztreonam, and oral azithromycin are commonly used.

Bilateral lung transplantation is an end-stage treatment option with a 65% 5-year survival rate.

Complications of CF include: respiratory failure, pulmonary hypertension with cor pulmonale, pneumothorax, and hemoptysis.

INTERSTITIAL LUNG DISEASES

OVERVIEW

Interstitial lung diseases (ILDs) are a diverse (> 100!) group of disorders that affect the supporting tissue of the lung, especially structural portions of the alveolar walls.

The name is partly a misnomer because there is often bronchial and alveolar involvement. Some call it diffuse parenchymal lung disease (DPLD)—which is more correct. However, we call it ILD in this discussion.

The interstitium usually is just a potential space between the capillaries and the alveoli. With ILDs, there is early alveolar disease with later collagen deposition in the interstitium, which causes scarring and changes the architecture of the alveoli and airways.

ILDs have common factors in their clinical presentation: dyspnea, diffuse disease on x-ray, restrictive PFTs with decreased DLCO, and an elevated A-a gradient (Image 3-5 and Image 3-6).

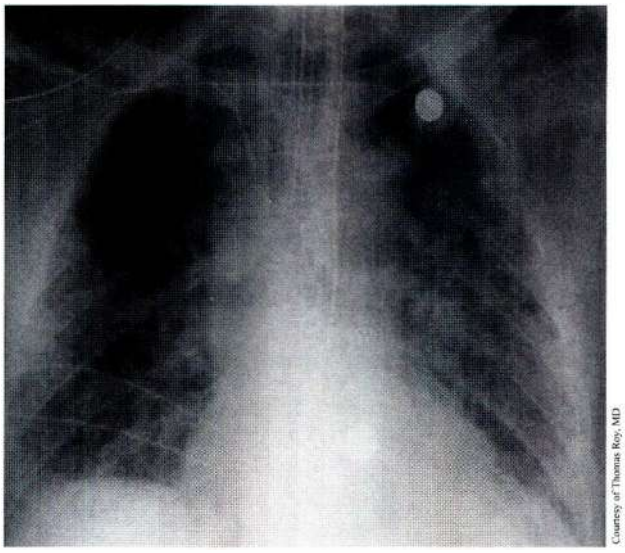


Image 3-5: PA chest: Diffuse interstitial fibrosis

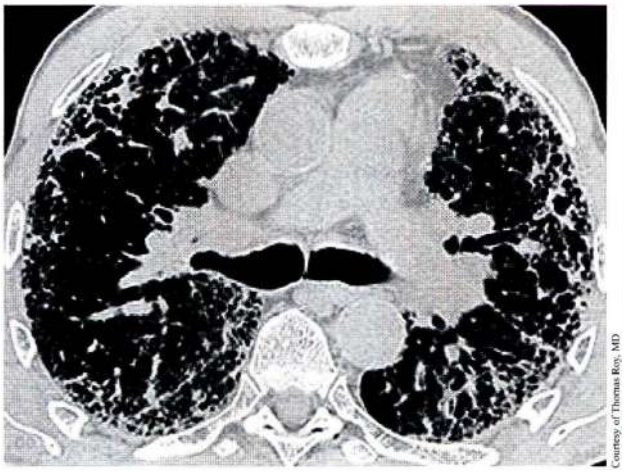


Image 3-6: Chest CT: Pulmonary fibrosis

ILDs most easily can be grouped into those of known cause and those that are idiopathic. Those of known cause are usually due to dust (organic or inorganic) from occupational or environmental exposures. We discuss these groups of ILDs as follows:

- Occupational and environmental causes of ILD
- Idiopathic interstitial pneumonias (IIP)
- Other causes of ILD

ILDs: OCCUPATIONAL AND ENVIRONMENTAL

Overview

There are 3 categories of occupational/environmental ILDs:

1) Hypersensitivity pneumonitis
2) Organic dust induced: byssinosis
3) Inorganic dust induced: asbestosis, silicosis, coal workers' pneumoconiosis, and berylliosis

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis is an immune-mediated granulomatous reaction to organic antigens. Not many people get it—just those susceptible to it.

Poorly formed granulomas are typical. (The granulomas in sarcoidosis are much denser.)

Hypersensitivity pneumonitis has a wide range of causes. An occupational and drug history can be highly revealing:

- Moldy hay (thermophilic actinomycetes), a.k.a. "farmer's lung"
- Pet birds, a.k.a. "bird-fancier lung" or "bird-breeder lung"
- Grain dust (workers in a grain elevator)
- Isocyanates
- Air conditioning systems
- Crack cocaine

Hypersensitivity pneumonitis has acute, subacute, and chronic forms. Typically, the onset is insidious. Think about it in a patient with "recurrent or persistent pneumonias" who gives you a history of exposure to 1 of the above.

Diagnose by history: Chest x-ray may reveal recurrent infiltrates, but these are fleeting. Serum precipitins are nonspecific for hypersensitivity pneumonitis because these indicate only exposure, and most people exposed to these antigens have no immune reaction. Eosinophilia is not a feature of acute hypersensitivity pneumonitis.

Subacute hypersensitivity pneumonitis eventually evolves into chronic hypersensitivity with irreversible parenchymal changes.

Quick Quiz

- Name the common clinical features of all interstitial lung diseases.
- What disease do you think of when a patient presents with recurrent pneumonia each time she changes her bird cage?
- Characterize the x-ray abnormalities in patients with a history of significant asbestos exposure.
- Smoking + asbestosis increase the risk of what types of lung cancer?

Differential diagnosis of acute hypersensitivity pneumonitis includes other causes of "recurrent or persistent pneumonias": eosinophilic pneumonia and cryptogenic organizing pneumonia (COP = idiopathic form of organizing pneumonia, previously idiopathic BOOP). Hypersensitivity pneumonitis also may be confused with sarcoidosis. Note that bronchoalveolar lavage (BAL) shows an increased number of lymphocytes, with a helper/suppressor ratio of < 1 (sarcoidosis has a ratio of > 4:1).

Best treatment is to remove the patient from the offending antigen. Corticosteroids are beneficial in acute disease.

Organic Dusts that Cause ILD: Byssinosis

Byssinosis is caused by inhalation of cotton, flax, or hemp dust. It is not immune-related, so no sensitization is needed. Early stage occasionally presents with chest tightness; late stage may present with regular chest tightness toward the end of the 1st day of the workweek (Monday chest tightness). The frequency of symptoms increases with continued exposure.

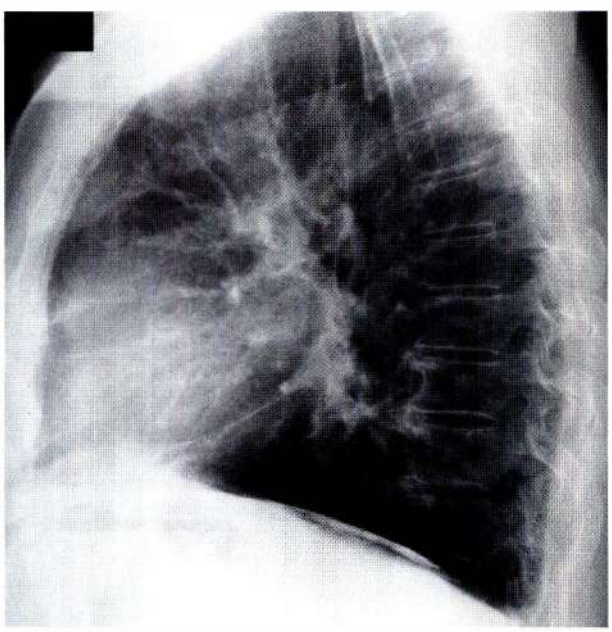


Image 3-7: PA lateral chest: Asbestos pleural plaques

Inorganic Dusts that Cause ILD

Overview

These ILDs are: asbestosis, silicosis, coal workers' pneumoconiosis, and berylliosis.

Asbestos

Asbestos exposure (not asbestosis) causes bilateral, mid-thoracic pleural thickening, plaques, and calcification. The pleural thickening usually involves the mid-thorax (posterolateral) and spares both the costophrenic angles and the apices. Remember that pleural plaques and pleural thickening are completely benign; they are not manifestations of asbestosis (Image 3-7).

The most common manifestation of asbestos exposure in the first 10 years is benign asbestos pleural effusions (BAPE). These vary from serous to bloody and tend to occur early in the exposure history (within 5 years). 1/3 of patients have eosinophils in the pleural fluid.

Malignant mesotheliomas are associated (80%) with asbestos exposure. (Again, merely exposure—not necessarily asbestosis!) It is a tumor arising from the mesothelial cell of the pleura—the area affected by asbestos exposure. Latency period can be > 40 years. It is not associated with smoking. It is usually a rapidly fatal disease.

Asbestosis is the pulmonary parenchymal disease—the parenchymal fibrosis and resultant impairment---caused by prolonged exposure to asbestos. The pulmonary parenchymal fibrosis develops mostly in the bases. Asbestosis generally occurs with > 10 years of moderate exposure, although the latency period is > 30 years! Smoking has a synergistic effect with asbestosis in the development of lung cancer. The associated lung cancers are squamous and adeno—but not small- or large-cell!

There is no specific treatment for asbestosis.

Silica

Silicosis is the most common occupational disease in the world. It requires years of exposure to crystalline silica to develop—as in mining, glassmaking, ceramics, sandblasting, foundries, and brick yards—with a latency of 20–30 years.

Silica ingested by alveolar macrophages renders them ineffective—so a +PPD (> 10-mm induration) in these patients makes the diagnosis of latent tuberculosis infection (LTBI); and these patients should be treated with antituberculous drugs per the ATS guidelines, regardless of age. Silica is a human carcinogen. All patients with silicosis have an increased risk for the development of active TB and malignancy, so consider screening for these conditions.

Simple nodular silicosis (i.e., small nodules) is "fibrocalcific" and usually involves the upper lung, so the differential diagnosis includes TB, coal workers' pneumoconiosis, and berylliosis. Silicosis is associated with

these silicotic nodules, involvement of the hilar lymph nodes ("hilar eggshell calcification"), and increased susceptibility to TB. See Image 3-8 and Image 3-9.

There is no specific treatment for silicosis, but if symptoms rapidly worsen, think of concurrent TB.

Complicated nodular silicosis (i.e., big nodules; also called progressive, massive fibrosis) has nodules > 1 cm, which tend to coalesce.

Silicoproteinosis: Overwhelming exposure leads to silicoproteinosis in ~ 5 years, which results in alveolar filling with eosinophilic material similar to that found in pulmonary alveolar proteinosis (page 3-33). These patients present with symptoms easily mistaken for pulmonary edema.

Cor icosteroids are thought to be beneficial in acute silicosis, but not in chronic disease.

Consider lung transplant for those with severe disease.

Note: Asbestosis involves the lower lung, while silicosis involves the upper lung.

Coal

Coal workers' pneumoconiosis (CWP) also has simple and progressive forms. The chest x-ray shows upper lung field nodules (similar to silicosis and berylliosis). Progression of simple CWP correlates with the amount of coal dust deposited in the lungs, whereas complicated CWP does not. Complicated CWP is a progressive massive fibrosis defined by nodules > 2 cm with no hilar involvement. With large depositions of coal dust, patients have melanoptysis. As expected, cigarette smoking accelerates the deterioration of pulmonary function. There is no association with TB, and there is no specific treatment.

Caplan syndrome is seropositive rheumatoid arthritis associated with massive CWP. This syndrome is heralded by the development of peripheral lung nodules (in addition to the upper lung field nodules seen in CWP).

Beryllium

Berylliosis (or chronic beryllium disease; CBD) is caused by a cell-mediated immune response that can occur from ≥ 2-year exposure to even slight amounts of beryllium. Especially suspect in persons who have worked with high-tech electronics, alloys, ceramics, the Manhattan Project nuclear program, and pre-1950 fluorescent light manufacturing.

It usually causes a chronic interstitial pneumonitis, which tends to affect the upper lobes (like silicosis, TB, and CWP). Patients often have hilar lymphadenopathy that looks identical on chest x-ray to that caused by sarcoidosis.

Diagnosis of CBD:

- History of beryllium exposure
- Positive beryllium lymphocy e transformation test (BeLPT)
- Lung biopsy showing interstitial cell infiltrates (with mononuclear cells) and/or noncaseating granulomas

This one can be treated! Corticosteroids are very effective.

Prescribe methotrexate (MTX) if no response or unable to tolerate corticosteroids.

ILDs: IDIOPATHIC INTERSTITIAL PNEUMONIAS (IIPs)

Overview

We will now discuss the second category of ILDs—idiopathic interstitial pneumonias (IIPs). Here is a listing in order of occurrence:

- Idiopathic pulmonary fibrosis (IPF; with usual interstitial pneumonitis [UIP] as the prototype)
- Nonspecific interstitial pneumonia (NSIP)
- Cryptogenic organizing pneumonia (COP, idiopathic form of organizing pneumonia; previously called idiopathic BOOP)

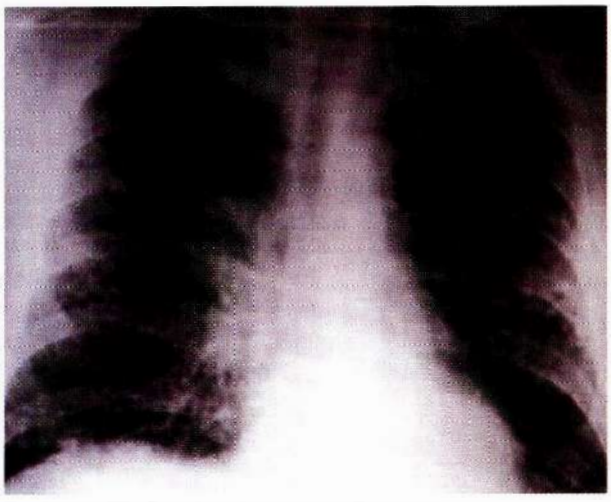


Image 3-8: PA chest: Simple nodular silicosis

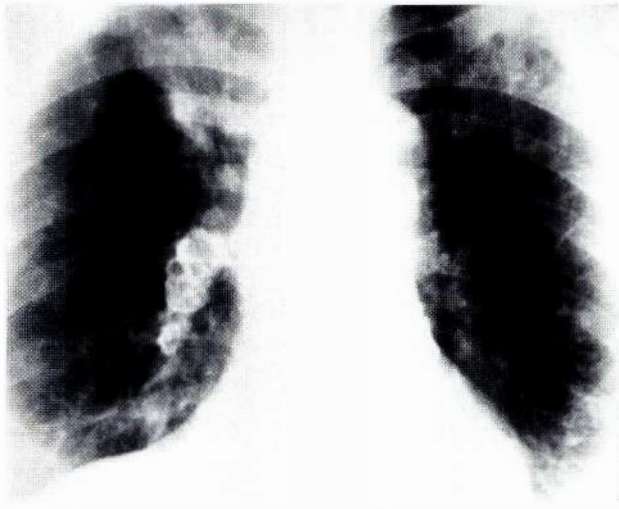


Image 3-9: PA chest: Eggshell hilar calcifications in silicosis

QuickQuiz

- What type of CT scan assists with diagnosis of IPF? What findings are seen with this in early IPF?
- What is the typical presentation of a patient with IPF?

- Acute interstitial pneumonia (AIP)
- Respiratory bronchiolitis-associated ILD (RB-ILD)
- Desquamative interstitial pneumonia (DIP)
- Lymphocytic interstitial pneumonia (LIP)

Each of these entities has specific histopathologic findings; IPF also has typical clinical and radiologic findings. We will discuss 2 of the most prominent IIPs: IPF and COP.

Idiopathic Pulmonary Fibrosis

As its name implies, the etiology of idiopathic pulmonary fibrosis (IPF) is uncertain, although it is thought to be autoimmune. IPF is a diagnosis of exclusion. It accounts for up to 50% of ILDs.

There are limited extrapulmonary manifestations of this disease, although clubbing may be seen in 50–60% of patients.

M = F, average age = 55 years, but it occurs in all age groups.

Smoking exacerbates the disease.

About 10% of patients may have low titers of ANA or RF which are acute phase reactions to the lung inflammation.

IPF, by definition, has the specific histopathologic findings of usual interstitial pneumonia (UIP).

IPF ranges from an early inflammatory stage, amenable to treatment, to an untreatable late fibrotic stage with severe restrictive disease, pulmonary hypertension, and cor pulmonale.

Early IPF is characterized by "leakiness" of the capillaries and alveolar wall (from damage to the capillary endothelial cells and the adjacent Type I alveolar epithelial cells). This leads to interstitial and alveolar edema, which ultimately causes intraalveolar hyaline membrane formation.

The fluid in the alveoli and in the interstitial edema has increased numbers of alveolar macrophages. These release cytokines and proinflammatory mediators (tumor necrosis factor [TNF], interleukin 8, and leukotriene B_4)—some of which attract neutrophils. This is reflected in BAL results of increased macrophages, neutrophils (PMNs = 20%), and eosinophils (2–4%). HRCT in early IPF shows a "ground-glass" pattern.

Late IPF leads to increasing alveolar-capillary permeability, desquamation of the alveolar wall, and fibrosis. Chest x-ray and HRCT show fibrosis with a honeycomb pattern.

Presentation: Consider IPF in a patient who presents with dyspnea, cough, dry mid-inspiratory "Velcro" crackles, and a diffuse interstitial process on chest x-ray.

Velcro crackles are loud and coarse. The crackles are mimicked when a Velcro® patch is opened. These crackles are different from the sounds of fine crackles that can be mimicked when hair is rubbed together.

Clubbing is common. See Table 3-6.

The chest x-ray changes correlate poorly with disease activity but generally show diffuse reticular or reticulonodular disease.

Like many ILDs, PFTs show a "restrictive intrathoracic" disease (low TLC, normal FEV_1/FVC, low DLCO). Know that, in IPF, a very low DLCO correlates with the presence of pulmonary arterial hypertension (and thus, poor prognosis).

Diagnostic workup of IPF includes: chest x-ray, HRCT (demonstrates "ground-glass" appearance in 1/3 of patients with true fibrosis), PFTs, ABG, and a functional assessment and oxygen requirements with exercise (e.g., 6-minute walk test).

When the diagnosis is in question because of an atypical presentation, perform lung biopsy to characterize the pathology of the x-ray abnormalities and to exclude cancer/infections/vasculitis—especially since empiric treatment with immunomodulators can cause serious harm in these conditions. Remember that UIP histology is consistent with IPF, although most diagnoses are now made with HRCT.

Definitely avoid lung biopsy if the patient has a negative environmental and drug history, is > 70 years of age, and has clubbing, coarse crackles, and honeycombed lungs. Honeycombed lungs suggest advanced disease that is not modifiable by immunomodulator.

Treatment: IPF progresses steadily to death without treatment. Some patients seem to respond favorably to treatment with corticosteroids. These are usually the patients with early IPF in which there is a suppressible inflammatory component. Recent studies combining corticosteroids with azathioprine or cyclophosphamide have not shown improved outcome. Current investigations using n-acetylcysteine and/or pirfenidone

Table 3-6: Occurrence of Clubbing

Clubbing is almost always seen with:	Clubbing is commonly seen with:	Clubbing is almost never seen with:
Advanced IPF	Cystic fibrosis	Emphysema
Asbestosis	Bronchiectasis	Sarcoidosis
	Lung cancer	

should be completed in the next year. Trials are ongoing to determine effective pharmacologic therapies for pulmonary artery hypertension complicating IPF.

The best tests for determining improvement in IPF is measurement of lung function, including lung volumes, DLCO, and ABGs with calculation of exercise-related A-a gradient. An objective improvement in response to corticosteroids, using these tests, is the best prognostic indicator available. (The ABIM emphasizes the less expensive exercise-related improvement in the A-a gradient.)

Cor pulmonale is treated symptomatically. Single-lung transplantation is an option for some late-IPF patients. Give IPF patients pneumococcal and influenza vaccines.

Organizing Pneumonia

Causes of Organizing Pneumonias

There are various types of organizing pneumonia that have the common finding of a chronic alveolitis.

50% of organizing pneumonia cases are idiopathic. The other 50% of cases are caused by/associated with the following:

- Inhalation of toxic fumes (e.g., smoke, paint aerosols, nylon flock fibers)
- Exposure to drugs (e.g., amiodarone, bleomycin, carbamazepine, minocycline, nitrofurantoin, phenytoin, penicillamine, sulfasalazine)
- Immunodeficiencies
- Lots of infections (e.g., respiratory viruses, *Mycoplasma*, *Pneumocystis*, GNRs)
- Connective tissue disorders (e.g., rheumatoid arthritis)
- Myelodysplasia
- Radiation

Cryptogenic Organizing Pneumonia (COP)

Cryptogenic organizing pneumonia (COP) is an idiopathic form of organizing pneumonia. Previously called idiopathic bronchiolitis obliterans organizing pneumonia (BOOP), it is a very specific entity with an unknown cause. COP is a bronchiolitis (inflammation of the small airways) and a chronic alveolitis (the organizing pneumonia). The bronchiolitis causes a proliferation of granulation tissue within the small airways and alveolar ducts.

Table 3-7: Comparison of COP/BOOP and IPF

	COP/BOOP	IPF
Signs	Acutely ill appearing; Fever	Not acutely ill No fever
Onset of symptoms	Days to weeks	Very slow— at least 6 months
Chest x-ray	Patchy infiltrates	Diffuse infiltrates

Consider COP in a patient with an insidious onset (weeks to 1–2 months) of cough, fever, dyspnea, malaise, and myalgias, possibly with 1 of the above risk factors. Often, patients have had multiple courses of antibiotics without effect. Rales are common. Chest x-ray shows some interstitial disease, bronchial thickening, and patchy bilateral alveolar infiltrate. Pulmonary function testing demonstrates a restrictive pattern with a reduced diffusion capacity.

You must differentiate COP from IPF because, contrary to IPF, COP has a good prognosis and response to steroids. To differentiate IPF from COP, know that IPF is even more insidious in onset (> 6 months), and the patients do not have fever (Table 3-7). Lung biopsy is the definitive means of diagnosing COP.

Corticosteroids are the treatment of choice for COP. COP does not respond to antibiotics. Slowly taper corticosteroids over ~ 6–12 months because exacerbations can occur with tapering that is too rapid. Corticosteroid-sparing treatment can be used—typically cyclophosphamide.

OTHER CAUSES OF ILD

Overview

Other causes of ILD and diffuse lung disease are:

- Collagen-vascular diseases
- Sarcoidosis
- Langerhans cell histiocytosis
- Lymphangioleiomyomatosis
- Vasculitides causing ILD: granulomatosis with polyangiitis (previously Wegener's), lymphomatoid, Churg-Strauss, bronchocentric, and PAN
- Eosinophilic ILDs: eosinophilic pneumonia, ABPA
- Alveolar proteinosis
- Idiopathic pulmonary hemosiderosis
- Goodpasture syndrome

Collagen Vascular Diseases and ILD

Rheumatoid arthritis (RA)—more than 1/3 of patients with RA get ILD! The most common lung problem in RA is pleurisy (with or without pleural effusion). Pleural effusions are exudative and can have uniquely very low glucose levels with pseudochylous findings. (See Pleural Effusions on page 3-41.) Occasionally, these patients have necrobiotic nodules—usually in the upper lung zones. ILD can also be due to a complication of gold and methotrexate treatment in the RA patients, while COP rarely results from penicillamine treatment.

Systemic lupus erythematosus (SLE) also causes painful pleuritis +/– effusion but additionally causes diffuse atelectasis and sometimes diaphragmatic weakness—and therefore orthopneic dyspnea that is out of proportion to the chest x-ray findings. However, the x-ray may show elevated diaphragms. SLE also occasionally causes hemoptysis similar to that in idiopathic

QuickQuiz

- What is the best test to document improvement of treated patients with IPF?
- Characterize the differences in presentation between IPF and COP.
- What finding in a pleural effusion may be helpful in distinguishing rheumatoid arthritis as an etiology?
- In what pulmonary disease is pulmonary hypertension out of proportion to the amount of pulmonary disease? What causes this?
- What PFT results are associated with sarcoidosis?

pulmonary hemosiderosis. SLE affects both lung and pleura more frequently than any other collagen vascular disease (60%), while systemic sclerosis (scleroderma) affects the lung alone more than any other (100%, but no pleural changes!).

Systemic sclerosis has 2 major lung effects:

1) Interstitial fibrosis
2) Intimal proliferation

It is this intimal proliferation in the pulmonary artery that causes pulmonary hypertension out of proportion to the pulmonary disease. So, it is not the ILD but the intimal proliferation that causes the real pulmonary problem in systemic sclerosis patients. Isolated pulmonary hypertension (without interstitial lung disease) occurs more often in patients with limited cutaneous sclerosis (previously CREST syndrome) than in patients with diffuse systemic sclerosis. Patients with systemic sclerosis are more susceptible to pneumonia. Chronic aspiration and gastroesophageal reflux are common and may have some relationship to the development of pulmonary fibrosis.

Both RA and systemic sclerosis are associated with exposure to silica, and both have an increased incidence of bronchogenic carcinoma!

Sjögren's causes desiccation of the airways and is also associated with lymphocytic interstitial pneumonia (LIP).

Table 3-8: Sarcoidosis Staging

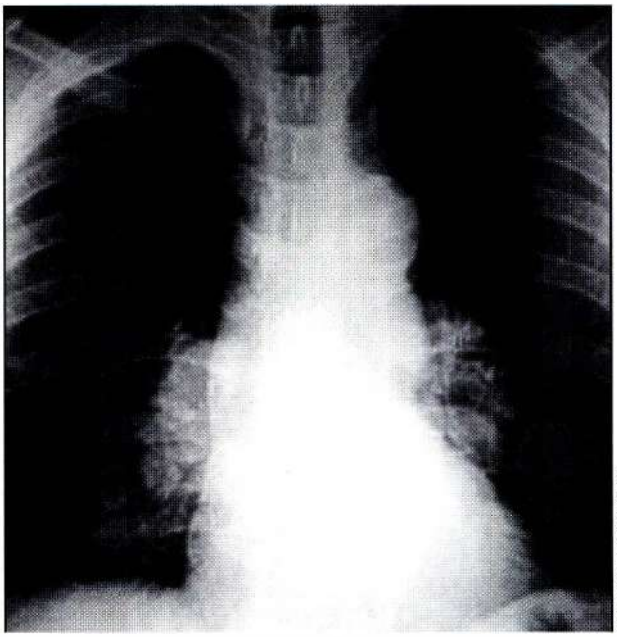
Stage	Chest X-ray Findings
0	Clear
I	Bilateral hilar adenopathy
II	Adenopathy + parenchymal infiltrates
III	Diffuse parenchymal infiltrates
IV	Fibrosis, bullae, cavities

Sarcoidosis

Sarcoidosis is a multisystem disease. Chest x-ray findings are variable. Usually, there is bilateral hilar and/or mediastinal adenopathy +/– reticulonodular or alveolar infiltrates. PFTs may either be normal or show restrictive +/– obstructive mechanics. The radiographic staging of sarcoidosis (Table 3-8) illustrates the interesting point that hilar adenopathy disappears as the disease progresses (Image 3-10 and Image 3-11).

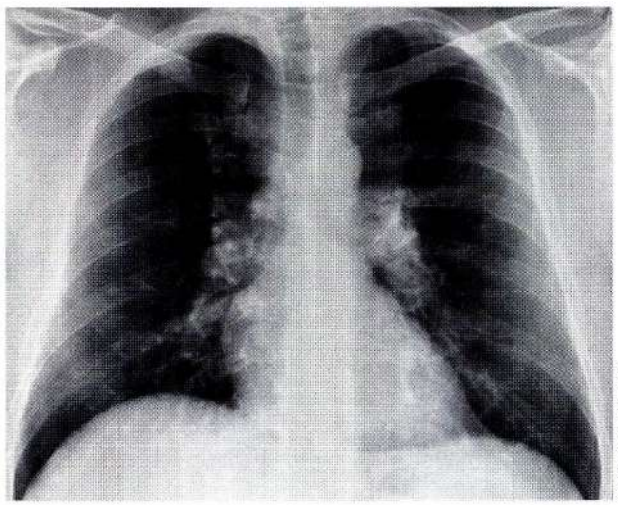
Serum angiotensin-converting enzyme (ACE) level is nonspecific, but it may be useful for monitoring progression of disease. A new elevation in ACE levels may be useful in determining if the disease is once again active. Hypercalcemia, hypercalciuria, and hypergammaglobulinemia are common.

Sarcoidosis is a diagnosis of exclusion. A positive BAL shows an increased number of lymphocytes, with a



Courtesy of Vinay Mallesh wari, MD

Image 3-10: PA chest: Stage I sarcoidosis



Courtesy of Thomas Ray, MD

Image 3-11: PA chest: Stage II sarcoidosis

helper/suppressor ratio of > 4:1 (hypersensitivity pneumonitis has a ratio of < 1). It is imperative to exclude the other granulomatous diseases, including hypersensitivity pneumonitis, berylliosis, and infectious diseases caused by mycobacteria and fungi. Material for histological exam should be cultured and examined for organisms.

While ensuring no organisms are present and cultures are negative, fiberoptic bronchoscopy with transbronchial or bronchial wall biopsies showing noncaseating granulomas is the best method for diagnosis of sarcoidosis. Endobronchial ultrasound sampling (EBUS) of lymphadenopathy is also useful.

Erythema nodosum is an associated skin lesion that denotes a good prognosis! This form of sarcoidosis is called Löfgren syndrome. When sarcoid presents in a classic form such as Löfgren's, biopsy confirmation is not necessary.

Treatment: Overall, 75% of sarcoid patients recover without treatment. It rarely progresses to pulmonary fibrosis or pulmonary hypertension. Treat only severe disease. There is no set regimen. Corticosteroids have not been proven to induce remissions in sarcoidosis, although they do decrease the symptoms, and PFTs improve. Inhaled corticosteroids decrease the respiratory symptoms and may be used instead of systemic corticosteroids if the disease is primarily in the bronchi.

Indication for systemic corticosteroids is persistent hypercalcemia and evidence of involvement of other organs:

- Eyes (conjunctivitis, uveitis)
- Heart (conduction abnormalities)
- CNS (signs of optic nerve or optic chiasm involvement)
- Lungs (severe pulmonary symptoms)
- Skin (severe skin lesions)

Other medications available include hydroxychloroquine (Plaquenil®), infliximab (Remicade®), methotrexate, and thalidomide.

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) causes characteristic lytic bone lesions (eosinophilic granulomas). Langerhans cells are the predominant cell form. LCH sometimes involves the posterior pituitary—leading to diabetes insipidus.

In the lung, it causes interstitial changes and small cystic spaces in the upper lung fields, both of which are visible on chest x-ray, giving a honeycomb appearance (as seen with other fibrotic ILDs).

Virtually all affected patients are smokers and M > F. Patients have an interstitial disease with normal or increased lung volume. (Most ILDs have decreased lung volume.)

10% of patients initially present with a pneumothorax, and up to 50% of these patients get a pneumothorax sometime in the course of their illness.

Diagnose by finding Langerhans cells on lung biopsy or BAL.

Treatment: Stop smoking! Many do a trial of steroids, although drugs generally do not help. Occasionally there is spontaneous resolution.

Again: Langerhans cell histiocytosis = pneumothorax, smoking.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) occurs almost exclusively in premenopausal women. It is the result of immature smooth muscle proliferation in the lymphatic, vascular, and alveolar wall/peribronchial structures. This proliferation results in the formation of constrictions and cysts in these structures. There is a genetic relationship to tuberous sclerosis.

Chest x-ray in LAM typically shows honeycombing (small cystic spaces) spread diffusely throughout the lung (in contrast to upper lung fields seen in Langerhans cell histiocytosis above).

Thoracic and abdominal lymphatics are often involved, resulting in chylous pleural effusions—with triglycerides > 110 mg/dL +/– chylomicrons in the fluid. Pneumothorax may occur.

Oophorectomy with progestin treatment is often recommended. Lung transplantation may be done, but the process may recur in the transplanted lung.

Again: LAM = premenopausal, pneumothorax, chylous effusion (TG > 110 +/– chylomicrons), and is associated with tuberous sclerosis.

Vasculitides that Cause ILD

Granulomatosis with Polyangiitis (GPA)

Previously termed "Wegener granulomatosis," GPA is a vasculitis that involves all of the following:

- Affects the upper respiratory tract and paranasal sinuses
- Causes a granulomatous pulmonary vasculitis with large (sometimes cavitary) nodules
- Causes a necrotizing glomerulonephritis

Sometimes, it is limited just to the lungs (called "limited" GPA).

The ANCA test (antineutrophil cytoplasmic antibody—thought to be a destructive autoantibody) is often used as an adjunctive test. It is ~ 90% sensitive and 90% specific. When positive in a patient with GPA, it is virtually always c-ANCA (96%).

The additional important positive antibody is anti-PR3.

Quick Quiz

- What are the indications for treatment of sarcoid with corticosteroids?
- What is a potential lung complication of lymphangioleiomyomatosis?
- Characterize the typical presentation of a patient with granulomatosis with polyangiitis.
- Which vasculitis is c-ANCA+ and anti-PR3+?
- An asthma patient with worsening symptoms and peripheral eosinophilia makes you think of what diseases?
- Churg-Strauss vasculitis is associated with what medications?
- Which hepatitis virus is associated with PAN?
- How does PAN present?
- What do you do to diagnose PAN?

Confirm diagnosis from either a biopsy of the nasal membrane or a lung biopsy. A kidney biopsy usually is not part of the diagnostic workup because it may not show the granulomas, is much more invasive, and doesn't allow for differentiation between forms of vasculitis.

Treatment for GPA is aggressive because, without treatment, most patients die within 2 years. To induce remission, use cyclophosphamide + corticosteroids—usually for a minimum of 4–6 months.

Methotrexate and azathioprine are typically used for maintenance therapy.

Again: kidney, lungs, and sinuses. Consider GPA in any patient who presents with a purulent nasal discharge, epistaxis, and/or signs of a glomerulonephritis with hematuria. The patient typically is not dyspneic and may not have a cough or hemoptysis. If you see a similar presentation but ANCA-negative, think anti-glomerular basement membrane disease.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis: 50% progress to histiocytic lymphoma. It is similar to GPA but has no upper respiratory lesions and only rarely affects the kidney. Although the principal site is the lungs, lymphomatoid granulomatosis less often has skin, CNS, and peripheral nerve involvement. Biopsy shows a mononuclear angiocentric necrotic vasculitis.

It is usually treated with corticosteroids and cyclophosphamide.

Churg-Strauss Syndrome

Churg-Strauss syndrome (CSS; also called eosinophilic granulomatosis with polyangiitis) is a necrotizing, small-vessel vasculitis with eosinophil infiltration. It can affect multiple systems and also cause neuropathy. It does not affect the sinuses.

Patients typically present with preexisting asthma and have eosinophilia in up to 80% of the WBCs. Think about CSS (and ABPA) when assessing a progressively worsening asthmatic.

CSS may be unmasked by treating the asthmatic patient with a leukotriene-receptor modifier while weaning oral corticosteroids.

Treatment of CSS is mainly with systemic corticosteroids. Refractory cases are treated with cyclophosphamide, azathioprine, or high-dose IV immune globulin.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis causes an ILD in which there are masses of granulomata in the walls and surrounding tissues of airways.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is the only one of this group that is not granulomatous. It is a systemic, necrotizing nongranulomatous vasculitis of small and medium-size arteries that can result in characteristic arterial aneurysmal dilatations.

The most common organs affected are intestinal mesentery, heart, skin, kidneys, testes, and peripheral nerves. PAN usually spares the lungs!

Many cases are associated with chronic hepatitis B infection.

Think about PAN in the patient with +HBsAg who presents with constitutional symptoms (anorexia, fever, malaise, weight loss) and any combination of:

- skin nodules,
- episodic abdominal pain, and
- tender testicles.

Lab studies show increased ESR and anemia of inflammation +/– p-ANCA and anti-myeloperoxidase.

Diagnosis rests on the demonstration of non-granulomatous vasculitis in the tissues of the lung, kidneys, skin, or testes (ouch!). If biopsy is nondiagnostic or tissue is unapproachable, angiogram that demonstrates aneurysms in small and medium-size vessels is enough for diagnosis.

Remember that necrotizing granulomas are associated with GPA, and granulomas with eosinophils in the tissue are associated with Churg-Strauss.

Treatment for PAN is combination cyclophosphamide and prednisone +/– treatment for HBV.

Eosinophilic ILDs

Overview

The eosinophilic ILDs are eosinophilic pneumonia, ABPA, and Churg-Strauss syndrome (discussed earlier). Remember that asthma, hypereosinophilic syndrome, certain parasite infections, and some drugs are non-ILD causes of peripheral eosinophilia.

Eosinophilic Pneumonias

In all types of eosinophilic pneumonia, you must rule out drugs and parasites as the cause. Eosinophilic pneumonia consists of 3 types:

1) **Löeffler syndrome**: This disease is usually self-limited and occurs as a result of transpulmonary passage of helminthic larvae early in their life cycle. Usual cause is *Ascaris,* but other helminthes—*Strongyloides* or hookworms—are less common causes. Generally found incidentally. Minimal respiratory symptoms. These patients have migratory peripheral infiltrates on chest x-ray. Eosinophils are in the blood and sputum. Treatment: Typically, no specific lung treatment is necessary. If severe, then prescribe corticosteroids. Antihelminthic therapy (albendazole, mebendazole, or pyrantel pamoate) also may be appropriate.
2) **Acute eosinophilic pneumonia**: an acute, febrile, pulmonary illness with hypoxemic respiratory failure resembling ARDS. Unknown cause. Rule out infection. BAL shows large number of eosinophils. Treat with ventilatory support and systemic glucocorticoids.
3) **Chronic eosinophilic pneumonia**: the most common eosinophilic pneumonia in the U.S.; usually occurs in middle-aged women. The illness is subacute with cough, wheezing, night sweats, and low-grade fever. 50% have a history of asthma. The chest x-ray shows bilateral, very peripheral infiltrates in a pattern that is the photographic negative of pulmonary edema. (Instead of a butterfly pattern of opacification, the chest x-ray butterfly pattern looks dark.) Increased number of eosinophils in the BAL, but 1/3 have no peripheral eosinophils. Very high ESR. Treat with long-term steroids. Relapses are common.

Allergic Bronchopulmonary Aspergillosis

As the term suggests, allergic bronchopulmonary aspergillosis (ABPA) is caused by an allergic reaction to *Aspergillus* that results in chronic cough, mucus plugging, and recurrent pulmonary infiltrates, with eosinophilia in some asthmatics and patients with CF.

Diagnosis: Think about ABPA in patients with either asthma or CF who have uncontrolled disease. Look for eosinophilia and *Aspergillus* in a sputum culture. In asthmatics, the clinical history may be one of recurrent exacerbations that improve with prednisone, with return of wheezing, coughing, and dyspnea shortly after stopping steroids.

Chest x-ray and HRCT show central mucus impaction and bronchiectasis causing a "fingers-in-glove" appearing central infiltrate. Sputum may show branching hyphae (nonspecific). If there is only lung eosinophilia with peripheral eosinophilia, consider a chronic eosinophilic pneumonia instead.

Screen for ABPA using the *Aspergillus* antigen skin prick test. If the skin test is positive, then work up the patient further by measuring a total IgE (usually > 1,000 IU/mL) and *Aspergillus* IgG and IgE. These antibody levels, plus the clinical history and other lab/x-ray data, can be reviewed in consideration of some major and minor criteria for ABPA (which you do not need to know for exams). Just know when to suspect ABPA and that diagnosis starts with the pin prick test.

Treat active ABPA with itraconazole and oral steroids. In most patients, the addition of itraconazole reduces the necessary duration of steroids, thus reducing long-term side effects.

Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis (IPH) causes intermittent pulmonary hemorrhage. DLCO can be elevated. IPH is similar to Goodpasture's, except IPH does not affect the kidneys. Macrophages are filled with hemosiderin. Fe deficiency anemia occurs. It may remit in young patients, but it is unrelenting in adults. Remember that pulmonary hemorrhage also occurs in SLE.

DIAGNOSIS OF ILDs

PFTs in ILD patients classically show a "restrictive" pattern. This means normal airway flow rates, but lung volumes are decreased. There is increased lung stiffness from increased elastic recoil (increased by pulmonary fibrosis; decreased in emphysema). A chest x-ray with diffuse interstitial infiltrates is often the 1st suggestion of disease, but it correlates poorly with severity of disease. The HRCT is integral to the workup of ILD.

X-ray clues suggesting cause of ILD:

- Asbestosis: lower lung field predominance of infiltrates +/– pleural calcifications and plaques
- Silicosis: hilar eggshell calcifications
- Sarcoidosis: bilateral symmetrical hilar and paratracheal lymphadenopathy
- LAM: ILD with a pneumothorax in a premenopausal woman; may also have chylous effusions and characteristic nodules and cysts on CT

Bronchoscopy with transbronchial biopsy is the usual method for confirming the diagnosis and establishing the etiology and severity of ILD. However, the tissue specimens are small, and the best use of this technique is to diagnose and rule out the following: diffuse infections, diffuse lymphangitic spread of carcinoma, and sarcoidosis.

Quick Quiz

- Describe the differences in the presentations of Löeffler syndrome, acute eosinophilic pneumonia, and chronic eosinophilic pneumonia.
- What is the workup of the uncontrolled asthmatic whom you suspect has ABPA?
- Which organisms are associated with chronic pneumonia in patients with pulmonary alveolar proteinosis?
- Name 4 autoimmune diseases associated with pulmonary hemorrhage.

Thoracoscopic biopsy (through the chest wall) and lung biopsy generally give the best yield for interstitial pneumonitis.

Remember that the DLCO is the 1st test to become abnormal in ILD, so this parameter should be followed in patients receiving potentially lung-toxic drugs; e.g., amiodarone and chemotherapy.

NONINTERSTITIAL DIFFUSE LUNG DISEASES

Alveolar Proteinosis

Alveolar proteinosis is usually more alveolar than interstitial. There are defective alveolar macrophages causing a buildup of pulmonary surfactant.

Consider this in males, ages 30–50 years, who present with an indolent but progressive nonproductive cough, dyspnea with exertion, weight loss, and occasional fever. Patients may be hypoxemic from a large R-to-L shunt with secondary polycythemia.

HRCT shows ground-glass appearance (similar to early IPF), along with thickened interlobular structures.

Diagnosis is usually confirmed with lung biopsy, but transbronchial biopsy or BAL is also acceptable.

Treatment: Smoking cessation is extremely important. If severe, do a whole lung lavage under general anesthesia. GM-CSF may restore proper function to the alveolar macrophages. Nonresolving pneumonias in these patients are most likely to be caused by *Nocardia*, mycobacteria, or endemic fungi.

Anti-GBM Disease

Anti-GBM disease can present as a pulmonary-renal disease, and a certain subset may present with diffuse pulmonary hemorrhage (Goodpasture syndrome). This is discussed in Nephrology, Book 2.

PULMONARY HEMORRHAGE

Immunologic lung diseases that cause pulmonary hemorrhage:

- Goodpasture syndrome
- SLE
- Granulomatosis with polyangiitis (previously Wegener's)
- IPH

Cardiopulmonary diseases that cause pulmonary hemorrhage:

- Pulmonary embolism
- Pulmonary AV malformations
- Aortic aneurysm
- Pulmonary hypertension
- Septic emboli
- Mitral stenosis

Other causes of diffuse alveolar hemorrhage and/or pulmonary hemorrhage include:

- Bronchitis
- Bronchiectasis
- Aspergilloma
- Tuberculosis
- Lung abscess
- Severe thrombocytopenia or coagulopathy
- Aspergillosis, zygomycosis (mucormycosis), and other acute fungal infections
- Chemotherapy and bone marrow transplantation

PULMONARY HYPERTENSION

OVERVIEW

Definition of pulmonary hypertension (PH): The mean pulmonary artery pressure is ≥ 25 mmHg at rest and ≥ 30 mmHg with exercise.

The World Health Organization (WHO) categorizes PH into 5 groups based on etiology:

- **Group 1 PAH** (pulmonary arterial hypertension) is composed of both idiopathic PAH (IPAH; previously primary pulmonary hypertension) and secondary PAH caused by diseases or toxins that damage small muscular pulmonary arterioles, such as collagen vascular diseases, intracardiac shunts, portal hypertension, HIV, and appetite suppressants/stimulants.
- **Group 2 PH** is due to left-sided heart disease (atria, ventricle, valve).
- **Group 3 PH** is associated with disorders of the respiratory system (ILD, COPD) or hypoxemia (e.g., sleep apnea).
- **Group 4 PH** is caused by chronic venous thromboembolic disease.
- **Group 5 PH** has unclear multifactorial causes, inflammation, mechanical obstruction, or extrinsic compression of the pulmonary vasculature.

Note that group 1 is pulmonary arterial hypertension (PAH); that is, PH caused by factors affecting the pulmonary arteries. Groups 2–5 are pulmonary hypertension (PH).

PH affects the entire vasculature of the lung, including the endothelium, smooth muscle, and even the extracellular matrix. This results in an obliterative process in which the pulmonary vessels become more tortuous and close off.

PHYSICAL FINDINGS OF PH

Physical exam: loud 2nd heart sound (P_2), tricuspid regurgitation, RV heave.

Tricuspid regurgitation is common with pulmonary hypertension and is due to the dilation of the right ventricle (holosystolic murmur along the LLSB—increases with inspiration—and a parasternal heave). The tricuspid regurgitation and right ventricular failure present as JVD with large *v* waves, liver pulsations, and lower extremity edema.

DIAGNOSIS OF PH

Chest x-ray may clue you in to an undiagnosed case—significant PH manifests on the chest x-ray as enlargement of the central pulmonary arteries with attenuation of the peripheral vessels, resulting in "oligemic," darker lung fields on chest x-ray.

ECG may show right axis deviation from RVH. The 1st tests to order when you suspect PH are ECG and an echocardiogram.

The echocardiogram is useful in the workup of PH to:

- Estimate pulmonary artery pressure
- Evaluate right ventricular size, wall thickness, and systolic motion
- Evaluate right atrial size
- Evaluate the presence of a R-to-L shunt through a patent foramen ovale (Usually an agitated saline infusion is given—sometimes termed a "bubble echo.")
- Rule out cardiac pathology

Right heart catheterization is then used to follow up PH diagnosed by echocardiogram. For a positive diagnosis, mean pulmonary artery pressure is, as stated earlier, ≥ 25 mmHg at rest and ≥ 30 mmHg with exercise.

Additional findings that support the diagnosis of group 1 PAH include:

- Pulmonary artery diastolic pressure (PADP) greater than PCWP
- Pulmonary artery mean pressure > 10 mmHg more than PCWP
- Pulmonary vascular resistance > 120 dynes-sec-cm^{-5}

Remember that most pulmonary function parameters are normal in PH, but the DLCO decreases. Know that a very low DLCO is associated with a poor prognosis in patients with PH.

TREATMENT

Exercise, Anticoagulants, Diuretics, and Oxygen

Exercise appears to improve the functional class of patients greatly but does not change the hemodynamics.

Give anticoagulants for those with IPAH (part of group 1) and for those with group 4 PH. Use warfarin titrated to an INR of 2.0.

Diuretics are recommended for fluid retention.

Oxygen helps symptoms in group 3 and also helps correct hypoxic vasoconstriction. Give oxygen to all who meet the criteria as discussed in COPD (page 3-17). Occasionally, single-lung transplantation or heart-lung transplantation are long-term solutions.

Vasodilators in PH

Pharmacologic agents for reducing pulmonary hypertension are intended for group 1 PAH, and most of the following have been tested only with IPAH.

Vasodilators — Endothelin Receptor Antagonists

Bosentan (Tracleer®) is an oral endothelin receptor antagonist. Endothelin is a polypeptide released by injured endothelium and is elevated in patients with PH and heart failure.

Ambrisentan and sitaxsentan are oral medications that are selective Type A endothelin receptor antagonists.

Vasodilators — Calcium Channel Blockers

The pulmonary vasodilators of choice are the calcium channel blockers—especially nifedipine, amlodipine, and diltiazem. Use amlodipine especially if intolerant of other calcium channel blockers and use diltiazem especially if tachycardic.

Short-acting pulmonary vasodilators, such as inhaled nitric oxide and IV adenosine, have only a transient effect. These are used in the workup of IPAH, testing for vasoreactivity.

Vasodilators — Prostanoids

Continuous IV (pump) infusion of epoprostenol (prostacyclin) has now been approved and is recommended as 1st line therapy for NYHA Class IV disease. It has shown good results for functional Class III also, but there are many other agents to choose from for Class III disease.

Know that patients getting epoprostenol exhibit tachyphylaxis and require slow "ramp-up" of the dosing over time.

Iloprost, an inhaled vasodilator, helps with symptoms, but improvement in survival has not been demonstrated.

Quick Quiz

- What common physical exam findings are seen in PH?
- What are the 1st tests you order in the workup of PH? What follow-up test is done if the 1st tests are suggestive?
- What test of lung function, when low, is associated with a poor prognosis in pulmonary hypertension?
- What is the usual cause of pulmonary emboli in hospitalized patients?
- Characterize the clinical findings seen with a massive PE.
- What symptoms and physical exam findings are seen more with a submassive PE?
- What is the 1st step in evaluating a patient with possible pulmonary embolism?

Vasodilators — PDE Inhibitors

Sildenafil (Viagra®, Revatio®) inhibits cyclic guanosine monophosphate (cGMP) phosphodiesterase type 5 (PDE-5) in smooth muscle of pulmonary vasculature, where PDE-5 is responsible for the degradation of cGMP. Increased cGMP concentration results in pulmonary vasculature relaxation, and vasodilation in the pulmonary bed may occur.

Vasodilators — Combination Therapy

Usually only 1 vasodilator is used. There is very little experience with combination therapy. Trials are ongoing.

VENOUS THROMBOEMBOLIC DISEASE

OVERVIEW

Venous thromboembolic (VTE) disease is the term that includes both deep venous thromboses (DVT) and pulmonary emboli (PE). DVT and PE are considered different parts of the same disease process; the majority of medically significant PEs are from DVT in lower extremities—virtually all from above the knee (ileofemoral area). Most calf vein thromboses do not embolize.

Other sources of PE are upper extremity, internal jugular, and subclavian thrombi. Usually the source for the upper body thrombi are IV catheters, especially PICC lines.

PE is the 3rd most common cardiovascular cause of death (after ischemic heart disease and stroke); 11% die within 1 hour of onset of symptoms. Despite our knowledge of the cause and effect of PE, the incidence has not declined. In hospitalized patients, inadequate VTE prophylaxis is the usual cause of PEs.

The sequence of events in a medically significant PE:

1) Embolic obstruction of a pulmonary artery
2) Increased alveolar dead space—ventilated but not perfused
3) Vascular constriction
4) Loss of alveolar surfactant with atelectasis—V/Q mismatch + shunt areas

These events result in an increased resistance to blood flow → increased pulmonary artery pressure → increased right ventricular work. The pulmonary circulatory system is highly compliant and therefore inherently has high capacitance. Because of this capability, up to 50% of the lung vasculature can be blocked before increased workload on the right ventricle becomes significant in a normal individual. Massive PE occurs when > 2/3 of the functioning lung is involved.

Note that lung-tissue infarction is rare (< 10%) because the tissue is perfused by multiple sources, including the bronchial artery, the PA, and back-diffusion through the pulmonary venous system.

DIAGNOSIS OF PE

Overview

There are many diagnostic tests that are used in the workup of DVT and PE. We will go over clinical findings of PE first, then go over all the diagnostic tests, and then have a brief (whew!) discussion on working up PE that brings it all together.

Physical Findings in PE

Clinical findings are varied and usually nonspecific, but there is a suggestive set of signs and symptoms. Sudden onset of dyspnea and tachypnea are most common. Hemoptysis and pleurisy indicate associated lung infarction.

PE are divided into 3 groups: massive, submassive, and low-risk. The definitions are important for determining prognosis and for ascertaining which patients should be given thrombolytics:

1) **Massive PE** is defined as having sustained hypotension, pulselessness, or persistent, profound, bradycardia.
2) **Submassive PE** is defined as having normal blood pressure but evidence of RV dysfunction. It often has elevated troponins.
3) **Low-risk PE** is defined as resulting in normal blood pressure and normal biomarkers.

The Wells prediction rules determine the pretest probability of PE based on clinical findings and medical history. As we will discuss later, assessing these (or similar verified pretest probability rules) is the 1st step of the diagnostic workup for PE (Table 3-9 and Table 3-10).

Malignancy is present in 50% of patients with phlegmasia cerulea dolens (an unusual type of DVT associated with additional thrombosis of collateral veins, which causes massive edema, pain, and blue discoloration due to arterial insufficiency). Malignancy also is suggested by superficial migratory thrombophlebitis, DVT resistant to anticoagulants, and thrombophlebitis in unusual places such as the arms and trunk.

Table 3-9: Wells Criteria for DVT

Criteria	Score
Active cancer (current Tx or palliation, or Tx within last 6 months)	1
Recent immobilization of lower extremities (plaster cast, paralysis, paresis)	1
Recently bedridden > 3 days or major surgery with general/regional anesthesia	1
Localized tenderness along the distribution of deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral nonvaricose superficial veins	1
Alternative diagnosis is at least as likely as DVT	–2
3 or higher = high probability of DVT 1–2 = moderate probability 0 = low probability	
Note: If symptoms are in both legs, use the more symptomatic one.	

Table 3-10: Wells Criteria for PE

Criteria	Score
Clinical signs of DVT	3.0
An alternative diagnosis is less likely than PE	3.0
Heart rate > 100 beats/minute	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy (being treated, treated in the past 6 months, or palliative)	1.0
> 6 = high probability 2–6 = moderate probability 0–1 = low probability of PE	

Review of Lab and Radiological Tests for PE

Here we discuss 11 tests and how they are used to diagnose PE and determine the patient's prognosis. In the next topic we put it all together and cover how PE actually is diagnosed.

These are the 11 tests. Know all of them:

1) ABGs
2) Chest x-ray
3) ECG
4) CTPA (using hCT)
5) V/Q scan
6) Venous studies
7) D-dimer
8) Pulmonary angiography
9) MRI/MRA
10) Echocardiography
11) Serum troponins

Draw an **arterial blood gas** (ABG) immediately. It is used to determine the A-a gradient and evaluate for hypoxemia. Analysis of data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) indicates that neither ABG nor A-a gradient is specific enough to be useful in the diagnosis or triaging of patients with pulmonary embolism.

Let's see why this is. An A-a gradient > 20 mmHg is seen in 89% of patients with a PE (pretty good sensitivity), but many people with cardiopulmonary disease have an increased gradient—and those hyperventilating or on O_2 may have an artificially low A-a gradient (low specificity). So, only in the absence of cardiopulmonary disease and if the patient is not on O_2 and is not hyperventilating is there a satisfactory specificity for diagnosing a PE solely from an elevated gradient.

Hypoxemia, after a large PE, is due to many factors—especially V/Q mismatch, R-to-L shunt, and dead space—although dead space must be very large to cause hypoxia. The V/Q mismatch is from decreased perfusion of ventilated areas. The shunt is from perfusion of poorly ventilated areas that occur as a side effect of PE (secondary to bronchoconstrictive mediators and atelectasis). Secondary right ventricular failure can also contribute to the V/Q mismatch.

Chest x-ray helps exclude other causes in the differential (pneumonia, pneumothorax). Chest x-rays are commonly either normal (12%) or nonspecific (infiltrate, effusion, atelectasis). Even so, a PE is suggested by:

- Pulmonary infiltrate with a normal WBC count on peripheral smear
- Pulmonary consolidation associated with an elevated ipsilateral hemidiaphragm (from atelectasis)
- "Hampton hump"—a pleural-based, wedge-shaped defect from infarction just above the diaphragm

QuickQuiz

- What happens to the A-a gradient in most patients with PE?
- What is the imaging of choice to diagnose pulmonary embolism in the nonpregnant patient with normal renal function and no dye allergy?
- In a low clinical probability scenario, what would a normal V/Q scan imply with regards to the probability of a pulmonary embolism?
- In a patient with a low clinical probability of venous thromboembolism, what is the significance of a negative D-dimer? A positive one?

- Oligemia (Westermark sign; rarely seen)—a lack of vascular markings in the area downstream of the embolus
- Large right descending pulmonary artery (Palla sign)

ECG: The only specific (but not sensitive) heart/ECG changes seen with PE are tachycardia and right ventricle strain from acute cor pulmonale. On ECG, right heart strain = S1Q3T3; that is, the S wave is large in I, the Q wave is large in III, and the T wave is inverted in III. This is not seen often, but it tends to be questioned about on exams. ECG also helps rule out MI.

CT pulmonary angiogram (CTPA; page 3-1). CTPA is the current standard for primary, noninvasive imaging to diagnose PE. It is especially required when the patient is pregnant or has cardiopulmonary problems that might obscure the results of the V/Q scan.

In the setting of chronic venous thromboembolic disease as a cause for recurrent PE, the V/Q scan is preferred over CTPA.

Ventilation/Perfusion lung scan remains useful in obese patients, in those with iodine allergy, and in patients with renal insufficiency when contrast dye is undesirable. The V/Q scan is the test of choice for diagnosis of recurrent PE due to chronic venous thromboembolic disease.

Normal: A normal chest x-ray plus a normal V/Q scan is associated with a very low risk of PE. When coupled with a low clinical probability, a normal V/Q scan essentially eliminates the diagnosis of PE.

Low-probability and moderate-probability scans are considered indeterminate because these patients have a 14–40% chance of PE.

Moderate-probability scans consist of subsegmental perfusion defects or matched ventilation and perfusion defects. A chest x-ray finding of an infiltrate in the area of perfusion defect indicates the same risk. If clinical suspicion of PE is low, no further testing is necessary. If it is high, do a pulmonary arteriogram or U/S of the lower extremities.

High-probability scans occur in 2 situations:

1) ≥ 2 segmental or larger perfusion defects are present with a normal ventilation study.
2) The perfusion defect is much larger than the ventilation defect.

The trouble with V/Q scans is that large numbers come back as low-probability/indeterminate. You greatly improve accuracy of the above scans by factoring in clinical probability of a PE. For instance:

- About 30% of patients with a low-probability scan have a PE; but with a low clinical probability, this rate drops to 2%! And with a high clinical probability, it jumps to 40%.
- About 85% of patients with a high-probability scan have a PE; but with a high clinical probability, this rate jumps to 96%! And with a low clinical probability, it plummets to 6%.

Determining the probability for PE (by means of verified criteria such as Wells) is included as the 1st step of the diagnostic workup.

Venous studies: Determining the existence of DVT of the lower extremities is important in diagnosing and preventing PE.

Note that the current trend is to label venous thrombosis in the calf as simply "calf vein thrombosis" rather than DVT—because these clots do not carry the same morbidity as the more proximal thromboses (i.e., DVT).

Duplex ultrasonography combines real-time, B-mode ultrasonography, which visualizes the vessel with Doppler flow detection, with looking for compressibility of vessel and flow. This test is reliable only in symptomatic patients being evaluated for their 1st DVT by an experienced operator (operator-dependent). In these patients, the sensitivity is 93%, while the specificity is 98%. It is poor for detecting distal DVT (because the vessels are hard to visualize) and abdominopelvic thrombi (from which most cases of PE arise).

hCT is better than ultrasound for detecting thrombosed vessels in the abdomen and pelvis. Some centers offer a "PE protocol" where they use some form of hCT technology to scan the lower extremity and lung vasculature to look for PE and DVT simultaneously.

D-dimer testing has become more sensitive and more useful. Used with any 1 of the above noninvasive tests, it increases the negative predictive value of the test. A negative D-dimer in a low-risk patient excludes DVT/PE as a diagnosis.

Because of the poor specificity, the D-dimer has a poor positive predictive value, so do not use it to screen for DVT or PE.

Pulmonary angiography is the gold standard for diagnosis of PE. Because pulmonary angiography is an invasive test, it is reserved for cases with inconclusive results from CTPA and/or V/Q scan. It is used in patients

who have a high clinical probability of disease but negative other studies, such as CTPA and Doppler U/S.

Pulmonary angiography, especially if selective (guided by V/Q or MDCT scan findings), is a relatively safe procedure. Mortality < 0.1%; morbidity = 1–2%.

MRI/MRA. MRI alone is showing good potential in visualization of the pulmonary vessels. MRA (angiography) is another newer test with promise. It can view up to 8th order vessels. It is not available on all MRI machines. There is no set procedure for treatment of PE in subsegmental and smaller pulmonary emboli.

Echocardiography has poor sensitivity and specificity and is not indicated for the diagnosis of PE. However, it sometimes is used in the patient who has a presentation consistent with massive PE, so the diagnosis can be made at the bedside, and thrombolytics can be considered.

Echo also is useful for making a prognosis in acute PE. Increased mortality is seen in patients who have normal blood pressure and evidence of RV dysfunction or presence of an RV thrombus.

Troponin I and **T** are elevated in 30–50% of submassive to massive PEs and are probably the result of right heart failure. They are mainly used to determine the prognosis. Elevated levels correlate with increased severity of PE and increased short-term mortality.

Putting It All Together: How to Diagnose PE

So, how is the diagnosis of PE made using these tests?

It is really quite simple [Know!]:

1) Use clinical prediction rules (Wells = most commonly cited) to determine pretest probability of PE (Table 3-9 and Table 3-10).
2) In patients with low pretest probability, a negative highly sensitive D-dimer indicates a low likelihood of PE and essentially excludes the diagnosis.
3) U/S of lower extremities is recommended for patients with intermediate-to-high pretest probability for PE. If high pretest probability and proximal (ileofemoral or higher) thrombi, treat for PE.
4) CTPA, V/Q scan, or standard pulmonary angiography is recommended in patients with intermediate or high pretest probability if lower extremity U/S does not show clot.

TREATMENT OF PE

Overview

Treatment for PE may include:

- Adjunctive treatment (O_2, hemodynamic support)
- Anticoagulants (heparins, fondaparinux, warfarin)
- Thrombolytics (streptokinase, tPA)
- Surgery (vena cava filters, thromboembolectomy)

Adjunctive Treatment for PE

Give oxygen for hypoxia. Many use dobutamine for right heart failure because it has both inotropic and pulmonary vasodilating effects.

Anticoagulants for PE

Overview

The main anticoagulants are heparins, fondaparinux, and warfarin. Achieve adequate anticoagulation ASAP with a heparin or fondaparinux! It is indicated in all patients in whom PE is suspected or confirmed unless there are contraindications.

Anticoagulants are relatively contraindicated in the following:

- Uncorrected major bleeding disorder (thrombocytopenia, hemophilias, liver failure, renal failure)
- Uncontrolled severe hypertension (systolic > 200 mmHg, diastolic > 140 mmHg)
- Potential bleeding lesions (active peptic ulcer, esophageal varices, aneurysm, recent trauma or surgery to head/orbit/spine, recent stroke, intracranial or intraspinal bleed)
- NSAIDs—increases risk of GI bleeding; if able, stop NSAIDs
- Repeated falls or unstable gait

Remember warfarin is teratogenic: Pregnancy is an absolute contraindication for warfarin.

Contraindications require consideration of an IVC filter or thrombectomy/embolectomy.

Heparins

Overview: There are 2 types of heparin, unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). LMWH is the drug of choice now for DVT and is at least as good as UFH for PE.

LMWH: Subcutaneous full-dose LMWH (tinzaparin, dalteparin, or enoxaparin) should be used whenever possible to treat PE (inpatients and outpatients) because of the lower risk of major bleeding compared to UFH. Either LMWH or UFH can be used for initial treatment of PE, although LMWH is preferred by most, especially if the patient is hemodynamically stable, because LMWH reaches the therapeutic state faster.

LMWH is made from the depolymerization of heparin, which produces some molecular fragments with 30–50% the weight and more anticoagulant activity. LMWH has no effect on thrombin like UFH does. Rather, it solely inactivates Factor Xa (so no effect on PTT). It has been proven to cause fewer instances of major bleed than UFH in DVT, and anticoagulation is established more quickly than with UFH in any VTE situation. LMWH still can cause heparin-induced thrombocytopenia (although less often than UFH), so monitor the platelet count.

Quick Quiz

- Know perfectly the 4 items in "Putting It All Together: How to Diagnose PE."
- In what situations do you use low-molecular-weight heparin to treat thromboembolism? Unfractionated heparin?
- What effect does LMWH have on PTT? On Factor Xa?
- Should PTT be monitored in patients on LMWH? How are Factor Xa levels used?
- What are the major complications with HIT Type II? Describe the treatment.

LMWH is preferred for treating VTE in pregnant women, cancer patients, and anybody who is treated for an extended period because the risk of osteoporosis is much lower than with UFH. You can monitor activity by assessing activated Factor Xa levels, but this is not usually necessary.

Use LMWH with caution in patients with estimated creatinine clearance of < 80 cc/min. Do not use it at all in patients with a clearance < 30 cc/min. Instead, use UFH because it can be titrated.

Patients who are at high risk for bleeding should be given UFH in an infusion, so it can be turned off and the effect reversed within a short period.

For both UFH and LMWH, protamine is the antidote for bleeding, but it is less effective against LMWH.

UFH binds with antithrombin (AT) to make it 1,000–4,000x more effective in inactivating thrombin and Factor Xa. To inactivate thrombin, heparin binds to both AT and thrombin.

UFH is no longer the drug of choice for DVT, but it still is used for initial treatment of PE---especially if the patient is unstable. UFH dosage is determined by means of a weight-based nomogram to achieve adequate anti-coagulation. Do PTT levels every 6–8 hours after dosage change to allow time to achieve steady state.

UFH is more often given to unstable PE patients because sub-Q LMWH requires good blood pressure and tissue perfusion for optimal delivery, and this situation is not present in unstable patients. (Thrombolytics are also used in unstable patients with PE. Know that you do not give tPA to stable patients with PE.)

Adjust the dose of IV UFH to keep the PTT at least 1.5x control for 7–10 days. Then continue anticoagulant treatment as discussed above (minimum 3–6 months), preferably with either LMWH based on body weight or warfarin (see next column). Adjusted-dose heparin is used by some---dosing to maintain PTT at 1.5x control. Greater increases than these result in increased incidence of bleeding.

Complications: The major problem with UFH use is hemorrhage. Before giving it, be sure the patient has no major bleeding syndrome, no recent bleed, and has heme-negative stool.

Heparin antidote: Again, for both UFH and LMWH, protamine is the antidote for bleeding. But it is less effective against LMWH.

Heparin-induced thrombocytopenia (HIT):

- HIT Type I develops within 1–2 days of initiation of heparins. HIT-I is common and of no clinical consequence.
- HIT Type II is an immune response where antibodies develop against the complex of heparin and platelet factor 4. The antibodies are named "anti-H-PF4." HIT-II starts 4–10 days after initiation of treatment. It occurs in 1–3% of patients receiving UFH and about 0.5% of patients receiving LMWH. Arterial and venous thromboemboli are the major life-threatening complications.

Always monitor the platelet count in patients on heparin; if it drops > 50% and/or thromboembolic symptoms develop, stop using heparin (even heparin flushes) and start treatment with a direct thrombin inhibitor, such as lepirudin or argatroban. Start warfarin when the platelet count recovers to ≥ 100,000 (and continue the thrombin inhibitor) because there is a long-term risk of clots as long as the antibodies are present. Know that lepirudin should not be used in patients with chronic kidney disease. ("Be careful with le-pee-ru-din in those who can't pee!") Use argatroban instead.

Fondaparinux

This drug is a Factor Xa inhibitor. Give it sub-Q, once daily. It is approved for use in DVT prophylaxis of the surgical patient and for treatment of venous thromboembolism (both DVT and PE) as an alternative to UFH and LMWH. Fondaparinux does not cause HIT, so it is a useful drug for patients who need anticoagulation or prophylaxis and who have a history of HIT. Rate of bleeding is similar to heparins.

The drug is cleared exclusively by the kidneys. Therefore, it is contraindicated in patients with creatinine clearance < 30 cc/min, and probably should not be used when the clearance is between 30 and 80 cc/min because it accumulates. There is no way to monitor the effects of the drug, and there is no antidote.

Warfarin

International normalized ratio (INR) is a product of the $PT_{patient}/PT_{control}$ ratio times an international sensitivity index (ISI). The ISI accounts for the sensitivity of the thromboplastin used by the lab, which varies from batch to batch. The formula is $INR = (PT_{patient}/PT_{control}) \times ISI$. INR is used to determine proper dosages of warfarin.

Warfarin is adjusted to increase INR to 2.0–3.0 (target 2.5). Initial dose is usually 5.0 mg/day, and this is often decreased to ~ 2.5 mg/day.

Note: Warfarin is a vitamin K antagonist that prevents activation of Factors II, VII, IX, and X.

Remember: After starting warfarin, Factor VII is the most rapidly decreasing procoagulant, but protein C (an anticoagulant) also decreases rapidly—so you may rarely see an initial net procoagulant effect. This may occur only until the slower-clearing Factor II decreases enough to result in a net anticoagulant state. This usually takes ~ 4 days. This potential problem is addressed by starting the warfarin right after heparin is started (within 8 hours), and keeping patients on heparin for at least 4 days.

Warfarin necrosis is an idiosyncratic side effect, which causes full-thickness skin necrosis requiring skin grafts.

Any decrease in the minimum level of dietary vitamin K results in an increase in the INR. Monitor the INR more frequently if the diet is changed or the patient is put on an antibiotic that might kill the gut flora required for proper vitamin K absorption.

Warfarin interacts with many drugs. There is more on this in General Internal Medicine, Book 5, under Drug Interactions.

Do not give warfarin to pregnant patients—deformities are common, especially if given in the 1st trimester. Use LMWH or adjusted-dose UFH instead.

Note: Warfarin can be started at the same time or anytime after heparin or fondaparinux is started. The overlap period should be at least 4–5 days (10 days with massive PE) with the INR at a therapeutic level for 2 days before discontinuing the heparin and continuing the warfarin.

Remember, treat patients who are pregnant or who have cancer with LMWH for the entire duration of therapy; warfarin is contraindicated in pregnancy.

Thrombolytics for PE

PE: Streptokinase, tPA, and other thrombolytics are indicated for patients with massive PE who have "acceptable" risks of bleeding.

Submassive patients with prognostic risk factors for increased mortality may also benefit, if they are low-risk for bleeding.

Thrombolytics are not indicated for treatment of low-risk PE.

Vena Cava Filters for PE / VTE

Indications for vena cava filters include recurring VTE with adequate anticoagulation or recurring VTE when anticoagulant treatment is contraindicated.

Retrievable vena cava filters may be used when only short-term protection is required and can be removed when the risk for PE has subsided or when anticoagulation may be resumed.

Surgical thrombectomy/embolectomy is a potential option but is associated with high operative mortality.

Newer devices allow for mechanical thrombectomy (i.e., catheter extraction or AngioJet®) or mechanical disruption (i.e., pigtail catheters).

Putting It All Together: How to Treat PE

[Know!]

First, stabilize the patient: Put on O_2 and give hemodynamic support as needed with IV fluids and/or dobutamine.

Then, determine which anticoagulant to start. It usually is subcutaneous LMWH—especially if the patient is pregnant, has cancer, or is bedridden. If there is a history of HIT, fondaparinux is a good choice unless the patient has creatinine clearance < 80 cc/min. In this case, argatroban, a direct thrombin inhibitor, is your only choice. If the patient is unstable without a history of HIT, IV UFH is used (PTT = 1.5x control). If massive PE, consider thrombolytics.

In hospital, anticoagulant treatment is continued for 7–10 days. Home treatment with LMWH or warfarin is continued for 3–6 months for PE due to transient risk factors, 12 months for idiopathic PE, and indefinitely for recurrent PE or thrombotic tendencies.

And remember, if switching to warfarin: Before stopping heparin or fondaparinux, the patient must have been on warfarin for 4–5 days and have had a therapeutic INR (2.0–3.0) for 2 days.

TREATMENT OF DVT WITHOUT PE

Know that if the patient has a high probability of DVT with a low probability of PE (or if these diagnoses have been confirmed), the treatment is exactly the same as that for PE (just above).

Although few calf vein thromboses migrate above the knee, the ones that do are usually painful! So historically, we have treated patients with a painful calf venous thrombosis with anticoagulants and observed the painless thromboses with serial ultrasound.

However, now there are conflicting recommendations among various IM societies about the treatment of painless and painful calf thromboses, with some societies advocating treating all cases with anticoagulation and other societies advocating treating only the painful ones—so, a potential Board question would include only a situation common to both. For instance, the question would ask about anticoagulation in a patient with painful calf thrombosis.

Quick Quiz

- In which patients is warfarin absolutely contraindicated?
- When are thrombolytics used to treat pulmonary embolism?
- What are the indications for a vena cava filter?
- Know perfectly the 4 paragraphs in "Putting It All Together: How to Treat PE."
- What is the 1st choice for VTE prophylaxis in the hospitalized medical patient?
- Name the causes of transudative pleural effusions.
- What 3 conditions must be met for an effusion to be called a "transudate"?

RISK AND PROPHYLAXIS OF VTE

Overview

Pulmonary embolism is the most common preventable cause of death in hospitalized patients. Prophylaxis for DVT (and therefore PE) is cost-effective. In spite of the existence of numerous evidence-based guidelines, adequate prophylaxis is still not being offered to many medical patients (which makes this topic ripe for Board questions).

VTE Prophylaxis

ACP issued guidelines in 2011 for VTE prophylaxis, and the recommendations have simplified things some.

Know that stockings are no longer recommended for any patients because stockings can cause skin damage.

It is recommended that a risk assessment tool be used, but one was not suggested by ACP. Any assessment tool that considers a patient's medical history and current conditions, then assesses for risk of bleeding, is adequate.

Unless patients are "very high risk" for bleeding, a drug for VTE prophylaxis is recommended. Types include subcutaneous LMWH and UFH. These drugs reduce the risk of PE, but not DVT or mortality. (Then why use prophylaxis?)

For patients at the "highest risk" for bleeding, use pneumatic compression instead of drugs for VTE prophylaxis.

The use of fondaparinux is unclear because the heparins are considerably less costly. Probably "fonda" should be used as prophylaxis only in patients who have had HIT (if kidney function is okay).

FAT EMBOLI

Fat emboli cause the triad of dyspnea, confusion, and petechiae—usually in the neck, axilla, and/or conjunctiva. Fat emboli can occur within 72 hours after a fracture of a large bone (e.g., femur), sometimes after CPR, and with sickle cell bone-occlusive crisis.

Treatment is supportive; corticosteroids have not proven helpful.

PLEURAL EFFUSIONS

EXUDATIVE vs. TRANSUDATIVE

Overview

Pleural effusions are either transudative or exudative (Image 3-12).

A **transudative effusion** is secondary phenomenon to systemic changes that affect hydrostatic balance via the Starling equation, i.e., influencing the formation and absorption of pleural fluid. The most common causes are LV failure, cirrhosis, and nephrotic syndrome.

An **exudative effusion** is due to a local cause, and the 2 most common are bacterial pneumonia and cancer—but don't forget pulmonary embolism, even though it is not as common.

Table 3-11 on page 3-42 details the results of fluid studies that help you determine whether a pleural effusion is a transudate or an exudate. These measurements and ratios that determine the diagnosis of "exudates" are called Light's criteria. Note that all 3 conditions must be met for an effusion to be called a transudate—failing any 1 criterion makes it an exudate.

Transudative effusions are due to hydrostatic imbalance—treat the main problem, usually with diuresis and sometimes with albumen.

Exudative effusions are associated with local disorders and require further tests on the fluid to establish the cause. For this reason, you want to send several tubes of pleural fluid to the lab. Evaluate the 1st tube; then tell the lab to save the rest. Once you know the type of effusion, then you can decide on the other tests.

Transudative Effusions

These effusions do not need further evaluation.

Know that LV failure is the #1 cause, and it is not unusual to see an isolated right-sided effusion. You may see left-sided pleural effusion in association with pancreatitis. Transudative effusions are common after abdominal surgery and are usually benign.

Some experts advocate that bilateral effusions, equal in size and responsive to diuretics, in patients with well-established LV failure, cirrhosis, or nephrotic syndrome, do not need thoracentesis because the overwhelming majority

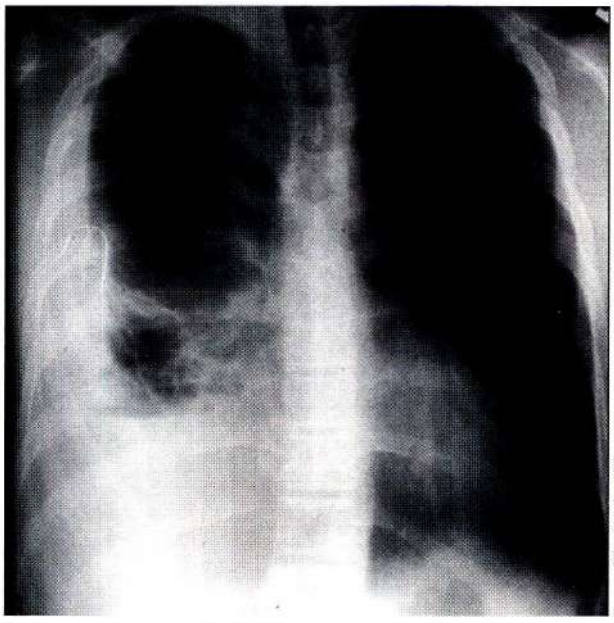


Image 3-12: PA chest: Right-side pleural effusion

are transudates. But always tap unilateral, asymmetric, or nonresponsive effusions to characterize the fluid.

Relief of dyspnea after therapeutic thoracentesis for an effusion is due to a decrease in intrathoracic volume! This is because most of the volume a pleural effusion occupies is obtained by distending the diaphragm (which causes the dyspnea). Only about 20% of the volume is obtained from compression of the lung. Know that removal of a large amount of pleural fluid may actually be accompanied by a transient fall in pO_2 during the first 12 hours, until atelectatic alveoli can re-expand and participate in gas exchange.

Exudative Effusions

Once you determine that your fluid is an exudate, tell the lab to do the following simple studies on the remaining fluid you sent:

- Glucose and amylase
- Cell count with differential
- Gram stain and bacterial culture
- Cytology
- Marker for tuberculosis (e.g., adenosine deaminase level), if available
- Analyze serum/pleural fluid albumin ratio
- If the above studies do not help you with diagnosis, consider CTPA to evaluate for pulmonary embolism.

Table 3-11: Light's Criteria for Pleural Effusions

	E/S Protein		LDH_{EFF}		E/S LDH
Transudative	< 0.5	and	< 200	and	< 0.6
Exudative	> 0.5	or	> 200	or	> 0.6

These initial studies, plus your clinical history and exam, help you determine the most likely cause, which we discuss next.

Bacterial pneumonia is the most common cause of an exudative effusion in the U.S. The effusion develops in association with bacterial pneumonia or lung abscess (rarely, also with bronchiectasis). Consider the possibility of effusion every time you consider bacterial pneumonia as a diagnosis. If clinical evidence of effusion is present in the setting of pneumonia, quantify the size using imaging (chest x-ray, CT, or U/S). The key is 10 mm! If there is more than 10 mm of fluid from lung surface to chest wall, the patient needs a thoracentesis—to get out the bulk of inflammatory material and organisms and to give the patient the best chance to heal.

The effusion is "complicated" if any of the following are found on analysis of fluid from the therapeutic thoracentesis:

- Loculations on imaging
- pH < 7.20
- Glucose < 60 mg/dL
- Positive Gram stain or culture

Empyema thoracis is the diagnosis when visible frank pus is found.

Treatment of a complicated effusion requires chest tube drainage at the least and may require surgical intervention.

Empyema thoracis often requires surgical therapy, and video-assisted thoracoscopic surgery (VATS) has recently become the best technique. VATS is supplanting thoracoplasty and decortication.

Malignancy is the 2nd most common cause of an exudative effusion. The most common malignant pleural effusions are lung cancer (1/3), breast cancer (1/4), and lymphoma (1/5). Lung, breast, lymphoma ... 1/3, 1/4, 1/5.

In a pleural-based malignancy, repeated cytologic examination of the effusion fluid has as high a yield as pleural biopsy! 3 effusion samples have a combined yield of > 90%. Thoracoscopy is done if the repeat cytologies are negative. Pleural biopsies are rarely needed anymore to diagnose cancer. The main use now for a closed pleural biopsy is to diagnose pleural TB.

Less common (but important!) causes of exudative pleural effusions: mesothelioma, pulmonary embolism, viral infections, and tuberculosis.

Mesothelioma: Think about mesothelioma (considered pathognomonic for asbestos exposure) in patients with dyspnea, chest pain, and a grossly hemorrhagic pleural effusion.

Pulmonary embolism: Consider this in the dyspneic patient with an exudative effusion showing normal fluid amylase, glucose > 60 mg/dL, normal or slightly increased cell count and differential, and Gram stain showing no organisms. PE as a cause of pleural effusion is often missed clinically!

Quick Quiz

- What clinical and laboratory features make a pleural effusion complicated?
- What is the definition of empyema?
- What specific tests for *M. tuberculosis* are available to diagnose TB using pleural fluid?
- What diagnostic tests are done for suspected pleural TB?
- What is the definition of hemothorax?
- Define chylous effusion. What causes it?

Virus: Many viruses cause self-resolving pleural effusions. Think of a probable viral cause in someone who improves quickly without intervention.

Tuberculosis: Think of tuberculous effusion in the patient with risk factors for primary TB and additional history of fevers and wasting. Pleural fluid cell count usually is lymphocytic. AFB smear and culture of the pleural fluid have a low yield, so the strategy incorporates mycobacterial-specific tests. These tests are now commercially available to diagnose TB in the fluid, and they are quite good. They include adenosine deaminase (ADA), interferon-γ release assay (IGRA), and polymerase chain reaction (PCR) for TB DNA.

If you do not have these special tests available, do a pleural biopsy. Send your tissue for routine pathology with AFB stains, and send a sample to the micro lab for AFB smears and culture. Aside from the special mycobacterial-specific research tests described above, path + cultures of pleura is the approach with the highest diagnostic yield for TB, between 65 and 90% (higher than any single approach).

In clinical practice, closed pleural biopsies are rarely performed. Most of the pleural sampling procedures are now done with VATS, which has a high diagnostic yield and can be used for both pleural fluid sampling and pleural biopsy.

Again: To diagnose cancer = repeat taps and cytology; to diagnose TB on a pleural effusion = special tests and pleural biopsy.

And a weird one: Think about yellow nail syndrome if the patient has a history of chronic peripheral edema and chronic exudative pleural effusions. Patients with this genetically transmitted syndrome also have yellow, dystrophic nails.

Some Key Effusion Findings

Cell count with differential findings. General clues:

- WBCs > 1,000, think exudate; > 10,000, think complicated parapneumonic effusion; WBCs > 100,000 = empyema or pus.
- Mesothelial cells normally line the cavity and are occasionally confused with malignant cells. There is a consistent finding that, with a tuberculous pleural effusion, there are very few mesothelial cells. So, if a high mesothelial cell count is reported in the fluid, then TB is highly unlikely to be the cause.
- Eosinophils > 10%: Think pneumothorax, drug reaction, post-thoracotomy, paragonimiasis (trematode: fluke), fungal infection, and asbestos exposure.
- Lymphocytes > 50%: Think TB or malignancy.
- Neutrophil predominance: Think pneumonia, pancreatitis, PE, peritonitis.
- Know the specific definition of hemothorax: grossly bloody pleural effusion with a hematocrit > 1/2 of the hematocrit of the peripheral blood. Think trauma!

Fluid chemistry findings:

- Glucose ~ 80 = TB; ~ 60 = cancer, empyema; < 30 = rheumatoid arthritis.
- Amylase increased in pancreatic fistula and esophageal rupture (salivary amylase).
- Adenosine deaminase (ADA) concentrations (especially isoenzyme ADA-2) are elevated in tuberculous pleural effusions. (Conversely, ADA level < 40 U/L is rarely TB.) This test is used as a diagnostic aid when a TB effusion is suspected but other tests are negative. Other tests include the γ-interferon and polymerase chain reaction to identify TB DNA.

What if the pleural fluid is milky white, but not pus?

Chylous effusions are white-colored, exudative effusions with a triglyceride level > 110 mg/dL (due to fat globules; i.e., chylomicrons). The chylous effusions are associated with leakage of thoracic duct lymph. Think trauma and cancer (especially lymphoma). Work hard to find the cause using imaging studies of the mediastinum.

Pseudochylous pleural effusions are associated with chronic inflammatory processes, especially TB and rheumatoid arthritis lung disease. Triglycerides in pseudochylous effusions are < 50 mg/dL; total cholesterol is > 65 mg/dL because the white color is due to cholesterol, not chylomicrons. Neither the chylous nor pseudochylous specimens clear with centrifugation.

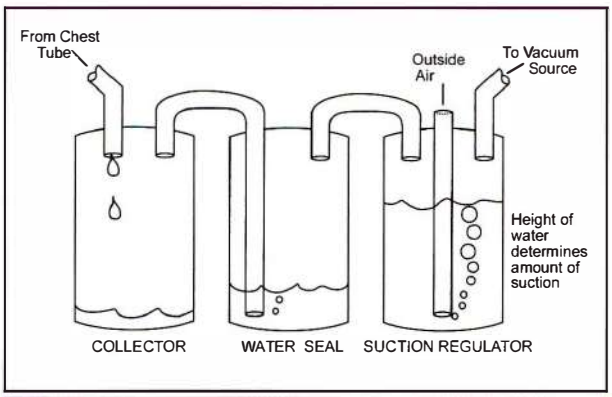


Figure 3-6: Chest Tube Drainage System

PNEUMOTHORAX

Primary spontaneous pneumothorax (PSP) was once thought to be a benign problem that most commonly affects tall, slender, smoking men ages 20–40 years. With high-resolution CT, we now know that many of these patients have subpleural emphysematous blebs, which may be an etiologic factor.

Secondary spontaneous pneumothorax (SSP):

- COPD is the most common cause.
- *Pneumocystis* pneumonia in AIDS patients occasionally causes a pneumothorax.
- Cystic fibrosis.
- Langerhans cell histiocytosis—smoking males.
- LAM—exclusively premenopausal women.
- Barotrauma—about 10–15% of patients on mechanical ventilators develop barotrauma, including pneumothorax.

Recurrence rate for PSP is 28%, while that for SSP is 43%. Risk of mortality is 1–4% for PSP and up to 17% for SSP.

Initial treatment: If the pneumothorax is small (< 15–20% or < 2 cm) and the patient is stable, observe the patient and give high-flow O_2. 3 L/min O_2 by nasal cannula is associated with a 3–4-fold increase in rate of reabsorption (vs. room air).

If the pneumothorax is larger (> 2 cm), place a small anterior chest tube. This may consist of an intravenous catheter inserted via the 2nd intercostal space, aspirated, and either closed off or connected to suction. A chest tube is mandatory in pneumothorax patients receiving positive pressure ventilation regardless of the size of the pneumothorax!

Review of chest tube drainage system components (Figure 3-6). 3 chambers:

1st chamber (nearest the patient) = Collection chamber—where whatever effluent from the pleural cavity is collected.

2nd chamber (middle) = Water-seal chamber—allows air to bubble out from the pleural cavity but does not allow air into the chest. Bubbles in this chamber indicate air is in (or still entering) the pleural space.

3rd chamber (attached to suction) = Suction regulator—height of water determines the amount of suction on the chest tube (when vacuum is applied to the chamber and there is bubbling in the water of the chamber).

If there is a persistent air leak with < 90% expansion of the lung, video-assisted thoracoscopic surgery (VATS) is used to either staple the blebs or instill talc.

A persistent air leak for > 7 days suggests a broncho-pleural fistula, which may require surgical intervention for stapling and pleurodesis to prevent recurrences.

Recurrence prevention: Pleurodesis decreases the recurrence rate significantly. Pleurodesis is not usually done with the 1st episode of SSP, but there is more evidence suggesting that you should do pleurodesis for even the 1st occurrence of PSP due to the recurrence rates. This may become the standard of care. Talc is the best and cheapest agent for pleurodesis. Doxycycline and minocycline are next. Bleomycin is toxic, expensive, and no longer recommended.

SINUSITIS / TONSILLITIS

Acute sinusitis is either viral or bacterial. Viruses (rhinovirus, influenza, parainfluenza) are the most common causes of acute sinusitis that lasts < 10 days. Bacterial sinusitis can complicate viral URIs. The most common bacteria are pneumococcus, *H. influenzae*, and *Moraxella*. Treat with TMP/SMX, AM-CL, clarithromycin, a 2nd/3rd generation cephalosporin, or fluoroquinolone. Treat recurrent sinusitis for 3 weeks. Osteomyelitis of the frontal bone is rare; it is indicated by a pale, cool edematous area over the forehead called Pott puffy tumor.

Postanginal sepsis (Lemierre syndrome) is an anaerobic sepsis secondary to thrombophlebitis of the jugular vein. This phlebitis is the result of spread from an adjacent tonsillar abscess.

PNEUMONIAS

OVERVIEW

Pneumonia is categorized in 1 of 4 ways:

1) Community-acquired (CAP)
2) Health care-associated (HCAP)
3) Hospital-acquired (HAP)
4) Ventilator-associated (VAP)

Currently, HCAP is defined to exclude HAP and VAP, but the next guidelines are likely to recategorize HAP and VAP as subsets of HCAP (logically!).

Quick Quiz

- What conditions are associated with secondary pneumothorax?
- Which organisms are the common causes of bacterial sinusitis?
- What is Lemierre syndrome?
- Identify the organisms associated with typical and atypical CAP.
- When is it appropriate to start doing a full workup in CAP?

COMMUNITY-ACQUIRED PNEUMONIA

Overview

CAP can be organized into 2 groups based on the organisms that cause disease:

1) **Typical** (pneumococcus, *H. influenzae*, *S. aureus*, gram-negative rods, and *Moraxella catarrhalis*).
1) **Atypical** (*Mycoplasma*, *Chlamydophila*, *Legionella*, endemic fungi [cocci, histo, blasto], and viruses [flu, adeno, RSV]). Atypical pathogens cannot be identified by Gram stain or routine bacterial culture (require special media), and they are resistant to β-lactam antibiotics, which are 1st line drugs for empiric treatment of CAP.

We rarely determine which bug is causing a patient's community-acquired pneumonia, but there are some risk factors associated with certain pathogens. And these associations are often tested. They are discussed in the section on empiric treatment of CAP (page 3-47).

In 2007, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) came together to issue guidelines for evaluating, diagnosing, and treating CAP. Think about CAP from 2 perspectives:

1) Empiric treatment; when the organism is not known
2) Pathogen-directed treatment; when it is known

Clinical Presentation of CAP

Symptoms are variable (from mild to severe) and include fever, anorexia, sweats, dyspnea, sputum production, cough, and pleurisy. Nausea, vomiting, and diarrhea occur in 20%. Elderly patients are also often confused.

Exam findings include tachycardia, tachypnea, evidence of consolidation (increased tactile fremitus, bronchial breath sounds, crackles), and/or parapneumonic effusion (decreased tactile fremitus and percussion).

There is overlap in signs and symptoms caused by typical and atypical pathogens—so you cannot reliably use the history of symptoms or the x-ray findings to differentiate typical from atypical pathogens.

Diagnosis of CAP

Overview

Per ATS/IDSA 2007 guidelines, the initial workup of CAP is very limited if the patient does not have severe disease (i.e., requiring ICU) and responds to empiric therapy.

More aggressive workup is recommended for patients:

- with risk factors for severe disease (e.g., underlying structural lung disease or uncontrolled comorbidities),
- with a severe presentation (requiring ICU), and
- who are unresponsive to empiric treatment.

Diagnostic Tests

Chest x-ray is required for diagnosis in patients with CAP. Some confusion in reading the x-ray may result from coexisting HF, COPD, and malignancy. Remember that an infiltrate may not appear in a volume-depleted patient until after the patient is volume-resuscitated. See Image 3-13 and Image 3-14 for a comparison of middle lobe and lower lobe pneumonias.

Do a **sputum Gram stain and culture** in patients with:

- severe or unresponsive CAP,
- COPD,
- a history of alcohol abuse,
- cavitary infiltrates, and/or
- a pleural effusion.

In the intubated patient, send a deep-suction aspirate or sample from BAL (better than sputum) as soon as possible because targeted antibiotics in the ICU do affect

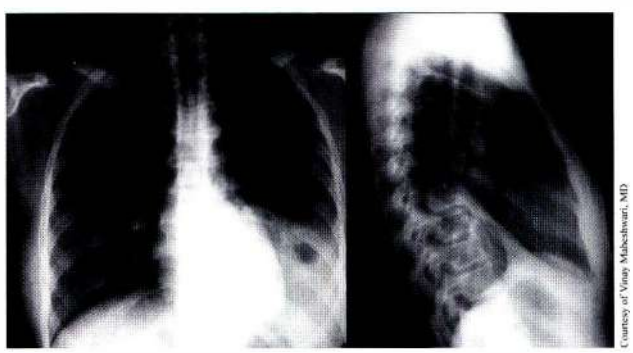


Image 3-13: Left lower lobe pneumonia

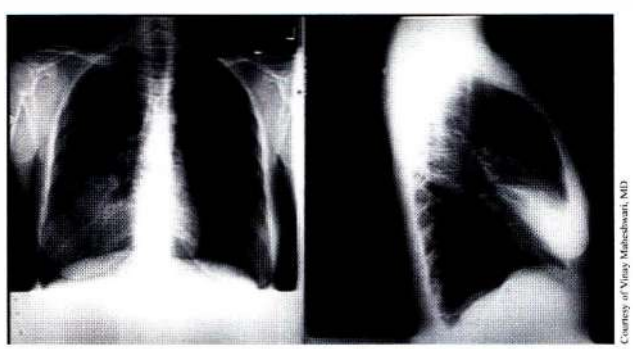


Image 3-14: Right middle lobe pneumonia

outcome (as opposed to outpatients who do just as well with empiric therapy).

Add an acid-fast stain if tuberculosis is in your differential based on the presentation and x-ray.

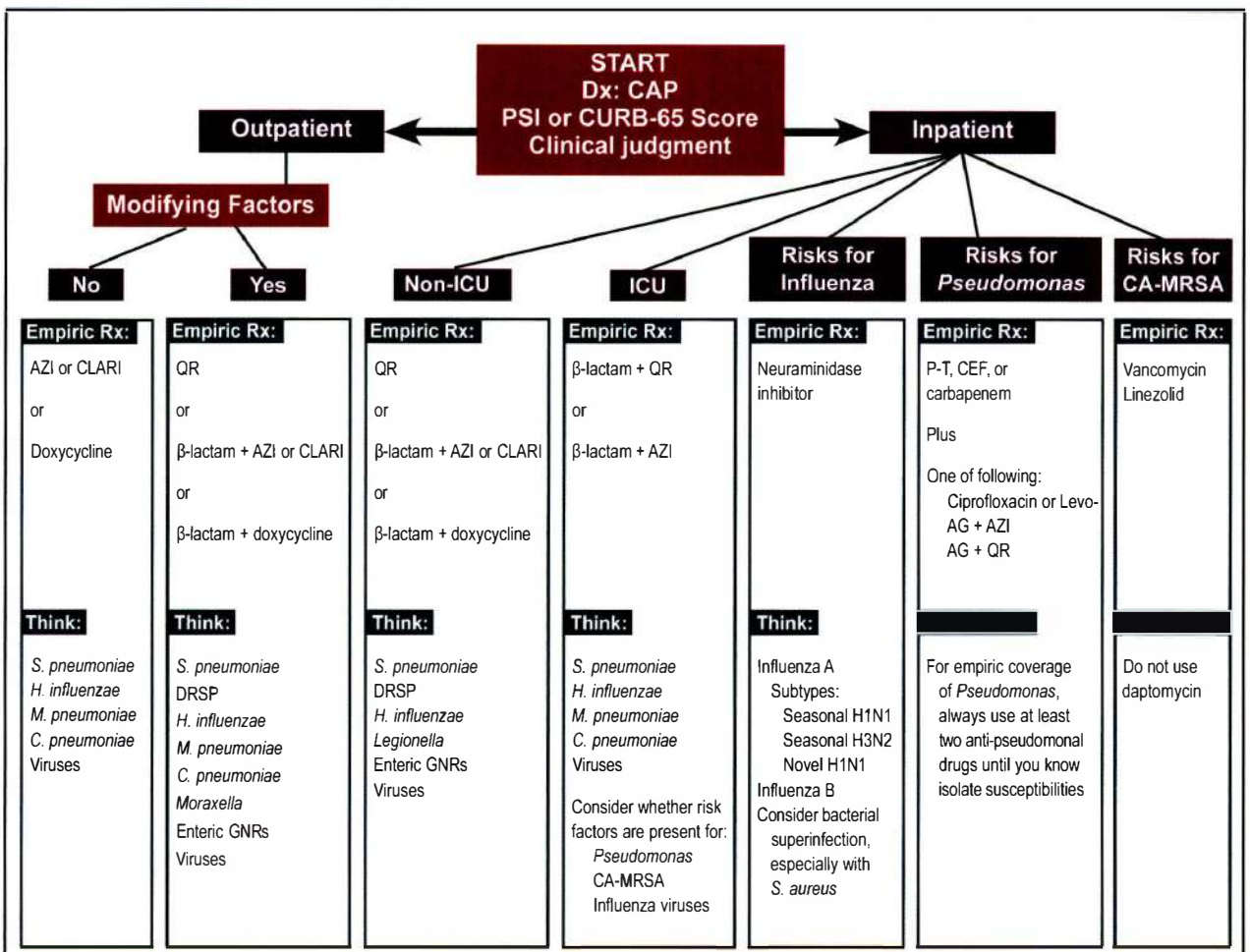
Do not do sputum tests on admitted patients who don't meet these indications or on outpatients with CAP.

Sputum interpretation: The C+S results are accurate only if there are > 25 neutrophils and < 10 epithelial cells per low power field. If more epithelial cells are present, then it is contaminated. If the patient gives you a cup with what looks like saliva mixed with a few mucoid globs, fish out these "goobers" and send them to the lab (higher yield)!

Blood cultures should be done on patients with:

- sepsis,
- severe or unresponsive CAP,
- COPD,
- liver disease,
- a history of alcohol abuse,
- cavitary infiltrates,
- asplenia,
- a pleural effusion,
- leukopenia, and/or
- a positive pneumococcal urine antigen test.

Do not do blood cultures in admitted patients who don't meet these indications or on outpatients with CAP.



"Modifying factors" = Risks for DRSP (age > 65 years, β-lactam Rx within past 3 months, alcoholism, immunosuppression, exposure to child in day care), and/or any of following comorbidities: COPD, diabetes, renal or congestive heart failure, malignancy

QR = respiratory quinolone (levofloxacin, gemifloxacin, or moxifloxacin)

AZI = azithromycin

CLARI = clarithromycin

DRSP = Drug-resistant *Streptococcus pneumoniae*

β-lactam choices for outpatients (oral): high-dose amoxicillin or amoxil-clavulanic acid in patients with RF for DRSP; alternatives: cefpodoxime or cefuroxime

β-lactam choices for inpatients (intravenous): cefotaxime or ceftriaxone

P-T = piperacillin-tazobactam

CEF = cefepime

AG = aminoglycoside (gentamicin, tobramycin, or amikacin)

Carbapenem = imipenem or meropenem

Figure 3-7: Treatment of Outpatient and Inpatient Community-Acquired Pneumonias

QuickQuiz

- Detail the characteristics that a sputum sample must have to be considered an adequate specimen.
- List the tests that you need to order in patients with severe or unresponsive CAP.
- Be familiar with the Pneumonia Severity Index (Table 3-12).
- Which patients are at increased risk for infection with DRSP?
- A patient with known influenza develops a cavitating pneumonia. Besides pneumococcus, what organism should you consider?

Other tests: In patients with severe CAP, add to blood and sputum cultures—urine antigen tests for pneumococcus and *Legionella*.

Additional admission tests are: CBC, Chem-6, liver function tests, O_2 sat, and HIV testing.

Serologic tests are usually not helpful in the initial evaluation. DNA probes and nucleic acid amplification are not indicated.

Treatment of CAP

Remember to think of CAP from 2 perspectives: empiric treatment and organism-specific treatment. The following treatment discussion is also based on the 2007 ATS/IDSA guidelines. Refer to Figure 3-7 during the following discussion.

Empiric Treatment of CAP

Empiric treatment is started before pathogen identification and is based on:

- Severity of the illness and need for hospitalization
- Likelihood of specific pathogen based on associated risk factors

What you prescribe empirically is partly determined by whether the patient will be admitted. (Usually, outpatients = oral; inpatients = parenteral.)

Pathogens

Remember that you are guessing the most likely causal organisms when you are treating empirically. [Know the following associations.]

Pneumococcus is more likely in these groups: chronic diseases (heart, stroke, seizures, dementia, COPD, HIV/AIDS), cigarette smoking, and alcoholism. Resistance to β-lactams is increasing in pneumococcus. If your patient has a resistant pneumococcus, they may not respond to empiric cephalosporin treatment (or not respond as well). Consider drug-resistant *S. pneumoniae* (DRSP) in these groups: age > 65 years, recent (3 months) β-lactam therapy, alcoholism, immunosuppression, multiple comorbidities, and/or exposure to child in day care. (When discussing DRSP, generally the concern is resistance against penicillins, cephalosporins, macrolides, tetracyclines, and TMP/SMX. But know that pneumococcus is developing resistance against the respiratory quinolones as well.)

S. aureus pneumonia is associated with influenza virus as a bacterial superinfection. Know that community-acquired MRSA (CA-MRSA) is now a cause of CAP and can be severe with necrotic complications. This CA-MRSA has special genetic endowments (superantigen genes, such as the Panton-Valentine leukocidin [PVL]) that make it a particularly aggressive bug in patients without any underlying disease. CA-MRSA is more common in Native Americans, homeless, gay men, prisoners, military, day care workers, and contact sport athletes.

Table 3-12: The Pneumonia Severity Index (PSI)

	Findings	Points Assigned
Demographic factors	Males Females Nursing home residents	Age (years) Age − 10 Age + 10
Comorbid illnesses	Neoplastic disease Liver disease Congestive heart failure Cerebrovascular disease Renal disease	+ 30 + 20 + 10 + 10 + 10
Physical exam	Altered mental status Resp rate ≥ 30 bpm Systolic BP < 90 mmHg Temp < 35° C or ≥ 40° C Pulse ≥ 125 bpm	+ 20 + 20 + 20 + 15 + 10
Laboratory	pH < 7.35 BUN > 10.7 mmol/L Na < 130 Glucose > 139 Hct < 30% P_aO_2 (art) < 60 mmHg or O_2 sat < 90% Pleural effusion	+ 30 + 20 + 20 + 10 + 10 + 10 + 10

Scoring	Points	Mortality (%)
I	< 51	< 0.5
II	51–70	≥ 0.5–0.9
III	71–90	≥ 1.0–3.9
IV	91–130	≥ 4.0–9.9
V	> 130	≥ 10.0

Gram-negative organisms are associated with uncontrolled chronic diseases, immunosuppression, and alcoholism. *Legionella* is typical in winter or summer and is associated with diabetes, cancer, kidney disease, HIV/AIDS, and a recent cruise ship or hotel stay. Note that some of these risk factors might cause the pneumonia to be reclassified as HCAP (health care-associated pneumonia), depending on circumstances.

Know these organism-specific associations:

- COPD or immunoglobulin deficiency (especially IgG): *Moraxella catarrhalis* and *H. influenzae*
- Cattle or sheep exposure: *Coxiella burnetii* (Q fever)
- Bird fanciers: *Chlamydophila psittaci* (psittacosis)
- Hunters: *Francisella tularensis* (tularemia)
- Bat caves especially in the **M**ississippi and **O**hio River valleys: *Histoplasma capsulatum* (histoplas**MO**sis)
- Travel to California or Arizona: *Coccidioides immitis* (coccidioidomycosis)
- Living in or travel to southeast, mid-Atlantic, and central states—especially Illinois and Arkansas: *Blastomyces dermatitidis* (blastomycosis)
- Risk factors for HIV/AIDS or other immunocompromise: *Pneumocystis jiroveci* (PJP) and TB

Empiric Antibiotics

Refer to Figure 3-7 for the treatment of CAP as we go through this discussion. Know that identifying the specific microbial cause of CAP is expensive and difficult (successful < 50% of the time).

Except in ICU cases, no data have shown that targeted treatment of a specific organism is superior to empiric treatment of possible organisms. Therefore, empiric treatment is accepted as appropriate and is emphasized by the guidelines as initially preferred over attempting to diagnose the specific pathogen.

Outpatients

The majority of patients with CAP are treated as outpatients based on a severity index indicating low risk—with either macrolides (azithromycin or clarithromycin) or doxycycline. Note that erythromycin is a choice, but GI side effects limit its use, and it is less effective against *H. influenzae* than the advanced macrolides.

If the patient has risk factors for DRSP or has comorbidities that could affect outcome (termed "modifying factors"), use a respiratory quinolone or high-dose amoxicillin (because the resistance can sometimes be overcome with larger β-lactam doses). An alternative is to pick an oral cephalosporin with known activity against DRSP.

Inpatients — Non-ICU

Non-ICU inpatients are treated with a respiratory fluoroquinolone or, alternately, an IV or oral β-lactam plus either a macrolide or doxycycline. Start treatment immediately once you determine admission is necessary.

Inpatients — ICU

ICU patients (with no risk factors for *Pseudomonas*) are treated with a β-lactam plus either a respiratory fluoroquinolone or a macrolide. If the ICU patient has risk factors for *P. aeruginosa*, start with 2 anti-pseudomonal drugs. If CA-MRSA is suspected based on historical risk factors, add linezolid or vancomycin. Start treatment immediately.

Narrowing Empiric Therapy

By day 3, you know whether your patient is improving, and you might have an organism identified if you sent any specimens for microbiology (sputum and blood cultures, urine antigen tests).

Switch to oral meds if your patient is improved with stable blood pressure and can take drugs by mouth.

If the lab identifies a bug, narrow treatment to focus on that organism.

Treatment varies from 5 days (clear cut, improving cases) to 14 days (extensive pneumonias). Follow up with a chest x-ray about 4–6 weeks after discharge, and consider malignancy in the patient whose lung has persistent abnormalities.

If your patient deteriorates over the first 3 days on empiric treatment, think of these possibilities:

- You have the wrong diagnosis, and it is not an infectious infiltrate; e.g., PE, CHF, connective tissue disease, hypersensitivity pneumonitis.
- Your empiric regimen is not covering the causative organism. Revisit the list of risk factors and associations. What did you miss? If you are giving the right drugs, are you giving the correct doses?
- There is a new infection, in addition to the original one; e.g., staph pneumonia in addition to original viral pneumonia. Think empyema if a parapneumonic effusion was present on admission. Chest x-rays that demonstrate development of pneumatoceles or lung abscesses over the first few days should make you think pneumococcus, CA-MRSA, and *Pseudomonas*.

Now let's talk about the individual organisms that cause CAP. Some of this information has been briefly covered before, but a focused discussion is necessary.

"TYPICAL" ORGANISMS OF CAP

It is important to know which organisms are common in your area and your local antibiotic resistance patterns as you make decisions on empiric therapy. This information may be available to you from your hospital microbiology lab in the form of an "antibiogram."

QuickQuiz

- A patient who works on an animal farm develops pneumonia. What organism should you think about?
- What organism should you consider if pneumonia develops in a patient who spent an afternoon in a bat cave in Mississippi?
- What organism should you think about if pneumonia develops in a patient who drove through an Arizona dust storm?
- What organism should you consider if a chronic, cavitating pneumonia develops in a male logger from Arkansas?
- Name 2 drugs that are recommended to treat outpatient CAP in patients without risk factors for DRSP.
- Name 2 regimens recommended to treat inpatient CAP in the non-ICU patient.
- What antibiotics would you use for empiric treatment of the ICU patient with cavitary pneumonia and risk factors for *P. aeruginosa*?
- What are the diagnostic possibilities for the unresponsive patient with apparent pneumonia?
- Name some potential pulmonary complications of pneumococcal pneumonia.
- Describe the patients who should be vaccinated with PPSV23.

Streptococcus pneumoniae

Pneumococci live in the nose and throat of up to 40% of healthy children. Any adult who has contact with children, day care centers, and other crowded conditions (military barracks, dormitories, homeless shelters, prisons) is at risk for becoming colonized and subsequently infected with *Streptococcus pneumoniae*.

Children who receive frequent antibiotic prescriptions for viral illnesses are a source of drug-resistant strains because the colonizing organisms mutate under the drug's selective pressure. Upper respiratory inflammation from a cold virus, in the colonized patient, then sets the stage for bacterial pneumonia and/or sinusitis.

Patients most at risk for pneumococcal disease are > 65 years of age or have comorbidities (e.g., diabetes, alcoholism, and lung, heart, or renal disease). Asplenic patients (e.g., sickle cell) and patients with humoral immunodeficiencies (e.g., AIDS, myeloma, CLL, lymphoma) are especially at risk because pneumococci are encapsulated organisms.

To review: DRSP is associated with age ≥ 65 years, recent β-lactam therapy, alcoholism, immunosuppression, multiple comorbidities, and exposure to child in day care.

In addition to generic signs and symptoms of pneumonia, think pneumococcus if your at-risk patient presents with shaking chills, pleuritic chest pain, and "rust-colored sputum." CBC reveals a high WBC count. (Leukopenia is associated with mortality.) Chest x-ray often shows lobar consolidation (Image 3-15). If sputum is sent for microbiology, suspect pneumococcus when the Gram stain result describes intracellular, lancet-shaped gram-positive diplococci. Blood cultures are positive in 25% of hospitalized cases of pneumococcal pneumonia.

Look out for these complications: lung abscess, pneumatoceles, and empyema in the patient with history of parapneumonic effusion.

Know that multilobar disease, bacteremia, and peripheral blood WBC < 6,000/μL are associated with increased mortality.

Diagnosis of *S. pneumoniae* pneumonia is supported when a good quality sputum Gram stain identifies the lancet-shaped gram-positive diplococci, and the organism is identified in sputum culture. A positive blood culture and/or pneumococcal urinary antigen test are diagnostic.

Treatment: For susceptible pneumococcus, many drugs are effective, including tetracyclines, macrolides, penicillin, cephalosporins, and respiratory quinolones. Don't forget about the evolving resistance.

DRSP strains are treated with a cephalosporin with known activity against DRSP, a respiratory quinolone, or with higher doses of a β-lactam (with hopes of overcoming the resistance—a useful strategy if the infection is not severe).

There are 3 vaccines now licensed for pneumococcal disease: the 23-valent polysaccharide vaccine (PPSV23, contains 23 prevalent serotypes), the 7-valent protein conjugate vaccine (PCV7, contains 7 prevalent serotypes), and the most recent 13-valent protein conjugate vaccine (PCV13, contains 13 serotypes).

Adults are given PPSV23 if they are > 65 years of age, are cigarette smokers, have a chronic disease (HF,

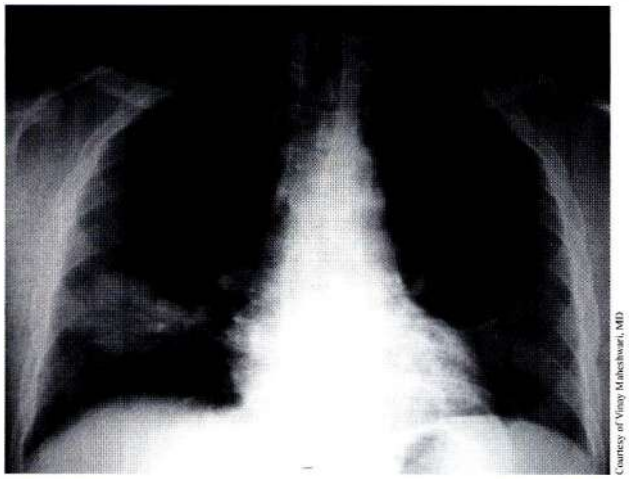


Image 3-15: Round pneumonia (often seen in pneumococcal pneumonia)

COPD, asthma, DM, cirrhosis), are functionally or anatomically asplenic, or are immunosuppressed. Many patients with comorbidities (i.e., those who need the vaccine most) do not develop an adequate antibody response. Current recommendations include a booster vaccine for patients over 65 years of age if > 5 years have elapsed since initial vaccination.

PCV7 and PCV13 are approved for use in children < 2 years of age because the protein conjugate is more effective at stimulating the immune system in this age group. PCV7 has dramatically reduced the incidence of invasive pneumococcal disease in children (which subsequently confers reduction in disease in adults). We are now seeing emergence of invasive disease caused by the less common serotypes not included in PCV7. This "replacement phenomenon" is most often mediated by capsular switching. Thus, PCV13 has been manufactured to include most of the circulating serotypes. PCV13 is intended to replace PCV7 in practice.

Haemophilus influenzae

Haemophilus influenzae may be encapsulated or unencapsulated ("nontypeable"). Because of widespread use of the Hib vaccination, most *H. influenzae* infections in the U.S. are nontypeable, caused by invasion of the bacteria across mucous membranes. Pneumonia from nontypeable strains is most often seen in patients with underlying lung disease (COPD) and AIDS.

Diagnosis: This pneumonia presents generically with fever, cough, and dyspnea. A good sputum sample often shows you the organism on Gram stain—pleomorphic gram-negative coccobacilli. Definitive diagnosis is made when you grow the organism in culture from a normally sterile site (e.g., pleural fluid or blood—both uncommon).

Treatment: Antibiotics effective against *H. influenzae* are ampicillin (or AM-CL if resistance is suspected or common in your area), 3rd generation cephalosporins, doxycycline, fluoroquinolones, and TMP/SMX.

Staphylococcus aureus

S. aureus colonizes the anterior nares and gets distributed to the skin with fingers. Regular staph strains don't cause problems in immunocompetent patients without skin breaks. But if the immune system or skin barrier breaks down, the staph can cause a problem.

Also, there are much stronger strains. A Panton-Valentine leukocidin-producing strain (PVL-SA) can cause a virulent necrotizing CA-MRSA in immunocompetent patients.

Staph species can be either susceptible to methicillin (and subsequently other β-lactams) or resistant to methicillin (MRSA, a surrogate marker for resistance to all β-lactam drugs).

Lastly, staph can be categorized by whether the strain is hospital-acquired (HCAP or HAP) or community-acquired (CAP)—generally predicted based on the patient's history, the organism's antimicrobial susceptibility, and toxin analysis.

Staphylococcus aureus CAP is usually seen in patients with a preceding influenza infection (as a superinfection), although *de novo* pneumonia due to CA-MRSA is being seen more frequently.

Presentation is typical for pneumonia with fever, dyspnea, and cough; but patients with staph may have hemoptysis with salmon pink sputum, and diffuse lung infiltrates and/or pneumatoceles.

Think superinfection with *S. aureus* if the history is consistent with resolving influenza that worsens with new symptoms of dyspnea and cough.

Think CA-MRSA in cases of severe pneumonia with pink sputum and pneumatoceles in an immunocompetent patient with a history of close contact with others or poor hygiene.

Diagnosis: As with other pneumonias, diagnosis is supported when a good sputum sample shows the organism on Gram stain (gram-positive cocci in clusters) and grows the organism in culture. Blood cultures are helpful if positive, but they usually are not.

Complications include empyema (frequent), an immune-complex type of glomerulonephritis, and pericarditis.

Treatment: Methicillin-sensitive *S. aureus* pneumonia can be treated with a β-lactam—nafcillin is usually the drug of choice.

Treat MRSA pneumonia with either vancomycin or linezolid. Daptomycin is ineffective for respiratory infections; do not use it to treat staph pneumonia!

CA-MRSA strains often have preserved susceptibility to TMP/SMX, quinolones, and clindamycin. These drugs are fine to use in treating skin infections with CA-MRSA but not lung infections. Use vancomycin or linezolid for serious MRSA lung infections.

Klebsiella

The major CAP-causing enteric gram-negative organism is *Klebsiella pneumoniae*, which colonizes the oropharynx of alcoholics and patients with uncontrolled lung disease or diabetes. It is an uncommon cause of CAP.

Klebsiella CAP presents with typical features of pneumonia (cough, dyspnea, fever). As the pneumonia worsens, the lung can become necrotic, and patients get sicker. Be aware of some buzzwords classically associated with gram-negative pneumonia: "currant jelly sputum" (bloody sputum that resembles jelly) and the "bulging fissure sign" (an x-ray finding in *Klebsiella* pneumonia that is associated with a lobar infiltrate).

Diagnosis is made via Gram stain and culture of sputum and blood (usually performed because the patient with gram-negative pneumonia often presents with severe disease and may end up in the ICU).

Quick Quiz

- Name some potential complications of staph pneumonia.
- What drug choices are available for targeted treatment of *S. aureus* pneumonia?
- The "bulging fissure sign" is associated with what organism that causes pneumonia?
- What antibiotics must be added for empiric treatment of pneumonia in the ICU patient with risk factors for *Pseudomonas*?
- Describe the microbiologic characteristics of *Moraxella*.
- What are the extrapulmonary manifestations of infection with *Mycoplasma pneumoniae*?

Treatment: Know that many enteric gram negatives are either innately resistant to ampicillin or have acquired ampicillin resistance. When you suspect gram-negative pneumonia, your empiric antibiotic choice should be broad in spectrum; i.e., an extended-spectrum penicillin with a β-lactamase inhibitor, such as piperacillin-tazobactam (because you need coverage for gram-positive organisms also, until the lab identifies an organism for you). Once cultures identify your organism, you can narrow treatment based on resistance testing—often an oral quinolone is adequate to finish therapy.

Pseudomonas aeruginosa

Pseudomonas grows in moist environments. Patients who are infected with this organism in their lungs have an underlying illness that allows their alveoli and airways to stay moist. And most often, the underlying disease process requires either chronic or intermittent antibiotic use, such that drug pressure selects for colonization with resistant and hearty gram negatives.

So *Pseudomonas* causes CAP in patients with underlying lung disease, especially cystic fibrosis, bronchiectasis, and in patients who use steroids or antibiotics frequently.

Patients without lung disease who inhale a large amount of steam from hot tubs that are heavily contaminated with *Pseudomonas* can also present with pseudomonal CAP. *Pseudomonas* is not a common cause of CAP—more often it causes HCAP.

Presentation is typical with cough, dyspnea, and fever. The patients with chronic lung disease usually look sicker, though, because this bug is bad and they don't have much reserve.

Diagnosis of *Pseudomonas* pneumonia is trickier than with other causes of CAP because the organism is harder to find. A sputum Gram stain with many polys + sputum culture that grows the organism suggests infection. Of course, it takes a while for the culture to grow, so you have to have a high index of suspicion for this bug and treat empirically.

Treatment: If you suspect *Pseudomonas* based on underlying chronic disease or hot tub exposure, empirically treat with 2 antipseudomonal drugs—1 of which should be a broad-spectrum antipseudomonal penicillin (e.g., piperacillin-tazobactam, ticarcillin-clavulanic acid, or imipenem-cilastin). Add ciprofloxacin or an aminoglycoside as the 2nd drug. Once culture results are available, with susceptibility results, narrow the regimen.

Moraxella catarrhalis

Moraxella catarrhalis colonizes the mouth and upper airway of both children and adults and is a frequent cause of otitis and sinusitis. Importantly, however, this organism causes CAP only in patients with underlying lung disease, generally COPD. In a large study, *Moraxella* never caused pneumonia in healthy individuals. CAP from this organism indicates severe lung disease; 50% of patients die from their disease within 3 months of infection.

Moraxella CAP is slightly less acute than disease caused by pneumococcus or *H. influenzae*. Symptoms are less severe. The x-ray pattern is variable, ranging from lobar infiltrates to diffuse involvement, and even interstitial disease in some cases.

Diagnosis is typically simple because a quality sputum sample shows an overwhelming number of obvious organisms that are described as gram-negative cocci. It is useful to look at the Gram stain yourself because the organisms line up side-by-side and look like a pair of kidneys (not usually reported by the micro tech on the Gram stain result).

Treatment is straightforward because the bug is generally susceptible to most drugs used to treat pneumonia: doxycycline, macrolides, cephalosporins, or amoxicillin/clavulanic acid. Up to 90% of isolates produce a β-lactamase, which breaks down penicillins but not cephalosporins.

"ATYPICAL" ORGANISMS OF CAP

Recall, these organisms are defined as "atypical" because they are not identifiable by Gram stain or routine bacterial culture, and they are resistant to β-lactam antibiotics. These organisms require special culture media +/– serologic tests to establish diagnosis.

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a common cause of CAP in young patients. Incubation is 2–3 weeks, and onset of dyspnea, cough, and fever is typically insidious, although occasionally presentation can mimic pneumococcal disease. Extrapulmonary manifestations of *Mycoplasma* infection include hemolytic anemia, splenomegaly, erythema multiforme (and Stevens-Johnson syndrome),

arthritis, myringitis bullosa, pharyngitis, tonsillitis, and neurologic changes—especially confusion.

Diagnosis is made by measuring acute and convalescent IgM antibody titers using enzyme immunoassay. If the convalescent titer rises by ≥ 4x the acute titer, then you can make the diagnosis retrospectively with > 95% sensitivity and specificity.

Cold agglutinins are nonspecific IgM antibodies that support the diagnosis in settings of high clinical suspicion but have low sensitivity and specificity.

Treatment of *Mycoplasma* pneumonia is with macrolide—or with doxycycline if the macrolide is not tolerated. Patients sometimes take a long time (> 6 months) to fully recover!

Chlamydophila pneumoniae

Chlamydophila pneumoniae (formerly *Chlamydia*) more commonly causes CAP in adults > 65 years of age.

Symptoms are similar to *Mycoplasma* pneumonia with the addition of pharyngitis and hoarseness. Often, there is a biphasic illness; the patient presents with a sore throat that is negative for group A strep; then 2–3 weeks later, hoarseness and pneumonia develop. Again: Sore throat → pneumonia + hoarseness = *Chlamydophila pneumoniae*.

Diagnosis of pneumonia due to *Chlamydophila pneumoniae* is confirmed by measuring acute and convalescent IgM and IgG titers using microimmunofluorescence or complement fixation; antigen detection using ELISA tests; or, PCR of respiratory secretions. The first 2 are most useful clinically.

Treatment: Effective antibiotic therapy includes doxycycline or macrolides for 3 weeks.

Legionella pneumophila

Legionella pneumophila causes CAP when the organism is inhaled from a contaminated water supply, typically in the winter and summer months. Epidemics are seen in hotels and on cruise ships, and the organism can also cause HAP when hospital water systems are contaminated.

Presentation can be similar to, and is often confused with, *Mycoplasma pneumoniae*. The disease begins with headache, GI symptoms (especially diarrhea), and occasionally confusion, then evolves into lung-related symptoms of cough and dyspnea. Pleural effusions are not uncommon in *Legionella* pneumonia.

Labs can show hyponatremia, hypophosphatemia, thrombocytopenia, and elevated lactate dehydrogenase and C-reactive protein.

When you see multisystem disease, think *Legionella*! Also think *Legionella* in the patient who is admitted for typical CAP but fails to improve on empiric therapy.

Diagnosis: Preferred diagnostic tests for *Legionella pneumophila* pneumonia are sputum culture on special media (buffered charcoal yeast extract agar, but results take longer than 3 days) and the urinary antigen test using enzyme immunoassay. The urinary antigen assay is less sensitive with milder disease.

Treatment: macrolides—especially azithromycin or quinolones. If severely ill, add rifampin as initial treatment.

Endemic Fungi

Coccidioides immitis

Coccidioides immitis infection (coccidioidomycosis) is endemic in the southwestern U.S., especially Arizona and California's San Joaquin Valley.

Typical history includes recent travel to Arizona and "got caught in a dust storm." Soon after, the patient develops fatigue, fever, and arthralgias. The resulting illness can be subclinical and self-resolve, or CAP can develop within 2–3 weeks of exposure. The fatigue and arthralgias can linger; thus, infection has been termed "desert rheumatism."

Erythema nodosum and erythema multiforme are associated skin findings.

Chest x-ray findings are variable from normal to adenopathy, infiltrates, nodules, and thin-walled cavities that can persist.

Disseminated coccidioidomycosis is seen in immunocompromised/HIV. This is a fulminant disease with meningitis and skin and bone involvement. Even with treatment (amphotericin B), it is frequently fatal.

Diagnose by isolating the organism using KOH smears and fungal cultures of sputum and identifying serum antibody using immunodiffusion.

Treatment of coccidioidomycosis: The common, self-limited form usually does not require treatment and may leave thin-walled lung cavities.

Treat with fluconazole or itraconazole. Use amphotericin B if there is hemoptysis or hilar enlargement on chest x-ray.

Histoplasma capsulatum

Histoplasmosis is uncommon, except in endemic areas of the southern and midwestern U.S. It is especially seen in the Mississippi and Ohio River valleys. Do not confuse this with San Joaquin Valley fever (above). Remember that the "**H**" and "**O**s" in **H**ist**O**plasm**O**sis goes with the "**H**" and "**O**s" in **OH**i**O**. Or, think of "histoplas**MO**sis" (**M**ississippi, **O**hio). It is associated with soil animals (chickens) and cave-dwelling animals, such as bats.

With acute disease, the chest x-ray shows hilar adenopathy and focal alveolar infiltrates. Heavy exposure ("epidemic," disseminating form) is suggested by a chest x-ray revealing multiple nodules in addition to the hilar adenopathy.

Quick Quiz

- Pneumonia caused by *C. pneumoniae* can be biphasic. What is the characteristic throat symptom in the 1st phase? The 2nd phase?
- Pneumonia in a patient with associated mental status changes and diarrhea should make you think of what organism?
- Your patient returns from a trip to the southwest U.S. and comes to you with erythema nodosum. What fungus do you include in your differential?
- Which endemic fungus causes hilar adenopathy, focal alveolar infiltrates, and multiple lung nodules?
- Describe the microbiologic characteristics of *Blastomyces*.
- Which patients are at increased risk for complications from infection with novel H1N1?

Diagnose histoplasmosis:

- If systemic disease, use antigen test of the blood, BAL, or urine.
- If pneumonia, use serologic tests. Complement fixation is more sensitive than immunodiffusion.

No treatment is indicated for the usual disease, although some recommend itraconazole.

Disseminated disease requires amphotericin B (usually liposomal because it gets into the lymph nodes, spleen, and marrow better—this is where histoplasmosis typically replicates most). HIV patients require chronic suppression with itraconazole.

Blastomyces dermatitidis

Blastomycosis is uncommon. It is usually acquired by middle-aged men in the central, southeast, and mid-Atlantic states. (Think of having a "blast" in Chicago.) M:F is 10:1!

Progression can be indolent to severe.

Chest x-ray shows mass-like infiltrates.

Diagnosis of blastomycosis: No skin test is available. Blastomycosis is more pyogenic than the others, and patients can cough up purulent sputum that reveals the organism with KOH prep. Buzz phrase for blasto is "broad-base, budding yeasts" (Image 3-16).

Treatment of blastomycosis:

- Indolent: observation or oral itraconazole.
- Mild-to-moderate: itraconazole x 6 months; also can use ketoconazole or fluconazole.
- Severe: amphotericin B; then may switch to itraconazole. HIV patients require chronic suppression with itraconazole (as with histoplasmosis, previous).

Image 3-16: Methenamine silver stain of pathology specimen shows the broad-base budding of blasto yeasts

Viruses

Influenza

Influenza A (common subtypes: H3N2, seasonal H1N1, and novel H1N1 [2009 "swine flu"]) and B viruses can cause primary viral pneumonia or be associated with secondary bacterial superinfection. Lung secretions grow the virus in culture.

Think primary viral pneumonia in a patient who has typical influenza symptoms with progressive worsening of cough and dyspnea. Exam is typical for pneumonia but with scant sputum production. Hypoxemia is common. In the 2009–2010 novel H1N1 influenza A pandemic, viral pneumonia was most common in young people and pregnant women.

Think secondary bacterial pneumonia as an influenza complication in the patient whose flu-like illness appears to be improving then suddenly worsens with signs of pneumonia (cough, dyspnea, and new fever). Think *S. aureus*, pneumococcus, and *H. influenzae*. Gram stain and culture of sputum usually show the suprainfecting organism.

More common than either of the above presentations is the mixed viral and bacterial pneumonia seen with influenza outbreaks. This is the patient who gets influenza and then eventually gets associated bacterial pneumonia, but time does not lapse between obvious flu and pneumonia—rather the clinical picture is one of blended disease. In this situation, the patient coughs up purulent sputum after a few days of influenza illness, then waxes and wanes between improvement and exacerbation. X-rays show areas of consolidation, and sputum may show an abundance of bacteria.

Diagnose influenza A and B with rapid antigen detection assay—especially recommended is an assay that distinguishes between influenza A and B. The rapid tests are not 100% sensitive, however, and false negatives are common. Subtyping analysis requires PCR testing and is done only at specialized labs.

Treatment: Primary prophylaxis is recommended for exposed individuals in nursing homes and in those with chronic diseases. Empiric treatment of influenza requires use of zanamivir (Relenza®) or oseltamivir (Tamiflu®) because most cases of influenza A/H3N2 have acquired resistance to amantadine and rimantadine. (Influenza B is inherently resistant to amantadine and rimantadine.) Some H3N2 and seasonal H1N1 subtypes of influenza A even have resistance to oseltamivir, but novel H1N1 (swine flu) remains susceptible.

Adenovirus

Adenovirus in adults initially causes cold symptoms (sore throat, runny nose, and cough) with eventual development of pneumonia in a small subset. Most cases of adenovirus pneumonia have been observed in the enlisted military.

Immunodeficient patients can develop life-threatening pneumonia from adenovirus.

Diagnostics are not usually done except in immunosuppressed patients (culture on respiratory secretions and PCR testing).

Treatment is supportive.

RSV

Respiratory syncytial virus generally causes only a "cold" in most adults, but the elderly and patients with immunosuppression can get pneumonia. Diagnosis can be made using a rapid test on respiratory secretions. Treatment is supportive.

VAP, HAP, and HCAP

Overview

The following is according to 2005 ATS/IDSA guidelines on hospital-acquired pneumonia.

VAP (ventilator-associated pneumonia) is defined as pneumonia that develops ≥ 48–72 hours after intubation.

HAP (hospital-acquired pneumonia) is defined as pneumonia that develops 48 hours after admission to hospital. So you can see that VAP is actually a type of HAP. But for distinction and clarity (and according to the 2005 guidelines), we treat VAP separately.

HCAP (health care-associated pneumonia) is defined as pneumonia in a patient who is not currently hospitalized but has had extensive health care contact; e.g., IV antibiotics or chemo or wound care in last month, lives in a nursing home, hospitalized more than 2 days in the last 3 months, or went to hospital or dialysis clinics for services within past month.

These 3 types of pneumonia are part of the same spectrum of disease, with the common concern that they are more likely than CAP to have multidrug-resistant (MDR) organisms.

Ventilator-Associated Pneumonia (VAP)

The organisms that cause VAP vary depending on how soon after admission patients are intubated. VAP in patients intubated within 1–4 days of admission is more likely to be caused by CAP organisms—and less likely to be drug-resistant. The more time elapsed (usually > 5 days) since admission before intubation, the more likely they are to develop pneumonia from hospital organisms that have colonized the oropharynx and upper airways—organisms that tend to be multidrug resistant (MDR).

The most commonly encountered VAP MDR infections are:

- MRSA
- *Pseudomonas* species
- *Stenotrophomonas maltophilia*
- *Acinetobacter* species

Any patient who develops new fever or clinical deterioration while on a ventilator should be suspected of having pneumonia. Incidence is highest in the first 5 days of ventilator use. Malnutrition in the ICU is an important predisposing condition.

For diagnostics, the best samples to get for culture are the deepest; e.g., protected specimen brush samples using a bronchoscope (as opposed to endotracheal aspirates) because they are less likely to be contaminated by colonizing flora.

Quantitative cultures are often used to help differentiate contaminated culture material from true infection. A threshold for culture growth is accepted for each type of specimen; when growth exceeds the threshold, pneumonia is considered present (e.g., endotracheal aspirate diagnostic threshold = 10^5 cfu/mL; protected brushings diagnostic threshold = 10^3 cfu/mL; BAL diagnostic threshold = 10^4 cfu/mL).

Treatment of VAP relies very much on results of culture to guide decisions based on local resistance patterns.

For empiric treatment of VAP:

- If the patient was recently admitted, treat for CAP organisms per Figure 3-7 on page 3-46.
- If the patient has risk factors for MDR gram negatives, then begin empiric treatment with 3 antibiotics—2 antipseudomonal drugs plus vancomycin or linezolid for MRSA (once specimens are obtained).

Note: As these terms are currently defined, patients who are admitted with pneumonia and then intubated do not have VAP. They have severe CAP or HCAP.

By definition, VAP is pneumonia that develops ≥ 48–72 hours after intubation. Remember that CAP organisms can be MDR; they are just less likely to be. Patients intubated for severe CAP are likely to have pneumonia caused by: pneumococcus, *Haemophilus*, CA-MRSA, *Klebsiella*, *Pseudomonas*, *Mycoplasma*, *Moraxella*, *Legionella*, or viruses.

Quick Quiz

- Name the drug options for empiric treatment of influenza.
- Which organisms are the usual causes when a patient requires intubation and then develops pneumonia within the first couple of days after admission?
- Characterize the organisms that cause pneumonia in patients who have been in the ICU on the ventilator for more than 5 days.
- Describe the presentation of the patient with aspiration pneumonia. With lung abscess?

Hospital-Acquired Pneumonia (HAP)

HAP (non-VAP) is not much different from VAP, except that patients are not on a ventilator. The organisms are much the same, except MDR organisms are less frequently involved, and patients are less sick.

Health Care-Associated Pneumonia (HCAP)

HCAP is similar to HAP and is treated the same. Note that HCAP patients are more likely to have MDR organisms when first evaluated, whereas HAP and VAP usually won't get an MDR pneumonia caused by hospital organisms until > 5 days after admission.

Note: Regarding HCAP/HAP/VAP guidelines, you will see the terminology change somewhat. It is probable that HAP and VAP will be defined as subsets of HCAP.

The non-changing, important point is highlighted above and again repeated here: The cause of pneumonia occurring 1–4 days after admission is likely to follow the spectrum seen with CAP; > 5 days after, more likely to be hospital-acquired organisms.

ASPIRATION SYNDROMES

With aspiration syndromes, infection generally occurs only after a large amount of material is aspirated; e.g., after endotracheal intubation, seizures, or in a severely intoxicated patient. The infiltrate usually occurs in the RLL. When a patient aspirates, it is not necessary to start antibiotics immediately because stomach contents often cause only a chemical pneumonitis.

Even so, observe the patient carefully because cavitating pneumonia and/or empyema can develop. The breath can be horrendously malodorous in those with anaerobic infection! Most common infection-causing bacteria are *Fusobacterium nucleatum*, *Bacteroides melaninogenicus*, and anaerobic streptococci.

Diagnosis is usually clinical, based on history of aspiration. Radiograph shows an infiltrate, possibly organizing into a cavity (Image 3-17 and Image 3-18). Gram stain shows mixed flora. Sputum is unreliable.

Treatment: The antibiotic used for aspiration pneumonia must cover above-the-diaphragm anaerobes (i.e., not metronidazole). A β-lactam + β-lactamase inhibitor (AM-CL or AMP-sulbactam) or clindamycin is generally recommended.

LUNG ABSCESS

A lung abscess forms after an infection causes necrotic lung to cavitate. The most common cause is aspiration of organisms from the oropharynx. Risk factors for aspiration include seizures, alcoholism, esophageal abnormalities, and swallowing problems. Typical organisms that live in the mouth are anaerobes, but alcoholics have a high incidence of gram-negative enterics (e.g., *Klebsiella*).

Lung abscess as a focus of metastatic infection can occur with right-sided staph endocarditis in injection drug abusers and in dialysis and chemotherapy patients who have chronic venous access.

Abscesses present as an indolent cough with purulent, often fetid, sputum (especially in anaerobic infections), although abscesses due to metastatic staph are more acute. The chest x-ray typically shows cavitary lesions (in the upper lobes and posterior segment of the lower lobes in cases of aspiration).

Diagnosis is usually clinical (need to exclude TB) because anaerobes are particularly difficult to culture.

Treatment with clindamycin is preferred over β-lactams because mouth anaerobes often make β-lactamases. Again, don't use metronidazole for anaerobic infections above the diaphragm! If gram-negative organisms are suspected, use a combination β-lactam/β-lactamase inhibitor drug, such as ampicillin-clavulanic acid.

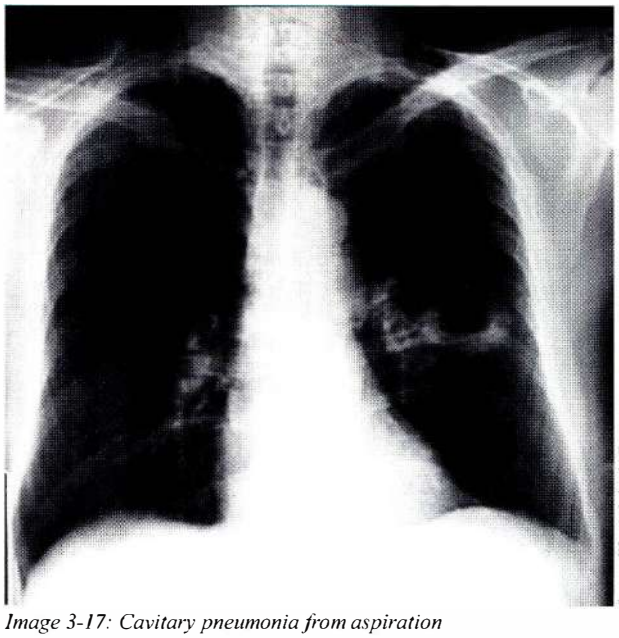


Image 3-17: Cavitary pneumonia from aspiration

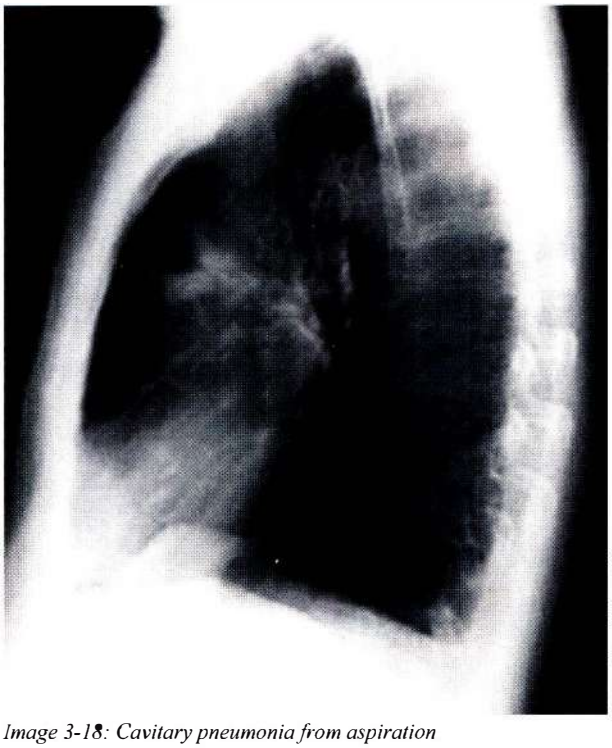


Image 3-18: Cavitary pneumonia from aspiration

MYCOBACTERIAL INFECTION

TUBERCULOSIS

Overview

Much of the following on tuberculosis (TB) is adapted from the CDC/ATS statements. You can download them from http://www.cdc.gov/tb/.

You must know TB thoroughly. For good reason—the incidence of TB began increasing after 1988. This is mainly due to TB associated with HIV infections.

Not much yellow highlighting is shown here because you must know this entire section perfectly!

The TB infection sequence goes: primary infection → latent infection → reactivation.

Primary tuberculosis occurs when aerosolized, contaminated droplets are inhaled and droplet nuclei reach the alveoli, where bacteria multiply locally for a while and then spread to areas of the body with high oxygen tension (bone, brain, kidneys, apices of lungs). Cell-mediated immunity kicks in to arrest dissemination and growth of organisms during this initial stage. Patients who do not have functional cell-mediated immunity can develop active tuberculosis during this phase—termed primary TB. Disease occurs throughout the lungs or in the sites of dissemination (e.g., meningitis), and symptoms manifest quickly after initial exposure. Children and AIDS patients are most at risk for primary disease.

Latent: In the exposed patient with a functional immune system, the organisms are held at bay by the formation of granulomas (and the patient does not develop primary infection). In the lung, the granulomas sometimes calcify and can be observed as Ghon complexes. Usually this sensitized person has no evidence of disease—but a TB skin test reacts, showing that they are infected with the organisms. A significantly reactive TB skin test in a patient with no evidence of active tuberculosis is called "latent TB infection" (LTBI).

Reactivation: With aging and development of comorbidities, the cell-mediated immune system sometimes loses its ability to keep the organisms in check, and the patient develops "reactivation TB." Reactivation disease occurs at the sites of initial dissemination (lung apices, brain, kidney, bones). The risk of reaction is highest after exposure (5% within the first 2 years and another 5% thereafter; HIV/AIDS patients are an exception and have 40% risk of reactivation within months).

Common presenting signs of reactivation tuberculosis include fever, weakness, night sweats, and weight loss. Pulmonary disease is indicated by cough, pleuritic chest pain, and hemoptysis.

The chest x-ray may show an upper lobe infiltrate and hilar lymphadenopathy (Image 3-19 and Image 3-20). Patients who develop cavities have the largest burden of organisms.

Most reactivation tuberculosis is pulmonary; 15% is extrapulmonary. Consider TB in a patient with indolent, chronic arthritis or chronic meningitis.

Miliary tuberculosis is the term given to uncontrolled hematogenous spread of *M. tuberculosis*. The clinical picture is variable—from overwhelming disease with multisystem organ failure (in primary infection) to chronic wasting (in reactivation infection). The classic chest x-ray is a faint and diffuse reticulonodular infiltrate (Image 3-21).

Diagnosis: The CDC-recommended approach to diagnose active pulmonary TB includes:

- TB skin test or interferon gamma release assay (IGRA)
- Chest x-ray
- Acid-fast smears and cultures of the sputum
- At least 1 nucleic acid amplification test (NAA; PCR)

Acid-fast bacteria (AFB) smears are cheap but are only ~ 80% sensitive (false negatives) and have a 50–80% positive predictive value. (The AFB could be non-tuberculous mycobacteria [NTM]—you don't know until you get the organism precisely identified.) Some of these issues are resolved with mycobacterial cultures, but they take a long time to grow.

NAA tests can be done on both smear-positive and smear-negative sputum samples and improve both sensitivity (to ~ 95%) and positive predictive value (because the PCR can distinguish between TB and NTM).

Do not wait for test results before treating reactivation TB if your clinical suspicion for disease is high; i.e., positive TB skin test or IGRA and risk factors.

Quick Quiz

- Describe the differences between primary TB, latent TB, and reactivation TB.
- How do you make the diagnosis of active pulmonary TB?
- What is the percentage of patients who have active pulmonary TB and nonreactive TB skin tests?

Report all persons with current reactivation tuberculosis or suspected current reactivation tuberculosis to the appropriate state or local health department.

We will cover treatment of LTBI and active TB after we discuss screening for LTBI.

Screening for Latent TB Infection

Who gets screened?

High-risk groups including:

- HIV or high-risk for HIV
- Close contacts of those with reactivation tuberculosis
- IV drug abusers
- Low-income, medically underserved populations
- Homeless
- Migrant workers
- Residents of long-term care facilities (nursing homes and jails)

How are they screened?

3 methods:

1) The tuberculin skin test is the best and most widely used.
2) Many centers now are using the IGRAs.
3) For people easily lost to follow-up, such as those in some jails and homeless shelters, screen for actual disease (chest x-ray and sputum for AFB)—or use the IGRA.

Tuberculin skin tests react in most infected people. Having said that, know that 25% of patients with active pulmonary TB have nonreactive TB skin tests. So, a negative TB skin test does not exclude TB in patients who have high pretest probabilities of disease. The tuberculin skin test is contraindicated only if there has been a necrotic skin reaction to previous tests.

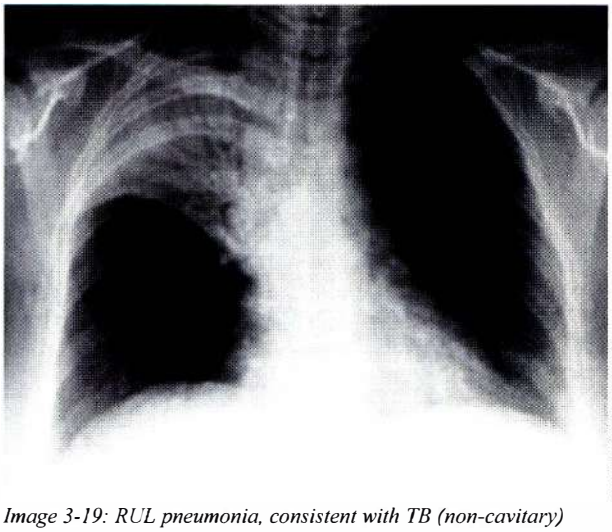


Image 3-19: RUL pneumonia, consistent with TB (non-cavitary)

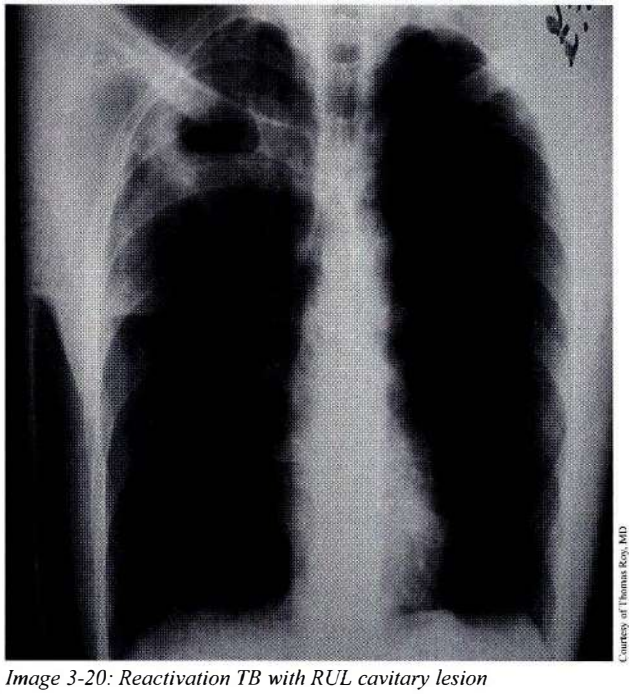


Image 3-20: Reactivation TB with RUL cavitary lesion

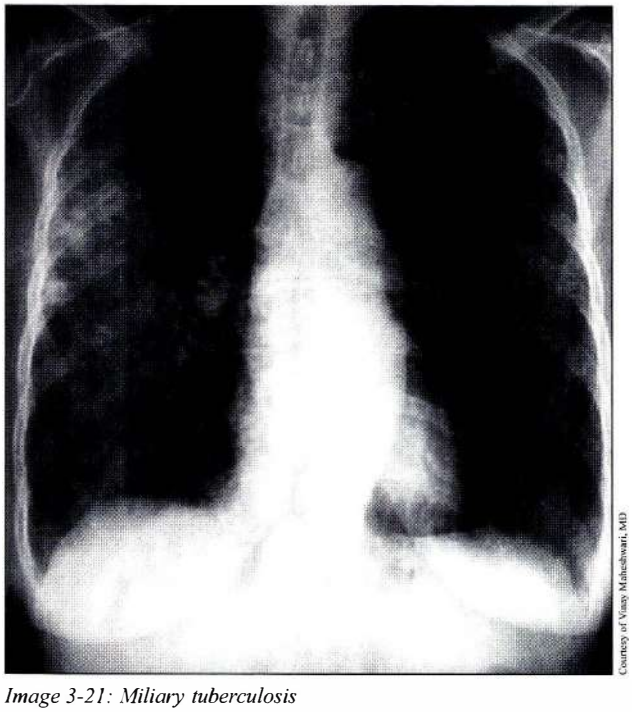


Image 3-21: Miliary tuberculosis

TB skin test may be given if the patient has had the BCG vaccine (used in some countries as a TB vaccine). Because most of these people were vaccinated as infants, the PPD result will probably be valid and should be interpreted in the standard fashion and treated accordingly.

The standard Mantoux test is an intradermal injection of 0.1 mL (5 tuberculin units) of purified protein derivative (PPD) tuberculin in the forearm. The injection site is evaluated 48–72 hours after the injection. The reading is based on the diameter of the indurated/swollen area—not the erythematous area—measured perpendicular to the long axis of the forearm (Image 3-22).

The current recommendations from the CDC as to what constitutes a significant reading take into account the degree of clinical suspicion of LTBI. The following list shows how a particular diameter of induration may be significant in one group and insignificant in another.

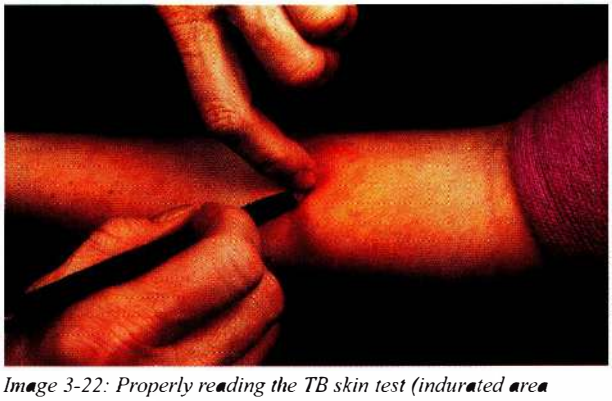
All of the following are considered significant (i.e., should be treated) skin tests:

≥ 5 mm is significant for those in the high-risk group:

- HIV or major cell-mediated dysfunction
- Fibrotic changes on chest x-ray consistent with prior TB
- Close contact with a documented case
- Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥ 15 mg/d of prednisone for 1 month or more, or receiving TNF-inhibitor or chemotherapy)

≥ 10 mm is significant for those in the intermediate-risk group:

- Homeless persons
- Recent immigrants (within 5 years) from high-prevalence countries
- Injection drug users who are HIV-negative
- Prisoners
- Health care workers!
- Nursing home patients and staff
- Patients with diabetes, silicosis, malignancy, and malnutrition
- "New converters" (discussed next)



Courtesy-CDC image library

Image 3-22: Properly reading the TB skin test (indurated area perpendicular to long axis of forearm)

≥ 15 mm is significant for the low-risk group. This includes most people in the community.

The most concise way to remember this: HIV, positive chest x-ray, close contacts, severely immuno-compromised ≥ 5 mm; no risk factors ≥ 15 mm; all the rest ≥ 10 mm.

The negative TB skin test: Sometimes the result is a true negative; sometimes it's a false negative. Interpretation of the negative test requires that you consider the following:

- Was the test placed too soon? It takes up to 10 weeks to react after an exposure. If a recently exposed patient has a negative TB skin test, recheck 10–12 weeks after exposure. Whether you treat this patient in the interim depends on whether you think the patient is really high-risk for TB (an individual judgment—not based on specific parameters). A nurse, for example, is more high-risk than an accountant.
- Can the patient actually react to the test? Is the patient possibly anergic? Worry about anergy in patients with immunosuppression (HIV/AIDS) and sarcoidosis. However, know that "control" tests are no longer recommended because, as we said, up to 25% of people with active disease have negative PPDs, even when their "control" test is reactive. Therefore, the control test does not help you interpret a nonreactive TB skin test—and in fact, has been a cause for misinterpreting test results in the past!

Here's the bottom line: If you strongly suspect TB in a patient (e.g., because they had an exposure and they are high-risk), then start empirical treatment even if the patient has a negative TB skin test result. And be aggressive about continuing the workup.

"New Converter" and the Booster Effect

The terms "new converter" and "booster effect" are used to discuss certain patients who are monitored with yearly skin tests; e.g., health care providers and nursing home patients.

The induration that occurs with TB skin testing is a delayed-type hypersensitivity reaction mediated by the memory T cell response to *M. tuberculosis,* non-tuberculous mycobacteria, or BCG.

Now, some people's T cells "remember" better than other people's T cells. Most people who have LTBI have induration within 48–72 hours of a skin test, but the sensitized people who have memory-impaired T cells do not respond within 72 hours (often, the elderly). Retesting a week later with a second TB skin test often stimulates the memory-impaired T cells to better recall previous antigen and indurate.

Stimulating T cells with bad memory in this manner is called "boosting." The significant induration that occurs on the 2nd test, but was not visible on the 1st test, is called a "booster effect." The booster effect can sometimes

QuickQuiz

- What do you do differently to read the TB skin test in the patient who has received the BCG vaccine?
- In what direction of the arm is the TB skin test read?
- In what groups of patients is a reactive TB skin test of 5 mm or more significant? 10 mm or more? 15 mm or more?
- List some reasons why a patient with true latent TB might have a negative TB skin test.
- What are you going to do for the patient who is high-risk for TB disease but has a negative skin test?
- What is the booster effect seen with TB skin testing?
- What is the definition of a "new converter"?
- Which patients should be screened with IGRA tests?
- Can a patient with a negative TB skin test still have TB? What about with a negative IGRA?

persist several months after the 1st TB test, so it becomes difficult to determine sometimes if new induration on a yearly screening skin test reflects the booster effect or new conversion from a recent exposure. (Then the patient is labeled a "new converter.") A new converter has a ≥ 10 mm increase in TB skin test induration within 2 years from the 1st nonreactive test.

Here's the classic way that boosting gets confused with new conversion:

A nursing home patient or health care worker, who has constant potential exposure to TB, gets her 1st annual TB skin test. She has no reaction. One year later, during the required yearly TB screen, she now has 10 mm of induration. Is this new induration because she has developed LTBI in the last year (and is thus a new converter), or is it due to boosting? You don't know.

Therefore, in patients who are scheduled for annual TB skin tests, a 2-step TB skin test regimen is often employed for the 1st screening. In the 2-step regimen, the patient gets an initial test, and if the initial test is nonreactive, then the patient is retested in a week, with the 2nd test establishing the patient's baseline result. If the patient has a negative baseline test but develops significant induration with the next year's test, you can say with certainty that the new induration is from recent exposure, and the patient is a new converter.

Know the definition of new converter and that TB skin tests are performed as a 2-step regimen for most patients who subsequently will be undergoing yearly TB screening.

Understand that 10 mm of induration in a nursing home patient or a health care worker is a "significant" result and merits treatment for LTBI regardless of whether it's a boosted result or a new conversion. The clinical difference is the patient's risk of reactivation TB within the next 2 years; risk is much higher after recent true conversion compared to a boosted result.

Interferon-γ Release Assays

Interferon-γ release assays (IGRAs) are used in clinical practice, and are endorsed by the CDC, to screen for active and latent TB in lieu of the TB skin test. Examples are the QuantiFERON®-TB Gold In-Tube test and the T-SPOT®.*TB* assay.

These test for the interferon-γ released during TB infection. The tests cannot distinguish active from latent disease, and they should not be used to diagnose active TB because false-negative tests in active disease can be a problem. The test is performed in a single day. There is no booster response. BCG does not cause a false-positive result.

The current CDC recommendations for use of the test include:

- IGRAs are preferred over TB skin testing for non-adherent patients and for those who have been given BCG.
- TB skin testing is preferred in children < 5 years of age.
- All other patients can get either the IGRA or the TB skin test—but not both.

The IGRA should not be used in the health care worker with a positive TB skin test, as a way to avoid isoniazid treatment if the IGRA is negative.

A negative IGRA, like a negative TB skin test, does not exclude infection in patients who have a high pretest probability of disease. Manage indeterminant tests based on likelihood of having TB.

Positive PPD Considerations

What do you do when a patient has a positive skin test or IGRA?

A positive test indicates that the patient has or has had LTBI, but not necessarily active disease. If the patient has had no previous TB workup, perform a workup for active disease: full review of systems and good physical exam, chest x-ray, sputum for acid-fast bacteria smear, culture, and at least 1 PCR test for *M. tuberculosis*.

(Sputum testing is not required if the chest x-ray does not demonstrate abnormalities and the patient's review of systems is inconsistent with active disease.)

If the PPD or IGRA is positive and active disease is present, treat for active tuberculosis, as discussed next.

If the PPD or IGRA is positive and no active disease is present, treat for LTBI—regardless of age! This includes the 80-year-old and the 1-year-old, HIV-positive and HIV-negative, and pregnant and non-pregnant (although care must be given to minimize teratogenicity and hepatotoxicity during pregnancy).

Treatment for LTBI

Give isoniazid (INH) to eradicate the TB infection before it can develop into active disease. Again, the risk of conversion is 5% within 2 years for the general population and ~ 40% within several months for HIV patients (Table 3-13).

Treatment with INH for 9 months is recommended for everyone except those with known exposure to INH-resistant organisms or history of INH intolerance—these patients should get rifampin for 4 months instead. Do not use pyrazinamide (PZA) in pregnancy because it causes birth defects.

Again, what about negative IGRAs or PPDs?

Patients who have been a close contact of someone with active TB but have a negative TB test can either be observed or treated for LTBI, depending on their risk; e.g., an HIV-positive patient would probably be treated, whereas a healthy person with no other risks would probably be observed. Children definitely get treatment. Retest the negative cases in 10–12 weeks.

Treatment of Active TB

The emergence of multidrug-resistant strains has changed the treatment of active tuberculosis. Let's first define the 4-drug and 3-drug regimens.

The 4-drug regimen:

- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)

and

- Either ethambutol (oral; preferred) or streptomycin (injection)

The 3-drug regimen consists of the first 3 drugs (INH, RIF, and PZA; "**R**est **I**n **P**eace" for the TB patient who doesn't get RIF, INH, and PZA). Remember: Do not use PZA in pregnancy.

In the U.S., all patients with active tuberculosis are initially to be treated for 2 months with 4-drug therapy, unless criteria for 3-drug therapy are met (see below). Give the first 3 drugs for the full 2 months, while the 4th drug may be dropped if the susceptibility testing shows sensitivity to the first 3 drugs. After the first 2 months, give INH + RIF for an additional 4 months—i.e., 6 months total.

HIV-infected patients on protease inhibitors are usually given rifabutin instead of rifampin. Duration of therapy for HIV-infected patients also is 6 months but may be increased in patients with CNS or skeletal involvement or with cavitary lung lesions that stay culture-positive.

Table 3-13: Positive PPD Determination Based on Preexisting Conditions

Treatment of latent tuberculosis infection	
Certain groups are at high risk of developing TB disease once infected. These people are candidates for treatment regardless of their age—after ensuring active infection is not present. The current optimum treatment regimen for all patients is 9 months of daily INH. See text for treatment of drug-resistant organisms. Treat all the following (all ages!):	
PPD result (induration)	**In people with the following conditions**
≥ 5 mm is positive in these high-risk groups	Known/Suspected HIV infection Close contacts of active cases Chest x-ray suggests previous inactive tuberculosis Organ transplants and other immunosuppressed patients with > 1 month of equivalent prednisone use (> 15 mg/d)
≥ 10 mm is positive in these intermediate-risk groups	Recent immigrant from country with high prevalence Injection drug users Employees and residents of high-risk settings (prisons, jails, hospitals, nursing homes and other long-term care centers, homeless shelters, mycobacteriology lab workers) Patients with certain comorbidities (silicosis, diabetes, advanced chronic kidney disease, leukemia, lymphoma, solid tumor malignancies, recent weight loss of > 10% of ideal body weight, gastrectomy, post-jejunoileal bypass surgery) Children < 4 years of age and others with high-risk comorbidities
≥ 15 mm is positive in low-risk patients	No known risk factors
PPD negative but high-risk	High-risk contacts of active cases

QuickQuiz

- What is the usual treatment (and for how long) for an asymptomatic, HIV-negative, 30-year-old with a positive TB skin test and normal chest x-ray?
- What is the usual treatment for latent TB? (Hint: The patient in the last question has "latent TB.")
- What are the 4 drugs used to treat active TB? How long is each given?
- What side effects are associated with the different anti-mycobacterial drugs? Required screening?
- What is Lady Windermere syndrome?
- What do you do for the healthy patient with a single sputum sample positive for *M. kansasii*?

Someone must observe all patients taking the medication unless compliance is absolutely assured. This "directly observed therapy" (DOT) is supervised by the local health department.

When can 3 drugs be used?

Only if there is a slight chance of drug-resistant infection. All the following criteria must be met:

- New TB patient and < 4% primary resistance to INH in the community
- No known exposure to a patient with a drug-resistant infection
- Is not from a high-prevalence country

Additional notes:

- Give vitamin B_6 (pyridoxine) with INH-containing regimens to prevent peripheral neuropathy and mild central nervous system effects.
- If the patient cannot take PZA, give INH and RIF for a total of 9 months.
- If the TB is resistant to INH only, stop INH and give the other 3 drugs for 6 months (total) or RIF and ethambutol for 12 months.
- Multidrug-resistant TB (i.e., to at least INH and RIF) is difficult to treat. Treatment is based on sensitivities. Consult a specialist.

Know these side effects:

INH, RIF, and PZA are all hepatotoxic.

INH: In all patients on INH, regardless of age, monitor monthly for signs and symptoms of liver toxicity. Laboratory testing is necessary only if signs or symptoms develop!

Ethambutol is not hepatotoxic, but it can cause a decrease in visual acuity. Often, decreased color perception is the 1st sign of this deterioration. It is usually reversible if the drug is quickly discontinued. Patients should have an ophthalmologic exam before treatment and periodic checks thereafter (Snellen chart, gross confrontation eye exam, and question the patient). Any inflammatory disease of the eyes is at least a relative contraindication for ethambutol.

Streptomycin is an older aminoglycoside. It is ototoxic and nephrotoxic.

NON-TUBERCULOUS MYCOBACTERIA

Non-tuberculous mycobacteria (NTM) include mycobacteria species other than *M. tuberculosis* and *M. leprae*. Many NTM species have been found to cause infections in humans, especially in immunoincompetent patients and in patients with bad lungs. Representative common examples include *M. avium* complex (MAC) which includes *M. avium* and *M. intracellulare*; *M. kansasii*; and *M. gordonae*. All of these species are sometimes found incidentally in the sputum of healthy individuals.

Pulmonary Infections with NTM

2 basic groups of NTM clinical lung disease are seen:

Pattern 1: middle-aged male with underlying lung disease (e.g., COPD or bronchiectasis) who presents with cough, weight loss, and lung infiltration—possibly even cavitary lesions. This presentation is very similar to TB, but the progression is more indolent. Radiographs often are difficult to interpret because of the underlying lung disease.

Pattern 2: middle-aged female nonsmoker who presents with cough productive of purulent sputum and interstitial infiltrates on radiograph. When the infiltrates are in the right middle lobe or lingual, the presentation is termed Lady Windermere syndrome—based on a character from one of Oscar Wilde's plays. Radiographs or CT scans often show bronchiectasis or nodules.

Because the humoral immune response of these two patient groups is generally intact, the NTM do not spread outside of the lungs.

Diagnosis is made using criteria by the ATS, which requires that a HRCT scan of the lungs show specific abnormalities (bronchiectasis and nodules) in addition to requirements for sputum results (2 or more culture-positive samples for the same organism, lung biopsy showing granulomas, or +AFB with 1 culture-positive). Nucleic acid probes are available to make a rapid diagnosis of MAC on sputum samples.

Employing the ATS criteria helps to avoid overdiagnosis of NTM lung disease and unnecessary treatment. Know that an isolated sputum sample growing NTM in a healthy person is not diagnostic of disease and does not require treatment!

Patients with severe immunodeficiencies (e.g., AIDS with CD4 counts < 100/μL) are unable to hold the infection at bay in the lungs and, instead, develop

disseminated disease with positive blood cultures and manifestations in the lungs, liver, and bone marrow. Patients present with constitutional symptoms and, often, diarrhea. Labs indicate systemic disease with leukopenia, anemia, and elevated transaminases—and blood cultures for mycobacteria are often positive.

Treatment of NTM is lengthy, tough, and should be guided by culture results. 2 antibiotics (clarithromycin and ethambutol) are given for isolated, non-cavitary, lung disease, while 3 antibiotics (clarithromycin, ethambutol, and rifampin) are used to treat cavitary lung disease and disseminated disease in AIDS patients.

Hospitalized patients with NTM do not require respiratory isolation (unlike patients with known or suspected TB).

Cutaneous Infections

Know that NTM can cause infections of surgical sites in immunocompetent patients. Patients with immune deficiencies can have disseminated disease that starts with a skin infection. Some post-surgical patients have gotten infected plastic surgery sites after exposing their healing wounds to soil and water; e.g., a trip to the beach status-post tummy tuck. Think about these organisms if you see the classic history of recent plastic surgery, travel with exposure to sand and water, and indolent drainage from the surgical site. Culprit organisms include *M. abscessus*, *M. fortuitum*, *M. chelonae*, and *M. marinum*.

TB Skin Tests and NTM

Memory T cells that have been stimulated by NTM react to the antigen in the TB skin test, but the reaction is usually not as robust as with true TB sensitization. Still, this reaction to NTM is why we have cut-off measurements for "significant" reactions with TB skin testing.

This is somewhat useful to know when you are evaluating a patient who has an indurated, but not significant, TB skin test result and AFB+ sputa (possibly the AFB ends up being identified as NTM in culture). Nucleic acid amplification testing for *M. tuberculosis* is really helpful in this situation to exclude true TB.

IMMUNOSUPPRESSED PATIENTS

IMMUNE DYSFUNCTION

Note: The following is covered in more depth in Infectious Disease, Book 1, and in Allergy & Immunology, Book 4.

Bacterial pneumonia is the most frequent cause of death in immunodeficient patients. Mortality is 50%.

Humoral dysfunction: B-cell dysfunction or decreased antibodies are seen in most patients with ALL, CLL, and multiple myeloma. These patients are especially susceptible to encapsulated organisms, including *S. pneumoniae*, *H. influenzae*, and meningococci.

Patients with hypogammaglobulinemia, asplenia, sickle cell, or abnormal complement also have a tendency to acquire infections caused by the same encapsulated organisms.

Cell-mediated dysfunction: T-cell defects are seen in patients with AIDS, lymphoma, uremia, post-organ transplant, and after use of steroids or alkylating agents. These patients are susceptible to infections caused by encapsulated bacteria (pneumococcus), *Pneumocystis jiroveci* (PJP, previously *P. carinii*), mycobacteria, viruses (CMV and HSV), fungi (*Cryptococcus*), *Legionella*, and *Nocardia*. Although the incidence of PJP has dramatically decreased with use of prophylactic drugs and HAART, *Pneumocystis* remains the most common cause of pneumonia in AIDS patients (second is encapsulated bacteria such as *S. pneumoniae*). A minority of patients with ALL have T-cell variant, and these patients may have a T-cell deficiency.

Neutrophil dysfunction: AML, CML (the myelogenous leukemias), bone marrow transplant, and in patients who are otherwise getting ablative chemotherapy. These patients tend to get infections with gram-negative organisms, staph species, *Corynebacterium jeikeium*, and fungi (*Candida* and *Aspergillus*).

ORGAN TRANSPLANT

Organ transplant patients get the same infections as patients with T-cell defects:

- During the first 30 days, patients most commonly get the usual nosocomial infections—especially gram-negative pneumonias and *Legionella*.
- 1–4 months, *P. jiroveci*, CMV, and mycobacteria.
- After 4 months, think of *P. jiroveci*, encapsulated organisms, fungus (*Aspergillus* and *Candida*), and viral infections (e.g., herpes). Also, community-acquired infections are common.

CMV infection is typically donor-to-recipient. The majority of renal and cardiac patients get CMV infections. It is the most common cause of fever after transplant! It usually occurs 6–8 weeks after transplant. CMV typically causes only a mild infection, but it is also responsible for 20% of deaths in cardiac transplants!

Think of CMV if there is a mixed bag of "-itises" because patients often get concurrent pneumonitis, hepatitis (generally mild), and adrenalitis-causing adrenal insufficiency!

Diagnosis: Finding inclusion bodies on BAL suggests CMV infection. Finding inclusion bodies on a tissue sample (lung biopsy) confirms the diagnosis.

Treatment: Ganciclovir, along with high-dose IV immunoglobulin infusion, has been beneficial in bone marrow transplant patients.

Quick Quiz

- A patient returns from a vacation to Mexico with complaints of chronic drainage from a recent tummy tuck incision. What is a likely organism?
- What are the 2 most common causes of pneumonia in patients with HIV/AIDS?
- What is the preferred regimen for treatment of *Pneumocystis jiroveci*? How about with $P_aO_2 = 60$?
- Discuss the various types of *Aspergillus* pulmonary infections.

MYELOPROLIFERATIVE DISORDERS

If a patient with a myeloproliferative disorder gets a localized infiltrate, it is usually caused by a gram-negative bacterial pneumonia. Treat empirically.

LUNG PATHOGENS IN THE IMMUNOSUPPRESSED

Pneumocystis jiroveci and PJP

P. jiroveci and encapsulated bacteria (especially pneumococcus) are the most common causes of pneumonia in HIV/AIDS. *P. jiroveci* pneumonia (PJP) also remains the most common opportunistic infection in AIDS patients. A history of PJP and/or a CD4 count of < 200 (or 14%) confer the greatest risk. The incidence of PJP in patients adherent to both antiretroviral therapy (ART) and PJP prophylaxis is near zero.

Patients present with indolent, progressive dyspnea and cough with scanty sputum +/– fever. Think about PJP in any HIV+ patient with pulmonary symptoms. Chest x-ray typically shows diffuse, bilateral, symmetrical interstitial + alveolar infiltrates.

Diagnose with sputum examination using immunofluorescent monoclonal antibodies (reveals the organism in 80% of cases, while BAL or transbronchial biopsy gets the rest). Other ways to examine sputum are Giemsa stain and Gomori methenamine silver stain, but these tests are less sensitive than the monoclonal antibody.

Treatment: IV or oral TMP/SMX or IV pentamidine are preferred 1st line drugs. Try TMP/SMX first because it can eventually be given orally. Alternatives include atovaquone, dapsone/TMP, or clindamycin/primaquine, but these alternatives are for mild cases of PJP only. A majority of PJP patients improve on the initial course of therapy (usually 3 weeks), but a good number have intolerable side effects from treatment (e.g., rash and bone marrow suppression with TMP/SMX).

Corticosteroids given concomitantly with initiating anti-PJP treatment reduce the likelihood of respiratory failure and death in patients with moderate-to-severe pneumonia. Give steroids to PJP patients with a P_aO_2 < 70 or an A-a gradient > 35.

Bacterial Pneumonia

Bacterial pneumonia, usually due to *Streptococcus pneumoniae* or *Haemophilus influenzae*, occurs in HIV/AIDS patients with CD4 counts ~ 300/µL—higher than those with PJP. HIV-positive patients have 6x increased risk of pneumonia and 100x increased risk of bacteremia with pneumococcus compared to HIV-negative individuals. Again: Pneumonia in a patient with risk factors for HIV, think about PJP and pneumococcus.

Mycobacteria

Mycobacteria: For TB in HIV/AIDS, the treatment is the same as for any other patient (see previous section). Most AIDS patients with TB come from areas where there is already a high prevalence of TB.

The most effective treatment for NTM (*M. avium* complex [MAC]) is to get the CD4 count > 100 (with antiretroviral therapy) and to initiate combination therapy against the MAC—typically using clarithromycin or azithromycin with rifabutin and ethambutol.

Fungi

Aspergillus

Aspergillus can cause invasive disease in patients with AML, ALL, Hodgkin disease, heart or bone marrow transplant, chronic corticosteroids, and with granulocytopenia lasting > 25 days (slow growing!). Occasionally, we see this disease in AIDS patients.

Previously, we discussed *Aspergillus* in the asthmatic (see ABPA, page 3-32), but that is not what we're talking about here. In this section, we're looking at invasive disease. Sputum cultures growing *Aspergillus* are usually ignored in patients with competent immune systems because *Aspergillus* is often found incidentally in normal sputum.

The spectrum of *Aspergillus* disease depends on the immune system of the patient and includes aspergilloma, invasive sinusitis, invasive pulmonary aspergillosis (IPA), and hematogenous dissemination to various organs (the most severe manifestation).

Prior to the last 5 years, IPA was one of the most feared complications of treating hematologic malignancies because mortality was very high.

Know that IPA presents as either an acute or an indolent pulmonary syndrome of fever, cough, dyspnea, and occasional hemoptysis in a severely immunocompromised patient. Occasionally, no symptoms are present in marrow transplant patients because they lack any immune response.

Diagnosis of IPA requires quick recognition of the clinical picture, HRCT of the chest (buzzword is "halo

sign" = early evidence of pulmonary infarction), and lab tests. Lung samples can be obtained and cultured—sometimes the organism is visible in path specimens and grows in culture. Galactomannan is a polysaccharide that is a major component of *Aspergillus* cell walls. Because it is a water-soluble carbohydrate, it is found in blood, urine, CSF, and BAL of infected patients. This aids in the diagnosis of aspergillosis. Know that piperacillin-tazobactam (Zosyn®) contains a significant amount of galactomannan antigen and may cause a false-positive test.

Aspergillomas are balls of fungus that grow in cavities from prior lung disease in immunocompetent people; e.g., TB, NTM, bullae. They present as very indolent disease of the lung with cough, hemoptysis, and constitutional symptoms. X-rays show cavities with fluid or fungus balls. Aside from chronic wasting and necrosis of remaining lung, the major complication is life-threatening hemoptysis. Sometimes patients do not develop typical fungus balls, but instead they have chronic infection of prior cavities with *Aspergillus*. This presentation is simply called chronic pulmonary aspergillosis. The galactomannan assay can also be used to diagnose chronic pulmonary aspergillosis, in addition to culture.

Treatment of *Aspergillus* infections depends on the form of disease:

- IPA in immunosuppressed: IV voriconazole (major reduction in mortality compared to amphotericin B)
- Aspergilloma (+/– hemoptysis): surgery
- Chronic pulmonary disease and ABPA: oral itraconazole + corticosteroids
- Sinus disease: surgery + antifungal (amphotericin B, azole, or echinocandin)

Cryptococcus

Cryptococcal pulmonary disease is associated with Hodgkin disease, corticosteroids, and transplants but not with PMN defects or neutropenia. Chest x-ray may show nodules or mass lesions. *C. neoformans* in sputum equals infection (contrary to *Aspergillus*). Needle aspiration and lung biopsy are also accurate means of diagnosing cryptococcal pneumonia. If found, perform a lumbar puncture to evaluate for CNS infection.

Patients with HIV/AIDS and CD4 counts < 100/μL are susceptible to cryptococcal meningitis.

Coccidioides

Coccidioides immitis is endemic in the southwestern U.S. (California and Arizona). Most immunocompetent patients with infection are asymptomatic or develop a mild flu-like illness that is self-limited. Disseminated or chronic infections are most common in patients with myeloproliferative disorders, Hodgkin disease, transplants, and AIDS.

Histoplasma

Disseminated histoplasmosis is common in AIDS patients with CD4 counts < 100/μL who live in endemic areas, such as the southern and midwestern U.S. It is especially found in the Mississippi and Ohio River valleys.

Nocardia

Nocardia asteroides lung infections are usually seen in T-cell deficient patients (not those with humoral deficiency) and in patients with pulmonary alveolar proteinosis. The pulmonary lesions may cavitate. Brain abscesses and subcutaneous dissemination may occur. Treat with sulfonamides.

Candida

Candida pneumonia is very rare and difficult to diagnose in immunosuppressed patients. *Candida* in the sputum is nonspecific.

Zygomycosis

Patients with leukemia are at especially high risk of pulmonary zygomycosis (a.k.a. mucormycosis). It is also seen in uncontrolled diabetics with frequent DKA. This infection has a poor prognosis.

Reactivation Infections

TB, toxoplasmosis, herpes infections, cryptococcosis, and strongyloidiasis can reactivate in the immunosuppressed.

NONINFECTIOUS INFILTRATES

Drugs may have cytotoxic or noncytotoxic lung effects:

- Methotrexate is the most common cause of noncytotoxic lung reactions and causes a hypersensitivity interstitial pneumonitis.
- Bleomycin is the most common cause of cytotoxic pulmonary toxicity.
- Gold-induced lung disease is reversible—just stop the drug.
- Bleomycin, amiodarone, and the nitrosoureas all cause dose-related pulmonary disease, while almost all other offending drugs have a hypersensitivity or idiosyncratic effect. Uremia, supplemental O_2, and radiation therapy exacerbate bleomycin lung toxicity. Transbronchial lung biopsy is the diagnostic procedure of choice, but it is usually not needed.
- Crack cocaine can cause a hypersensitivity pneumonitis, diffuse alveolar hemorrhage, and COP.

QuickQuiz

- What is the recommended treatment of invasive pulmonary aspergillosis?
- Name some causes of noninfectious pulmonary infiltrates.

Hemorrhage is common in patients with AML—it can be the sole cause of pulmonary infiltrates in these patients. But remember: In AML, rule out *Aspergillus* infection as the cause of the hemorrhage. (Also remember, hemorrhage may be caused by idiopathic pulmonary hemosiderosis, Goodpasture's, SLE, and post-bone marrow transplantation.)

Leukemic pulmonary infiltrates most commonly occur in ALL, and they always imply a high percentage of blasts. Leukostatic infiltrates (globs of WBCs in the pulmonary vessels) occur in myeloid leukemias when the WBC count is > 100,000. Half of lymphoma patients have infiltrates.

Radiation changes in the lung usually present within 6 months of treatment. These changes are divided into 5 phases with radiation pneumonitis (the acute inflammatory reaction) occurring within 6 weeks. Radiation changes (pneumonitis/fibrosis) have a characteristic chest CT appearance with sharp boundaries corresponding to field of radiation exposure.

CRITICAL CARE

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Overview

ARDS is a hypoxemic acute respiratory failure due to bilateral inflammatory lung injury with bilateral pulmonary edema.

ARDS can have a direct or indirect precipitating event. Direct causes include aspiration, pneumonia, and inhalation injuries. Indirect events are sepsis, pancreatitis, multiple transfusions, and trauma. Aspiration and sepsis are the most common. Risks increase with multiple precipitating events.

Diagnosis

The 2012 Berlin Conference Definition has replaced the 1994 American European Consensus Conference definition.

The Berlin definition eliminates the acute lung injury (ALI) category and categorizes ARDS as mild, moderate, or severe based on the ratio of P_aO_2/F_iO_2 and the response to applied positive end expiratory pressure (PEEP).

The Berlin definition requires that all of the following 4 criteria are met for diagnosis of ARDS:

1) Onset of respiratory symptoms within 1 week.
2) Chest x-ray or lung CT findings consistent with pulmonary edema—not otherwise explainable.
3) Increased hydrostatic pressure is ruled out (echocardiogram if needed) so that the respiratory failure cannot be fully explained by increased hydrostatic pressure from fluid overload or cardiac failure.
4) Moderate-to-severe hypoxemia. The degree of hypoxemia defines the severity of ARDS:
   - Mild ARDS:
     - $P_aO_2/F_iO_2 > 200$ but ≤ 300
     - On ventilator with PEEP ≥ 5 cm H_2O or on continuous CPAP with ≥ 5 cm H_2O
   - Moderate ARDS:
     - $P_aO_2/F_iO_2 > 100$ but ≤ 200
     - On ventilator with PEEP ≥ 5 cm H_2O
   - Severe ARDS:
     - $P_aO_2/F_iO_2 \leq 100$
     - On ventilator with PEEP ≥ 5 cm H_2O

In the above, P_aO_2/F_iO_2 is the ratio of P_aO_2 in mmHg over F_iO_2 as a decimal (0.21 – 1.0).

ARDS mnemonic:

- **A** (acute onset)
- **R** (restrictive lung mechanics from pulmonary edema)
- **D** (diffuse panendothelial inflammatory injury manifested in the lungs—i.e., not due to hydrostatic pressure)
- **S** (shunt hypoxemia—degree of hypoxia defines severity of ARDS)

There is typically a 48–72-hour lag time between injury and ARDS (quicker with TRALI and neurologic insults). As yet, it is unknown what all of the factors are that cause the leaky lungs in ARDS. Injury results in local edema with subsequent fluid accumulation in the interstitium and alveoli, compounded by the presence of inflammatory cells and their mediators. The inflammation causes all sorts of chaos in the lungs: microthrombi clot local vessels; protein aggregates, surfactant, and cellular debris that clog up the alveoli in "whorls." Inflammatory cells invade the interstitium and alveoli en masse, releasing more mediators and causing a ruckus. Eventually large sections of lung simply collapse, which causes shunting and hypoxemia. The microthrombotic occlusion of pulmonary vessels leads to nonperfusion of ventilated areas, causing dead space and hypercapnia—in addition to the hypoxemia (Image 3-23 and Image 3-24).

Patients initially present with symptoms of the underlying cause plus dyspnea, increased work of breathing, and eventual respiratory fatigue.

With supportive care, patients improve and enter a "proliferative phase," where their lungs repair and

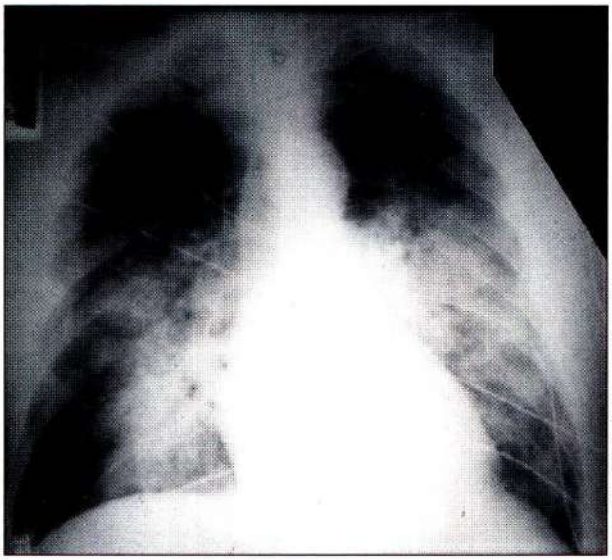


Image 3-23: PA chest showing ARDS

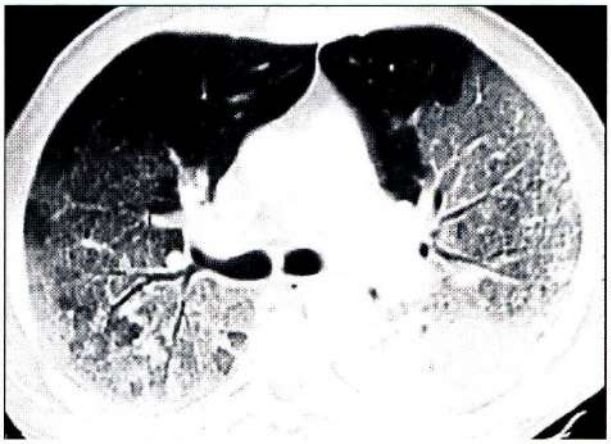


Image 3-24: CT chest showing ARDS

organize. Usually this is when they can be weaned from ventilator support. A few patients will go on to develop fibrosis as part of healing and will remain ventilator and/or oxygen dependent for a prolonged period. As yet, there is no prophylaxis for ARDS.

Death rate is 25–58% and has decreased with the use of lung protective ventilatory support strategies and improved critical care support. Death due to respiratory failure in ARDS is uncommon! The most common cause of death within the first 3 days after onset of ARDS is the underlying problem. After 3 days, nosocomial pneumonia and sepsis are the most common causes of death.

Making the diagnosis of pneumonia in the patient with ARDS is difficult because infiltrates and leukocytosis are common in ARDS. Lavage fluid in ARDS without pneumonia has nearly 80% PMNs (normal < 5%). Quantitative airway cultures (as discussed in the section on HCAP) are a valid approach to diagnosing pneumonia in these patients. Give antibiotic therapy as indicated by Gram stain and C+S results.

Treatment

Overview

Prevention of pneumonia and other complications of critical illness in the ARDS patient are important. Adequate handwashing and using sterile technique are mandatory. Selective decontamination involves using antiseptic solutions or topical antibiotics to reduce colonization in the upper airway and GI tract. It does decrease the risk of VAP, but it does not reduce mortality and it is expensive and time consuming.

Treatment of ARDS: Treat the underlying condition and provide optimized cardiopulmonary support. If the patient has an abscess, push surgeons to remove it or interventional radiology to drain it. Give empiric antibiotics if sepsis is thought to be the cause.

Keep patients slightly hypovolemic, but it is very important to provide enough volume to maintain adequate cardiac output and tissue-oxygen delivery—thereby preventing worsening lactic acidosis (and the resultant multiorgan failure).

ARDS Network FACT trial demonstrated that conservative fluid replacement (targeting normal central venous pressure [CVP], pulmonary artery occlusion pressure [PAOP], and hemodynamic function) was better than a liberal strategy. It led to decreased ICU and ventilator time and decreased organ dysfunction. Mortality, however, was similar. This trial also concluded management with CVP is as good as using a PA catheter. This fluid algorithm can be found at www.ardsnet.org.

Nutrition should be enteral rather than parenteral, if possible. This reduces the risk of catheter-induced sepsis and may also prevent translocation of endotoxin and gram-negative colonic bacteria. Recent studies with special formulae high in omega-3 fatty acids have not shown benefit in ARDS and septic shock and are now discouraged.

Ventilator Support for ARDS

PEEP stands for positive end-expiratory pressure; on the ventilator, a valve shuts when the patient is near end-expiration, while there is still positive intrathoracic pressure.

ARDS is shunt physiology, and the best way to improve oxygenation is to recruit, or "pop open," atelectatic and fluid-filled alveoli. At the same time, you want to avoid barotrauma and oxygen toxicity. To avoid oxygen toxicity, try to get a pO_2 of 60 mmHg with F_iO_2 < 60% ASAP. To "pop open" alveolar units, use PEEP; but to avoid ventilator-induced lung injury (VILI), use adequate, but not excessive, PEEP (the minimum level of PEEP that allows an adequate MAP and safe F_iO_2 of 60%).

Ventilator management has now changed with the recognition of the potential for VILI, which arises from overdistended alveoli (from an ↑ TV or ↑ end-inspiratory plateau pressure) and cyclic opening and closing of atelectatic alveoli (recruitment-derecruitment). An

QuickQuiz

- Characterize the ARDS Network approach to fluid management in patients with ARDS.
- Describe the ventilator-induced lung injury that can happen when treating ARDS.
- For ARDS, what is considered the optimal ventilator setting for tidal volume?
- Describe the specifics of permissive hypercapnia.

adequate level of PEEP prevents repetitive closure and opening of lung units. Recommendations from the NIH ARDS Network indicate improved outcome with low tidal volumes (TV) = 6 mL/kg and PEEP at adequate levels (discussed below; lung protective ventilatory support strategy). Maintaining low TV appears to be critically important, and 6 mL/kg is considered the optimal TV. Generally, we start worrying about VILI due to excessive plateau pressures at > 30 cm H_2O.

Previously, TV in the range of 12–15 mL/kg had been used, but this is too high for many patients with ARDS because their total lung capacity is much smaller than normal. There is a trend to lower tidal volumes in all patients on ventilators, whatever the cause, although there is no strong data to support a benefit as there is in ARDS.

No single ventilator mode has proven better than another for ARDS patients. An assist-control, volume-cycled ventilator mode was used in the ARDS Network trial.

Initial settings:

- F_iO_2 = 1 (then follow P_aO_2 goal as per Figure 3-8).
- TV = start at 8 mL/kg ideal body weight and work down (6 is optimal). Monitor end-inspiratory plateau pressure! Maintain < 30 cm H_2O.
- Inspiratory flow = 60 L/min.
- PEEP: See the NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary in Figure 3-8. The PEEP is determined using a nomogram of F_iO_2 and achieving the P_aO_2 goal of 55–80 mmHg.
- Some physicians use a PEEP pressure just greater than the lower inflection point on the ventilator P_V curve. And yet others use an empiric regimen, in which they adjust the PEEP to maintain adequate S_aO_2 of at least 90% and low enough F_iO_2 (< 60%). PEEP typically starts at ≤ 5 cm H_2O and usually goes up to 10–20 cm H_2O. More on PEEP on page 3-70.

Surfactant replacement, inhaled nitric oxide (investigational), and recruitment maneuvers are often added to help improve oxygenation, but have not been demonstrated to improve survival.

Recent meta-analysis suggests a survival benefit from "proning," but this has not been validated by the ARDS network. Issues around proning:

- Data support increasing the P_aO_2/F_iO_2 ratio with prone positioning, which stabilizes the anterior chest wall, causing improved physiology and recruitment of previously unused alveolar units.
- The prone position was found to get the heart off of the left lower lobe and help with expansion.
- The prone position is associated with pressure necrosis complications of the face and anterior body surface. In fact, if the ICU team is not experienced with prone positioning, all kinds of bad things can happen; e.g., extubation, venous catheters fall out, even fractures.

The only intervention currently touted as effective in reducing mortality is the lower lung volume protective ventilation strategy with 6 cc/kg tidal volume. A recent multicenter trial has demonstrated improved survival and oxygenation status associated with prone positioning of patients with severe ARDS. A recent French multicenter trial also demonstrated improved oxygenation and survival associated with use of neuromuscular blockade during the first 48 hours of ventilator management of patients with moderate-severe ARDS.

Permissive hypercapnia: The "ARDS Network low TV lung protective ventilatory support protocol" is now the standard of care for ventilatory support of ARDS. The study results show a mortality decrease. Specifically, some evidence suggests that respiratory acidosis may decrease lung injury and be protective. Permissive hypercapnia is acceptable in patients with ARDS; however, most nonparalyzed patients with ARDS on AC mode maintain a satisfactory minute ventilation.

The goal in an ARDS patient is to maintain adequate tissue oxygenation—maintain the S_aO_2 > 88%. Do not worry so much about the P_aCO_2. Allow hypercapnia to develop. The resultant acidosis can be corrected by any of the following:

- Increasing respiratory rate (RR)
- Increasing TV if end-inspiratory plateau pressure is low
- Use $NaHCO_3$

Remember: Giving $NaHCO_3$ typically results in a subsequent increase in CO_2 as $NaHCO_3 + H^+ \leftrightarrow Na^+(Cl^-) + H_2O + CO_2$.

Renal compensation for the respiratory acidosis usually ensues, and typically you do not need to give an alkali or increase the V_E. Permissive hypercapnia is acceptable in severe exacerbations of obstructive lung disease as well. Again, the therapy-determining measurement is S_aO_2, not P_aCO_2.

Permissive hypercapnia is not recommended in patients with intracranial hypertension or hemodynamic instability.

NIH NHLBI ARDS Clinical Network
Mechanical Ventilation Protocol Summary (Part I)

INCLUSION CRITERIA: Acute onset of
1. $P_aO_2/F_iO_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

PART I: VENTILATOR SETUP AND ADJUSTMENT
1. Calculate predicted body weight (PBW).
   Males = 50 + 2.3 [height (inches) – 60]
   Females = 45.5 + 2.3 [height (inches) – 60]
2. Select any ventilator mode.
3. Set initial TV to 8 mL/kg PBW.
4. Reduce TV by 1 mL/kg at intervals ≤ 2 hours until TV = 6 mL/kg PBW.
5. Set initial rate to approximate baseline minute ventilation (not > 35 bpm).
6. Adjust TV and RR to achieve pH and plateau pressure goals below.

OXYGENATION GOAL: P_aO_2 55–80 mmHg or SpO_2 88–95%
Use incremental F_iO_2/PEEP combinations below to achieve goal. [Note: Higher PEEP options (lower row) will decrease F_iO_2 and may be preferred in patients with high F_iO_2 who can tolerate higher PEEP (stable blood pressure, no barotrauma). Survival is similar with both PEEP approaches.]

F_iO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
	12-14	14	16	16	18-20	20	20	20

F_iO_2	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0
PEEP	14	14	14	16	18	20	22	24
	20	20-22	22	22	22	22	22	24

PLATEAU PRESSURE GOAL: ≤ 30 cm H_2O
Check Pplat (0.5 second inspiratory pause) at least q 4h and after each change in PEEP or TV.
If Pplat > 30 cm H_2O: Decrease TV by 1 mL/kg steps (minimum = 4 mL/kg).
If Pplat < 25 cm H_2O: TV < 6 mL/kg, increase TV by 1 mL/kg until Pplat > 25 cm H_2O or TV = 6 mL/kg.
If Pplat < 30 and breath stacking or dys-synchrony occurs: May increase VT in 1ml/kg increments to 7 or 8 ml/kg if Pplat remains < 30 cm H_2O.

pH GOAL: 7.30–7.45

Acidosis Management: (pH < 7.30)
If pH 7.15–7.30: Increase RR until pH > 7.30 or P_aCO_2 < 25 (Maximum RR = 35).
If pH < 7.15: Increase RR to 35.
1) If pH remains < 7.15, TV may be increased in 1 mL/kg steps until pH > 7.15 (Pplat target may be exceeded).
2) May give $NaHCO_3$.

Alkalosis Management: (pH > 7.45)
Decrease vent rate if possible.

Figure 3-8: NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary

Trials show no proven survival advantage in the following treatments for ARDS: early high-frequency oscillation, extracorporeal respiratory support, surfactant administration, NSAIDs, anti-endotoxin therapy, inhaled nitric oxide, and n-acetylcysteine (as an antioxidant).

To summarize, when using the ventilator in the treatment of ARDS, avoid VILI and oxygen toxicity by doing the following:

- Start TV at 8 mL/kg and reduce to 6 mL/kg when able.
- Start F_iO_2 at 1 and follow the recommendations by the ARDS Clinical Network (Figure 3-8).
- Use adequate but not excessive PEEP.
- Use permissive hypercapnia if needed.
- Use the mentioned ARDS Network PEEP dosing tables (on ardsnet.org and reproduced in Figure 3-8) as guidelines, but adjust as necessary to meet the needs of the individual patient.

Corticosteroids for ARDS

The pendulum has swung away from the use of steroids solely for ARDS inflammation. If steroids are used, ensure that there are no untreated foci of infection.

SEPSIS

Critically ill patients (especially patients with sepsis +/– ARDS) can have a normal P_aO_2 and still have abnormal O_2 uptake by the tissues. This is thought to be a major contributor to multiple organ failure.

Hypophosphatemia decreases diaphragmatic contractility in addition to shifting the O_2 saturation curve to the left. Sucralfate can cause this!

Careful! Mixed venous O_2 may be misleading in the septic patient because there is significant peripheral shunting. Lactic acid levels may be misleading as an indicator of tissue hypoxia because an increase can also be caused by failure of the liver to clear it. Nevertheless, the measurement of these data is used in decision making in the Surviving Sepsis Campaign.

Always correct the underlying problem. You may need to do surgery/drainage on a focal infection if that is causing the sepsis, even if the patient is unstable.

The utility of pulmonary artery catheterization is controversial in most cases of sepsis. Remember the following general principles regarding pulmonary capillary wedge pressure (PCWP):

- PCWP reflects LVEDP, and LVEDP is an indicator of LV function; it reflects compliance and stroke volume.
- Always read the PCWP at end-exhalation.
- Read wedge pressure in all patients on a graphed wave form (not digital printout).
- Never take patient off PEEP to read the PCWP.

QuickQuiz

- Discuss the different modes of mechanical ventilation.

LVEDP is now more often determined directly during left heart catheterization just before contrast ventriculography (rather than during a right heart cath). More on PCWP in Cardiology, Book 3.

MECHANICAL VENTILATION

Overview

The cuff of the tracheal tube should be inflated to the lowest possible effective pressure, ~ 15 mmHg. When the pressure exceeds ~ 25 mmHg, serious damage can occur to the tracheal mucosa.

Timing of a tracheostomy is controversial and takes into account specific patient variables and likelihood of requiring prolonged ventilatory support. Typically, a tracheotomy is not performed during the 1st week of intubation (barring other indications). Tracheostomy is not indicated solely to decrease airway resistance during weaning.

Ventilator-associated pneumonia is a frequent complication of mechanical ventilation. We discussed this in the section under VAP (page 3-54). Quick review: All patients are colonized with gram-negative bacteria in upper and lower airways within 74–96 hours of endotracheal intubation. It may be very difficult to sort out true pneumonia vs. colonization. For a diagnosis of pneumonia, you should see:

- New or worsening infiltrate
- Leukocytosis
- Purulent sputum or endotracheal secretions
- Fever or hypothermia

Even with this clinical scenario, there is an ongoing debate about whether more invasive tests should be done to confirm the diagnosis. More invasive tests include PSB/BAL with quantitative cultures. Empiric antibiotic treatment for VAP should cover both *Pseudomonas* and MRSA. The CDC has recently proposed new definitions for ventilator-associated events (VAE) and infectious ventilator-associated complications (IVAC), which also include the presence of possible and probable VAP.

Modes of Mechanical Ventilation

Continuous Ventilation

Controlled mechanical ventilation (CMV) has a set rate and set tidal volume that does not allow spontaneous breathing. Patient-ventilator asynchrony is a big problem. Therefore, this mode is best used in patients who are under anesthesia, paralyzed with muscle relaxants, or in deep coma.

Assist/Control (AC): This is a CMV with a set rate and tidal volume, but this mode allows the patient to initiate additional breaths "above the vent." When the machine senses that the patient is attempting to take a breath, it kicks in with a full machine-supported breath at the selected tidal volume. This is a commonly used mode of ventilation. One caveat: If patients are anxious and hyperventilating, they continue to trigger additional full machine breaths, get even more hyperventilation, and are at risk for developing auto-PEEP.

Intermittent Ventilation

Synchronized intermittent mandatory ventilation (SIMV) is similar to AC in that you dial in a set rate and tidal volume, but spontaneous breath overrides the machine. Because this spontaneous breath requires a lot of work from your patient to suck in a breath through the endotracheal (ET) tube and the ventilator circuit, we often add pressure support ventilation (PSV) to the SIMV mode so that, when the patient takes a spontaneous breath, there is a boost of pressure (you set the amount) to help overcome the resistance of the ET tube and the ventilator circuit. Typically, use pressure support of 8–20 cm H_2O, but you need to titrate this pressure for an individual patient after you see what kind of spontaneous tidal volume the patient can generate.

Note: The above volume-cycled ventilators have a "pop-off" valve set at a certain inflation pressure to prevent over-pressurization of the lungs.

Pressure support ventilation (PSV), as discussed previously: In a spontaneously breathing patient, you can supply only pressure support, and there is no need for mandatory breaths. This is a very comfortable mode for the patient because he or she determines his respiratory rate and tidal volume. However, you must have a patient with a stable respiratory drive (i.e., not heavily sedated and not paralyzed). More importantly, remember: There is no guarantee as to what tidal volume will be generated at a specific level of pressure support (no consistent direct correlation between tidal volume and pressure). If your patient is prone to—and develops—acute CHF, the lungs may acutely become "stiffer," and the unchanged level of pressure support produces a much smaller tidal volume, causing tachypnea and respiratory distress.

Pressure control: a newer form of ventilation that is actually a throwback to the first ventilators. Machine breaths are pressure-cycled, not volume-cycled. You determine the pressure you want the patient to receive on each breath and the rate at which the breaths are delivered. If the patient attempts a spontaneous breath, they get a machine breath at the pressure you have designated. This may be helpful in limiting airway pressures in patients with high end-inspiratory plateau pressure in other volume-cycled modes that leave them susceptible to barotrauma. As with PSV, there is no guarantee with respect to the tidal volume; hence, this mode must be titrated carefully at the bedside to determine the proper pressure settings.

Weaning and Failure to Wean

Weaning is now felt to be best accomplished using protocols. Generally, you do it in one of the following ways:

- Spontaneous breathing with a T-tube (SBT) protocols generally recommend progressively longer periods of breathing on a T-tube—from 10 minutes to 2 hours. Usually, once the patient tolerates 2 hours on the T-tube, the ET tube is removed. SBT can also be accomplished on the ventilator (to allow tracking of RR, TV, and V_E), using low level of PS (PS + 5 cm H_2O) or tube compensation.
- PSV, wherein the pressure is gradually reduced to the point where it is just overcoming the resistance of the ET tube. This is, in practice, pretty difficult to determine because resistance of the ET tube can vary from 3–14 cm H_2O (!) due to differing diameters and lengths, kinks, and deformations.

Failure to wean—possible causes (**DESAT**):

- **D**rugs (e.g., sedatives).
- **E**ndotracheal tube and **e**lectrolyte imbalance. Sometimes the intraluminal diameter of the tube is too small. It is common for ET tubes to decrease in diameter with time after placement related to secretions/biofilm adherent to the internal lumen. Automatic tube compensation is a newer ventilatory mode that dynamically compensates for the increased resistance of the ET tube, thereby making the final stages of weaning more predictable. Hypocalcemia hypophosphorous and hypomagnesium impair weaning.
- **S**ecretions.
- **A**lkalemia (decreases respiratory drive).
- **T**oo high a P_aO_2 and too low a pCO_2 just before extubating (should keep it near the patient's baseline).

There is potential danger in suddenly switching from positive pressure ventilation in patients with limited cardiac function or occult cardiac ischemia to full spontaneous breathing. Stopping positive pressure ventilation --→ increased venous return --→ increased cardiac filling pressures --→ need for increased cardiac output --→ CHF/cardiac ischemia in susceptible patients.

COPD patients with respiratory failure are less able to get rid of CO_2, and CO_2 production is increased with fever and with large amounts of glucose and other carbohydrates in the diet. Severe COPD patients, then, may be harder to wean if they have a fever or have had a high-carbohydrate diet.

Adjusting a Ventilator

Remember: When we are adjusting a ventilator to improve a patient's ABGs, we have to separate our actions into 2 categories:

1) Those that change alveolar ventilation (TV and rate) = changes the patient's pCO_2 and pH. Remember alveolar ventilation is inversely proportional to P_aCO_2. Alveolar ventilation = $(TV - V_P) \times RR$ (where TV = tidal volume and V_P = dead space).
2) Those that alter a patient's oxygenation = F_iO_2, PEEP, inspiratory/expiratory ratio.

PEEP

Positive end-expiratory pressure (PEEP) is a positive pressure left in the chest at the end of exhalation. This can be done purposely to a patient on a ventilator by closing a valve during exhalation and not allowing the pressure in the airways to return to zero.

You dial in a PEEP pressure—the desired end-expiratory pressure—typically 5–15 cm H_2O (can go higher in ARDS). The purpose of utilizing PEEP in mechanically ventilated patients is to help prevent the alveoli from completely collapsing at end-expiration. This prevents atelectasis and, more importantly, leads to better matching of V/Q while having less shunt fraction. PEEP also prevents atelectrauma, which is damage caused by shear forces that arise during repeated reexpansion of collapsed lung units.

Use PEEP only with diffuse lung disease! It can actually decrease the P_aO_2 if used in focal lung disease. Use PEEP in cases of diffuse lung disease if required to maintain the $F_iO_2 < 60\%$, while keeping the $P_aO_2 > 60$.

An elevated PEEP can cause:

- Pneumothorax, ventricular failure, and/or alveolar damage, which can precipitate or worsen pulmonary edema. The PEEP level recommended in ARDS is based on a nomogram as discussed previously. Some advocate using the lowest level of PEEP required to oxygenate the patient with a safe F_iO_2 (60%).
- Decreased venous return, causing decreased cardiac output and hypotension.

Auto-PEEP

Auto-PEEP usually happens when the time constant of the lung is violated in patients with high compliance and/or high airway resistance (high respiratory rate, high TV, bronchospasms).

In essence, the patients are not fully emptying their lungs during expiration prior to the initiation of the next breath. This is known as "stacking breaths" or generating auto-PEEP. A patient on a ventilator gets auto-PEEP if the ventilator is set up in a way that does not allow the patient to fully exhale before initiating the next breath. This is particularly worrisome in patients who have exacerbations of COPD or who are in status

Quick Quiz

- Name the DESAT causes of failure to wean.
- What are the 2 categories of actions you keep in mind when adjusting a ventilator?
- When should you use PEEP?
- A patient with severe COPD is placed on the ventilator. She suddenly becomes hypotensive. What steps should you follow to stabilize her?
- What is the best route to provide nutrition for a mechanically ventilated patient?
- What is the refeeding syndrome, and how do you prevent it?

asthmaticus. The auto-PEEP may become severe enough that the patient may suffer barotrauma or hemodynamic collapse secondary to the inability of blood to return to the chest. Auto-PEEP can also occur in spontaneously breathing patients with obstructive lung disease and is responsible for creating "dynamic hyperinflation" with all of the consequences of auto-PEEP combined with increased work of breathing.

Auto-PEEP can be measured in mechanically ventilated patients using either of the following 2 methods:

1) Insert an end-expiratory pause in the ventilator circuit and observe the airway pressure monitor during the pause.
2) Use newer generation ventilators that automatically measure this.

Treatment of auto-PEEP is directed toward shortening inspiration and lengthening expiration and includes 1 or more of the following to increase the time for exhalation:

1) Decrease respiratory rate
2) Decrease TV
3) Increase PIFR (peak inspiratory flow rate)
4) Decrease secretions

What do you do if your patient with severe airway obstruction has hypotension after being placed on mechanical ventilation?

1) Disconnect the patient from the ventilator and slowly bag the patient through the endotracheal tube. Check for tension pneumothorax, mucus plugs, and otherwise ensure that the ventilator is functioning properly.
2) Return the patient to the ventilator with new settings that allow for a longer expiratory phase. Specific changes: Lower the respiratory rate, increase the peak flow (shortening the time the patient gets for inspiration and, hence, allowing longer time for expiration), and reduce the tidal volume.

Note that the patient must be sedated or sedated + paralyzed to accurately measure auto-PEEP.

As a historical reference, inverse ratio ventilation is a technique that was employed in patients with ARDS, whereby auto-PEEP was purposely generated as a mechanism for "recruiting" alveoli. It's fallen out of favor because of the significant potential for harm and rare utility.

NUTRITIONAL SUPPORT

Nutritional support is extremely important and often underemphasized. Use the enteral route whenever possible. After major surgery or the onset of sepsis, metabolic requirements increase dramatically. Requirements peak in 3–5 days. If the patient is unable to eat, start enteral feedings as soon as feasible after the initial insult. Even though enteral feeding increases the possibility of aspiration, it is preferred over TPN because it tends to maintain the intestinal epithelium and its natural defenses against bacteria.

Enteral feeding is contraindicated in only 2 cases:

1) Patients with severe pancreatitis and associated abdominal pain
2) Prior to, and just after, abdominal surgery (Even in this situation, surgeons feed immediately post-op when using a jejunostomy.)

Otherwise, feed enterally! With enteral feeding, you can decrease the risk of aspiration and pneumonia by keeping the head of the bed elevated $\geq 30°$. Position of head is more important than where the feeding tube is placed; e.g., pre- vs. post-pyloric.

Refeeding syndrome occurs when severely malnourished patients are fed high-carbohydrate loads. These patients develop low total body levels of phosphorus, magnesium, and potassium.

With refeeding syndrome:

- There is a dramatic increase in circulating insulin levels and a resulting swift uptake of glucose, K+, phosphate, and magnesium into the cells—with a precipitous drop of these agents in the serum. The resulting severe hypophosphatemia causes heart and respiratory failure, rhabdomyolysis, RBC and WBC dysfunction, seizures, and coma.
- The body also begins to retain fluid (unknown why), and heart failure may result.

Prevent refeeding syndrome by starting the feeding of severely malnourished patients slowly, and by aggressively replacing phosphate, potassium, and magnesium.

PULMONARY ARTERY CATHETERIZATION

Overview

Right heart and pulmonary artery catheterization is done with a balloon-floated (Swan-Ganz) catheter.

- As the catheter is introduced—usually via the internal jugular vein—take pressure readings of the central venous pressure, right atrial (0–8 mmHg = normal), right ventricle (0–8 end-diastolic; 15–30 systolic), and pulmonary artery (3–12 end-diastolic; 15–30 systolic) pressures.
- When the catheter has been flow-directed to a small pulmonary artery, the balloon at the tip temporarily obstructs forward flow and the reading (wedge pressure, a.k.a. pulmonary artery occlusion pressure) is a reflection of left ventricular end-diastolic pressure (LVEDP). LVEDP is a reflection of LV preload (assuming compliance is not changed). This LVEDP is the all-important indicator of the likelihood for LVF and pulmonary edema.

Thermal-dilution cardiac output (CO) is done by injecting a known temperature (usually ice water at 32° F but may be room temperature) and known volume of water 30 cm proximal to the tip of the PA catheter, then measuring temperature at the tip of the catheter. These values are put into a formula that calculates CO, taking into account temperature at the tip and the volume and temperature of the fluid (D5W) injected.

The greater the difference in temperature, the higher the CO—because more warm blood is mixed with the fluid injected from the proximal catheter port before it reaches the distal tip.

Mixed venous oxygen saturation (S_vO_2) is the last measurement of venous blood before it gets oxygenated. Normally, the S_vO_2 is 78%. This number drops as the global tissue oxygen debt increases. If it gets too low, you must boost delivery of O_2 to the tissues (increase O_2 sat, cardiac output, or Hgb concentration-—discussed at the beginning of this section).

Systemic vascular resistance (SVR) measurement reflects vascular tone: vasodilated vs. vasoconstricted.

$$SVR = (MAP - CVP) \times 80/CO$$

(MAP = mean art press; CVP = central venous press)

Complications of PA Catheterization

Establishing central venous access can cause unintentional puncture of nearby arteries, bleeding, neuropathy, air embolism, and pneumothorax.

Advancing the catheter may cause dysrhythmias, which are usually transitory but may be persistent. Cardiac advancement can cause right bundle-branch block; and, in a patient with left bundle-branch block, this may result in complete heart block.

Catheter residing in the pulmonary artery may cause pulmonary artery rupture (53% mortality), venous thrombosis, thrombophlebitis, pulmonary embolism, and pulmonary infarction.

The majority of ICU physicians believe PA catheterization is helpful in select groups of critically ill patients. Even so, despite over 30 years of use, there is little proof that Swan-Ganz catheters have improved patient outcomes.

You should weigh the risks and benefits carefully for each patient.

FACT study by ARDS Network found similar outcomes using CVP vs. PAOP to guide management of ARDS patients. (See treatment of ARDS on page 3-66.)

Optional devices: Trials/developments of noninvasive hemodynamic monitoring are ongoing, such as echocardiography, tissue tonometry, surface impedance plethysmography, and esophageal and tracheal sensors that give cardiac output readings.

Know Table 3-14 and know the following hallmarks:

- Hallmark of hypovolemia: low wedge pressure. This low LV preload → low stroke volume → low CO (once HR is maxed out; CO = HR x stroke volume) → high SVR. Treat by giving fluid.
- Hallmark of cardiogenic shock: low CO (i.e., the pump ain't working) → high wedge pressure (pump backs up) and increased SVR.
- Hallmark of distributive shock: loss of SVR → initially low wedge pressure → initially have high CO (e.g., "warm" septic shock), which becomes low with shock progression. Treat septic shock by implementing all of following:
  - Remove source and treat with antibiotics.
  - Give fluids.
  - Give vasopressors (to increase SVR).
  - Know that this is the only subset of shock in which the SVR is low. In all other cases, the high SVR is the only thing keeping blood pressure high enough to sustain life.
- Hallmark of obstructive shock: low filling pressure → low wedge pressure → low CO → high SVR. Treat by resolving the obstructive problem +/– fluids.

Table 3-14: Catheterization and Shock

PA Cath: Hemodynamic Subsets of Shock

Type	CO	Wedge	SVR
Hypovolemic	Low	LOW	High
Cardiogenic	LOW	High	High
Distributive†	High-Nl-Low	Low	LOW
Obstructive‡	Low	Low	High

†Distributive as seen in sepsis, spinal, and anaphylactic shock—have total loss of SVR.
‡Obstructive as in massive PE or tension pneumothorax. From John Morrissey, MD

Quick Quiz

- Discuss the potential complications of pulmonary artery catheters.
- A patient presents with *E. coli* sepsis. Predict cardiac output, wedge pressure, and SVR in relation to normal values. (See Table 3-14.)
- Predict PA catheter values in hypovolemic shock. In cardiogenic shock. (See Table 3-14.)
- Discuss the causes of obstructive sleep apnea.
- What should be avoided in patients with OSA?

By the way, tension pneumothorax causes torsion of the heart and increased intrathoracic pressure. Torsion of the heart → twisting the great vessels, thereby causing obstruction. Increased intrathoracic pressure → decreases venous return, also causes obstruction.

SLEEP-DISORDERED BREATHING

OVERVIEW

There are various types of abnormal respiratory patterns that may occur during sleep. These vary from apnea (with obstructive and/or central origins) and hypopnea to "respiratory effort-related arousals."

Apnea is defined as cessation of breathing for > 10 sec (generally 20–30 sec) during sleep. It becomes clinically significant at 10–15 episodes per hour, and severe cases may have > 40 per hour. Oxygen saturation usually decreases by > 4% during the apneic episodes.

The 2 main classes of sleep apnea are central and obstructive, although both can coexist in a single patient.

Hypopnea is a decrease of at least 30% of baseline airflow with oxygen saturation typically decreasing by ≥ 4%.

Respiratory effort-related arousals relate to multiple arousals from sleep due to obstructive symptoms.

Patients may have daytime hypersomnolence. When severe, pulmonary hypertension/cor pulmonale (from the chronic hypoxia) and personality changes may develop.

Diagnosis is confirmed only by polysomnography (sleep study). The patient is hooked up to multiple electronic gadgets (ECG, EEG, EMG, oximeter, tidal CO_2 recorder) during sleep. Presence or absence of inspiratory effort during the apneic episode differentiates between obstructive and central apnea. O_2 desaturation to < 85% or of > 4% is significant. The frequency of hypoxic apneic episodes determines the severity of the disease. Normal is < 5–10/hr, mild is 5–20/hr, moderate is 20–30/hr, and severe disease is > 30/hr (again, various definitions).

OSA

Obstructive sleep apnea-hypopnea (OSA) is sleep apnea or hypopnea occurring despite continuing ventilatory effort. The obstructive episode is usually followed by a loud snore. Patients have daytime hypersomnolence and snoring, and may have headaches, and recent weight gain.

OSA is frequently associated with an abnormal upper airway, myxedema, and obesity (but none of these, including obesity, is a necessary feature). Causes of an abnormal airway include tonsillar hypertrophy or lymphoma, micrognathia, acromegaly, goiter, and TMJ disease.

Know that OSA is associated with several severe disease states including, hypertension, coronary heart disease, stroke, and arrhythmias.

Perioperative complications and motor vehicle accidents also are common in these patients. Patients with untreated, severe disease and those who are untreated with CHD have decreased survival.

Treatment of OSA

Treat the most persistent and significant OSA with either nCPAP or bi-level PAP. With nCPAP (nasal continuous positive airway pressure), air at constant pressure (5–15 cm H_2O) is supplied via a well-sealed nose mask. This "splints" the pharynx open at night. It is very effective. BiPAP (bi-level positive airway pressure) is similar but can be used with a nasal or full face mask and allows independent adjustment for inspiratory and expiratory pressures. This improves comfort and compliance.

You can often treat mild-to-moderate OSA successfully with weight loss, avoidance of alcohol/sedatives/hypnotics, and avoidance of sleeping in the supine position. Nasal and intraoral patency devices may also help.

Treat moderate OSA with uvulopalatopharyngoplasty and/or either nCPAP or bi-level PAP. Uvulopalatopharyngoplasty often eliminates the snoring, but, overall, it cures only 50% of OSA. It is most effective in young, thin patients with mild-to-moderate obstructive sleep apnea and in those with certain specific sites of obstruction. It is sometimes used in severe sleep apnea to decrease the amount of PAP required.

Severe OSA may require tracheostomy, which is effective.

Modafinil (Provigil®) is used if the patient is getting daytime sleepiness despite documented compliance with full therapy as discussed above.

The tricyclic protriptyline is used with varying success.

OHS

Obesity hypoventilation syndrome (OHS; Pickwickian syndrome) is defined as hypoventilation while awake, although most also have OSA.

Patients with OHS have 2 main findings:

1) BMI > 35 kg/m^2 in most
2) pCO_2 > 45 mmHg when awake

If no ABGs are available, look for an elevated bicarbonate on the serum chemistry as a clue (due to compensation for the chronic respiratory acidosis).

Treatment: Aim therapy at decreasing obesity and increasing ventilatory drive. Patients should lose weight. Progestins are respiratory stimulants and help with daytime symptoms but do not benefit concurrent OSA. OSA must be addressed separately. Treatment for the OSA may benefit the OHS.

CENTRAL SLEEP APNEA SYNDROME

Central sleep apnea syndrome (CSAS) occurs in < 5% of sleep apnea patients. Cheyne-Stokes breathing is a type of central apnea and is usually seen with CNS disease, but it frequently occurs in healthy persons when they're at high altitudes for the 1st time and is also seen in patients with CHF. Ondine's curse is a very rare syndrome, in which breathing is a voluntary function only.

Treatment of CSAS: Avoid CNS depressants, such as alcohol, sedatives, and hypnotics. Weight loss prn and avoid sleep deprivation.

Mild CSAS treatment is not standardized. Try different therapies. Supplemental nighttime oxygen has been helpful for those with hypoxemia. Acetazolamide is often helpful; it causes a metabolic acidosis that stimulates a central compensatory response. Theophylline is also being studied.

Nasal CPAP or even bi-level PAP may be useful—they are thought to decrease frequency of apneas by propping open airways that might be narrowed or closed with the apneic episodes. Note that nCPAP and bi-level PAP are also useful in patients with Cheyne-Stokes breathing.

Question: When do nocturnal O_2 desats occur without apnea? Answer: COPD/emphysema, kyphoscoliosis, and muscular dystrophy.

LUNG CANCER

NOTE

Lung cancer is the #2 cancer among men (after prostate); and the #2 cancer among Caucasian, Native American, and Alaska Native women (after breast); and #3 among African-American and Hispanic women (after breast and colorectal).

Lung cancer is the leading cause of cancer-related death in men and women (except Hispanic women, in whom breast cancer is the leading cause of death).

85% of lung cancers are linked to smoking! The risk decreases after smoking is stopped and continues to decrease for as long as the patient remains smoke free, but the risk never returns to the baseline risk of a person who has never smoked. (Similarly, lung function also improves after smoking cessation—but not to normal.)

RISK FACTORS FOR LUNG CANCER

With significant asbestos exposure alone, risk of lung cancer is 6x normal; with smoking alone, it is 10x normal. With asbestos and smoking, the risk is 60x normal (synergistic). Asbestos is associated with the 2 most common lung cancers: adenocarcinoma and squamous cell carcinoma. There is also an increased incidence of lung cancer with uranium and nickel mining and exposure to hexavalent chromium and arsenic. Heavy doses of radon in underground miners are associated with lung cancer, but home/office exposure as a cause is controversial.

Atmospheric pollution is a risk factor for lung cancer. Second-hand smoke in childhood (> 25 pack years) increases the chance of lung cancer in adulthood. Non-filter cigarettes are worse than those with filters. There is a definite genetic factor in susceptibility.

Malignant mesothelioma is associated with asbestos, but not with smoking. It is usually considered pathognomonic for asbestos exposure. Note that the death rates from mesothelioma are lower for smokers than nonsmokers (!) ... because the smokers often die of another lung cancer first! Malignant mesothelioma generally presents with pleuritic chest pain and a unilateral hemorrhagic pleural effusion.

Silica, when it causes silicosis, is considered a carcinogen.

TYPES OF LUNG CANCER

Overview

There are 4 major categories of lung cancer (shown with proportion of incidence):

1) **A**denocarcinoma (1/3)
2) **S**quamous cell (1/3)
3) **S**mall cell (1/4)
4) **L**arge cell (1/5)

(h**ASSL**e: 1/3, 1/3, 1/4, 1/5. Lung cancer is a "h**ASSL**e"!)

Adenocarcinoma just beats out squamous cell as the most common lung cancer.

Squamous and **s**mall cell cancers are usually central lesions (**S**-**S**-**S**ENTRAL). Adeno and large cell are peripheral.

Quick Quiz

- Describe the obesity hypoventilation syndrome and how it relates to OSA.
- List some risk factors for development of lung cancer besides smoking cigarettes.
- Which lung cancers are usually central in the chest?
- Which lung cancers are usually peripheral?
- Which lung cancer is most likely to cavitate?

Nowadays, lung cancer is discussed as small cell and non-small cell (NSCLC). NSCLC collectively represents adeno (with bronchoalveolar subclass), squamous, and large cell.

Non-Small Cell Lung Cancer (NSCLC)

Types of NSCLC

Adenocarcinoma is typically peripheral and is usually found incidentally. Adenocarcinoma metastasizes early, especially to the CNS, adrenals, and bones. It generally presents as a solitary nodule. A "bronchoalveolar carcinoma" is a subclass of adenocarcinoma and is now referred to as adenocarcinoma *in situ*, and may be mucinous, nonmucinous, or mixed type. This tumor may produce a large amount of frothy sputum; it has the least association with smoking and a strong association with pulmonary scars (as in IPF). In milder cases, it may be mistaken for pneumonia and in severe cases, the chest x-ray is indistinguishable from ARDS. Another new classification of adenocarcinoma is minimally invasive adenocarcinoma (MIA), which typically is a slowly growing small nodule or group of nodular abnormalities.

Squamous cell cancer, unlike adenocarcinoma, does not metastasize early. It usually is a central/hilar lesion with local extension and often presents with obstructive symptoms (atelectasis, pneumonitis), and occasionally (7%) as a thick-walled (> 4 mm) cavitation. Squamous cell lung cancer is by far the most likely lung cancer to cavitate.

Large cell cancer is typically a peripheral lung lesion and tends to metastasize to the CNS and mediastinum (may cause hoarseness or SVC syndrome).

If there is a history of asbestos exposure, think of squamous cell cancer, adenocarcinoma, and mesothelioma.

See Image 3-25 and Image 3-26.

In June of 2012, the American College of Chest Physicians, in collaboration with several societies, published a set of guidelines that recommend low-dose CT scanning as a method for lung cancer screening.

They recommend annual screening with low-dose CT only to patients who are between 55 and 74 years of age, have smoked ≥ 30 pack years, and are either current smokers or have quit within the past 15 years. Additional caveats to those who should be screened include:

- The patient should be counseled about the potential for a false-positive screening test—what it entails, including risk of harm and excess cost, as well as benefits. The greatest potential harm is the identification of nodules that end up being benign but may result in invasive procedures, such as bronchoscopy, needle biopsy, thoracoscopy, mediastinoscopy, and thoracotomy. Many patients who were diagnosed with a nodule as a result of screening also reported significant psychological distress.
- Patients should be screened only if the screening can occur at a multidisciplinary facility that can coordinate the CT scan along with interpretation, management of findings, and treatment of results.

Younger patients who do not smoke much should not undergo any form of lung cancer screening.

NSCLC: Diagnosis and Staging

First, do a careful H+P and lab tests—CBC, calcium, bilirubin, AST, ALT, and alkaline phosphatase.

Then, order a contrasted CT scan of the chest, abdomen, and pelvis to assess the lungs, liver, and adrenal glands. Further imaging, such as CT/MRI of the brain, PET scan, and bone scans, depends on the results of a full review of systems, physical exam, labs, and chest/abd/pelvis CT.

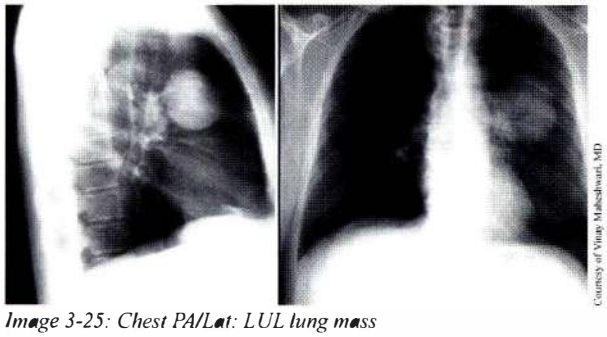


Image 3-25: Chest PA/Lat: LUL lung mass

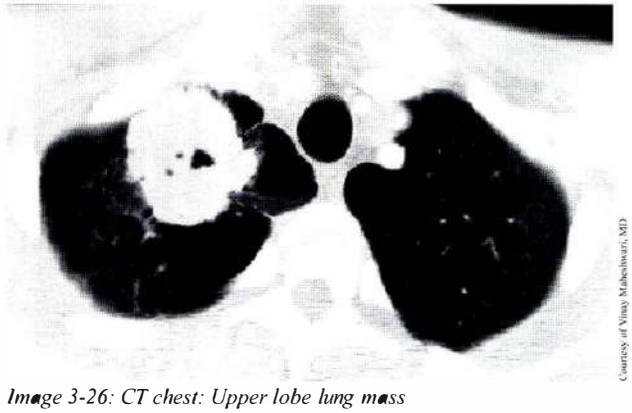


Image 3-26: CT chest: Upper lobe lung mass

Then get tissue for diagnosis.

Many different procedures exist to get lung tissue: different types of bronchoscopy, image-guided percutaneous needle biopsy, mediastinoscopy, etc. The procedure of choice is based on location of the lesion, need to assess other areas (local lymph nodes), and patient comorbidities/tolerance for procedures. Nowadays, the combination of imaging studies (including PET scans) and transbronchial procedures are making more invasive diagnostics unnecessary.

Know: If a patient has palpable supraclavicular or cervical lymphadenopathy, fine needle aspiration or excisional biopsy helps with both diagnosis and staging and is less invasive.

Pleural effusion cytology is helpful in staging, if an effusion is present. If the 1st sample does not show malignant cells, submit a 2nd (diagnostic yield > 90% on 3 samples if malignancy is cause of effusion). Closed pleural biopsies are no longer needed to diagnose cancer.

The approach differs based on patient-specific parameters. Know that after imaging, you want tissue of the primary tumor for diagnosis, unless you can get diagnosis and staging done in a single procedure using lymph nodes. Aim to biopsy the safest site that gives you both a diagnosis and the most advanced stage, so that only 1 procedure is needed.

For NSCLC, there are 4 staging categories used in conjunction with the TNM staging criteria of the past (although the specifics of TNM have also recently been revised):

1) Clinical stage (cTNM)
2) Surgical-pathologic stage (pTNM, includes clinical info plus surg-path data). Clinical and surg-path staging agree only 50% of the time. Obviously, surgical staging is most definitive.)
3) Retreatment stage
4) Autopsy stage

This 7th edition TNM staging system describes tumor, node, and mets (updated 2009):

T indicates primary tumor size:

- T1 is < 3 cm (with subsets).
- T2 is > 3 but ≤ 7 cm or tumor involves main bronchus but ≥ 2 cm distal to carina or invades visceral pleura or is associated with atelectasis/obstructive pneumonitis and extends to hilum but does not involve entire lung (with subsets).
- T3 is > 7 cm or invades the chest wall, diaphragm, or phrenic nerve, mediastinal pleura, pericardium, main bronchus < 2 cm from carina; or is associated with atelectasis/obstructive pneumonitis of entire lung; or exists as separate nodules in same lung lobe.
- T4 is tumor of any size that invades major structures (mediastinum, heart, esophagus, vertebrae) or exists as separate nodules in ipsilateral but different lung lobes.

Lymph node involvement:

- N0 = none
- N1 = ipsilateral peribronchial and/or ipsilateral hilar nodes
- N2 = ipsilateral mediastinal and/or subcarinal nodes
- N3 = contralateral nodes or ipsilateral supraclavicular nodes

Metastases:

- M0 = absent
- M1 = present (with subsets); includes malignant pleural/pericardial effusions and tumor nodules in the contralateral lung

Treatment of NSCLC Lung Cancer

- Stage I disease is defined as T1–T2a with N0, M0.
- Stages I–III patients are treated with surgery, chemotherapy, and radiation with intent to cure.
- Stage IV disease is defined as any T, any N, with M1. Treatment of Stage IV disease is palliative.
- Most patients present with Stage III or IV disease, so 5-year survival rate is only 10–15%.

Stage I and II patients are treated with lobectomies when possible. Post-resection radiation reduces the rate of local recurrence but does not appear to affect survival.

Radiation is an alternative for non-surgical candidates.

Adjuvant treatment using platinum-based doublet chemo is given to Stage Ib and II patients because it does improve survival in these groups.

Post-treatment surveillance should include an exam with x-ray 4x/year x 2 years, then twice yearly through year 5, then annually. Substitute a chest CT for 1 x-ray yearly.

Small Cell Lung Cancer

Small cell cancer is extremely aggressive, so its treatment is usually discussed separately from the others. Cavitation never occurs (unlike other lung cancers). Small cell lung cancer can cause SIADH, ectopic ACTH production, and Eaton-Lambert syndrome and various paraneoplastic syndromes (see below).

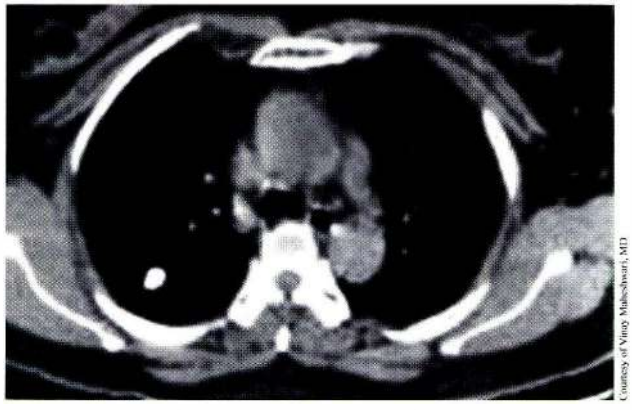


Image 3-27: CT chest: Calcified pulmonary nodule

Quick Quiz

- For patients with a lung mass and palpable cervical lymphadenopathy, what procedure is useful for diagnosis?
- How sensitive are pleural fluid analyses for diagnosing lung cancer?
- Define Stage I non-small cell lung cancer.
- Characterize the course of patients with small cell lung cancer.
- What type of calcifications indicate a benign solitary pulmonary nodule?
- What do you do with the solitary pulmonary nodule in the patient with risk factors for cancer?
- Which lung cancers are associated with SIADH? With hypercalcemia? With gynecomastia? With HPO?
- List causes of superior vena cava syndrome, both malignant and non-malignant.
- What are the most common causes of anterior mediastinal masses? Posterior? Middle? (See Table 3-15.)

Small Cell: Diagnosis and Staging

Compared to NSCLC, small cell lung cancer is just bad disease. The tumor grows fast and metastasizes early.

Most patients present with advanced disease, and the tumors do not respond as well to treatment as NSCLC. The staging system that is most useful is the Veterans Affairs Lung Study Group (VALSG), where the patient has "limited disease" if tumor is confined to the ipsilateral hemithorax or "extensive disease" if tumor has metastasized outside of the ipsilateral hemithorax. Up to 70% of patients present with "extensive" disease.

Diagnosis requires a good physical exam and review of systems, x-ray, and chest CT. Once tissue is obtained for diagnosis, lots of imaging studies are performed (contrasted CT of head, abdomen, pelvis, bone scan, and marrow biopsies, if indicated).

Know that small cell lung cancer is rapid-growing (usually all symptoms evolve within 8 weeks prior to diagnosis), so you absolutely cannot delay staging a patient more than a week after diagnosis—because the patient can get very sick very quickly.

Treatment of Small Cell Lung Cancer

Survival periods for majority of small cell lung cancer patients (and 5-year survival rates):

- Limited disease = 15–20 months (10–13%)
- Extensive disease = 8–13 months (1–2%)

For small cell cancer, use chemotherapy, radiation therapy, or occasionally adjuvant surgery. Because of the poor prognosis, all treatment for small cell cancer is only palliative.

SOLITARY PULMONARY NODULE

The solitary pulmonary nodule is a nodule in the middle-to-lateral 1/3 of the lung, surrounded by normal parenchyma. 35% are malignant.

Most solitary pulmonary nodules are found on chest CT and require rescanning with CT at intervals. Size of the nodule and patient's risk for lung cancer determine whether to follow the nodule with several scans at intervals or to take it out.

When a nodule is > 1–2 cm in diameter, a PET scan usually is done prior to surgery to help with diagnosis and staging.

Calcification of a solitary pulmonary nodule suggests it is benign. It is virtually always benign if the calcification is "popcorn" (hamartoma), laminated ("bulls eye" = granuloma), or has multiple punctate foci or dense central calcification (Image 3-27).

In low-risk patients (e.g., age < 35 and a nonsmoker), it is acceptable to follow a solitary calcified nodule with chest x-rays q 3 months. It is considered benign if, after 2 years, there is no growth. There is still controversy regarding semi-solid nodules (ground glass nodules), and most feel that a follow-up of 4–5 years for stability is required due to the risk of bronchoalveolar cell carcinoma.

High-risk patients require a diagnosis. This can be accomplished using any of the following:

- Fine needle aspiration (must be able to hit the center of the nodule; 10–15% risk of pneumothorax).
- Bronchoscopy (won't reach peripheral lesions).
- Surgical lobectomy (can remove the nodule at the same time).
- If nodules are > 1 cm in diameter, 5-fluorodeoxyglucose + PET scan also may be able to sort out benign from malignant lesions, but PET is very unhelpful in bronchoalveolar or carcinoid tumors.

PARANEOPLASTIC SYNDROMES

Paraneoplastic syndromes (favorite topics for exam questions) occur in ~ 2–20% of lung cancer patients:

- **Hypercalcemia** (from PTH-secreting cancer) is associated with squamous cell cancer (think sCa++mous!). The calcium level is proportional to the tumor bulk. Hypercalcemia is seen less often in large cell (12%).
- **SIADH**, **ectopic ACTH production**, and **Eaton-Lambert syndrome** are associated with small cell cancer. (Wow, small cells do all that?) Note: Diabetes insipidus is not a paraneoplastic

Table 3-15: Mediastinal Masses — Type Based on Location

Anterior		Middle	Posterior
1) Thymoma	6) Aortic aneurysm	1) Lymphoma	1) Neurogenic tumors
2) Thyroid tumor	7) Lymphoma	2) Cysts	2) Gastroenteric cysts
3) Parathyroid tumor	8) Thymus	3) Lymphadenopathy	3) Esophageal lesions
4) Teratoma	9) Other endocrine tumors	4) Aortic aneurysm	4) Aortic aneurysm
5) Lipoma		5) Hernia	5) Hernia

Of the primary mediastinal tumors:

20% = Cysts
20% = Neurogenic tumors
20% = Thymomas*
10% = Lymphomas
10% = Teratomas
20% = Miscellaneous

*Note that the thymomas are associated with autoimmune diseases, such as myasthenia gravis.

syndrome. If a patient presents with this and a lung cancer, consider brain metastases!

- **Gynecomastia** is associated with large cell cancer.
- **Hypertrophic pulmonary osteoarthropathy** (HPO) is especially associated with adenocarcinoma, but it is seen in all 3 NSCLC types. With HPO, patients get clubbing and new bone formation on the long bones, which appear dense on x-rays. These patients often present with only painful ankles and clubbing.

SUPERIOR VENA CAVA SYNDROME

Superior vena cava syndrome (SVC) is a medical emergency. 85% of malignancy-associated cases are caused by small cell or squamous cell lung cancers (less often, lymphoma and metastatic tumors). Permanent central venous access is an emerging cause.

Presentation includes swelling of the neck and face (especially the periorbital region), shortness of breath, and cough. Exam is very significant: distended neck veins with visible collaterals, edema across the chest and onto the face, and difficulty breathing. Hypotension may also be present.

Diagnosis is usually obvious by looking at the patient. Contrasted CT is the recommended imaging. If the patient does not already carry a diagnosis of malignancy, and the chest CT does not show one, look for it! Tracheal obstruction is a major concern.

Treat less acute cases with diuretics and elevation of the head. Steroids help reduce tumor size only in lymphomas. Radiation helps NSCLC and other solid tumor mets. Chemotherapy helps small cell lung cancers. All of these interventions are strictly palliative.

In the rare case where the cause of SVC is nonmalignant (e.g., aortic aneurysm, goiter, benign tumors), surgery can help. If the cause is venous thrombosis due to an indwelling central venous catheter, the catheter should be removed and the patient should be anticoagulated.

MEDIASTINAL MASSES

See Table 3-15 on page 3-78.

FOR FURTHER READING

[Guidelines in blue]

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SIXTEENTH EDITION

INTERNAL MEDICINE REVIEW

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NEPHROLOGY

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Nephrology

RENAL TESTS

URINALYSIS (U/A)

Proteinuria is an important indicator of underlying renal pathology; normal 24-hour urine protein is < 150 mg. Greater than 2.0 g/d (or 40–50 mg/kg/d) indicates significant glomerular pathology. Patients with proteinuria < 1 g/d are more likely to have interstitial renal disease. Medullary cystic disease and obstructive uropathy are the only exceptions in which there can be pathology and a normal urine sediment with minimal proteinuria. Know that urinary light chains in myeloma are not picked up on urine dipstick, and also know the causes of false-positive urine albumin on dipstick: very alkaline urine with a pH > 8, fever, heart failure (HF), urinary tract infection (UTI), hematuria, and very concentrated urine.

Transient proteinuria is common in people during a febrile illness, after strenuous exercise, and in patients with HF and COPD. Recheck urine when the acute situation has passed. If the repeat urinalysis is negative, the condition can be considered benign. There is an entity called benign orthostatic proteinuria, in which the proteinuria reverts to near-normal values when the patient is supine.

Spot protein:creatinine ratio has become the standard method to determine proteinuria because it requires only a random urine sample. The ratio of the protein:creatinine equates roughly to the 24-hour urinary protein in grams (i.e., a protein:creatinine ratio of 3.5 = a 24-hour urine of 3.5 gm). This test has become the recommended test to determine and follow proteinuria in patients with renal disease. Proteinuria ranges, using spot ratio:

- < 0.15 (150 mg) = normal
- 0.03–0.3 (30–300 mg) = microalbuminuria
- 0.3–1 = overt proteinuria, usually due to interstitial disease
- > 3–3.5 = nephrotic range

Microalbuminuria is the earliest indicator of diabetic and hypertensive nephropathy—and is too small to be detected on the standard urine dipstick.

RBC casts or "**dysmorphic**" RBCs indicate probable glomerulonephritis/nephritic syndrome. When there are few RBCs on microscopic analysis, but the urine dipstick is positive for blood, think of hemoglobinuria or myoglobinuria (rhabdomyolysis). One unusual cause of hemoglobinuria is lysis of RBCs in very dilute urine.

The big challenge is determining if **hematuria** is due to intrinsic renal disease or genitourinary bleeding. Hematuria associated with proteinuria, especially if dysmorphic cells and/or RBC casts are present in the urine, is always due to glomerular bleeding. The most common causes of isolated glomerular hematuria (normal renal function, no proteinuria) are IgA nephropathy, thin basement membrane disease, and early Alport syndrome. Strenuous exercise can cause transient hematuria. Patients with sickle cell trait may also have hematuria. Isolated microscopic or gross hematuria is more likely to be urologic in origin. In older patients, complete GU imaging with renal U/S, MRI, or CT must be performed to exclude renal cell or other GU tract carcinomas.

With eosinophiluria, think of drug-induced interstitial nephritis.

With coarse granular casts or "muddy brown" casts, think acute tubular injury.

Oval fat bodies ("maltese crosses" under polarized light) may be seen in nephrotic syndrome.

SERUM CREATININE

Creatinine is the common screening measure of renal function but varies depending on the amount produced by muscle tissue. The more muscle tissue one has, the higher the creatinine. Also, if muscle tissue breaks down (as in rhabdomyolysis or myositis), creatinine values can rise acutely. An unusually rapid rise in serum creatinine (more than 1.5 mg/dL over 24 hours) suggests rhabdomyolysis-induced renal failure. With aging, there is less muscle mass, and the creatinine may be normal despite reduced renal function.

Serum creatinine (sCr) is artificially increased by cimetidine, probenecid, tenofovir, and trimethoprim. These drugs decrease the tubular secretion of creatinine (elevating the serum value), but true glomerular filtration is not affected. Acetone and cefoxitin interfere with the test for creatinine and may give falsely elevated results. An elevated (> 20:1) BUN:Cr ratio indicates either prerenal azotemia (low flow and increased absorption) or increased protein breakdown. The increased protein breakdown can be due to increased protein intake, GI bleed, total parenteral nutrition (TPN), catabolic states, or steroids that increase protein turnover.

Cystatin C is a nonglycosylated protein that is produced at a stable rate from all nucleated cells and is almost exclusively removed by glomerular filtration. Serum cystatin C concentration therefore better reflects the glomerular filtration rate than sCr. However, it is not currently readily available, though it can be obtained when a more accurate measure of glomerular filtration is necessary.

GFR

Glomerular filtration rate (GFR) is a measure of overall renal function. Creatinine clearance is used to estimate GFR. Creatinine is released from skeletal muscle at a fairly constant rate and is not filtered entirely by the glomerulus, although GFR has been traditionally calculated as:

$$GFR = U_{Cr}V/P_{Cr}$$

where UV is the total urine creatine/24 hours divided by the serum creatinine (sCr).

The most accurate method in patients with impaired renal function is to calculate GFR using one of the creatinine-based formulas.

There are 2 main creatinine-based GFR formulas:

1) Modification of diet in renal disease (MDRD) GFR formula requires serum creatinine, race, sex, and age.
2) The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) GFR equation is another creatinine-based formula that is more accurate than MDRD at near-normal kidney function (eGFR > 60 mL/min/1.73 m^2).

Laboratories are now routinely providing either the MDRD or CKD-EPI GFR on their reports. Online calculators are also available to determine GFR accurately.

The Cockcroft-Gault formula is another acceptable way to estimate GFR as CrCl =

[(140 – age) x (Wt) x (0.85 if female)] / (72 x sCr) [eq 1]

[CrCl = mL/min; age = years; wt = kg; sCr = mg/dL]

Especially at higher levels of GFR, the CKD-EPI equation is the equation of choice in the general population. The CKD-EPI equation was developed to provide a more accurate estimate of GFR among individuals with normal or only mildly reduced GFR. A calculator for the estimation of GFR using the CKD-EPI equation may be obtained at the following website: www.kidney.org/professionals/kdoqi/gfr_calculator.cfm.

Both the MDRD and Cockcroft-Gault equations are less accurate in populations with normal or near-normal GFR. MDRD equation frequently underestimates GFR when it is greater than 60 mL/min/1.73 m^2.

Only use these GFR equations when the serum creatinine level is in a steady-state and the patient does not have acute kidney injury (AKI).

Estimation equations for GFR are not very accurate when there is an extreme of age and weight and in patients with amputations, cirrhosis, or pregnancy. In these situations, collect a 24-hour urine to estimate GFR (UV/P). Another option is to measure serum cystatin C and utilize a cystatin C-based equation to accurately determine GFR.

FE_{Na}

The fractional excretion of sodium (FE_{Na}) is the ratio of excreted Na^+ to the total filtered load of Na^+. It is most useful in evaluating oliguric acute kidney injury and is primarily used to differentiate prerenal azotemia from acute tubular necrosis (ATN):

- Prerenal azotemia = FE_{Na} < 1%
- Acute tubular necrosis = FE_{Na} > 2%

Other causes of AKI with FE_{Na} < 1% include: contrast-induced ATN, cardiorenal syndrome, hepatorenal syndrome, nonoliguric ATN, pigment nephropathy (hemoglobinuria, myoglobinuria), and acute glomerulonephritis.

$$FE_{Na}(\%) = (sCr \times uNa) / (sNa \times uCr) \times 100 \quad [eq\ 2]$$

Values for FE_{Na} that are not low are difficult to interpret when there is concurrent use of diuretics, which are commonly used in patients with AKI. The natriuresis from a diuretic may increase FE_{Na}, even in patients with prerenal disease. In these situations FE_{Urea} can be used.

FE_{Urea}

The fractional excretion of urea (FE_{Urea}) is a measurement of excreted urea over the total filtered load of urea. FE_{Urea} is more accurate than the FE_{Na} in patients receiving diuretics when the FE_{Na} is higher than expected for prerenal disease.

$$FE_{Urea}(\%) = (sCr \times U_{Urea}) / (BUN \times U_{Cr}) \times 100 \quad [eq\ 3]$$

FE_{Urea} < 35% is suggestive of a prerenal state.

RENAL BIOPSY

Biopsy is used to diagnose unexplained causes of acute kidney injury, nephrotic syndrome, and glomerulonephritis. In transplant patients, it is routinely utilized to evaluate increases in the sCr to distinguish between medication toxicity, ATN, viral infections, and acute rejection.

ACID-BASE DISORDERS

Disorders that affect pH resulting in an acidosis or alkalosis are acid-base disorders. Primary acid-base disorders are either respiratory or metabolic in origin:

- Primary respiratory disorders: The change in P_aCO_2 causes the initial change in pH; and the kidney slowly responds in an opposite direction by dumping or holding on to HCO_3^-.
- Primary metabolic disorders: The change in HCO_3^- causes the initial change in pH; and the respiratory rate immediately increases or decreases.

Again: The kidneys respond slowly to changes in pH while the respiratory rate responds immediately.

MECHANISMS

There is really only 1 chemical equation you must know to calculate and understand all acid-base problems.

This is the Henderson-Hasselbalch equation. It is derived from the bicarbonate buffer equation shown here:

$$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2 \quad [eq\ 4]$$

HCO_3^- is bicarbonate. H_2CO_3 is carbonic acid. CO_2 is carbon dioxide. These 3 molecules are in equilibrium with one another. From the above equation is derived the

QuickQuiz

- What lab findings suggest that hematuria is caused by GN?
- What effect does respiratory rate have on pH? How quickly does this occur?

Henderson-Hasselbalch equation. (Derivation is shown in Appendix A at the end of this section.)

$$pH = pK + \log (HCO_3^- / [0.03 \times P_aCO_2]) \quad [eq\ 5]$$

… which can be more easily used as:

$$H^+ = 24 \times (P_aCO_2 / HCO_3^-) \quad [eq\ 6]$$

This equation tells us that the body has only 2 ways to control the serum pH:

1) Regulate the respiratory rate and tidal volume; thus, control the P_aCO_2.
2) Regulate the kidney's reabsorption of HCO_3^-.

It further shows that it is the ratio of P_aCO_2 to HCO_3^- that determines pH and not the absolute levels.

Soon we will go over a quick and more exact method of calculating acid-base status; but first, let's discuss anion gap, osmolal gap, and causes of acid-base abnormalities.

Remember: Significant alkalemia of any etiology can cause the diffuse paresthesias/numbness and muscle spasms we usually associate with acute hyperventilation; the high pH increases the fraction of bound calcium. The resulting decrease in ionized calcium produces these symptoms of hypocalcemia. There is no change in total serum calcium (ionized + bound). This effect also can be induced by rapid overload with intravenous HCO_3^- or with citrate (massive blood transfusion). On the other hand, patients with both metabolic acidosis and hypocalcemia are protected from the hypocalcemia since acidosis decreases the fraction of bound calcium and increases the ionized calcium. Correction of acidosis prior to correction of hypocalcemia in this setting removes the protective effect of the acidosis, and can precipitate seizures.

ANION GAPS

Serum Anion Gap

The serum anion gap, simply called "anion gap" (AG), is always determined using measured ions found in the chemistry panel.

$$AG = Na^+ - (HCO_3^- + Cl^-) \quad [eq\ 7a]$$

Alternatively, you can use:

$$AG = [(Na^+ - HCO_3^-) - Cl^-] \quad [eq\ 7b]$$

These are the same formula. Regardless of which way you use it, be very certain about your order of operations, so you get the correct value. Note that K^+ is left out. This is because it does not change enough to affect the gap since it is mainly an intracellular ion. The normal AG values already reflect a normal K^+ level.

Table 4-1 describes how a normal anion gap is generated.

The AG is a determination of unmeasured anions, which, when elevated, indicates an increase in unmeasured acids. Why is this? Because most of the chemicals that add extra anions to the blood in a pathologic fashion are acids (e.g., ketoacids, lactate, metabolites of ethylene glycol, and methanol).

And these acids are composed of an unmeasured anion with a positively charged hydrogen, H^+ (which decreases pH).

Normal values for the AG vary depending on the lab you use. Typically, normal is 10 +/– 3 (i.e., 7–13), and these are the values used in this section.

Table 4-1: Derivation of the Anion Gap (AG)

The anions (A^-) in blood include HCO_3^-, Cl^-, phosphate (phos), sulfate, albumin, and organic acids. The cations are Na^+, K^+, Ca^{++}, and Mg^{++}. Because plasma remains neutral, the anions and cations must balance, or:

$$(Na^+ + K^+ + Ca^{++} + Mg^{++}) - (HCO_3^- + Cl^- + phos + sulfate + albumin + organic\ acids) = 0$$

This is very cumbersome so some normally unmeasured ions that stay relatively constant have been dropped, leaving only the major measured ions. Pulling these unmeasured ions out of the equation results in a gap, called the anion gap:

$$*Anion\ Gap = Na^+ - (Cl^- + HCO_3^-)$$

But, didn't we remove unmeasured anions and cations? Why is it called the anion gap? Good question! The answer is that because the unmeasured cations' concentrations rarely change much, it is easiest to just think of the AG as a measurement of the unmeasured anions (mostly albumin). Any change in this gap is due to added anions such as ketones or lactate. So, this gap is commonly taught as the "anion gap" rather than the "unmeasured anions minus the unmeasured cations gap"! The anion gap is usually about 10 mEq/L (+/– 3).

Remember that any increase in unmeasured anions always is 1:1 with the increase of H^+—so high AG always indicates metabolic acidosis.

*Note that anions used in the AG are extracellular, while K^+ is intracellular and therefore not part of the abbreviated equation.

Under normal conditions, albumin is the main contributor to the AG; therefore, hypoalbuminemia lowers the "normal" AG (~ 2.5 mEq/L decrease in the AG for each 1 g/dL decrease in albumin).

Always calculate the AG when presented with acid-base and electrolyte problems. As shown in Table 4-1, an elevated anion gap means an increased H^+, which always means metabolic acidosis. The differential diagnosis is different for a high anion gap metabolic acidosis (HAGMA) vs. a normal anion gap metabolic acidosis (NAGMA).

Note: Ethanol intoxication itself does not cause an elevated anion gap, but alcoholic ketoacidosis does.

Urine Anion Gap

The Urine Anion Gap (UAG) is used to evaluate the etiology of NAGMA to differentiate between gastrointestinal loss of HCO_3^- and renal tubular acidosis (RTA; see page 4-14). UAG is determined using the measured ions in the urine: Na^+, K^+, and Cl^-, expressed in mEq/L.

$$UAG = Na^+ + K^+ - Cl^- \quad [eq\ 8]$$

UAG is an estimate of the unmeasured ions in the urine, the most important one being NH_4^+:

- Normal value of UAG is close to 0.
- A positive UAG value suggests low urinary NH_4^+ (e.g., RTA Type 4).
- A negative UAG value suggests high urinary NH_4^+ (e.g., diarrhea). Remember ne**GUT**ive UAG in cases of diarrhea.

In the setting of metabolic acidosis due to extra-renal bicarbonate losses, renal H^+ excretion should be high, and H^+ is excreted in the form of NH_4^+.

Table 4-2: AG and OG in the Obtunded Patient

Anion Gap	Osmolal Gap	Consider
High	Very High	Methanol and ethylene glycol; ketoacidosis and lactic acidosis; chronic kidney disease
High	High	Ketoacidosis and lactic acidosis; chronic kidney disease
High	Normal	Salicylate poisoning; methanol or ethylene glycol ingestion after substrates have been converted to acid metabolites.
Normal	High	Isopropyl alcohol, acetone, or ethanol ingestion
Normal	Normal	Think carbon monoxide poisoning—before lactic acidosis develops.

OSMOLAL GAP

The osmolality of the blood is determined mainly by concentrations of Na^+, glucose, and urea.

The osmolal gap (OG) helps you determine whether unmeasured osmotically active substances (osmoles) are circulating in the blood (and possibly causing an acidosis). The OG is the difference between the measured serum osmolality (from the lab) and a calculated estimation of what the osmolality ought to be—if the only effective osmoles present are the normal ones (sodium, glucose, and urea). Use the following formula to calculate the serum osmolality (sometimes 3 and 20 are used to substitute for 2.8 and 18—it makes the math easier):

$$Osm_{calc} = 2[Na^+] + (BUN/2.8) + (glucose/18) \quad [eq\ 9]$$

Subtract this value from the lab-measured serum osmolality to get the OG. Therefore:

$$OG = Osm_{meas} - Osm_{calc} \quad [eq\ 10]$$

$$OG = Osm_{meas} - (2[Na^+] + BUN/3 + glucose/20) \quad [eq\ 11]$$

Know that a normal OG is < 10. Table 4-2 contains a list of disorders that cause a high OG.

Important causes to know specifically are methanol and ethylene glycol ingestions and propylene glycol. Chronic kidney disease causes a high OG from retention of small solutes. Similarly, lactic acidosis and ketoacidosis cause a high OG from the accumulation of unknown small solutes and not from the actual lactic acid or ketoacids.

Know that isopropyl alcohol ingestion is not associated with acidosis, even though the osmolal gap is increased (so the AG is normal). Nontoxic causes of an increased OG and normal AG are mannitol, sorbitol, and glycerol.

The main use of OG is in the workup of a patient with possible acid alcohol ingestion (e.g., ethylene glycol, methanol, or propylene glycol). Especially consider these possible poisonings if the OG > 25 mOsm/kg:

- Ethylene glycol is a common primary ingredient in radiator antifreeze solutions.
- Methanol is a common ingredient in paint thinners and deicing solutions (e.g., windshield washer fluids). Rarely, methanol is an inadvertent contaminant of "moonshine." Methanol is a by-product of grain fermentation.
- Propylene glycol is a solvent used in IV lorazepam. It may cause a HAGMA + OG if the lorazepam is given as a continuous infusion.

Know that these poisons quickly convert to toxic metabolites—which do not cause an increased OG. These acidic metabolites actually cause the HAGMA. It is fairly early after ingestion when you see both the HAGMA and the elevated OG because the initial substrate is still around as the metabolites are being formed.

High OG without acidosis (with a normal chemistry and anion gap) suggests ethanol, isopropyl alcohol, or acetone ingestion. Table 4-2 gives you clues as to causes of an increased AG and OG in the obtunded patient.

QuickQuiz

- What is the calculation used to determine the serum osmolality? The osmolal gap?
- What substances are associated with an increased OG and normal AG?
- What substances cause both an increased AG and OG?
- What are the 2 main causes of NAGMA?
- Which NAGMA is associated with hyperkalemia?
- What are 2 causes of NAGMA and hypokalemia?

The metabolite of isopropyl alcohol is acetone, which is less toxic than the original alcohol. Patients can develop stupor, coma, and hypotension. Ventilatory support, intravenous fluids, and vasopressors are sometimes needed, but symptoms sometimes resolve with supportive care once the original ingestion is completely metabolized.

METABOLIC ACIDOSIS

Etiology

Metabolic acidosis occurs with the following:

- Overproduction of lactic acid or ketoacids
- HCO_3^- wasting (renal tubular acidosis [RTA] or diarrhea)
- Failure to excrete daily acid production (renal failure)
- Ingestion of agents that are acids (salicylates) or are metabolized to acids (methanol, ethylene glycol, paraldehyde) or cause a lactic/ketoacidosis (salicylates, isoniazid, and iron)

Normal Anion Gap Metabolic Acidosis

Normal Anion Gap Metabolic Acidosis ([NAGMA]; also called "hyperchloremic" acidosis) has a commensurate increase in Cl^- with the decrease in HCO_3^-. The Cl^- is retained to maintain electrical neutrality. Table 4-3 reviews common causes of NAGMAs and HAGMAs.

The 3 causes of NAGMA:

1) Usual: Loss of HCO_3^- due to diarrhea or proximal RTA
2) Increased organic acids (NH_4^+; e.g., patients on total parenteral nutrition)
3) Inability of the kidney to excrete endogenous acids (renal failure or distal RTA)

Again, the main causes of NAGMA are diarrhea and RTA. More on RTA on page 4-17.

NAGMA plus hyperkalemia, think Type 4 RTA (hypoaldosteronism).

NAGMA plus hypokalemia is caused by:

- GI loss (sometimes)
- RTA Types 1 (distal) and 2 (proximal)

On the rare occasion when you cannot distinguish RTA from diarrhea (or other GI loss of HCO_3^-, such as a urinary fistula), calculate the UAG. (See equation 9 on page 4-4.) Again:

- UAG is positive with NAGMA due to RTA.
- UAG is negative with NAGMA due to GI losses. Remember: neGUTive—negative UAG in bowel cases.

Toluene is a common solvent in glues and paints and can cause NAGMA. Suspect toluene exposure under these conditions: glue-sniffing, use of oil-based paints, and use of varnishes in a poorly ventilated area.

Treat NAGMA with replacement of bicarbonate losses, whether due to GI losses or RTA. Depending on the clinical situation and presence of other electrolyte abnormalities, replace with sodium bicarbonate intravenous fluid or sodium bicarbonate tablets.

High Anion Gap Metabolic Acidosis

With high anion gap metabolic acidosis (HAGMA), no equivalent increase in Cl^- is observed. Because the net charge in the serum is always neutral, there must be an increase in the unmeasured anions.

These tests should be performed immediately in a patient with unexplained HAGMA:

- Funduscopic exam
- Toxicology screen
- Serum glucose; urine and serum ketones
- Lactic acid level
- Serum osmolality with calculation of the osmolal gap (high in methanol and ethylene glycol ingestions)
- U/A to assess for calcium oxalate crystals

Table 4-3: HAGMAs and NAGMAs

Common Causes of HAGMA
Severe CKD: decreased acid (especially NH_4) excretion—most common
Uremia: sulfate, phosphate, urate
Ketoacidosis: diabetic, alcoholic, starvation
Lactic acidosis: drugs, toxins, circulatory compromise
Poisonings: salicylates, methanol, ethylene glycol, propylene glycol
Common Causes of NAGMA
Renal tubular acidosis
Diarrhea
Carbonic anhydrase inhibitors
Hyperalimentation with TPN

The 4 common causes of HAGMA include:

1) **Ketosis** (diabetic, alcoholic, and starvation): Check ß-hydroxybutyrate and urine ketones.
   - Diabetic ketoacidosis (**DKA**): Classic findings include volume depletion, a normal Cl^-, hyperglycemia, and HAGMA in a diabetic. DKA responds to restoration of intravascular volume, replacement of electrolytes, and insulin. DKA is discussed in Endocrinology, Book 4.
   - Alcoholic ketoacidosis (**AKA**): Key clue is an alcoholic who presents with HAGMA. Classic findings include HAGMA, hypophosphatemia, and hypoglycemia in a known alcoholic. AKA responds well to dextrose infusion.
2) **Uremia** causes an accumulation of anions, including sulfate, phosphate, and urate. (Check BUN and creatinine.)
3) **Lactic acidosis** (check blood lactic acid level):
   - **Type A** is due to muscle hypoperfusion during shock, cardiac failure, or sepsis.
   - **Type B** (findings of systemic hypoperfusion are lacking) can be caused by drug-induced mitochondrial dysfunction (zidovudine, metformin, propofol), tumor-induced lactic acidosis (leukemia, lymphomas), and alcoholism.
   - **Propofol-related infusion syndrome**:
     - High doses of propofol for more than 48 hours can result in type B lactic acidosis and a syndrome associated with renal failure, rhabdomyolysis, hyperlipidemia, J-point elevation on EKG, and various arrhythmias.
   - **D-lactic acidosis** can occur in patients with short bowel syndrome; they present with typical neurologic abnormalities, from slurred speech to obtundation. D-lactic acid is not the normal L-lactic acid seen with anaerobic metabolism. D-lactic acid takes much longer to break down and therefore accumulates more quickly and hangs around longer.
4) **Toxins** (salicylates, ethylene glycol [makes glycolic and oxalic acid], methanol [makes formic acid], and propylene glycol):
   - **Salicylate overdose**: Key clue is mixed respiratory alkalosis + HAGMA. Salicylate intoxication initially causes the respiratory alkalosis, then additionally, the HAGMA. Suspect in elderly patients taking medications for arthritis.
   - **Ethylene glycol**: Key clue is calcium oxalate crystals in the urine. Ethylene glycol forms glycolic acid and oxalic acid, resulting in HAGMA.
   - **Methanol**: Key clue is visual symptoms. Methanol metabolizes to formaldehyde and formic acid, resulting in HAGMA. Patients present with nausea, vomiting, abdominal pain, and may have visual complaints described as "walking through a snowstorm." Formic acid is directly toxic to the optic nerve. Methanol and ethylene glycol are toxic because of their metabolites. Like ethanol, these substances are metabolized by alcohol dehydrogenase. The previous treatment was to start an ethanol drip to act as a competitive inhibitor of alcohol dehydrogenase. Fomepizole + dialysis now make up the standard of care for both of these ingestions.
   - **Propylene glycol**: Propylene glycol is used as a solvent for intravenous lorazepam. Continuous infusion or large IV doses of lorazepam can cause propylene glycol toxicity, which manifests as HAGMA with an osmolal gap.

Treat HAGMA by correcting the underlying cause of the acidosis, including removal of toxic alcohols via dialysis if necessary.

Treat propofol-related infusion syndrome by discontinuing the propofol; and in cases with AKI and severe acidosis, initiate hemodialysis.

Always treat salicylate poisoning with aggressive sodium bicarbonate therapy, as alkalemia protects the CNS from the salicylate.

Do not treat DKA with bicarbonate unless the pH is < 7.0.

Do not treat lactic acidosis with bicarbonate unless the pH is < 7.1.

Chronic acetaminophen use (pyroglutamic acidosis) at therapeutic doses rather than in the setting of an overdose, can result in an elevated anion gap metabolic acidosis. The accumulating acid is pyroglutamic acid (also called 5-oxoproline). Chronic illness and malnutrition are the 2 big risk factors. The pathogenesis is thought to be related to chronic glutathione deficiency. Treat acetaminophen overdose with n-acetylcysteine (NAC), which blocks the hepatotoxic effects caused by acetaminophen.

METABOLIC ALKALOSIS

Metabolic alkalosis commonly results from volume contraction caused by diuretics or vomiting/gastric suction. Metabolic alkalosis always involves a generation phase (initial H^+ loss or HCO_3^- gain) and maintenance phase (failure of the kidney to excrete HCO_3^- to correct the alkalosis):

- With vomiting and NG suction, HCl is lost via gastric secretions.
- With primary hyperaldosteronism, there is renal acid loss.
- With diuretic-induced "contraction" alkalosis, there is renal loss of bicarb-free fluid, resulting in reduction in the extracellular fluid volume around a fixed quantity of extracellular bicarbonate.

The maintenance of the alkalosis is the failure of the kidney to excrete the excess HCO_3^-. This is most often mediated by volume depletion, which leads to decreased distal Cl^- delivery and high aldosterone levels. Aldosterone enhances distal sodium reabsorption by activating distal tubular Na^+/H^+ and Na^+/K^+ pumps,

QuickQuiz

- What are the causes of HAGMA?
- What abnormality is sometimes noted in the urine of patients who have ingested ethylene glycol?
- What are the potential PE findings in a patient who has ingested methanol?
- What is the treatment for methanol and ethylene glycol ingestions?
- Know the 4-step method for solving acid-base disorders!
- When looking at a blood gas result, how do you determine which acid-base disorder is the primary disturbance?

at the expense of H^+ loss (alkalosis) and K^+ loss (hypokalemia). This can result in "paradoxical aciduria," a low urine pH in the setting of metabolic alkalosis. Also in alkalemia, K^+ shifts from the extracellular space to the intracellular space in exchange for H^+, exacerbating hypokalemia.

The 2 types of metabolic alkalosis, chloride responsive or chloride resistant, are based on the urinary chloride measurement. U_{Na} and FE_{Na} are elevated during metabolic alkalosis even in the face of volume depletion because bicarbonaturia results in Na being excreted as the accompanying cation. In cases of volume depletion, urinary Cl^- is < 10 mEq/L because NaCl is avidly reabsorbed to maintain intravascular volume. If urinary Cl^- is > 10, think of other causes of alkalosis such as Cushing syndrome, Bartter syndrome, Gitelman syndrome, primary hyperaldosteronism, Liddle syndrome, licorice ingestion, severe hypokalemia, or increased intake of HCO_3^- (i.e., milk—alkali syndrome).

In chloride-responsive alkalosis (when urinary $Cl^- < 10$), aim treatment at restoration of volume with IV fluids (with either NaCl and/or KCl) and interruption of the cycle, which causes persistent volume loss. Potassium correction is integral to resolving the alkalosis, as well. Both interventions interrupt aldosterone production.

Please refer to Figure 4-1, which summarizes urinary chloride responsive vs. resistant causes.

The carbonic anhydrase inhibitor, acetazolamide, which increases sodium bicarbonate excretion, can be used in patients who have alkalosis with contraindications to saline or potassium administration (e.g., severe edematous states such as decompensated heart failure).

Severe metabolic alkalosis (> 7.55) can be treated with HCl, which must be infused over an extended period of time through central venous access. This is done only in rare circumstances and usually only in the ICU.

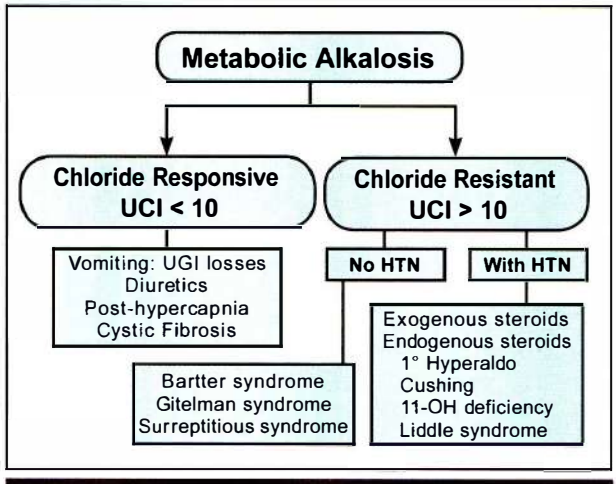


Figure 4-1: Metabolic Alkalosis: Chloride Responsive vs. Chloride Resistant Causes

ANALYSIS OF ACID-BASE PROBLEMS

Introduction

The goal of acid-base analysis is to establish a clinical differential diagnosis based on an analysis of the problem. There are several methods used for figuring out acid-base problems. Here we give you a good method to quickly crank out reasonably accurate acid-base diagnoses—even oddly mixed ones.

In this topic, we use pCO_2 for P_aCO_2. And we drop the brackets to indicate concentration of a substance. For instance, we use HCO_3^- instead of $[HCO_3^-]$.

The Step Method of Acid-Base Analysis

Overview

The process is simple and quick. This method can easily handle multiple, concurrent acid-base disorders.

The information required to determine exactly what the acid-base status is:

- Arterial blood gas (ABG): $pH/CO_2/O_2/HCO_3$
- Anion gap = $Na^+ - (HCO_3^- + Cl^-)$

The Steps

There are 4 major steps to this method. Always remember to interpret the blood gas in the setting of the patient presentation.

Refer to Table 4-4 on page 4-8 as you read the following explanations:

Step 1: Look at the pH. Is the patient acidemic or alkalemic?

To review, remember that the body does not fully compensate for primary acid-base disorders; therefore, the pH narrows down what the primary disturbance is (assuming no treatment). If the patient has an acidemia, the primary disturbance is a metabolic or respiratory acidosis. If the patient has an alkalemia, the primary disturbance is a metabolic or respiratory alkalosis.

Serum pH < 7.35 defines acidemia.

Serum pH > 7.45 defines alkalemia.

Physiologic explanation for upcoming Steps 2 and 3: Recall from basic physiology that the body has complex buffering systems for acidosis (intracellular and extracellular systems). The main extracellular buffer is bicarbonate, and its primary job is to complex with acids to neutralize them and keep the blood pH stable. It follows, then, that for every 1 increase in an acidic anion in the blood, the bicarbonate level should reduce by 1 (because of the neutralization). (In some instances, the ratio of anions to bicarb reduction is 1.6:1, but generally 1:1 works.) The point is: As anions go up, bicarb goes down proportionally.

In Steps 2a, 2b, and 3a, we calculate the ΔAG (the difference between the calculated AG and normal), and then determine what the expected bicarb level should be, based on any increase in AG (recognizing that bicarb should fall by 1 for every 1 increase in the AG). If there are no extra anions, then the bicarb should be normal.

Steps 2–3 evaluate the patient for a metabolic component.

Step 2a: Calculate the anion gap = $Na^+ - (HCO_3^- + Cl^-)$.

Use 10 +/– 3 as normal. In patients with hypoalbuminemia, the normal anion gap falls by about 2.5 for every 1 g/dL fall in the serum albumin concentration below 4 g/dL.

So, if the AG > 13 = HAGMA is present.

Step 2b: ΔAG.

Calculate the change in the anion gap (ΔAG)

= (calculated AG) – 10 or $[Na^+ - (HCO_3^- + Cl^-)] - 10$.

What is the primary acid-base disturbance? Metabolic acidosis or alkalosis or respiratory acidosis or alkalosis?

First look for a metabolic disorder.

Step 3a: expected bicarb.

Calculate the expected bicarbonate level.

If the AG is elevated, the expected bicarbonate = [25 – (ΔAG)].

If the AG is not elevated, the expected bicarbonate = 25.

Essentially, what you're doing in this step is reducing the bicarbonate by 1 for every 1 acidic anion that the bicarbonate neutralizes.

Step 3b: expected – measured bicarb.

Compare the expected bicarbonate from Step 3a (either 25 or [25 – (ΔAG)]) to the actual bicarbonate from the chemistry panel.

If the measured bicarbonate is less than what is expected, a NAGMA is present.

If the measured bicarbonate is more than what is expected, a metabolic alkalosis is present.

NAGMA or a metabolic alkalosis can coexist with a HAGMA. A standard deviation of 3 exists on each of these calculations, so if the calculated and observed values are within 3 numbers, call them "close enough."

Table 4-4: Evaluating Acid-Base Disorders
The 4-Step Method

Step	Questions	How to Determine Answer	What it Means
1) pH	Determine serum pH	Look at ABG results	pH > 7.45 = alkalemia pH < 7.35 = acidemia
2) Anion Gap	a) What is the anion gap?	$Na^+ - Cl^- - HCO_3^-$	If AG is > 13 = HAGMA
	b) What is change in AG? (measured – normal)	AG – 10	Use in Step 3
3) HCO_3	a) What is expected HCO_3^-?	25 – (ΔAG)	If actual HCO_3 > expected HCO_3 = metabolic alkalosis
	b) What is the change in HCO_3^-?		If actual HCO_3 < expected HCO_3 = NAGMA
4) pCO_2	a) What is expected pCO_2?	15 + measured HCO_3^-	If actual pCO_2 > expected pCO_2 = respiratory acidosis
	b) What is the change in pCO_2? (expected – measured)		If actual pCO_2 < expected pCO_2 = respiratory alkalosis

Now look for a respiratory disorder.

Step 4a: Calculate the expected pCO_2.

In metabolic acidosis, the expected pCO_2 = 15 + actual HCO_3^- from the chemistry.

In metabolic alkalosis, the expected pCO_2 increases by 0.7 mmHg for every 1 mEq/L increase in the HCO_3^-.

Step 4b: Compare the expected pCO_2 to the actual pCO_2 from the blood gas.

If higher than expected pCO_2 is present in the blood gas results, a respiratory acidosis is present.

If lower than expected pCO_2 is present in the blood gas results, a respiratory alkalosis is present.

These respiratory disorders can coexist with any of the metabolic disorders. A standard deviation of 3 exists on each of these

Quick Quiz

- What happens to a patient's serum bicarbonate level when acid anions accumulate in the blood?

calculations, so if the calculated and observed values are within 3 numbers, call them "close enough."

Caveats

Other key points to keep in mind:

- ABG and chemistries must be drawn at the same time.
- If HCO_3^- < 9 or > 40, expected pCO_2 may be unreliable.
- All of the diagnoses are independent disorders; compensation is built into the formulas.
- Always make sure the diagnosis is consistent with the clinical history.
- Look for a discrepancy between the direction of Na and Cl to signal an acid-base disorder!
- Even in chronic respiratory acidosis, the serum bicarbonate does not increase above 38 mEq/L. Also, pCO_2 > 55 usually suggests an additional primary respiratory acidosis.

Acid-Base Example #1

Blood gas: 7.50 / 20 / 96 / 15

Na = 140, Cl = 103, Bicarb = 15

Step 1: First look at the pH. It is 7.50, which tells us our primary disorder is either a respiratory or metabolic alkalosis.

Step 2a: Calculate the anion gap.

140 – (103 + 15) = 22

Because the AG is > 10, HAGMA is present.

Step 2b: Calculate the ΔAG.

AG – normal AG = (22 – 10) = 12

Step 3: Now look for metabolic disorders.

Calculate the difference between expected and normal HCO_3^-. Expected HCO_3^- = 25 – ΔAG = 25 – 12 = 13.

Measured HCO_3^- is 15. This is close enough. No additional metabolic disorder is present.

Step 4: Now look for respiratory disorders.

Calculate the expected pCO_2 and compare it to the actual. Expected = 15 + 15 = 30. Actual pCO_2 is 20. There is less CO_2 than you expect there to be, so a respiratory alkalosis is present. This is the primary disorder because Step 1 defines the primary disorder as an alkalemia.

So, the patient has a primary respiratory alkalosis + HAGMA. This scenario is seen with salicylate poisoning. As discussed under HAGMA (page 4-5), salicylates initially increase the respiratory drive causing respiratory alkalosis; then metabolic acidosis develops.

Acid-Base Example #2

Blood gas: 7.30 / 40 / 92 / 24

Na = 145, Cl = 100, Bicarb = 24

Step 1: First look at the pH. It is 7.30, which tells us our primary disorder is either a respiratory or metabolic acidosis.

Step 2a: Calculate the anion gap.

145 – (100 + 24) = 21

Because the AG is > 10, HAGMA is present.

Step 2b: Calculate the ΔAG:

AG – normal AG = (21) – (10) = 11

Step 3: Now look for metabolic disorders.

Calculate the difference between expected and normal HCO_3^-. Expected HCO_3^- = 25 – ΔAG = 25 – 11 = 14. Measured HCO_3^- is 24. There is more bicarb than expected, so an additional metabolic alkalosis is present.

Step 4: Now look for respiratory disorders.

Calculate the expected pCO_2 and compare it to the actual. Expected = 15 + 24 = 39. Actual pCO_2 is 40. This is close enough. There are no additional respiratory disorders.

Because the patient is acidemic, the patient has a primary HAGMA + metabolic alkalosis.

Diagnosing the Cause of the Abnormal Acid-Base Status

Note: To make the diagnosis of causes of the abnormal acid-base state (discussed previously), you often need more information. This may include the following:

- Urine anion gap (if NAGMA) = $(U_{Na} + U_K) – U_{Cl}$ to differentiate RTA from GI losses (page 4-4).
- Serum K^+ to help differentiate RTAs (page 4-17).
- Osmolal gap = $Osm_{meas} – Osm_{calc}$ to help with poisonings (page 4-4).
- Salicylate levels, lactic acid level, glucose, etc.

Review Table 4-2 and Table 4-3 for causes of osmolal gaps, anion gaps, NAGMAs, and HAGMAs.

You can get pretty quick at crunching through the 4-step method. It is also important to get an innate feel for the ABGs, so you can quickly pick up an abnormal situation. Review Table 4-5 on page 4-10 to see what ABGs are expected with certain conditions.

FLUID AND ELECTROLYTES

OSMOLALITY AND VOLUME STATUS

Normal serum osmolality is usually 282 +/– 2 mOsm/kg H_2O. If no osmolal gap exists from an acid alcohol ingestion, then measured osmolality should be equal to calculated osmolality, which is (roughly):

$$Osm_{calc} = 2[Na^+] + (glucose/20) + (BUN/3)$$

If glucose and BUN are normal, use 2 x $[Na^+]$ to quickly see if the patient's osmolality is ~ 270.

Antidiuretic hormone (ADH) is the common term for arginine vasopressin (AVP). ADH is the primary regulator of renal water excretion; it is a neurohypophysial hormone that acts on the late distal tubule and cortical collecting duct to increase water permeability and mediate the urine concentration.

ADH levels are regulated by several mechanisms. The 2 most important are:

1) **Osmoreceptors** in the hypothalamus
2) **Volume (stretch) receptors** in the left atrium (and possibly in the pulmonary veins) and blood vessels

The strongest stimulant for ADH release is significant volume loss resulting in hypotension; e.g., hemorrhage. This stimulates both the stretch receptors and baroreceptors. High plasma osmolality is a weaker but more sensitive stimulus for ADH release. More on ADH in Endocrinology, Book 4.

Volume status of the patient with a sodium abnormality is critical in determining the treatment. In general, if the patient is edematous, there is volume overload. If the patient has the clinical signs of volume loss, there is a volume deficit. If there is neither of these, the patient is considered euvolemic.

Remember these clinical clues to hypovolemia: tachycardia, narrowed pulse pressure, orthostatic hypotension, and resting tachycardia with hypotension. Central venous pressure is low.

Table 4-5: Examples of Abnormal ABGs

Examples	Acid-Base Status	pH	pCO_2	pO_2	HCO_3
Acute hyperventilation episode	Acute respiratory alkalosis	7.56	20	90	22
Acute asthma/PE/ chest trauma	Acute resp alk due to hypoxia	7.56	20	50	24
CNS problem, chronic hyperventilation	Chronic resp alk w/metab compensation	7.44	25	90	16
COPD with chronic bronchitis	As above, but w/hypoxia	7.43	30	60	20
Pt in transition to respiratory failure	Normal except hypoxia	7.40	40	50	24
Sedative overdose	Acute resp acidosis	7.24	60	80	26
Resp failure from hypoxia	Acute resp acidosis w/hypoxia	7.16	70	50	25
Emphysematous COPD	Resp acidosis w/metabolic compensation	7.37	60	60	34
Bicarbonate overdose	Metabolic alkalosis w/resp comp	7.44	60	90	39
Sepsis, ASA overdose, renal failure ...	Metabolic acidosis w/resp comp	7.36	28	90	15

Assuming consistent HCO_3^- and chloride

HYPONATREMIA

Isoosmolar and Hyperosmolar

Low serum Na^+ is the most common electrolyte abnormality. It is further classified by osmolality as isoosmolar, hyperosmolar, or hypoosmolar.

The 1st step after discovering hyponatremia is to determine the serum osmolality:

- **Isoosmolar hyponatremia**: An artifactual decrease in the serum Na^+ associated with older lab instruments that miscalculated sodium in settings of high protein (e.g., myeloma) or lipids. The current standard in laboratory practice is to use ion-specific electrodes, thus eradicating this problem.
- **Hyperosmolar**: Both glucose and mannitol cause an osmotic shift of water out of cells, which dilutes plasma Na^+. Remember: For each 100 increase in glucose over 100 mg/dL, the sodium concentration decreases by 1.6.
- **Hypoosmolar**: (See next.)

Hypoosmolar

By far, the largest low-Na^+ subgroup is the hypoosmolar group. Refer to Figure 4-2 as you read along. Note that the terms hypoosmolar and hypotonic are interchangeable.

The low osmolality causes water movement into cells, leading to intracellular swelling, which may result in neuromuscular

Quick Quiz

- What are the 2 important regulators of ADH secretion from the posterior pituitary?
- What causes hyperosmolar hyponatremia?
- For each 100 mg/dL increase in glucose over 100, how should you correct the serum sodium?
- What are causes of low-volume, hypoosmolar hyponatremia?
- What are causes of high-volume, hypoosmolar hyponatremia?

excitability, seizures, and coma—usually when the Na^+ falls acutely (< 120). If the sodium level decreases slowly, the cells re-equilibrate and do not swell enough to cause these symptoms. The hypoosmolar group is further subdivided by volume status: low, high, and normal.

Always think of the serum sodium concentration as the ratio of total body sodium to water, with increased total body water content as the key disorder in most cases of hyponatremia. Therefore, hypotonic hyponatremia is a water problem. Whenever the serum sodium is low, it means the patient has more water relative to total body sodium either from loss of sodium, true water excess, or total body sodium excess that is exceeded by water excess.

In the patient with hypotonic low Na^+, the first thing to do is assess the volume status, which is done clinically. Volume status essentially reflects total body sodium content.

Low Osmolality ... Low Volume (Hypovolemia)

Low-volume patients have lost both water and Na^+, but more Na^+ than water. This has several causes:

- Diuretics
- GI losses (vomiting and diarrhea)
- Third spacing of fluid
- Adrenal insufficiency (Addison disease)

In primary adrenal insufficiency, both cortisol and aldosterone are deficient. The low aldosterone causes renal Na^+ wasting and decreased K^+ and H^+ excretion, resulting in hypovolemia (sometimes with hypotension), hyperkalemia, and metabolic acidosis. The low cortisol stimulates ADH production, resulting in hyponatremia.

Low Osmolality ... High Volume (Hypervolemia)

High-volume hyponatremic patients usually retain water and Na^+, but more water than Na^+. These patients have dependent edema and JVD.

Causes of low osmolality, high-volume status include:

- Edema-forming states: heart failure, cirrhosis, and nephrotic syndrome
- Kidney failure: acute or chronic

Normal treatment is restriction of water and Na^+. Lithium and demeclocycline can improve hyponatremia by inducing tubular resistance to ADH, but should not be used routinely because they can lead to chronic kidney disease. Also, avoid chronic, oral thiazide diuretics because they impair urinary-diluting ability, which can worsen hyponatremia. Loop diuretics can be very effective in patients with high-volume hyponatremia.

It's easy to precipitate acute kidney injury with rapid diuresis of a high-volume cirrhotic patient. Cirrhotics tend to have a low GFR, even with a normal serum creatinine. They have decreased muscle mass, so a decrease in their GFR is not necessarily reflected in their serum creatinine concentration.

Low Osmolality ... Normal Volume (Euvolemia)

SIADH

Normal-volume patients usually have SIADH or are taking drugs that either mimic ADH or cause ADH release.

Know that pain and chronic nausea are potent natural stimulators of ADH release.

Normal-volume hyponatremia also can be caused by psychogenic polydipsia (but in a patient with normal renal function and solute intake, it takes over 15 L/day of water intake to produce hyponatremia), hypothyroidism, and isolated glucocorticoid deficiency.

Causes of SIADH include the following:

- CNS disease (e.g., meningitis)
- Lung disease (e.g., pneumonia)
- Neoplasms (especially small cell lung cancer)
- Drugs

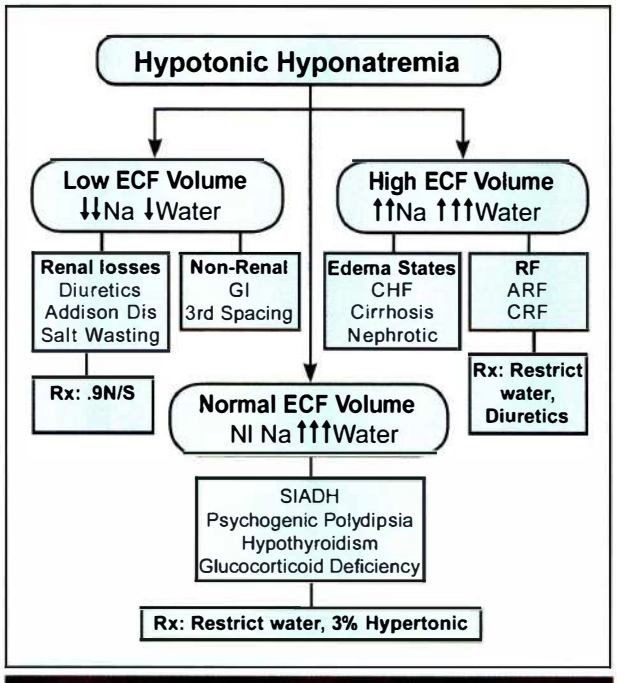


Figure 4-2: Causes of Hypotonic Hyponatremia

Most common drugs associated with SIADH:

- NSAIDs
- SSRIs
- Carbamazepine and oxcarbazepine
- Psychotropic drugs: haloperidol, amitriptyline
- IV cyclophosphamide
- Vincristine/Vinblastine
- Cisplatin
- Chlorpropamide (now rarely used)
- Ecstasy (methylenedioxymethamphetamine)

Diagnose SIADH by comparing the urine and serum osmolalities. The normal response to hyponatremia would be to excrete free water in the urine; e.g., healthy patients would have a low serum osmolality and a low urine osmolality (< 200 mOsm/L) because they are making dilute urine; this is what you see in psychogenic polydipsia. In SIADH, however, the urine is inappropriately concentrated (> 250 mOsm/L) in the setting of a low serum osmolality. The patients are not excreting free water, so the serum osmolality is low, but the urine osmolality is high.

The mechanism for ADH release in moderate-to-severe hypothyroidism is decreased cardiac output, which stimulates the carotid baroreceptors. Rule out hypothyroidism and glucocorticoid deficiency in all patients with hyponatremia before making a diagnosis of SIADH because both causes can have low serum osmolalities and high urine osmolalities—more commonly seen in SIADH. Sometimes you cannot tell the difference using these tests, so look for the hormone deficiencies in everyone first, before diagnosing SIADH.

Thiazide Diuretics

Thiazides also can cause euvolemic low osmolality hyponatremia via several possible mechanisms, both ADH-related (by inducing mild volume depletion and directly stimulating ADH release) and non-ADH–related (by impairing urinary dilution in the early distal tubule). Elderly patients are highly susceptible to this effect of thiazides.

Treatment of Hyponatremia

Treat asymptomatic hyponatremia (no CNS changes) based on etiology:

- **Normal serum osmolality** hyponatremia: This is artifact and does not require treatment.
- **High osmolality** hyponatremia: sometimes attributable to glucose or mannitol. Treating the underlying disease process (e.g., DKA) normalizes the sodium with time.
- **Low osmolality** and:
  - Hypovolemic: normal saline to replenish deficit (watch for over-rapid correction!).
  - Hypervolemic: fluid restriction (~ 800 cc/day) +/– loop diuretics.
  - Euvolemic: SIADH is treated with fluid restriction (~ 800 cc/day). Refractory cases can be treated with an ADH receptor antagonist, such as conivaptan or tolvaptan, although these agents are expensive and are generally reserved for use in patients with severe, chronic hyponatremia with serum Na^+ < 120 mg/dL. ADH antagonists are not approved for use in symptomatic hyponatremia (use hypertonic saline; see below). Treat hypothyroidism or glucocorticoid deficiency with appropriate replacement. Remember: Isotonic saline worsens hyponatremia in patients with SIADH.

If the symptoms of hyponatremia are severe (e.g., neurologic symptoms such as lethargy, confusion, coma, seizures) and the patient is not hypovolemic, treat with 3% saline. Correction of hyponatremia should never exceed 9 mEq/L over 24 hours due to the risk of osmotic demyelination syndrome (see below).

Standard therapy: Give enough 3% saline to increase the serum sodium by 6–8 mEq/L over 24 hours. For severe symptoms (seizure, coma), a 100 mL bolus of 3% saline is recommended to quickly raise the serum sodium by 2–3 mEq/L. If symptoms persist, 2 more boluses can be given in 10-minute intervals. For moderate symptoms (confusion, lethargy) and suspected SIADH, hypertonic saline can also be used. A reasonable initial rate is 0.5–1.0 mL/kg lean body weight/hour. The serum sodium should be checked frequently (every 2–4 hours) and the rate adjusted to achieve the target correction of 6–8 mEq/L over 24 hours. Watch carefully for the abrupt onset of a water diuresis, which can cause the serum sodium concentration to rise too fast, especially in patients with psychogenic polydipsia, hypovolemic hyponatremia, and hyponatremia due to thiazide diuretics.

Osmotic demyelination syndrome was previously referred to as central pontine myelinolysis because it is most prominent in the pons. If the sodium concentration is raised too rapidly, the cells can shrink (water rushes out of cells into the blood stream, where the osmolality has risen), potentially causing this demyelination syndrome. This rare effect is more likely to occur in the patient with chronic, severe hyponatremia (Na^+ < 115 mEq/L for > 2 days) whose sodium is corrected rapidly (> 10 mEq/L over 24 hours). Symptoms are delayed by about a week, compared to the rise in the sodium concentration, and are usually not reversible. Presentation includes speech and swallowing difficulties, weakness or paralysis, cognitive deficits, and coma. Seizures occasionally occur.

A related cause of severe and sometimes symptomatic hyponatremia is **exercise-induced hyponatremia**, reported in marathon and other endurance exercise participants and caused by both nonosmotic production of ADH and excessive intake of hypotonic fluids.

Quick Quiz

- What drugs cause SIADH?
- What endocrinopathies must be ruled out in all patients with hyponatremia?
- What is the suggested rate of correction for severe hyponatremia?
- When is osmotic demyelination syndrome most likely to occur?
- What is the usual cause of hypernatremia?
- What is the usual serum sodium in a patient with DI who has access to water?

3% hypertonic saline should be promptly administered when diagnosed.

HYPERNATREMIA

Overview

Severe hypernatremia is fairly rare but always represents a water deficit. It does not occur unless the patient is unable to get to water (debilitated or H_2O unavailable) or the thirst mechanism is defective. Unlike hyponatremia, these patients are always hyperosmolar, so the 1st step is determining volume status. Low volume implies water and total body Na^+ loss (water deficit exceeding Na^+ deficit). Refer to Figure 4-3 for causes of hypernatremia.

Treat severe hypovolemic hypernatremia with normal saline first to correct the volume deficit, and only then with hypotonic fluids to further replace the water deficit. Remember: Even normal saline has a lower osmolality than serum in a patient with hypernatremia.

The amount of free water needed in a hypernatremic patient is calculated by multiplying the total body water (60% of weight in kg) by the fractional difference between a patient's Na^+ and normal Na^+:

$$Vol_{water} = (\text{total body water}) \times ([Na^+_{serum} - 140]/140) \quad [\text{eq } 12]$$

$$Vol_{water} = 0.6 \times (\text{body weight}) \times ([Na^+_{serum} - 140]/140) \quad [\text{eq } 13]$$

So if a 100-kg patient has a serum Na^+ of 156, the amount of free water needed to fully correct the hypernatremia is 6.9 liters. This usually is given over 1–2 days to decrease the sodium concentration at a rate of 0.5 mEq/L/hr or 10–12 mEq/L/day.

Cellular swelling can occur from too rapid a correction of any severe hyperosmolar state, such as hypernatremia, nonketotic hyperglycemic coma, and severe uremia. (These are just the variables in the osmolality equation.) Cellular swelling can cause cerebral edema, seizures, and coma. So be careful with the fluid rate and measure serum sodium frequently.

High-volume hypernatremia: This is unusual and typically not serious. It most often occurs with mineralocorticoid excess, such as primary hyperaldosteronism. Usually, the only time a serious result occurs is after giving large amounts of sodium bicarbonate or hypertonic saline during advanced cardiac life support. Treat with loop diuretics and free water.

Normal-volume hypernatremia is most often seen in patients with diabetes insipidus (DI) and reduced access to water (and thus become hypernatremic) but have not yet developed frank volume depletion. Typical DI patients with normal access to water have normal or borderline-high serum Na^+ levels because they are constantly drinking water (hyperosmolar, and therefore always thirsty). Their primary complaint is usually polyuria and polydipsia.

Think of **central DI** in the patient with high Na^+ and high urine volume who also has a history of recent neurosurgery, head trauma, or brain cancer/metastases. Otherwise, DI is typically **nephrogenic DI** (also called "ADH resistant").

Nephrogenic DI can be hereditary, with most cases presenting in childhood (mutations in the vasopressin 2 receptor or aquaporin 2 genes) or due to:

- hypercalcemia (serum $Ca^{2+} > 11$ mg/dL),
- chronic hypokalemia (serum $K < 3$ mEq/L),
- intrinsic renal disease (especially Sjögren syndrome), or
- drugs (especially lithium).

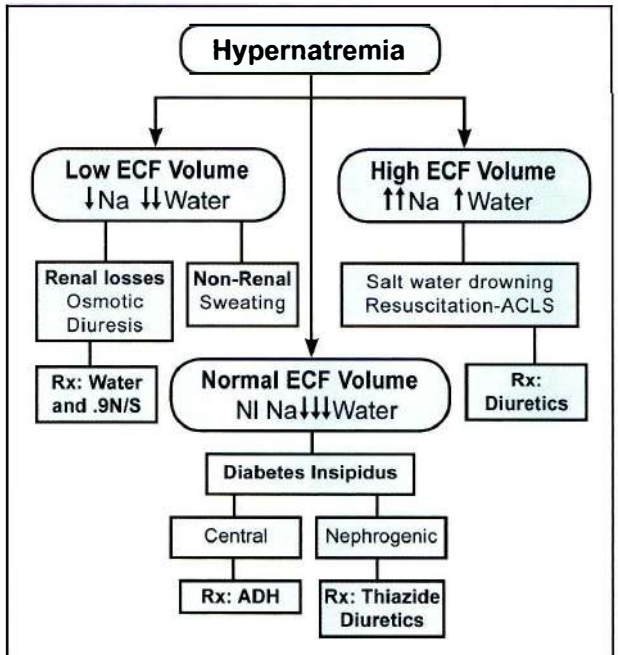


Figure 4-3: Causes of Hypernatremia

Water Restriction Test

The water restriction test not only diagnoses DI but also differentiates between central and nephrogenic types. In a healthy person, when plasma osmolality increases to 295, ADH level is high and urine is maximally concentrated (> 700 mOsm/L).

In central DI, even with water restriction, the ADH stays low and the urine dilute.

Treat mild cases of central DI with thiazides and salt restriction. Chlorpropamide and carbamazepine can be used in cases of partial central DI, when desmopressin might be too potent or limited in supply. These drugs stimulate further ADH production if the patient has a partial defect.

Treat more resistant central DI with oral or intranasal desmopressin (synthetic vasopressin analog). Because the kidneys immediately respond to ADH, giving desmopressin results in a quick increase of the urine concentration and reduction in urine output. The intranasal preparation is the most potent. Be careful to titrate the dose properly and counsel the patient to drink only when thirsty, because volume overload and hyponatremia can easily occur (i.e., drug-induced SIADH).

In nephrogenic DI, the ADH is appropriately high, but the urine is dilute: The collecting duct is resistant to the effect of ADH. Giving extra ADH (desmopressin) does not increase the concentration of the urine. Treat nephrogenic DI with thiazide diuretics or amiloride. NSAIDs are used to treat rare hereditary forms.

Remember: SIADH (high ADH) usually presents as hyponatremia with normal volume. DI typically presents as polyuria/polydipsia, with or without hypernatremia, also with normal volume! See Endocrinology, Book 4, for a discussion on how to interpret graphs frequently encountered during water restriction testing.

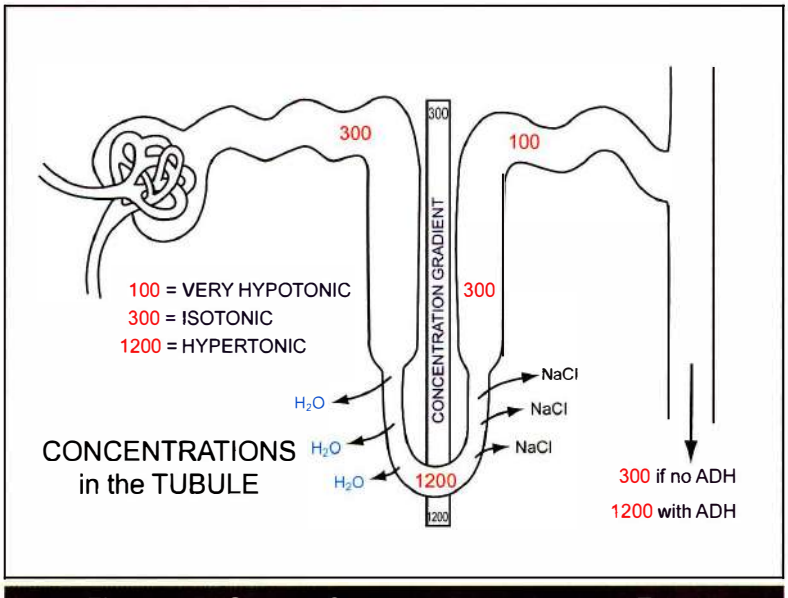


Figure 4-4: Osmolar Concentrations in the Renal Tubule

Urine Osmolality

Urine osmolality can range from 50–1,200 mOsm/L. To make sense of the osmolality, you must also know the urine output (L/d). Multiply the osmolality x output (1 kg = 1 L) to get total osmoles output per day. Normal is about 500. This is important in the case of a patient with high Na^+ and high urine output. If the 24-hour solute output is > 900 mOsm, think of an osmotic cause of the hypernatremia (e.g., hyperglycemia); whereas in DI, the 24-hour osmoles are normal, so the urine is very dilute.

NORMAL RENAL PHYSIOLOGY, DIURETICS, AND RTAs

OVERVIEW

The following topics discuss aspects of normal tubular function, hormonal regulation of the tubules, and the effects of the 4 categories of diuretics (carbonic anhydrase [CA] inhibitors, loop diuretics, thiazides, and aldosterone antagonists).

After glomerular filtration, the filtrate flows through the following sections of tubules—some of which are grouped together because of identical function:

- Proximal tubule
- Loop of Henle
  - Thin descending segment
  - Thin ascending segment
  - Thick ascending segment
- Early distal tubule
- Late distal tubule and cortical collecting duct
- Medullary collecting duct

Refer to Figure 4-4 and Figure 4-5.

Know that diuretics are mentioned throughout this discussion of renal physiology. They are also covered when discussing drugs for HTN on page 4-26.

PROXIMAL TUBULE

65% of filtered Na^+, Cl^-, and water is reabsorbed in the proximal tubule (PT). The PT is very permeable to water, which is reabsorbed in a 1:1 fashion with Na^+, such that the volume of filtrate is reduced along the tubule, but the concentration of Na^+ remains stable.

Solutes are reabsorbed by the following:

- Counter-transport of Na^+ (into interstitium) and H^+ (into filtrate) via secondary active transport; stimulated by angiotensin II (AT II) and inhibited by carbonic anhydrase inhibitors and thiazide diuretics (slightly)

QuickQuiz

- Which tubules are permeable to water?

- Counter-transport of Na^+ (into interstitium) and K^+ (into filtrate) via an ATPase active transport pump; stimulated by AT II
- Cotransport of Na^+, Cl^-, K^+, glucose, and amino acids (into interstitium)
- Paracellular absorption of other solutes, such as Ca^{2+}

Regarding the first of the 4 bullets above, know that 90% of filtered HCO_3^- is reabsorbed in the PT—but the process is indirect and driven by the Na^+/H^+ counter-transport pump:

- H^+ is counter-transported into the filtrate and combines with filtered HCO_3^- to form H_2CO_3 (carbonic acid).
- Carbonic anhydrase converts $H_2CO_3 \rightarrow H_2O + CO_2$.
- CO_2 is absorbed into the tubular cells and again, with the help of carbonic anhydrase, is converted to HCO_3^-.
- HCO_3^- is then reabsorbed into the interstitium.

So, for each H^+ that is secreted, one Na^+ and one HCO_3^- are reabsorbed. Although this is represented in Figure 4-5, it is better explained here in the text.

Carbonic anhydrase inhibitors (acetazolamide) disrupt this entire process by reducing the availabilities of H^+ in the tubule cells and H_2CO_3 in the lumen. Then, the Na^+/H^+ counter-transporter does not have substrate. Na^+ is not absorbed and H^+ is not secreted. A mild diuresis ensues (as well as generation of a metabolic acidosis, similar to proximal, Type 2 RTA).

Know that this Na^+/H^+ counter-transporter is also affected by the potassium concentration:

- Hypokalemia: stimulates H^+ secretion (and thus, stimulates bicarb reabsorption) → alkalosis
- Hyperkalemia: inhibits H^+ secretion (and thus, inhibits bicarb reabsorption) → acidosis

So, when something goes wrong in the proximal tubules, clinically we can see:

- Failure to reabsorb water
- Failure to secrete acid and reabsorb bicarbonate = generation of proximal (Type 2) NAGMA
- Failure to reabsorb solutes (Na^+, Cl^-, K^+, glucose, amino acids) = Fanconi syndrome +/– hypokalemia

LOOP OF HENLE

Follow along in Figure 4-5 as we discuss the physiology of the loop of Henle. Think of the loop as divided into 2 halves with the 1st half (descending) handling reabsorption of water and a little bit of solutes, and the 2nd half (ascending) handling reabsorption of only solutes. The action of the 2nd half of the loop drives the action of the 1st half.

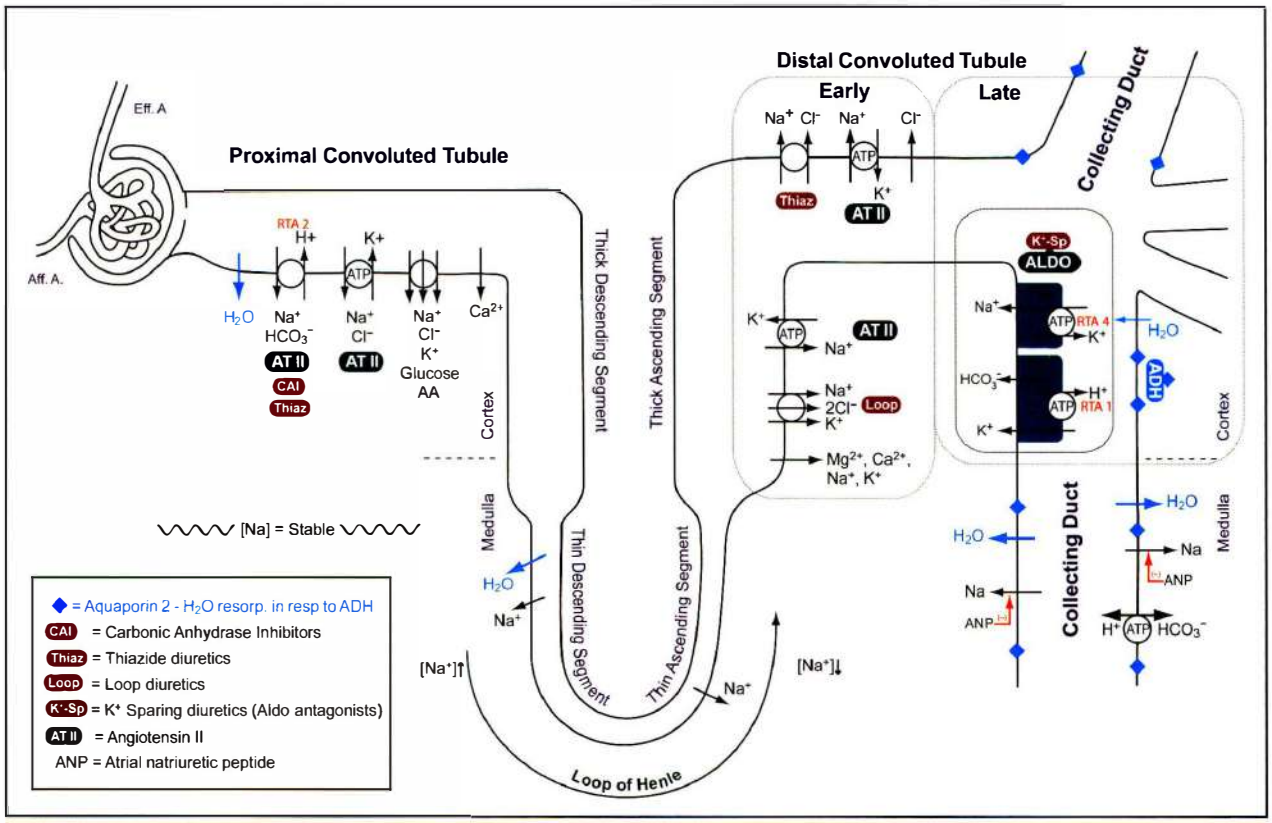


Figure 4-5: The Renal Tubule — Basic Physiology

In the thin, descending segment, another 20% of remaining H_2O moves from the filtrate into the interstitium, following an osmotic gradient, with maximum concentration of fluid at the base of the loop. (The renal medulla is very hypertonic—why?) In the thin ascending segment, NaCl passively diffuses into the interstitium, slightly diluting the filtrate. In the thick ascending segment, solutes are actively transported from the filtrate into the interstitium—increasing the tonicity of the medulla. (That's why!) This active transport is the mechanism that sets up the osmotic gradient in the descending segment and stimulates reabsorption of H_2O.

In the thick ascending segment, 25% of filtrate solutes are reabsorbed by these clinically relevant processes:

- Counter-transport of Na^+ (into interstitium) and K^+ (into filtrate) via an ATPase active transport pump; stimulated by AT II
- Cotransport of Na^+, 2 Cl^-, and K^+ (into interstitium); inhibited by loop diuretics
- Paracellular absorption of other solutes, such as Mg^{2+}, Ca^{2+}, Na^+, and K^+ (into interstitium)

Think about this a minute and look at Figure 4-5—be sure you understand before moving on.

Loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid) are dose-dependent. They remain effective when GFR is low (CrCl < 20 cc/min), but you have to increase the dose and/or give IV. Ethacrynic acid is mainly used for patients with sulfa allergies in whom furosemide, bumetanide, and the thiazide diuretics are contraindicated—because these drugs are sulfa derivatives. Know that furosemide and ethacrynic acid are associated with permanent ototoxicity at high IV bolus doses.

Loop diuretics cause diuresis by preventing reabsorption of Na^+ in the thick ascending segment—but also by preventing development of the interstitial osmotic gradient, relied upon by the thin descending segment for water reabsorption. The net effect is loss of both Na^+ and water. Look at the specific cotransporter that is inhibited by loop diuretics. Notice that K^+ is also cotransported with that pump, so now it makes sense how patients taking loop diuretics also develop hypokalemia.

Loop diuretics also increase Ca^+ loss in the urine and have been used in the past to treat severe hypercalcemia. Normal saline was infused at a high rate (to replace the volume losses), and a loop diuretic was added. The saline expands the volume and delivers increased flow to the proximal tubule, which prevents paracellular Ca^{2+} reabsorption. The greatly increased Ca^{2+} load is then delivered to the early distal tubule, overwhelming its ability to absorb Ca^{2+}, so calciuresis ensues.

In current clinical practice, saline is still given to volume-depleted patients with hypercalcemia; but loop diuretics are considered questionable, unless the patient becomes volume overloaded—since we have the bisphosphonates that control calcium better and are associated with fewer electrolyte side effects.

By the time filtrate reaches the end of the thick ascending limb, it is fairly dilute because more solutes than water have been reabsorbed through the loop.

DISTAL TUBULE

The distal tubule is divided into "early" and "late" segments because the actions of the sections differ.

The early distal tubule reabsorbs another 5% of remaining solutes with the following clinically relevant processes:

- Cotransport of Na^+ and Cl^- (into interstitium); inhibited by thiazide diuretics
- Counter-transport of Na^+ (into interstitium) and K^+ (into filtrate) via an ATPase active transport pump; stimulated by AT II
- Paracellular absorption of Cl^- (into interstitium)

Thiazide diuretics (chlorothiazide, hydrochlorothiazide, chlorthalidone, metolazone) have to be secreted into the filtrate to be effective and, hence, are less effective in patients with extremely low GFR. Remember that thiazides also slightly inhibit carbonic anhydrase in the proximal tubule. The effect of that is an increased delivery of Na^+ to the early distal tubule and upregulation of the counter-transport of the Na/K ATPase. So, the more Na^+ that gets delivered to the distal pumps, the more K^+ that gets excreted. So, hypokalemia is also a feature of thiazide use.

Know that thiazides actually increase calcium reabsorption, which is in contrast with the action of loop diuretics. This is important to remember; do not prescribe these drugs to patients with primary hyperparathyroidism or hypercalcemia of malignancy. On the other hand, thiazides can be useful in reducing urinary calcium in patients with kidney stones.

Clinically, the drug chlorthalidone is becoming a more popular diuretic than hydrochlorothiazide (HCTZ) because it is more potent and lasts 24 hours. Also, some major studies on hypertension (e.g., ALLHAT) used chlorthalidone, not HCTZ.

The late distal tubule and cortical collecting duct act the same. This area allows for further solute and water reabsorption, but, unlike the remainder of the tubules, the behavior of these segments is controlled by aldosterone and ADH.

There are 2 important cell types in the late distal tubule and cortical collecting duct that reabsorb solutes:

1) **Principal cells**: Counter-transport Na^+ (into interstitium) and K^+ (into filtrate) via an ATPase active transport pump; stimulated by aldosterone and hyperkalemia and inhibited by potassium-sparing diuretics (amiloride, triamterene, spironolactone, eplerenone).
2) **Intercalated cells**: Secrete H^+ (into filtrate) via an ATPase active transport pump against a concentration gradient; for every H^+ secreted, one HCO_3^- is reabsorbed via the action of carbonic anhydrase. Thus,

Quick Quiz

- Which tubule sets up the osmotic gradient for the thin, descending segment in the loop?
- Where do loop diuretics exert their effect?
- What type of diuretic is useful in patients with poor kidney function?
- Which 2 hormones exert their effects in the distal tubules?
- What is the serum potassium level in distal, Type 4 RTA?
- Stones are associated with which RTA?
- Multiple myeloma is associated with which RTA?

these cells are one of the major regulators of acid-base balance. Intercalated cells also reabsorb K (to a minor extent).

Water reabsorption in these segments is controlled by ADH. Through a complicated series of processes involving cyclic AMP and protein kinases, ADH calls forth an aquaporin protein (AQP-2) from the cytoplasm. Several AQP-2 molecules gather at the cell membrane and make a water channel, through which water is absorbed into the interstitium. In the absence of ADH, these segments are relatively impermeable to water. ADH receptors are inhibited by the ADH-receptor blockers—also termed "vasopressin receptor antagonists": conivaptan (IV formulation only) and tolvaptan (oral). These agents are sometimes used to treat hyponatremia.

Two diseases affect the late distal tubules and cortical collecting ducts:

1) Impairment of the H-ATPase active transport pump in the intercalated cells, which leads to inability to secrete acid (and reabsorb bicarbonate) = generation of distal (Type 1 RTA) NAGMA; urine pH is always > 5.3.
2) Tubular aldosterone resistance = impairment of the Na/K ATPase counter-transporter → generation of distal (Type 4) NAGMA; hyperkalemia is present. Type 4 RTA can also be seen in disorders of low aldosterone, such as diabetes mellitus.

MEDULLARY COLLECTING DUCT

The remaining 10% of Na^+ and water are absorbed in the medullary collecting duct. Clinically relevant processes include the following:

- Presence of the H-ATPase, which allows for further acidification of the urine (and reabsorption of bicarb).
- Passive absorption of Na^+.
- ADH-regulated reabsorption of water via aquaporins (proteins in cell membranes that regulate flow of water).
- Atrial natriuretic peptide (produced by the cardiac atrium in response to distention) inhibits Na^+ and water absorption in this segment (counteracting the effects of the renin-angiotensin-aldosterone cascade).

As discussed in the section on hyponatremia (page 4-10), new data suggest that thiazide diuretics increase permeability of the medullary collecting duct to water, but not via ADH. This phenomenon is not entirely understood.

RENAL TUBULAR ACIDOSIS

Overview

This section goes into more detail about Types 1, 2, and 4 RTA. RTAs are hyperchloremic NAGMAs. There is one proximal type (2) and two distal types (1 and 4).

Serum K^+ level is low to normal in Types 1 and 2, and high in Type 4.

Type 1 RTA

Type 1 distal RTA is a problem in the H^+-ATPase of the intercalated cells in the late distal tubule and cortical collecting duct that results in failure to acidify the urine. It is associated with hypokalemia (mechanism not completely understood) and hypercalciuria +/– nephrocalcinosis or stone formation. Urine is alkaline.

Most common causes:

- Genetic (presents in childhood)
- Autoimmune disease (Sjögren's, SLE, and rheumatoid arthritis)
- Hereditary hypercalciuria
- Drugs (amphotericin B, lithium)

Treatment is alkali therapy (i.e., sodium bicarbonate—low doses are usually sufficient), K^+ replacement, and addressing the cause.

Type 2 RTA

Type 2 proximal RTA is a problem with proper functioning of cells in the proximal tubule (review on page 4-14). Remember that the proximal tubule is the area where most bicarbonate is reabsorbed by the kidney; therefore, bicarbonate wasting is the natural outcome of Type 2 RTA. So, just think Type 2 RTA = bicarbonate wasting.

In Type 2 RTA, the proximal tubule is deficient in:

- Bicarbonate reabsorption
- Cotransport of Na^+ with glucose, amino acids, Cl^-, and K^+

Most common causes of Type 2 RTA:

- Monoclonal gammopathies (i.e., multiple myeloma) with buildup of light chains that damage the tubule cells
- Carbonic anhydrase inhibitors

Type 2 RTA may present as Fanconi syndrome (glucosuria, amino aciduria, and wasting of other solutes, including Mg, uric acid, and phosphorus). Urine is initially acidic, but becomes alkaline with bicarbonate treatment.

Treatment is bicarbonate (often very large doses are needed), potassium replacement, and vitamin D supplementation.

Type 4 RTA

Type 4 distal RTA is a result of hyporeninemic hypoaldosteronism or aldosterone resistance in the principal cells of the late distal tubule and cortical collecting duct. The Na/K ATPase counter-transporter does not function. It is associated with hyperkalemia. The acidosis is mild.

The hyporeninemic hypoaldosteronism is usually a result of:

- Diabetic nephropathy
- Obstructive uropathy
- Chronic interstitial nephritis

Several common drugs can also suppress renin/aldosterone and lead to a hyperkalemic metabolic acidosis similar to Type 4 RTA:

- Spironolactone
- ACEIs, ARBs
- NSAIDs (exacerbates a concurrent hyporeninemic state)

Although it makes theoretical sense to treat this cause of Type 4 RTA with fludrocortisone (Florinef®; a synthetic adrenal corticosteroid with very potent mineralocorticoid effects), this therapy often leads to too much fluid retention.

Table 4-6: Renal Tubular Acidoses (RTAs)

	Type of Acidosis	Urine pH	Serum K^+	Misc.	Mechanism	Main Causes
Type 1 Distal	NAGMA (severe, but responds to HCO_3 treatment)	> 5.5	Low-nl	Stones, nephrocalcinosis	In intercalated cells: Decreased H^+ secretion in late distal tubule and cortical collecting duct	Autoimmune (SLE, Sjögren's, RA) Hereditary hypercalciuria Drugs (amphotericin B, lithium)
Type 2 Proximal	NAGMA (mild, but difficult to correct with HCO_3 treatment)	Varies	Low-nl	Fanconi's	Decreased resorption of HCO_3^- in proximal tubule	MM Acetazolamide Amphotericin B Heavy metals Amyloidosis
Type 4 Distal	NAGMA (mild, responds to HCO_3 treatment)	< 5.5	High	Diabetes	In principal cells: Decreased Na^+–K^+ exchange in late distal tubule and cortical collecting duct; reduced NH_4^+ excretion	Diabetic nephropathy Chronic interstitial nephritis NSAIDs ACEI Obstructive uropathy Spironolactone

Table 4-7: RTAs — Serum and Urine Chemistry

	Plasma					Urine	
	Na^+	K^+	Cl^-	HCO_3^-	pH	K^+	Na^+
Normal	135–145	3.5–5	95–105	22–30	Variable	25–100	100–260
A	140	2.6	113	17	7.9	50	100
B	140	5.5	117	13	6	50	100
C	140	4.0	115	15	6	50	100
D	140	4.0	105	15	6	50	100
E	140	4.0	115	15	6	10	10

QuickQuiz

- Diabetic nephropathy causes which type RTA?
- Know Table 4-6 and Table 4-7! Answer all of the questions.
- What K^+ derangement can be seen in Cushing syndrome?

Dietary restriction of sodium or bicarbonate administration may be sufficient treatment. Otherwise, give furosemide—a commonly used, effective treatment.

Review of RTAs

Clues to analyzing possible RTA:

All types are non-anion gap metabolic acidosis.

Type 1 RTA is associated with hypercalciuria +/– nephrocalcinosis or stones; high urine pH; definite hypokalemia.

Type 2 is characterized by bicarbonate wasting and Fanconi's; urine pH and serum K are variable. Think myeloma.

Type 4 is associated with aldosterone deficiency or resistance and is marked by mild acidosis and hyperkalemia. Think causes of hyporeninemic hypoaldosteronism (interstitial disease, diabetes, NSAIDs, and ACE inhibitors).

Exam questions concerning RTA may not even mention the term "RTA." Instead, questions may present patients with a history of nephrocalcinosis or diabetes or signs/symptoms suggestive of myeloma; then you may be asked to select the most likely serum and urine chemistry or the best treatment based on your interpretation of the given labs.

RTA Questions

After reviewing Table 4-6, answer the following questions that refer to Table 4-7.

Which chemistry profile, A thru E, in Table 4-7 is associated with the following clinical scenario?

1) DKA
2) Patient with diabetes and chronic kidney disease
3) Patient with myeloma
4) Woman with nephrolithiasis
5) Patient with heavy metal poisoning
6) Patient with chronic diarrhea

Here is one approach to analyzing a table like this:

First, peruse the values. Notice that all of the HCO_3^- values are low, and all of the Cl^- values are high (disproportionate to the Na^+). Think to yourself, "Oh yeah, hyperchloremic acidosis … This may be one of those RTA problems."

Next, calculate the AG for each, and label the ones with an increased AG, HAGMA. (Note: Usually HAGMA has a normal Cl^-.)

Next, look for an alkaline urine (pH > 6.0), despite the low HCO_3^-. If yes, check to see if the serum K^+ is also low to normal. If yes, label it "Type 1 distal RTA—autoimmune, hypercalciuria."

Next, look for a high serum K^+, and label it "Type 4 RTA—hyporeninemic hypoaldo (diabetes, NSAIDs, ACEIs)."

Then, label the (probably) last one "Type 2 RTA—MM, Fanconi's, heavy metals."

NAGMA with a low urine sodium value is almost certainly diarrhea-induced volume contraction. Any HAGMA could be ethylene glycol, methanol, lactic/ketoacidosis, or salicylates. And what if you see a low anion gap? This means there is probably some artifactual lowering of the Na^+. This occurs in hyperlipidemia and multiple myeloma (MM). We suspect that it would be in a MM patient with Type 2 RTA.

Correct answers are 1) D; 2) B; 3) C; 4) A; 5) C; 6) E.

MINERALS

POTASSIUM

Overview

Aldosterone

Basically, aldosterone can be considered the hormone that regulates potassium level. Recall from page 4-16, K^+ secretion occurs in the late distal tubule and cortical collecting duct via aldo-regulated Na^+/K^+ active transport.

Any situation that causes aldo release (or mimics aldosterone) lowers the serum K^+. These include:

- Increased renin as a result of decreased effective arterial blood volume:
  - Volume depletion (GI losses, diuretic therapy)
  - Decreased renal perfusion (HF, renovascular disease, NSAIDs)
- Increased renin as a result of inappropriate release:
  - Renin-secreting renal tumors
- Increased aldo as a result of inappropriate release:
  - Bilateral adrenal hyperplasia
  - Aldo-secreting adrenal adenoma
- Increased excretion of hormone with aldo-like effects:
  - Cushing syndrome

Conversely, any situation that inhibits aldo release or aldo action increases the serum K^+:

- Potassium-sparing diuretics (Remember: Spironolactone blocks the aldosterone receptor; amiloride blocks the channel its action depends on.)
- Dysfunctional kidneys that do not release renin (termed "hyporeninemic hypoaldosteronism"); chronic interstitial nephritis; diabetes; exacerbated by NSAIDs
- ACE inhibitors, angiotensin receptor antagonists, and renin inhibition
- Primary adrenal disease (Addison's), because it affects both the zona glomerulosa (site of aldo production) and fasciculata (site of cortisol production)—but not secondary adrenal insufficiency because lack of ACTH affects only the zona fasciculata
- Heparins (Both unfractionated and low molecular weight are directly toxic to the zona glomerulosa.)

Know: NSAIDs typically decrease renin, so they can make K^+ go up—but generally only if the patient has an existing problem that affects the kidneys. Basically, NSAIDs make hyporeninemic states worse than they already are. See Other Drug-Induced Nephropathies on page 4-49 for more explanation.

Cellular Shifts

Cellular uptake also affects serum K^+ level:

- Alkalosis, beta-agonists, and insulin increase uptake → hypokalemia
- Acidosis and alpha-agonists decrease uptake → hyperkalemia

So this works both ways. Remember from the discussion on the proximal tubule (page 4-14) that hypokalemia can cause alkalosis, and hyperkalemia causes acidosis. And the reverse is true: Alkalosis causes hypokalemia and acidosis causes hyperkalemia.

Other Factors Affecting K^+ Level

Potassium excretion by the kidney is stimulated by increased urine flow, increased distal Na^+ delivery, aldosterone, the presence of non-resorptive anions in the tubules, and metabolic alkalosis. The following factors also affect serum K and are important to know:

- Increased cell turnover is associated with hyperkalemia (tumor lysis syndrome, rhabdomyolysis, acute leukemia).
- Trimethoprim in TMP/SMX interferes with K^+ secretion in the principal cells of the late distal tubule and cortical collecting duct, especially in patients with preexisting renal disease, causing hyperkalemia.
- Type 1 distal RTA is associated with hypokalemia for unclear reasons.
- Type 2 proximal RTA can be associated with hypokalemia because of cotransport problems.
- Loop and thiazide diuretics block reabsorption of solutes and water. Thiazides increase distal delivery of solutes and up-regulates the Na^+/K^+ ATPase in the early distal tubule causing hypokalemia.

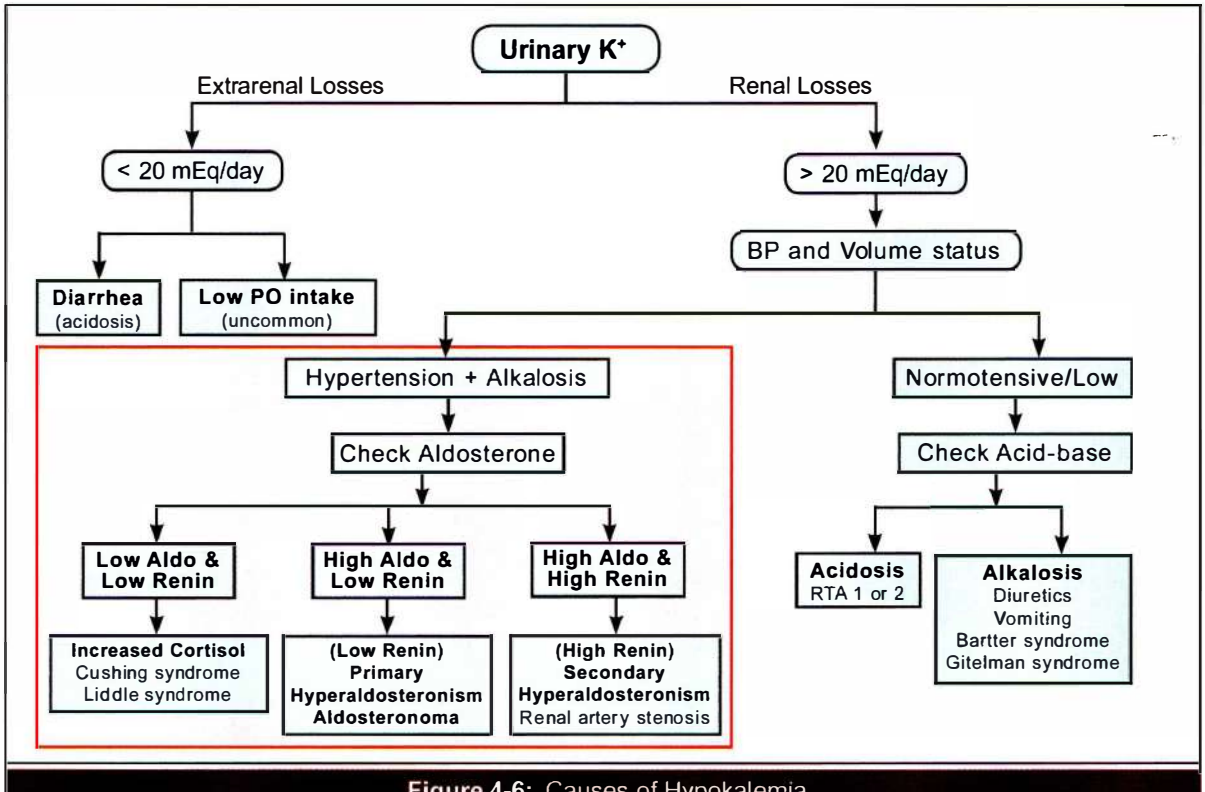


Figure 4-6: Causes of Hypokalemia

Quick Quiz

- Addison disease causes what type of potassium derangement?
- Discuss the effects of NSAIDs on serum K^+.
- How does the acid-base status affect K^+ levels?
- What are the ECG changes associated with hyperkalemia?
- What is special about the treatment of hyperkalemia in patients taking digoxin?

- Cisplatin and penicillins are associated with renal K^+ wasting, causing hypokalemia.
- 3 genetic syndromes are associated with hypokalemia: Liddle's, Bartter's, and Gitelman's.

Summary

The following is the same information just discussed, slightly reorganized and in list form. Please refer to Figure 4-6 as you read the following.

Causes of Hypokalemia

Hypokalemia with metabolic alkalosis:

- Reduction in effective arterial blood volume
  - Volume contraction: vomiting, NG suction, bleeding, or diuretics (thiazides and loops)
  - Renovascular disease: renal artery stenosis or fibromuscular dysplasia
  - Secondary hyperaldosteronism: severe HF, cirrhosis, nephrotic syndrome
- Primary hyperaldosteronism
- Aldo-secreting tumor ("Conn syndrome")
- Renin-secreting tumor
- Cushing syndrome
- Liddle's, Bartter's, and Gitelman's (see next page)

Hypokalemia with metabolic acidosis:

- Types 1 and 2 RTA
- Diarrhea

Hypokalemia associated with shifts into cells:

- Beta-agonists
- Insulin

Other causes of hypokalemia:

- Penicillins
- Cisplatinum

Causes of Hyperkalemia

- Chronic interstitial nephritis
- Type 4 RTA (hyporeninemic hypoaldosteronism)
- Primary adrenal insufficiency (Addison disease)
- Acidosis
- Drugs
  - Potassium-sparing diuretics
  - NSAIDs
  - ACEIs/ARBs and renin inhibitors
  - Heparins
  - TMP/SMX
  - Cyclosporine, tacrolimus
  - Alpha-agonists

Hyperkalemia Manifestations

Most patients have no symptoms if the increase in the potassium has been chronic, even with a level near 7 mEq/L. Symptoms can manifest at lower serum levels when the increase is acute. Presentation can include significant weakness or paralysis, conduction abnormalities or arrhythmias. Typically, if a patient is experiencing weakness, they also have ECG changes, although the opposite is not necessarily true.

Know the sequence of ECG changes that occur with progressive hyperkalemia:

- peaked T wave and short QT interval, then
- progressive lengthening of PR and QRS intervals, then
- loss of P wave + QRS widening into sine wave, then
- ventricular fibrillation or cardiac standstill.

Hyperkalemia Treatment

Treatment is aimed at decreasing the serum concentration and stabilizing cardiac membranes. Problems usually occur when $K^+ = \sim 7$ mEq/L, but there is no absolute number that requires treatment. IV calcium is always given to patients with ECG changes.

Treatment of acute hyperkalemia with ECG changes:

- **IV calcium** gluconate (OK for peripheral injection) or IV calcium chloride (requires central access); use only if there is a wide QRS or absence of P waves. IV calcium can enhance the effect of digoxin; therefore do not give to patients on this therapy.
- **Insulin with glucose** infusion (15 minutes for effect).
- **Sodium bicarbonate** injection or infusion, if acidosis is present (30 minutes for effect; minimal response in patients without acidosis).
- **Albuterol** nebulization (90 minutes for effect) or injection (30 minutes for effect), but be careful in patients with heart disease.
- **Loop diuretics** (in patients who make urine).
- **Dialysis**.

Sodium polystyrene sulfonate ([SPS]; Kayexalate®, Kionex®, Marlexate™) is a cation-exchange resin given orally or as an enema that exchanges Na^+ for K^+ across the gut wall and also induces an osmotic diarrhea full of potassium. SPS can be used to treat hyperkalemia, but it should not be used for treatment of severe hyperkalemia because it may take hours to work. Know that SPS in

sorbitol (most common preparation) has been associated with colon necrosis, especially within a week after surgery and especially in patients with ileus.

Patients with severe chronic kidney disease or on dialysis should be treated as above, but they may also need immediate dialysis. SPS without sorbitol can be given if there is a delay in dialysis.

Treat $K^+ \geq 6.5$ without symptoms or ECG changes with insulin + glucose, beta-agonists, sodium bicarbonate (if acidosis), and SPS enema. $K^+ \leq 6.5$ can be treated with loop diuretics and dietary restriction.

Know that sodium bicarbonate infusions can cause edema and may precipitate cardiac decompensation.

Make sure you check the patient's medication list and discontinue all of the drugs that cause hyperkalemia (ACE/ARBs, K-sparing diuretics, beta-blockers, heparin, NSAIDs, trimethoprim-sulfamethoxazole).

Hypokalemia Manifestations and Treatment

Overview

Severe hypokalemia may cause U waves, decreased deep tendon reflexes, and rhabdomyolysis. Serum K^+ does not decrease to below normal until there is a net loss of 200–300 mEq. The consequence of this is that large amounts of KCl are usually required for replacement.

Treat contributing factors such as volume depletion and/or metabolic alkalosis; also, do whatever tests are necessary to diagnose the cause (e.g., measure urine free cortisol to diagnose Cushing's; consider hyperaldosteronism). Replace potassium orally when possible. Poor response generally means the deficit is large, and the patient merely requires more potassium. Comorbid magnesium deficiency causes renal potassium wasting, so always check and replenish mg stores.

Hyperaldosteronism

This entity is also discussed under Hypertension on page 4-25.

Primary hyperaldosteronism is caused by disease in the adrenal gland. Hyporeninemia, hypertension, and hypokalemia occur—as in other states of mineralocorticoid excess, such as Cushing syndrome. The adrenal disease is either bilateral adrenal hyperplasia or an aldo-secreting tumor in the zona glomerulosa ("Conn syndrome").

Secondary hyperaldosteronism is caused by disease in the kidneys or a restricted blood flow in the renal arteries. Hyperreninemia, hypertension, and, sometimes, hypokalemia occur. Decreased renal blood flow → increased renin → increased angiotensin II → increased aldosterone. Renin-secreting tumors of the kidney are rare. Renovascular disease can be due to either atherosclerotic renal artery stenosis or fibromuscular dysplasia.

In both primary and secondary disease, aldosterone is increased, so the Na^+/K^+ ATPase in the late distal tubule and cortical collecting duct is up-regulated, resulting in increased reabsorption of sodium and increased secretion of potassium and hydrogen ions.

Hypokalemia without an obvious cause, in a patient with hypertension and metabolic alkalosis, should always cause you to deliberately consider hyperaldosteronism. The evaluation of these patients is discussed under Secondary Hypertension, page 4-30. Hyperaldosteronism also is discussed in Endocrinology, Book 4.

Liddle Syndrome

Liddle syndrome is a rare genetic cause of hypertension and hypokalemic metabolic alkalosis in which there is primary Na^+ retention, mediated by an activating mutation of the epithelial Na+ channel in principal cells of the late distal tubule and cortical collecting duct. Renin and aldosterone levels are decreased. Liddle's is treated with amiloride or triamterene.

Bartter and Gitelman Syndromes

Bartter's and Gitelman's usually are due to rare genetic or sporadic defects that cause abnormal solute transport in the thick ascending segment and the early distal tubule. Both are associated with severe sodium losses and eventual volume contraction with activation of the renin-angiotensin-aldosterone system. Renin and aldo levels are increased. Release of aldosterone is the mechanism for development of hypokalemia and alkalosis.

Bartter syndrome (4 types) is typically an autosomal recessive disorder, in which there is abnormal solute transport in the thick ascending segment that results in loss of Na, Cl, Ca, and Mg in the urine. Clinically, patients look like they are taking a loop diuretic. Bartter's type 4 has associated deafness. This syndrome sometimes presents in the neonatal period or early childhood due to salt-wasting and significant hypercalciuria, with stones or nephrocalcinosis.

Gitelman syndrome is caused by a defect in the Na^+/Cl^- cotransporter in the early distal tubule. This transporter is normally inhibited by thiazide diuretics; hence, patients with Gitelman's appear clinically as if they are taking a thiazide diuretic, except the patients have severe magnesium-wasting that is incompletely understood. Gitelman's is milder than Bartter's and generally presents later with symptoms of muscle weakness, cramps, and spasms due to hypomagnesemia.

Summarizing these 2 syndromes:

- Both cause hypokalemic metabolic alkalosis and salt-wasting without HTN.
- Bartter's: defect = furosemide-sensitive transporter; less common, childhood, disease of thick ascending limb, sometimes deafness, significant hypercalciuria.

QuickQuiz

- When hypokalemia is associated with HTN and alkalosis, what is the probable cause?
- What are the differences among Liddle's, Bartter's, and Gitelman's?
- What are the most common causes of asymptomatic hypercalcemia?

- Gitelman's: defect = thiazide-sensitive transporter; more common, later presentation, disease of early distal tubule, significant hypomagnesemia, and hypocalciuria.
- The easiest way to distinguish Bartter's from Gitelman's: Bartter's patients have hypercalciuria, Gitelman's patients have hypocalciuria. This is easy to remember because loop diuretics are sometimes used to treat hypercalcemia (increase urinary calcium excretion), and thiazide diuretics are sometimes used to treat calcium-containing kidney stones (decrease urinary calcium excretion).
- Refer to Table 4-8 for a comparison of Bartter and Gitelman syndromes.

A Clinical Approach to Hypokalemia

It's hard to remember all of the conditions associated with low serum K^+. The most helpful way to approach hypokalemia is to categorize patients according to whether or not they have a metabolic acid-base disorder, then whether or not they have hypertension.

Hypokalemia + NAGMA without HTN:

- K^+ loss is usually from diarrhea or Type 1 or 2 RTA.
- Clinical history and the UAG help differentiate. UAG is neGUTive in diarrhea, UAG is positive in RTA.

Hypokalemia + metabolic alkalosis + HTN:

- Diuretics (most common) causing contraction alkalosis. The urine sodium is increased in spite of the volume contraction.
- Hyperaldosteronism (primary or secondary).
- Cushing syndrome.
- Liddle syndrome.
- Adrenal hydroxylase deficiencies.

Hypokalemia + metabolic alkalosis without HTN:

- Bartter syndrome
- Gitelman syndrome

Table 4-8: Comparison of Bartter and Gitelman Syndromes

	Bartter Syndrome	Gitelman Syndrome
Onset	Infants/Children	Early adults
Low K, metabolic alkalosis	+	+
Low Mg	+	+
Hypocalciuria	–	+
Chondrocalcinosis	–	+
Defect	Ascending loop	Distal convoluted tubule
Looks like patient is taking …	A loop diuretic	A thiazide diuretic

CALCIUM

Overview

Calcium is regulated by PTH and vitamin D metabolites, which affect rates of absorption in the kidneys and gut and rates of resorption of bone. Calcium derangements are discussed extensively in Endocrinology, Book 4.

The measured plasma calcium concentration is a total of free/ionized calcium (45%), calcium bound to albumin (40%), and calcium bound to other substances (15%). Ionized calcium is the state available for immediate use by the body and correlates with consequences of hyper- or hypocalcemia. Measure ionized calcium directly to get the most reliable assessment of a patient's calcium status.

Routinely, however, we measure the total plasma calcium. If albumin decreases, the measured plasma calcium decreases, and you need to make a mathematical correction to estimate true calcium concentration (or measure an ionized calcium level to be precise). For each 1 g/dL decrease in albumin, increase the measured plasma calcium by 0.8 mg/dL. In pregnancy, calcium absorption and excretion is increased because the active form of vitamin D, 1,25-$(OH)_2$-D, is > 2x normal.

Hypercalcemia

Hypercalcemia found incidentally in an asymptomatic patient is usually due to use of thiazide diuretics or to 1° hyperparathyroidism (especially consider if there is a history of neck irradiation), but always consider multiple myeloma, hypercalcemia of malignancy, and granulomatous disease.

Most patients with significant hypercalcemia are volume depleted and should receive normal saline replacement fluid. Calcitonin and bisphosphates are now standard of care for persistent hypercalcemia. Loop diuretics are no longer used to treat hypercalcemia, unless overt volume overload develops.

Hypocalcemia

Hypocalcemia has multiple causes.

Most commonly:

- Vitamin D deficiency
- Chronic kidney disease
- Severe pancreatitis
- Rhabdomyolysis
- Hypermagnesemia (always check magnesium level!)

Less commonly:

- Hungry bone syndrome following parathyroidectomy
- Hypoparathyroidism
- Pseudohypoparathyroidism
- Citrate

Citrate is used as an anticoagulant in whole blood. It chelates calcium in the serum, causing hypocalcemia after massive whole blood transfusions. Know that the total plasma calcium concentration remains normal, and only the ionized fraction is reduced (but patients can have symptoms). Monitor patients who receive large amounts of blood or plasmapheresis by measuring their ionized calcium frequently.

Chronic kidney disease results in secondary hyperparathyroidism because of decreased renal conversion of 25-OH vitamin D to the active 1,25-$(OH)_2$-D.

MAGNESIUM

Hypomagnesemia

Hypomagnesemia is very common. Causes are:

- GI disease, especially small bowel-associated malabsorption, chronic diarrhea, acute pancreatitis, and small bowel bypass procedures
- Kidney losses, especially tubular disease (acute tubular necrosis, Bartter's, Gitelman's) and drugs that affect the tubules (loop and thiazide diuretics, aminoglycosides, amphotericin B, cisplatin, pentamidine, cyclosporine, tacrolimus)
- Miscellaneous causes, e.g., proton pump inhibitors ([PPI]; unknown mechanism, but patients can be so severely depleted that levels rise only after the PPI is discontinued), hungry bone syndrome (after parathyroidectomy), alcohol abuse, post-surgical state, and foscarnet use (due to chelation)
- Hypercalcemia

The relationship between calcium and magnesium is difficult to remember. Here's the quick synopsis:

- Both increased and decreased magnesium can cause hypocalcemia.
- Increased calcium can cause hypomagnesemia.

Low magnesium also causes hypokalemia, so always check for low magnesium in patients presenting with hypocalcemia and/or hypokalemia because these deficiencies are not correctable until magnesium stores (not just the serum level) are replenished!

Clinical manifestations of hypomagnesemia most often occur with other electrolyte and/or mineral derangements such as hypokalemia or hypocalcemia. Muscle weakness, spasms, and tetany are the more common neuromuscular manifestations. ECG abnormalities precede cardiac manifestations (wide QRS and peaked T waves). Refractory cardiac arrhythmias are associated with depleted magnesium stores (even with a normal serum level). Treatment can be oral in patients without symptoms, using a sustained release preparation—appreciating that the deficit is usually huge if the serum Mg level is low. Symptomatic patients should receive 50 mEq parenterally over 8–24 hours.

Hypermagnesemia

Hypermagnesemia, on the other hand, is rare and occurs from the use of:

- Mg-containing laxatives, antacids, or enemas in patients with renal failure (all are contraindicated in this group of patients)
- $MgSO_4$ over-infusion during eclampsia treatment
- Less common, but noteworthy, causes: tumor lysis syndrome, milk-alkali syndrome, lithium overdose, Epsom salts ingestion (even as a gargle)

Symptoms begin when magnesium level is > 4–6 mEq/L. There is initial nausea, followed by sedation, muscle weakness, and a loss of deep tendon reflexes, progressing to paralysis (including heart and respiratory muscles).

Treatment: Treat acute symptoms with volume and calcium as an antagonist. Hemodialysis is necessary in renal failure. Do not forget about hypocalcemia, which can develop as a result of increased magnesium concentrations.

PHOSPHATE

Hyperphosphatemia

Hyperphosphatemia—acute increase can be from:

- ATN (especially if due to rhabdo)
- IV solutions
- Rapid cell turnover (tumor lysis or acute leukemia)

Chronic increase of phosphate is seen in:

- Chronic kidney disease
- Hypoparathyroidism

See page 4-49 for a discussion of the treatment of chronic hyperphosphatemia in CKD (the most common situation).

Hypophosphatemia

Hypophosphatemia—think alcoholism and alcoholic ketoacidosis. If severe (PO_4 < 1 mg/dL), it may cause

QuickQuiz

- What is the relationship between calcium and magnesium?
- Hypomagnesemia is associated with what other electrolyte abnormality?
- What is "refeeding hypophosphatemia"?

rhabdomyolysis (as can low K^+), cardiomyopathy, respiratory insufficiency with failure of diaphragm function, and nervous system problems, initially consisting of irritability and hyperventilation, then profound muscle weakness, then seizures, coma, and death. Refeeding of malnourished patients, (think ICU patients) can cause severe hypophosphatemia by redistribution of phosphorus into cells.

Chronic malnutrition (as in alcoholics) results in increased catabolic release of phosphate, which then gets excreted by the kidneys, depleting total body stores. Even though an alcoholic may have a normal phosphate level on admission, he or she may become symptomatic with extreme muscle weakness a few days after a normal diet is established. This is because, as the glycogen level is returned to normal, the muscle cells become anabolic and take up phosphate, thereby reducing serum levels. This form of "refeeding hypophosphatemia" is a common clinical scenario.

Additionally, alcoholic patients with hepatic encephalopathy often have a respiratory alkalosis and may receive glucose solutions, both of which cause phosphate to enter cells, in turn causing severe hypophosphatemia, which may precipitate acute rhabdomyolysis.

Treatment of hypophosphatemia: Give supplemental phosphate to patients with DKA or those having alcohol withdrawal; it should be included in hyperalimentation fluid.

Patients with reduced renal function require less supplemental phosphate; phosphate supplementation may actually cause severe hyperphosphatemia.

Table 4-9: Volume Contraction

	Serum			Urine	
	Na^+	Cl^-	HCO_3^-	Cl^-	Calculated Osmo
Vomiting	Low-nl	95	35	10	700
Diarrhea	Low-nl	115	15	10	700
Thiazides	Low-nl	95	35	100	700
Osmotic diuresis	Low-nl	nl	nl	100	300 (but high volume)

VOLUME CONTRACTION

Look for the following unique combination of factors in the answers to exam questions asking about volume contraction states (Table 4-9).

Vomiting (especially frequent, surreptitious vomiting) causes metabolic alkalosis and:

- Low serum Cl^- (losing stomach HCl in the emesis—makes sense)
- Hypokalemia from renal K^+ wasting mediated by aldosterone

Diarrhea causes metabolic acidosis (NAGMA) and an appropriately high serum Cl^-. (Bicarbonate is lost in the stool, and chloride is avidly reabsorbed to increase intravascular volume.)

Thiazide diuretics, like vomiting, cause a metabolic alkalosis with low serum Cl^-, but, unlike vomiting, cause a high urinary Cl^- if the patient is actively taking the drug. Thiazides cause more Na^+ to be delivered distally, where it is available for reabsorption and, therefore, stimulates H^+ and K^+ secretion. (See the discussion of thiazides under Normal Renal Physiology on page 4-14 and under Drugs for HTN on page 4-26.)

Volume contraction and diuretic use are associated with a concentrated urine. On the other hand, osmotic diuresis (mannitol, hyperglycemia) causes a high urine output with a normal urine osmolality, but increased solute and volume loss per day.

Remember: Diabetes insipidus (nephrogenic or central/neurogenic) may cause hypernatremia and volume contraction, but the patient can have a normal intravascular volume and sodium concentration if water intake is sufficient—so it is only the patients who are unable to drink who become hypernatremic. This is discussed in Endocrinology, Book 4.

HYPERTENSION

NOTE

The following is adapted from the JNC 8 2014 Evidence-based Guideline for the Management of High Blood Pressure in Adults; report from the panel members appointed to the eighth Joint National Committee (JNC 8), published in 2014 in JAMA®.

Classification

Classification of blood pressure ranges remains the same:

- Normal = < 120/< 80
- Pre-hypertension: 120–139/80–89
- HTN, Stage I: 140–159/90–99
- HTN, Stage II: > 160/> 100

NEPHROLOGY

PRIMARY HTN

95% of all HTN is primary (i.e., essential, idiopathic). The systolic blood pressure (SBP) and diastolic blood pressure (DBP) define the stages of HTN (the average of ≥ 2 readings taken from each of ≥ 2 visits after the initial screening):

Stage I: SBP 140–159 or DBP 90–99

Stage II: SBP ≥ 160 or DBP ≥ 100

In any of these stages, morbidity and mortality are higher for men than women, and higher for African-Americans than Caucasians. HTN itself is also more frequent in African-Americans than Caucasians. This may be due to a decreased Na^+ excretion. HTN is well correlated with obesity in young persons. Of course, primary hypertension does have causes—they just have not yet been discovered.

If the diastolic blood pressure is < 85, recheck it in 2–3 years. If 85–90, recheck it in 1 year. If 90–104, recheck it within 2 months. If 105–114, work up within 2 weeks. If > 115, work up immediately.

EVALUATION OF HTN

This is the standard evaluation for newly diagnosed hypertension. Initially, you look for major cardiovascular disease risk factors and identifiable causes of hypertension (Table 4-10).

History: Ask about personal and family history or symptoms of CHD (coronary heart disease), PVD (peripheral vascular disease), cerebrovascular disease, renal disease, DM, and lipid problems. Ask about the use of alcohol, smoking, street drugs, prescribed meds, and diet and psychosocial history.

Perform a full physical exam, including all of the following.

Table 4-10: Identifiable Causes of Hypertension

Labile HTN, medullary thyroid cancer, primary hyperparathyroidism (MEN2)	Pheochromocytoma
Continuous abdominal bruit	Renovascular HTN
Decreased BP in lower extremities or absent/delayed femoral pulses	Coarctation of the aorta
Abdominal or flank masses	Polycystic kidneys
Elevated creatinine or abnormal urinalysis	Renal parenchymal disease
Hypercalcemia	Hyperparathyroidism Granulomatous disease
Hypokalemia	Hyperaldosteronism

General: height, weight, and waist size. Extremities: 2 BP checks (with verification in the other arm), other extremities for decreased pulses, bruits, and edema. Head: funduscopic for hypertensive changes. Neck: bruits, enlarged thyroid. Chest: rales, wheezes. Heart: full heart auscultation. Abd: abnormal masses, bruits, abnormal pulsations.

Initial lab tests for all hypertensive patients: serum chemistry (Na^+, K^+, Cl^-, HCO_3^-, creatinine, fasting glucose), fasting lipid panel (total cholesterol, TG, LDL, HDL), serum Ca^{+2}, U/A, and a 12-lead ECG.

Indications for further evaluation for secondary causes of HTN include abnormal initial lab tests (hypercalcemia or hypokalemia), an abrupt onset, onset at age < 30 years or > 55 years, malignant HTN, refractory HTN (BP above target despite at least 3 medications, one being a diuretic). Secondary HTN comprises only 5% of HTN cases. Renovascular HTN (renal artery stenosis and fibromuscular dysplasia) causing secondary hyperaldosteronism is the most common cause of secondary HTN. The presence of a systolic-diastolic epigastric bruit, asymmetric kidneys (> 1 cm size difference), and a significant decline in renal function with an ACE inhibitor are additional clues suggestive of renovascular hypertension. In the patient with hypokalemia and hypertension, consider whether the patient should be screened for hyperaldosteronism (discussed on page 4-22).

Primary aldosteronism is another relatively common cause of secondary hypertension (up to 5%). Patients with hypokalemia, resistant hypertension, hypertension with an adrenal "incidentaloma," or hypertension with primary aldosteronism in one or more 1st degree relatives should be screened, according to 2008 Endocrine Society Guidelines. Screen with a random plasma aldosterone to renin ratio (ratio > 30 is considered positive).

Other causes of secondary hypertension are Cushing syndrome, primary hyperaldosteronism, coarctation of the aorta, thyroid/parathyroid disease, chronic kidney disease, sleep apnea, drugs, and pheochromocytoma. Rare causes include Liddle syndrome, licorice ingestion, and 11ß-hydroxylase deficiency.

DRUGS FOR HTN

Overview

First, we discuss the specifics of the drugs used for HTN; then we discuss treatment of HTN.

Diuretics

Recall the 4 types of diuretics which were introduced along with normal renal physiology starting on page 4-14:

1) **Carbonic anhydrase inhibitors** (acetazolamide):
   - Inhibit Na^+/H^+ counter-transport in the proximal tubule
   - Complications: acidosis, hypokalemia

Quick Quiz

- Newly diagnosed hypertension in what age groups suggests that the cause might be secondary?
- What is the most common cause of secondary HTN?
- Review the 4 types of diuretics.
- Which diuretic is especially important to give to patients with systolic dysfunction and low ejection fraction?

2) **Loop diuretics** (furosemide, torsemide, bumetanide):
   - Inhibit the $Na^+/2Cl^-/K^+$ cotransporter in the thick ascending segment
   - Diminish the medullary osmotic gradient in the thin descending segment; effective at low GFRs but require higher dosing; contraindicated in sulfa allergy
   - Increase renal calcium excretion
   - Complications: hypokalemia, calciuresis, ototoxicity (high dose IV), and metabolic ("contraction") alkalosis
3) **Thiazides** (hydrochlorothiazide, chlorthalidone, metolazone):
   - Inhibit the Na/Cl cotransporter in the early distal tubule
   - Slightly inhibit carbonic anhydrase in the proximal tubule
   - Decrease renal calcium excretion
   - Less effective at low GFRs; contraindicated in sulfa allergy
   - Complications: hypokalemia, hypercalcemia, metabolic alkalosis; may cause severe hyponatremia in elderly patients
4) **K-sparing diuretics** (spironolactone, amiloride):
   - Inhibit the aldosterone-controlled Na/K ATPase in the principal cells of the late distal tubule and cortical collecting duct
   - Complications: hyperkalemia

Treat edematous patients with heart failure or chronic kidney disease with a loop diuretic. Treat patients with systolic dysfunction and low ejection fraction or problems with hypokalemia with spironolactone.

Diuretic-induced hypokalemia can be severe and is worrisome in patients with underlying cardiac problems and cirrhosis because of the potential for arrhythmias (especially if on digoxin) and hepatic coma. Hypokalemia usually develops within the first 3 weeks of diuretic use, after which new homeostasis develops. Because higher doses only increase side effects, use the lowest diuretic dose needed to achieve the desired effect and monitor levels each time a dose is changed.

Know that 12.5 mg of HCTZ provides the greatest antihypertensive effect; 25 mg only causes more K wasting.

In HF and cirrhotic patients, it's best to keep the K > 4 with supplementation or K-sparing drugs.

Thiazide diuretics can produce severe hyponatremia in patients with poor solute intake, particularly the elderly.

ACE Inhibitors, ARBs, and Renin Inhibitors

Brief review: Renin is a protease released from the kidney in response to decreased blood pressure and decreased effective arterial blood volume. Renin converts angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II by proteolytic enzymes, including angiotensin-converting enzyme (ACE). Angiotensin II increases blood pressure by direct vasoconstriction, potentiation of the sympathetic nervous system, increasing sodium reabsorption in the proximal tubule, and stimulation of aldosterone production by the adrenal gland.

ACE inhibitors (ACEIs: captopril, enalapril, benazepril, fosinopril, lisinopril, quinapril, moexipril, ramipril, perindopril, trandolapril) inhibit conversion of angiotensin I to II, causing a decrease in angiotensin II and aldosterone. Angiotensin receptor blockers (ARBs) act at the angiotensin II receptor level. By blocking angiotensin II production/effect, ACEIs/ARBs result in dilatation of the efferent arteriole (after the glomerulus) → decreased glomerular capillary pressure. This decreased glomerular pressure decreases progression of both diabetic and hypertensive nephropathies, and other types of chronic kidney disease. It can also lead to decreased GFR in patients with decreased effective circulating volume.

ARBs (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) are recommended in diabetics and other patients with indications for ACE inhibitors but who are unable to tolerate them, usually due to cough.

Indications for ACEIs/ARBs

Absolute indications for ACEIs/ARBs: systolic dysfunction, history of STEMI or anterior NSTEMI, chronic kidney disease (especially with proteinuria).

Complications of ACEIs/ARBs

Complications of ACEIs include an increase in serum K^+ by ~ 0.5 mEq/L (possibly significant in patients with chronic kidney disease). Renal function can also decline. Recommendations are to stop the ACEI or ARB if the creatinine increases to > 30% over baseline, and/or the serum K is uncontrollable. The combination of heart failure + ACEI and sudden initiation of NSAIDs is particularly noteworthy for complications.

Up to 20% of patients have to stop an ACEI because of cough. Angioedema is a possible fatal side effect. ARBs have a lower incidence of angioedema and cough.

Know that the combination of an ACEI + ARB for treatment of HTN has been shown to cause increased adverse events (ONTARGET trial). Pick an ACEI or an ARB but do not combine them.

ACEIs/ARBs are absolutely contraindicated in pregnancy because they are teratogenic. Avoid in hyperkalemic patients and use with caution in bilateral renal artery stenosis, heart failure, polycystic kidney disease, and hypertensive nephrosclerosis because the ACEI-induced decreased GFR can precipitate acute kidney injury. ACEIs/ARBs have minimal CNS and sexual side effects.

Renin Inhibitor

The renin inhibitor, aliskiren, acts similarly to ACEIs/ARBs by blocking renin production. It has been approved since 2007 and has an average antihypertensive effect. Potential complications include hyperkalemia, diarrhea, and angioedema. Renin inhibitors are also teratogenic.

In 2012, an interim analysis of international data on the use of aliskiren plus an ACEI or ARB in Type 2 diabetics showed an increased risk of stroke, hyperkalemia, low blood pressure, and renal insufficiency. Again, aliskiren should not be combined with an ACEI or ARB.

Calcium Channel Blockers

Calcium channel blockers (CCBs) depress cardiac contractility and are either:

- **dihydropyridines** (amlodipine, clevidipine, felodipine, isradipine, nicardipine, and nisoldipine), or
- **non-dihydropyridines** (verapamil and diltiazem), that also reduce heart rate.

Both drug types are used to treat hypertension, angina, and arrhythmias.

Complications may include significant edema (especially with dihydropyridines) and constipation (especially with verapamil). Edema seems to form because the drugs vasodilate and fluid leaks into the interstitium. Diuretics are ineffective at treating this edema. Edema is much less likely to occur if the dihydropyridine is given with an ACEI. Because of negative inotropic and chronotropic effects, do not give verapamil or diltiazem to patients also taking beta-blockers or who have heart blocks or severe heart failure.

Several studies have shown adverse associations (e.g., increased risk of death post-MI) with short-acting CCBs (but not long-acting ones). Dihydropyridines (but not verapamil or diltiazem) may increase proteinuria in patients with diabetes and chronic kidney disease.

Beta-Blockers

Beta-blockers are not recommended as 1st line treatment for hypertension. These agents (acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, pindolol, and propranolol) decrease cardiac output, sympathetic tone, and renin production. Each drug differs by its amount of lipid solubility, cardioselectivity, and sympathomimetic activity. JNC 8 panel does not recommend β-blockers for the initial treatment of hypertension because they result in a higher rate of the primary composite outcome of cardiovascular death, myocardial infarction, or stroke compared to use of an ARB, a finding that was driven largely by an increase in stroke.

Some indications for beta-blockers:

- Post-MI
- Stable heart failure
- Atrial fibrillation (rate control)
- Angina

Try to avoid beta-blockers in patients with:

- Reactive airway disease
- Frequent hypoglycemic episodes
- Hyperlipidemia
- PVD

Recall that nonselective beta-blockers (propranolol and labetalol) increase the serum K^+ level slightly (~ 0.5 mEq/L), but this can be significant in patients with chronic kidney disease. Other complications include fatigue, erectile dysfunction, depression, and weight gain of up to 6 lbs.

TREATMENT OF ESSENTIAL HTN

According to the JNC 8 panel, evidence supports BP control, rather than a specific agent used to achieve that control, as the most relevant consideration in their recommendations. Several trials demonstrate that the degree of blood pressure lowering is more important than the specific drug used to lower the BP unless the patient has a specific comorbidity that would benefit from a specific drug.

In the general non-African–American population, including those with diabetes, treat initial antihypertensive with a thiazide-type diuretic, CCB, ACEI, or ARB. In the African-American population, including those with diabetes, treat initial antihypertensive with a thiazide-type diuretic or CCB.

In heart failure, initially treat hypertension with a thiazide-type diuretic, which is more effective than a CCB or ACEI; and an ACEI, which is more effective than a CCB in improving heart failure outcomes. However trials show that evidence is not compelling enough to preclude the use of the other drug classes for initial therapy in heart failure.

Bottom line: Use any drug or drug combination with the fewest side effects to get the BP < 140/90 (or 150/90 for population > 60 years). Look at the goals of treatment as mentioned below.

Quick Quiz

- ACEIs and ARBs are absolutely contraindicated in what patients? Renin inhibitors?
- Why are beta-blockers not recommended as 1st line drugs for monotherapy?
- What are the JNC 8 recommendations to treat hypertension in elderly patients?

Acceptable 1st line drugs for monotherapy in non–African-American patients include thiazide diuretics, ACEIs, or ARBs, and CCBs.

Acceptable 1st line drugs for monotherapy in African-American patients, including those with diabetes, are thiazide diuretics or CCBs.

As monotherapy, beta-blockers are not recommended as the 1st line agents because they are associated with an increased risk of stroke and heart disease. Use beta-blockers initially only if the patient has specific comorbidities (discussed below), because long-term data show increased adverse effects, especially in the elderly.

Some specifics regarding monotherapy for HTN:

- Monotherapy with a thiazide, ACEI/ARB, or long-acting CCB is fine for patients with mild hypertension.
- African-Americans do better with a thiazide or a long-acting CCB.
- Young patients do best with an ACEI. As patients age, they often require additional drugs.

Patients who are not controlled with monotherapy usually have a better response with the addition of a low-dose 2nd drug, rather than an increase in dose of the 1st drug.

Initially treat patients with BP > 160/100 with 2 drugs.

Summary of JNC 8 Guidelines

According to JNC 8, emphasize healthy diet, weight control, and regular exercise in all patients with hypertension. JNC 8 supports the recommendations of the 2013 Lifestyle Work Group.

These general lifestyle guidelines for preventing and controlling hypertension are:

- Stop smoking.
- Lose weight/DASH diet.
- Get regular aerobic activity.
- Moderate alcohol and Na^+ intake.
- Maintain sufficient intake of K^+, magnesium, and calcium.
- Reduce intake of saturated fat and cholesterol.

Goals of treatment: Threshold for pharmacologic treatment are defined in JNC 8 based on age, diabetes, and chronic kidney disease:

- General population < 60 years: < 140/90
- General population > 60 years: < 150/90
- All ages, no CKD, diabetes: < 140/90
- All ages, CKD, with/without diabetes: < 140/90

Drug Therapy

This is pretty simple. You must know the 4 classes of recommended agents (ACEI or ARB, CCB, diuretics) and know that these medication classes are recommended based on 2 factors: race and CKD. So, given that:

- Regarding race (general population [all ages], diabetics without CKD).
  - Non-African–American (including those with diabetes): ACEI or ARB, CCB, or thiazide diuretics
  - African-American (including those with diabetes): thiazide or CCB; i.e., in this group an ACEI/ARB is not 1st line therapy
- Presence of CKD (regardless of race or diabetes, population > 18 years): Treat with ACEI or ARB.

Summary: No one drug class is recommended over others for mono- or dual therapy for initial treatment, except in patients with CKD (ACEI or ARB) or based on race (African-American: thiazide or CCB; non-African–American: thiazide, CCB, ARB/ACEI). ACC/AHA recommendations differ from JNC 8 in that they recommend thiazide diuretic as the preferred monotherapy for Stage I hypertension followed by ACEI or ARB, CCB, or combo. For Stage II hypertension, they recommend starting with a combination of thiazide + either ACEI or ARB, CCB.

Patients > 60 years

Hypertension is common in the elderly—a 60–80% incidence! Elderly persons generally have isolated systolic hypertension (SBP > 160); but diastolic HTN also occurs, so treat both. The data now strongly support treating isolated systolic hypertension, even in patients older than 80 years. The degree of systolic hypertension and the increase in pulse pressure are directly correlated with poor outcomes.

Treatment recommendation for general population age ≥ 60 years (JNC 8; moderate-to-strong evidence):

- Initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) ≥ 150 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. Treat to a goal SBP < 150 mmHg and a goal DBP < 90 mmHg. (Strong Recommendation – Grade A).
- In those ≥ 60 years, treat high BP to a goal of lower than 150/90 mmHg, which reduces stroke, heart failure, and coronary heart disease (CHD).

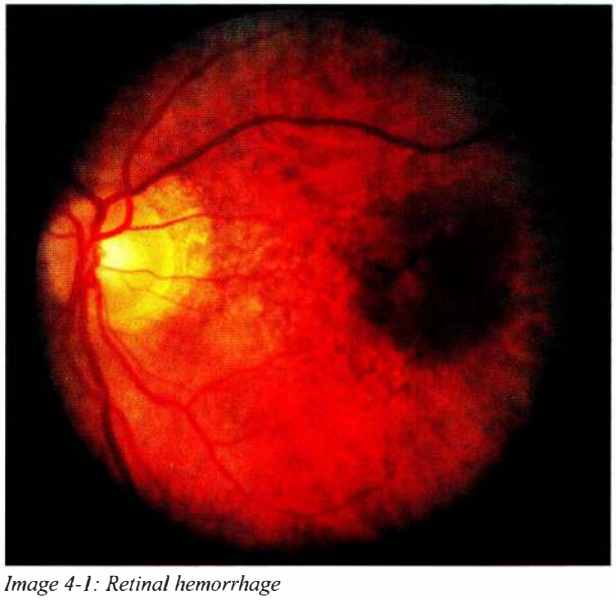


Image 4-1: Retinal hemorrhage

If pharmacologic, treatment for high BP results in lower achieved SBP (e.g., < 140 mmHg), and treatment is well tolerated, then do not adjust it (moderate-to-high–quality evidence).

HYPERTENSIVE CRISES

There are 2 main clinical expressions of end-organ damage caused by severe HTN:

1) Malignant HTN, which is severe HTN with papilledema, retinal hemorrhages (Image 4-1), or exudates that may also be associated with nephrosclerosis (which presents as acute kidney injury, proteinuria, hematuria).
2) Hypertensive encephalopathy, which is severe HTN with signs of cerebral edema (which presents as headache, nausea/vomiting, confusion, coma, and/or seizures). (This condition must be differentiated from acute stroke with imaging.)

Treatment goal is a controlled, steady decrease of the diastolic BP to 100–105 mmHg within 2–6 hours, while minimizing the drop so as not to reduce the presenting BP by > 25%. Generally, IV agents are used (e.g., nitroprusside, nicardipine, labetalol) because oral drugs reduce the BP in a less rapid and less predictable way. If the patient is asymptomatic or there are no parenteral drugs available, you can use oral drugs. Keep in mind that too rapid of a drop in BP may cause an ischemic stroke or MI. Drugs used are loop diuretics, beta-blockers, ACEIs, alpha-blockers, and CCBs. Oral agents are not the standard of care, however, if the above parenteral options are available.

SECONDARY HYPERTENSION

Renovascular HTN

Renovascular disease causing secondary hyperaldosteronism is the most common cause of secondary HTN.

The 2 main causes of renovascular hypertension:

1) Atherosclerotic renal artery stenosis (often bilateral, mainly affecting men > 50 years old, especially diabetics)
2) Fibromuscular dysplasia (also often bilateral, mainly affecting women < 40 years old)

Less common causes of renovascular HTN include scleroderma and various vasculitides (e.g., Takayasu arteritis).

So consider renovascular HTN when you see moderate-to-severe HTN with onset in patients < 30 years of age (fibromuscular), onset of HTN in patients > 55 years of age (atherosclerotic), HTN + unexplained hypokalemia, and accelerated HTN.

Diagnosis: Renovascular HTN may cause a continuous renal bruit, not an isolated systolic bruit. Know that the combination of a continuous abdominal bruit and hypokalemia in a hypertensive patient is strongly suggestive of renovascular HTN—especially if they have other risk factors (> 55 years old, diabetic).

Screen patients with possible secondary hypertension caused by renovascular disease with noninvasive tests first—if their serum potassium levels are normal. Choices are CT angiography, MR angiography, and duplex Doppler ultrasound of the renal arteries, with the first 2 being the most sensitive. Work up only those patients who are moderate-to-high risk for disease and who are candidates for intervention (surgery or, more commonly, angioplasty with stent placement).

Patients with suspected fibromuscular dysplasia are almost always candidates for intervention, because these patients can frequently be cured. Patients with suspected atherosclerotic renal artery stenosis are generally considered candidates for intervention only if 1 of the following criteria is met:

1) Uncontrolled blood pressure despite 3 or more antihypertensive medications
2) Recurrent "flash" pulmonary edema
3) Renal salvage (progressive decline in renal function)

Definitely do not screen elderly patients with mild hypertension and a normal serum potassium.

Several older screening tests for renovascular disease do not perform as well as CT and MR angiogram and are no longer recommended (captopril renal scintigraphy, selective renal vein renin measurements, isolated plasma renin activity, or an IV pyelogram.)

For patients with possible secondary hypertension and hypokalemia, proper screening includes an evaluation for disease in the adrenal gland, termed "primary hyperaldosteronism." In these patients, start with the PAC:PRA test (discussed next).

So, just to review, in patients with possible secondary hypertension, if the serum K is:

- Normal: Go straight to evaluation of the renal vasculature with helical CT, MRI, or Doppler.

Quick Quiz

- What is the goal for blood pressure reduction in patients who present with hypertensive crisis?
- What is the main cause of renovascular hypertension in men > 50 years old?
- What is the main cause of renovascular hypertension in women < 40 years old?
- What does the combination of a continuous abdominal bruit and a low K^+ imply in a hypertensive patient?
- How do you confirm the diagnosis of primary hyperaldosteronism?
- How do you screen for pheochromocytoma?

Do not screen patients who are not candidates for intervention (see earlier criteria).

- Low: Screen for primary hyperaldosteronism using the serum PAC:PRA (discussed next).

Arteriography is the gold standard for diagnosis of renovascular HTN, but the procedure is invasive, with potential for serious complications. Use it to confirm positive noninvasive screening tests. Fibromuscular dysplasia shows up as a "string of beads" with multiple, little aneurysmal dilatations. An atherosclerotic lesion is usually a single, unilateral, proximal stenosis with distal dilation. Not all lesions found on angiogram are functionally significant, so it is very important to consider a patient's likelihood of true disease prior to ordering the test.

Treatment: Fibromuscular dysplasia can frequently be treated with angioplasty/stenting, but intervention in atherosclerotic renal artery disease is controversial and does not always improve hypertension. Blood pressure in renovascular hypertension often responds well to ACEI or ARB, but you need to watch for a decline in renal function.

Primary Hyperaldosteronism

Aldosterone is secreted by the adrenal zona glomerulosa in response to renin stimulation and ADH secretion causes Na^+ uptake/K^+ secretion in the principal cells of the late distal tubule and collecting duct. Suspect hyperaldosteronism (primary or secondary) in a person not on diuretics who has hypokalemia of unknown hypertension and etiology. There are 2 main causes of the primary form: adrenal adenomas (70%; sometimes called "Conn syndrome") and idiopathic bilateral adrenal hyperplasia (~ 25%). Adrenal carcinoma is a rare cause.

Screening and diagnosis: Screen with a plasma aldosterone concentration (PAC) and plasma renin activity (PRA). The paired hormones can be analyzed as a ratio (PAC:PRA).

In primary hyperaldosteronism (disease in the adrenal), the PAC is increased, but the PRA is suppressed such that the ratio is usually > 20. If this screening suggests primary hyperaldo, assess whether you can suppress aldosterone after salt and fluid loading. Give 2 liters of normal saline IV over 3–4 hours while the patient is recumbent, then check the aldo level. Alternatively, you can give an oral salt load over 3 days and check the aldo level. In either situation, if aldosterone is not suppressed, the patient has primary hyperaldosteronism.

Also, if the patient is already on an ACEI or ARB, draw renin and aldosterone levels to see if aldosterone is suppressed; if not, this also supports the diagnosis of 1° hyperaldosteronism.

Once you know you're dealing with aldosterone excess, do a CT scan of the adrenals to characterize the gland: Is there hypertrophy/hyperplasia or an adenoma?

Initial treatment of primary hyperaldosteronism:

- Salt and water restriction
- K^+-sparing diuretics:
  - Spironolactone
  - Triamterene
  - Amiloride
- +/– Thiazide diuretic

Unilateral adrenal adenomas are surgically removed with excellent results, whereas patients with bilateral adrenal hyperplasia are managed with diuretics alone because bilateral adrenalectomy resolves the HTN in only 33% of these patients.

Cushing Syndrome

Cushing syndrome is covered in Endocrinology, Book 4.

Pheochromocytoma

Pheochromocytomas are very rare tumors arising from chromaffin tissue. 90% occur in the adrenal medulla. The rest are abdominal or thoracic. 10% are bilateral; 10% are malignant; and 10% are familial.

Paroxysmal signs and symptoms include palpitations, dizziness, and hypertension. 1/2 to 2/3 of patients have sustained HTN. Especially suspect this if the HTN is refractory to treatment. It is associated with multiple endocrine neoplasia (MEN) 2A and 2B.

Diagnosis: Screen with 24-hour urine for fractionated metanephrines and catecholamines in patients with low pretest probability.

In higher-risk patients (family history of pheo, MEN2, or neurofibromatosis [von Hippel-Lindau disease]), screen with fractionated metanephrines on a random plasma sample. This test is the least specific and may be false-positive in patients with less risk of disease. If the biochemical tests suggest a pheo, get a CT or MRI of the abdomen and pelvis using contrast. If imaging does not show a tumor, and you still suspect one given the

biochemical tests and history, consider metaiodobenzylguanidine scintigraphy. Metaiodobenzylguanidine is a norepinephrine analog that concentrates in an adrenal pheo. Tricyclic drugs interfere with the 24-hour urine tests, so wean your patients before testing. More on pheochromocytomas in Endocrinology, Book 4.

Pregnancy and HTN

In normal pregnancy, the blood pressure is reduced due to a decrease in systemic vascular resistance. Therefore, the BP should always be < 120/80 in pregnancy.

As recommended by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, there are 4 categories of HTN in pregnancy:

1) **Chronic HTN**: preexisting HTN or HTN before 20th week of gestation
2) **Preeclampsia**: HTN + proteinuria after 20th week of gestation in woman with no history of HTN
3) **Gestational HTN**: occurs after 20th week and has no proteinuria in woman with no history of HTN
4) **Chronic HTN with superimposed preeclampsia**: worsening HTN + new onset proteinuria after 20th week of gestation in a woman with history of controlled, chronic HTN

The JNC 8 stages of HTN do not apply in pregnancy, because this population of patients was not addressed by the panel. HTN in pregnancy is defined as:

- mild if BP is 140–159/90–109, or
- severe if BP ≥ 160/110.

Eclampsia is defined as grand mal seizures in a woman with preeclampsia or gestational HTN. Preeclampsia more commonly occurs in primigravidas, usually in the 3rd trimester, and resolves after delivery.

Note: The defining features of preeclampsia are proteinuria and hypertension, not symptoms. Signs and symptoms are an indication of preeclampsia severity. These can be mild (headache, vision changes) or severe (seizures [eclampsia], low platelets, stroke or intracerebral hemorrhage, pulmonary edema, hepatic and/or renal failure, and placental abruption). **HELLP** syndrome is a severe form of preeclampsia with **h**emolytic anemia, **el**evated **l**iver enzymes, **l**ow **p**latelets. Risk factors for preeclampsia include diabetes mellitus, chronic hypertension, multiple gestations (twins, triplets), and prior preeclampsia.

In 2014, USPSTF issued a strong recommendation that pregnant women with a moderate-to-severe risk for preeclampsia be put on 81 mg ASA daily. Risk of preeclampsia is reduced 24%! Also risk of premature birth is decreased by 14% and intrauterine growth restriction by 20%.

Guidelines for treatment differ between severe and non-severe hypertension. Treat all severe hypertension occurring during pregnancy (regardless of category) to < 160 systolic and < 110 diastolic. Note that treatment of chronic hypertension does not deter or prevent preeclampsia (weird … but true).

Know that pregnant women with hypertension are at risk for adverse fetal outcomes if blood pressure is driven too low. This is one patient group in whom we actually have higher BP goals, not lower! Each 10 mmHg reduction in SBP is associated with a reduction in fetal birthweight.

For women with preeclampsia, recommendations are usually to start treatment:

1) if symptoms are present, or
2) in asymptomatic women when SBP ≥ 150 or DBP ≥ 95 (although these specific numbers are controversial), with a target BP goal of < 130–150/80–100.

Bed rest is still recommended for asymptomatic or mild preeclampsia (especially if before 34-weeks gestation), although there are no clinical trials to suggest it affects outcome. For severe, symptomatic preeclampsia, definitive treatment is delivery. Ultimately, care providers walk a fine line between delivering a baby too early to relieve preeclampsia and allowing for longer gestational development.

Carefully review medications in women with chronic HTN who are contemplating pregnancy or are already pregnant. Discontinue ACEI and ARBs, and most recommend discontinuing thiazides. Take women who are pregnant and have chronic HTN that is controlled (BP < 120/80) off BP meds—but get frequent BP and symptom monitoring. (That's right! This is the one instance where antihypertensives are actually removed!) Reinstitute meds for the same BP as mentioned above for preeclampsia (SBP ≥ 150 or DBP ≥ 95) with a target of < 130–150/80–100. Agents that may be substituted include methyldopa and labetalol, though nifedipine is also acceptable. Safety of methyldopa, including long-term outcomes in children, has been demonstrated.

Any pregnancy complicated by malignant HTN (see page 4-30) or severe, symptomatic preeclampsia requires parenteral antihypertensives—labetalol is the preferred drug, though hydralazine also is used extensively. Rapid falls in maternal blood pressure must be avoided to prevent fetal hypoperfusion; nicardipine is 2nd line (but is also a tocolytic—inhibits labor).

Know that the following antihypertensives are contraindicated: ACEIs/ARBs, renin inhibitors, and nitroprusside (cyanide poisoning in the baby).

Oral agents used to treat chronic, asymptomatic preeclampsia, gestational hypertension, and chronic hypertension in pregnancy include labetalol (other beta-blockers impair placental perfusion, so labetalol is preferred), methyldopa, and extended-release nifedipine. 2nd line agents include diltiazem, verapamil, and thiazide diuretics (but watch for signs/symptoms of volume contraction, including oligohydramnios).

Quick Quiz

- What are the 4 categories of hypertension in pregnancy?
- What is the definition of eclampsia?
- What are the defining feature of preeclampsia?
- What is the definition of oliguria?
- What is the underlying cause of prerenal kidney injury?
- What causes do you consider in a patient with hypertension and hypokalemia?

Be aware that eclampsia can definitely occur postpartum, although rarely. A woman who presents hypertensive with generalized seizures within 12 weeks after delivery should be considered eclamptic.

Other Causes of HTN

Other important 2° causes of HTN that must be excluded include birth control pills and coarctation of the aorta. Treatment of obesity, decreasing alcohol intake to ≤ 2 drinks per day, and addressing a deficiency in calcium or potassium in the diet may normalize blood pressure in some patients with mild HTN.

ACUTE KIDNEY INJURY

OVERVIEW

The general term "acute renal failure" has been replaced with "acute kidney injury" (AKI) to better represent a wide spectrum of potential kidney damage—not just failure.

Small changes in serum creatinine can be associated with significant adverse clinical consequences. AKI should be evaluated by excluding prerenal and postrenal causes while evaluating for intrinsic kidney disease.

AKI can be either non-oliguric, oliguric, or anuric. AKI is defined as an increase in the serum creatinine by 0.3 mg/dL or by 1.5-fold over baseline within 48 hours, or by oliguria (urine output < 0.5 mL/kg/hour) for at least 6 hours. Anuria is < 50 mL/d.

Refer to Table 4-11 while reading about acute kidney injury.

Prerenal AKI is caused by underperfusion, either from true loss of volume or decreased effective arterial blood volume.

Postrenal AKI is caused by obstruction within the urinary system.

Intrinsic AKI is caused by a problem with the glomeruli, tubules, or interstitium.

In all patients with AKI, specifically focus on drug exposures, volume status, and episodes of hypotension as part of the history and physical. Initiate the diagnostic workup with orthostatic vital signs, a U/A, fractional excretion of sodium, and renal ultrasound.

PRERENAL AKI

Prerenal AKI is always due to a real or "effective" decrease in renal blood flow:

- Severe intravascular volume loss from volume depletion, blood loss, hypotension, or diuretics
- Renal artery stenosis or fibromuscular dysplasia causing reduced blood volume to the kidneys
- Systolic dysfunction ("cardiorenal syndrome")
- Drugs that cause vasoconstriction of the afferent arterioles:
  - NSAIDs (afferent)
  - Posttransplant immunosuppression drugs (afferent)
- Hepatorenal syndrome
- Abdominal compartment syndrome

If the patient has no indication of hypovolemia on physical exam, consider the other causes listed above—all are associated with reduced glomerular perfusion.

Additional clues as to the specific prerenal cause of AKI include:

- NSAIDs in the history: As we discuss on page 4-49 (Other Drug-Induced Nephropathies), NSAIDs cause constriction of the afferent arteriole and a decrease in GFR in patients who are prostaglandin-dependent to maintain GFR, specifically patients who have comorbidities with preexisting, decreased effective arterial blood volume, such as systolic dysfunction or cirrhosis.
- Baseline hypertension and hypokalemia or recent prescription of an ACEI or ARB: Consider renal artery stenosis or fibromuscular dysplasia.

Hepatorenal syndrome as a cause of prerenal AKI: Evidence of portal hypertension (ascites, esophageal varices, splenomegaly, leukopenia, thrombocytopenia, anemia) and jaundice: Think hepatorenal syndrome. AKI due to hepatorenal syndrome is a severe vasomotor disturbance caused by splanchnic dilation.

There are specific diagnostic criteria to establish a diagnosis of hepatorenal syndrome:

- Cirrhosis with ascites and evidence of portal hypertension
- A serum creatinine > 1.5 mg/dL that progresses over days to weeks
- Lack of improvement in renal function after withdrawal of diuretics and volume expansion with albumin (1 g/kg of body weight per day up to 100 g/day) for at least 2 days

Table 4-11: Acute Kidney Injury Labs and Clues

Category	Causes	FE_{Na}	$FE_{Uric\ acid}$	FE_{Urea}	U_{Osm}	Urine Na^+	Urine Sediment	Suspect in Patient with ...
Prerenal	Volume depletion Decreased EABV* NSAIDs ACEI	< 1%	< 12%	< 35%	> 400 mOsm/L	< 20	Normal Granular casts Hyaline casts	Bleeding CHF Cirrhosis/hepatorenal Abdominal compartment syndrome (ACS) Nephrotic syndrome GI fluid loss (nausea/vomiting/diarrhea)
Intrinsic renal	Diseases of, or damage to, the glomeruli, tubules, or interstitium	ATN* > 2% GN* < 1%	> 20%	> 50%	300–350 mOsm/L	> 20	Red cell casts and/or protein (GN) Dirty brown casts (ATN*) Eos (AIN*)	Infections SLE Vasculitis Drugs (aminoglycosides, amphotericin, cisplatin, NSAIDs) Contrasts/IV dyes Atheroembolism Heroin Myeloma Diabetes HTN Hypotension, shock
Postrenal	Obstruction	Varies	Varies	Varies	Normal	Normal	Hematuria	Elderly males Colicky pain

Fractional excretion**	Level indicating prerenal AKI	Changed by diuretics
FE_{Na}	< 1	Yes
FE_{Urea}	< 35	No
$FE_{Uric\ acid}$	< 12	No

*EABV = effective arterial blood volume
ATN = acute tubular necrosis
GN = glomerulonephritis
AIN = acute interstitial nephritis
**Recent diuretics use can alter the FE_{Na} and, in this setting, FE_{Urea} and $FE_{Uric\ acid}$ are more reliable.

- No evidence of parenchymal kidney disease (normal U/A, proteinuria < 500 mg/d, normal renal ultrasound)
- Absence of any other apparent cause of AKI, including shock, nephrotoxins, and infection (except peritonitis)

Therapy with midodrine and octreotide is aimed at stabilizing patients until they receive a liver transplant.

Abdominal compartment syndrome as a cause of prerenal AKI: Abdominal compartment syndrome (ACS) refers to organ dysfunction caused by intraabdominal hypertension. Intraabdominal pressure (IAP) is the steady state pressure concealed within the abdominal cavity. Abdominal perfusion pressure (APP) is calculated as the mean arterial pressure (MAP) minus the IAP (APP = MAP – IAP).

Elevated intraabdominal pressure reduces blood flow to the abdominal viscera. ACS is defined as a sustained intraabdominal pressure > 20 mmHg (with or without APP < 60 mmHg) that is associated with new organ dysfunction. ACS can occur with abdominal trauma, massive ascites, intraperitoneal bleeding, acute pancreatitis, and any other condition that raises the intraabdominal pressures. AKI in ACS most likely occurs secondary to renal vein compression, which increases venous resistance and impairs venous drainage.

Similar to other causes of prerenal AKI induced by reduced perfusion, the renal indices usually are decreased (FE_{Na} < 1% and FE_{Urea} < 35%).

Treat with either surgical decompression (trauma patients) or high-volume paracentesis (in patients with massive ascites).

Prerenal AKI: Labs

BUN:Cr ratio is typically increased to > 20.

Urine is very concentrated with osmolality > 400, and often > 700.

Urine Na^+ is < 20, indicating normal tubular function (and avid reabsorption of Na^+ to increase glomerular pressure).

QuickQuiz

- With postrenal AKI, how does the amount of urine produced relate to the degree of obstruction?
- ATN is usually due to what 2 causes? Name the major nephrotoxins.

Urine sediment is generally normal but can show granular or hyaline casts.

FE_{Na} is < 1% in both prerenal AKI and acute glomerulonephritis ([GN]; see equation 3 on page 4-2). To differentiate, AKI with an FE_{Na} < 1% and a normal urine sediment +/– few granular or hyaline casts = prerenal azotemia. Dysmorphic red cells, red cell casts, and protein indicate GN.

Patients who are on diuretics can have FE_{Na} > 1% and still have prerenal AKI. In these situations, FE_{Urea} is more accurate than FE_{Na}, and FE_{Urea} < 35% is suggestive of a prerenal state. You can also use $FE_{Uric\ acid}$ in these situations ($FE_{Uric\ acid}$ < 12% is suggestive of prerenal AKI). See Table 4-11.

POSTRENAL AKI

Postrenal AKI results from either external compression of the urinary tract or intraluminal/intratubular obstruction. Intratubular obstruction can be caused by uric acid precipitation, oxalate depositions, hypercalcemia with intrarenal deposits (remember Type 1 distal RTA!), multiple myeloma with light chains, and certain drugs, especially methotrexate, indinavir, acyclovir, ganciclovir, and sulfa antibiotics, which can crystallize in the urine.

Having 2 kidneys protects from unilateral obstruction because the 2nd kidney simply takes over total function. Consider obstruction if the patient develops AKI and has normal kidneys—or the patient has AKI and only 1 kidney (other kidney removed).

Prostatic hypertrophy and stones are the usual causes of postrenal AKI in internal medicine patients. Recall that Type 1 (distal) RTA is associated with calcium stone formation. Stones are specifically discussed on page 4-55. Urethral stenosis and cancer less commonly cause outlet obstruction.

Know that the amount of urine produced does not really give you an indication about the degree of obstruction. Obstructed patients can even have increased urine output because of chronic damage to the tubules that impairs their ability to reabsorb water and solutes. Anuria, however, almost never occurs with obstruction unless it is complete (commonly associated with shock).

Postrenal AKI: Labs

Creatinine is usually normal in unilateral complete or partial obstruction and elevated in bilateral complete obstruction.

U/A is typically "bland" (no abnormalities). Papillary necrosis (the papillae are just before the renal pelvis) occurs in pyogenic kidneys with postrenal obstruction, chronic analgesic abuse, and sickle cell disease. U/A shows sterile pyuria with WBC casts. Another clue: Obstruction can cause a clinical picture consistent with Type 4 RTA: NAGMA associated with hyperkalemia.

Diagnose obstruction with renal U/S or CT scan (if you suspect stones).

INTRINSIC RENAL AKI

The 3 main categories are discussed next as major headings:

1) Acute tubular necrosis (ATN)—discussed first because, in association with a prerenal state, it is the most common cause of intrinsic renal AKI
2) Interstitial disease
3) Glomerular disorders

ACUTE TUBULAR NECROSIS

OVERVIEW

Acute tubular necrosis (ATN) is a more common cause of intrinsic AKI than interstitial disease or glomerulonephritis. ATN causes about 1/2 of the cases of AKI in the hospital.

CAUSES OF ATN

ATN is caused by ischemia (progression from prerenal AKI) or a nephrotoxin. Ischemia may be due to shock or any other condition that causes an abrupt decrease in renal perfusion.

Ischemic ATN is caused by progression of prerenal AKI.

Nephrotoxic ATN has endogenous and exogenous causes:

- Endogenous
  - Free myoglobin (rhabdomyolysis, page 4-37)
  - Free hemoglobin (intravascular hemolysis)
- Exogenous
  - Contrast-related
  - Drugs (aminoglycosides, amphotericin B, foscarnet, cidofovir, tenofovir, cisplatin, and many others)
  - Osmotic nephropathy—IVIG with sucrose/mannitol/dextran, especially in patients with underlying chronic kidney disease
  - Acute phosphate nephropathy
  - Use of bowel purgatives containing sodium phosphate

Notes on drug-induced ATN:

- Amphotericin B causes ATN but requires a cumulative dose, and is especially likely to occur at > 3 gm total dose. Amphotericin B has a direct nephrotoxic effect and can cause a Type 1 or 2 RTA.
- Aminoglycosides (AG) cause proximal tubule damage, resulting in a non-oliguric ATN and hypomagnesemia. Typically, GFR begins to fall 5–7 days after the start of treatment. Once-daily AG dosing is less nephrotoxic than multi-daily doses. Gentamicin is the most toxic AG.
- Cisplatin is a common chemotherapeutic cause of ATN. It also causes a magnesiuria and hypomagnesemia.
- Both tenofovir and cidofovir can cause a Fanconi-like syndrome in addition to AKI.

Tubular dysfunction is the hallmark of disease. Renal epithelium necrotizes, and the tubules essentially fill up with debris so they no longer function. Failure of tubules to appropriately reabsorb water and solutes leads to activation of tubuloglomerular feedback, leading to a profound decrease in GFR.

Acute phosphate nephropathy (APN) is a form of acute kidney injury that occurs after the use of bowel purgatives containing sodium phosphate. Transient hyperphosphatemia after ingestion or enema containing sodium phosphate leads to an increased intratubular phosphate concentration, resulting in the precipitation and tissue deposition of calcium phosphate salts that cause luminal obstruction and direct tubular epithelial injury.

Risk factors for developing APN include underlying kidney dysfunction (GFR < 60), advanced age, volume depletion, hypertension, diabetes, and use of ACEIs or ARBs.

The diagnosis of APN is suggested by the temporal association between AKI and the administration of bowel purgatives that contain sodium phosphate.

Clue: hyperphosphatemia out of proportion to the degree of kidney injury.

Treatment and prevention: Identify patients who are at higher risk for the development of acute phosphate nephropathy and then avoid the administration of bowel purgatives that contain oral sodium phosphate.

Contrast-related AKI causes 2 different renal problems:

1) Immediate contrast-induced ATN (improves and has no skin findings)
2) Cholesterol atheroemboli (livedo reticularis, eosinophilia, obvious systemic emboli, kidney injury)

Consider cholesterol atheroembolic kidney disease if the AKI develops several days after the procedure. (Look for blue toes, livedo reticularis, stepwise progression, eosinophilia, eosinophiluria, and low complements.) With this disease, there are showers of cholesterol emboli that settle systemically in the extremities and in the kidneys, causing a "stepwise progression" of renal failure, abdominal pain, livedo reticularis, and blue toes.

Hollenhorst plaques may occur. These are cholesterol emboli in the retinal arterioles that appear as orange-white dots interrupting the circulation.

Labs often show eosinophilia +/– eosinophiluria, and hypocomplementemia, or may show proteinuria and/or hematuria (which would represent more of an intrinsic AKI manifestation). If diagnosis is in doubt, a skin biopsy of 1 of the systemic lesions can show a cholesterol embolus.

Treatment of AKI due to cholesterol emboli is supportive only. Do not anticoagulate.

Emboli may also occur after vascular surgery (especially of the aorta) or arterial catheterization in the atherosclerotic patient.

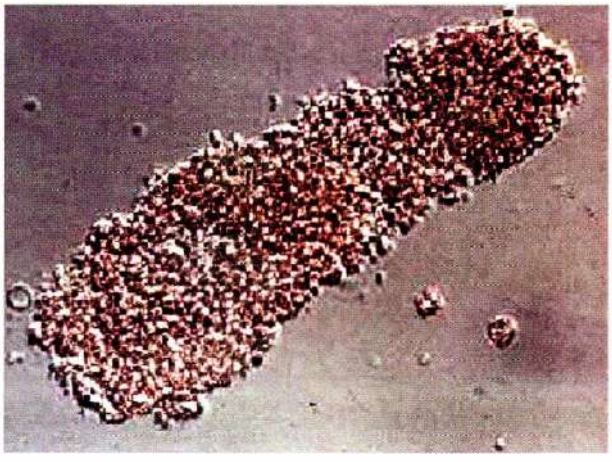


Image 4-2: Coarse granular (dirty brown) casts

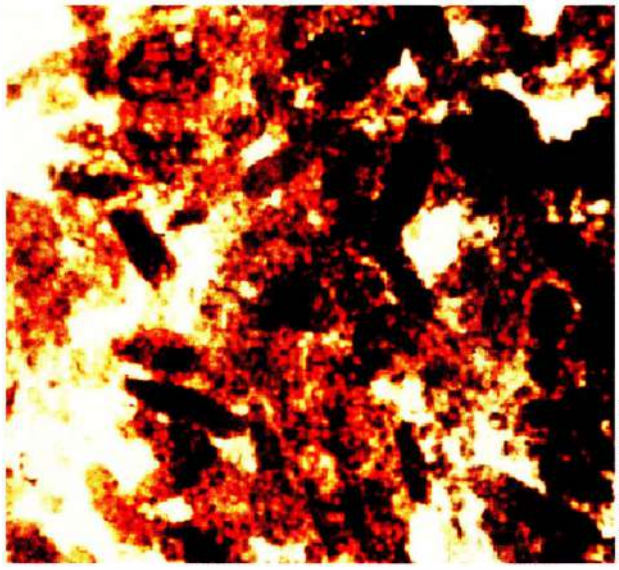


Image 4-3: Coarse granular casts

QuickQuiz

- What are some manifestations of cholesterol emboli?
- What is a Hollenhorst plaque?
- What are the lab findings in ATN?
- What are the lab findings in rhabdomyolysis?

LABS IN ATN

BUN:Cr ratio is 10–15:1.

Urine osmolality is usually < 350 because tubules cannot concentrate the urine.

Urine Na^+ is > 40 (however, if reabsorption of water is significantly affected, the urine Na^+ becomes dilute).

FE_{Na} is > 2%. However, FE_{Na} can be low in contrast-induced nephropathy.

Casts in the urine are the hallmark finding: muddy brown, "dirty" granular casts (nonspecific but very sensitive) and epithelial cell casts (Image 4-2 and Image 4-3). Sometimes tubular epithelial cells are seen. But the urine sediment can be normal.

If the patient is volume-contracted as a cause for ATN, then the above labs are more consistent with a prerenal picture.

TREATMENT OF ATN

Initial management of ATN includes treating the precipitating cause and any hyperkalemia. Maintain normovolemia, adequate blood pressure, and nutritional support (which decreases catabolism). Discontinue nephrotoxins, including ACEIs/ARBs and NSAIDs. Avoid contrast exposure.

Oliguric ATN usually resolves in 1–4 weeks. Note that oliguria is not required for the diagnosis of ATN. If oliguric, patients with ATN are more prone to becoming hyperkalemic and volume-overloaded, so dialysis is typically initiated earlier.

ATN AND RHABDOMYOLYSIS

Rhabdomyolysis is muscle degradation that results in the release of muscle enzymes, myoglobin, and electrolytes into the bloodstream. All of the following are causes:

- Crush injuries (compartment syndromes), coma, or traumatic immobilization
- Prolonged surgeries
- Strenuous exercise such as a marathon run or football in extreme heat
- Generalized seizures
- Heat stroke
- Severe volume contraction
- Drugs: cocaine, amphetamines, statins, colchicines, anesthetics causing malignant hyperthermia, neuroleptic malignant syndrome
- Infections: usually viral, especially influenza A and B
- Endocrinopathies: DKA, hypothyroidism, hyperthyroidism, and pheo
- Electrolyte abnormalities: severe hypokalemia, hypophosphatemia (in alcoholics during refeeding)

Patients present as a result of the underlying cause and/or with muscle pain and cola-colored urine. Labs show increased CPK (> 100,000 IU/L) with nonspecific increases in AST and ALT. It is important to be sure that there is no component of prerenal azotemia contributing to the AKI. Creatinine is usually elevated. Hyperkalemia, hyperphosphatemia, increased uric acid, and hypocalcemia are common complications. U/A shows muddy brown casts consistent with ATN. The urine is colored brown due to myoglobin pigment. The urine tests positive for blood, but no RBCs are visible in the sediment.

Rhabdomyolysis-associated hypocalcemia results from 2 mechanisms: 1) decreased production of $1,25\text{-}(OH)_2\text{-}D$ due to renal injury, and 2) hyperphosphatemia due to both renal injury and tissue breakdown. In recovery, patients can have significant hypercalcemia from secondary hyperparathyroidism (among other causes). For this reason, do not treat hypocalcemia unless it is severe or the patient is symptomatic.

Most recommend treatment as soon as possible with isotonic fluid resuscitation or forced diuresis with alkalinization of the urine (urine pH is raised above 6.5 to diminish the renal toxicity of heme) to prevent the myoglobin-induced tubular damage, though clinical evidence is limited. Watch out for hyperkalemia. Dialysis is used in severe cases.

Hemoglobinuria has urine findings similar to those seen in rhabdomyolysis. Hemoglobin can be released from severe intravascular hemolysis. It also can cause ATN—not due to toxicity, but rather mechanical obstruction. Treatment is the same as that for rhabdomyolysis.

INTERSTITIAL DISEASE

OVERVIEW

Interstitial disease is caused by inflammation and/or fibrosis of the interstitium. Acute interstitial nephritis (AIN) is more likely to be caused by drugs.

Tubular and interstitial diseases have only low-grade proteinuria (< 1–1.5 g/d), and they may cause a non-anion gap metabolic acidosis.

ACUTE INTERSTITIAL NEPHRITIS

Acute (or allergic) interstitial nephritis (AIN) is most often a drug-induced hypersensitivity reaction that can cause

fever, eosinophilia, and rash. Only 10% of patients have all 3. More often, presentation is an unexplained increase in the sCr and occasionally symptomatic renal failure.

Most commonly implicated drugs include: NSAIDs, antibiotics, proton pump inhibitors, cimetidine, thiazides, and allopurinol. AIN is an idiosyncratic response to the drug and generally is not related to the amount or duration of use.

The most common antibiotic culprits:

- Beta-lactams
- TMP/SMX
- Rifampin
- Ciprofloxacin and, less often, other fluoroquinolones

Remember: Proton pump inhibitors are now being identified as a major cause of interstitial nephritis.

NSAID-induced AIN is different in that the NSAIDs are typically ingested for months before symptoms occur. Rash, fever, and eosinophilia are frequently absent. Contrary to all other types of AIN, NSAID-induced AIN typically causes nephrotic-range proteinuria and glomerular changes consistent with those of minimal change disease. Acute interstitial nephritis also can be caused by sarcoidosis, SLE, Sjögren's, transplant rejection, and infection (e.g., pyelo, *Legionella*, streptococci).

The urine sediment in AIN contains few red cells, white cells +/– WBC casts, and mild protein (< 1 g/day, if quantitated). Red cell casts are generally not seen. The Hansel stain may show urinary eosinophils. Peripheral blood eosinophilia is sometimes observed in severe cases. FE_{Na} is usually > 1%. NAGMA and Fanconi syndrome are not uncommon if the proximal tubules are significantly damaged.

Treatment includes discontinuing the offending drug and observing the patient. Recent data suggest a potential benefit for steroids if started within the first 2 weeks of the injury.

CHRONIC INTERSTITIAL NEPHRITIS

Chronic interstitial nephritis is caused by:

- Drugs: analgesic-abuse, cyclosporine, cisplatin, and Chinese herbs
- Hypertension
- Heavy metals (especially lead and cadmium)
- Obstruction
- Infections: reflux nephropathy, tuberculosis
- Sarcoidosis
- Sjögren disease
- Sickle cell disease
- Multiple myeloma

Analgesic-abuse nephropathy had been associated with phenacetin, a key ingredient in OTC meds, but this has been removed from the U.S. market. Use of acetaminophen (the major metabolite of phenacetin) particularly in combination with ASA is associated with an increased risk of chronic interstitial nephritis—especially if it's further combined with mixtures containing caffeine or codeine. Chronic use of NSAIDs is associated with renal failure in some patients, but the association here is not as strong as with phenacetin and acetaminophen.

Analgesic-abuse nephropathy typically occurs in a patient with a history of frequent pain and presents with a low urine specific gravity, minimal proteinuria, sterile pyuria, and an elevated creatinine. Papillary necrosis is the most common ultimate consequence. A noncontrast CT of the kidneys may show the papillary necrosis, but not always. Treatment is supportive, with discontinuation of offending analgesics.

Although rare now, patients can be exposed to lead via their occupation (working with batteries, solder, cabling, ceramics, tin), drinking "moonshine" (yes, people still do this), taking alternative herbal medications from India and China, eating from lead-glazed plates or cookware, and smoking marijuana. Nephropathy may develop after years of high-level exposure and presents as azotemia, a tiny bit of proteinuria, hyperuricemia, and a bland urine sediment. Patients may have a comorbid crystalline arthropathy, termed "saturnine gout." Diagnosis is made by noting the potential exposure history and measuring the serum lead level.

Remember that lithium can also cause nephrogenic DI as well as chronic interstitial nephritis.

An unusual kind of renal interstitial fibrosis can occur in the setting of Chinese herbs ingested as weight-loss agents, specifically the ingredient aristolochic acid.

GLOMERULAR DISORDERS

OVERVIEW

The glomerulus is a specialized capillary plexus surrounded by the Bowman capsule (Image 4-4). The capillary walls filter blood, allowing an ultrafiltrate of the plasma to pass into the Bowman capsule, which collects the ultrafiltrate in the tubules for further processing. Recall the depiction of the glomerulus within the renal tubule diagram (Figure 4-5 on page 4-15).

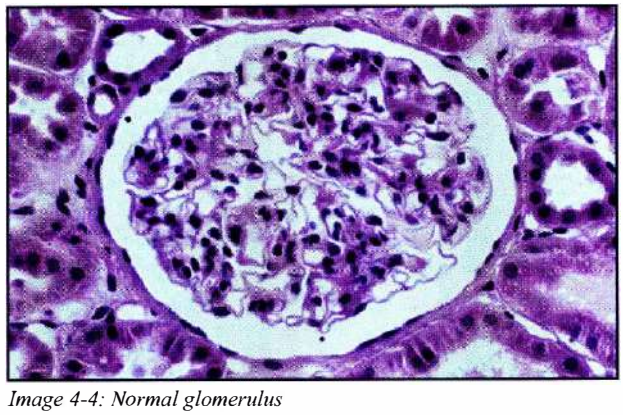


Image 4-4: Normal glomerulus

QuickQuiz

- Characterize the clinical presentation of acute interstitial nephritis.
- The biopsy picture of AIN due to NSAIDs resembles which glomerulonephropathy?
- Characterize the differences between nephritic and nephrotic urine sediments.

The wall of the glomerulus filters with:

- Endothelial cells
- The glomerular basement membrane (GBM)
- Slit pores between the epithelial cell foot processes

Glomerular diseases primarily affect the glomerular apparatus only and are collectively termed "glomerulonephritides." Glomerular diseases can be divided into 2 patterns, based on clinical presentation and mechanism of disease:

1) **Nephritic**: an acute, subacute, or chronic, potentially reversible, inflammatory process that presents with hematuria, proteinuria (usually < 2 g/day), +/– RBC casts. Disease can be focal and mild (active sediment without hypertension or edema) or diffuse and severe (active sediment with heavy proteinuria, renal failure, hypertension, and edema).
2) **Nephrotic**: a noninflammatory process that presents with > 3.5 g/day proteinuria and edema +/– urine oval fat bodies, often without red cells and casts in the urine sediment; renal function may be preserved. Hypercholesterolemia, hypertension, and hypoalbuminemia are classic features of nephrotic syndrome.

Know that patients with glomerular disease typically have either a nephritic or nephrotic presentation; however, either presentation can occur in patients with SLE or MPGN (membranoproliferative glomerulonephritis).

The causes of glomerular disease can be either primary renal (usually idiopathic) or systemic. Somewhat reliably, the renal pathology can be predicted based on the pattern of presentation and the patient's age. In clinical practice, however, a step-wise approach to diagnosis is followed, which we lay out on the following pages.

In progressive glomerulonephritis associated with worsening kidney injury, the glomerulus is the main site of pathology, but the tubules and interstitium are always affected as well. Therefore, clinical presentation of the progressive GNs reflects disease in multiple locations.

A few other categories of glomerulonephritides are useful to help remember the more common and frequently tested causes:

- Pulmonary-renal syndromes (Goodpasture's, granulomatosis with polyangiitis [previously Wegener's], microscopic polyangiitis, Churg-Strauss, Henoch-Schönlein purpura, cryoglobulinemia)
- Basement membrane syndromes (anti-GBM disease [also called Goodpasture's], Alport's, thin basement membrane disease)
- Infectious disease syndromes (post-infectious GN, endocarditis, HIV, HBV, HCV, syphilis, malaria)
- Other: lupus, IgA, antiphospholipid syndromes, HSP, cryoglobulinemia

Achieve definitive diagnosis of all glomerular diseases with a renal biopsy, though typical diabetic nephropathy is almost always diagnosed clinically.

It can be hard to determine whether isolated microscopic hematuria is coming from the kidney or lower urinary tract, but hematuria with proteinuria, dysmorphic red cells, and/or RBC casts is likely to be of glomerular origin. Nonrenal hematuria could be caused by malignancies in the urinary tract (bladder cancer), kidney stones, or urinary tract infections.

Patients with sickle cell trait may also have isolated hematuria. Red cell casts, however, are definitive for GN.

Refer to Figure 4-7 on page 4-41, and Table 4-12 and Table 4-13 starting on page 4-42 as you go through this section.

NEPHRITIC vs. NEPHROTIC

Nephritic pattern has variable proteinuria, and an "active" urine sediment. An "active sediment" is urine that contains proteinuria; red cells > 10/hpf; white cells; and often red cell, white cell, or granular casts.

Casts always originate in the tubules. Know the following:

- **Red cell casts** are a very specific finding. They are seen only in glomerulonephritis.
- **White cell casts** are typically seen in pyelonephritis or AIN.
- **Granular** casts can be nonspecific; in the setting of acute kidney injury with an appropriate clinical picture, they are characteristic of acute tubular necrosis.
- **Waxy** casts typically indicate advanced renal disease.
- In patients with a lot of proteinuria, free fat can assemble into a cast (called a **fatty** cast) or oval fat bodies, characterized by "Maltese crosses" under polarized light; or fat can suspend in the urine as droplets.
- **Hyaline casts** do not indicate disease and are seen with concentrated urine.

Nephrotic urine reflects defects in the selectivity of glomerular ultrafiltration, even though there is little inflammation. This can be due to changes in the charge or size of the selective barrier in the glomerular basement membrane (GBM). In nephrotic syndrome, there is typically heavy proteinuria, and urine fat may be visible as oval fat bodies, fatty/waxy casts, and renal tubular cells with lipid droplets. The urine sediment is usually normal except for the fat.

Nephrotic-range proteinuria is > 3.5 g/d (or 40–50 mg/kg/d). Because of this protein loss, nephrotic patients tend to have hypoalbuminemia (with 2° edema), hypogammaglobulinemia (with a tendency for infections with encapsulated organisms, especially *H. influenzae* and *S. pneumoniae*), loss of thyroid and iron-binding globulins (so low total thyroxine and iron levels), and loss of antithrombin III (so they have a hypercoagulable state and are at risk for pulmonary emboli and renal vein thrombosis).

Nephrotic patients also have hyperlipidemia. When the albumin is very low, these patients often have severe peripheral edema, pleural effusions, and even ascites—yet they do not have pulmonary congestion/edema unless they have heart failure. This is because the pulmonary interstitium loses albumin at the same rate as the blood, so there is not a big osmotic differential.

A strategy that helps classify the glomerular diseases (use this!):

1) Is the urine nephritic or nephrotic? If the urine is nephritic, are the complements low or normal?
2) Does the patient present with a systemic disorder by history and physical exam, or is the presentation primarily a kidney disorder (e.g., edema, hypertension only)?

While reading below, follow along in Figure 4-7 on page 4-41. Know this flowchart! It gives structure to this otherwise quite confusing set of renal problems.

NEPHRITIC SYNDROMES

Complement in Nephritic Syndromes

Nephritis from lupus is associated with hypocomplementemia, but complement levels are usually normal in cases of pulmonary-renal vasculitis (i.e., ANCA vasculitis, Goodpasture's/anti-GBM disease).

C3 is always low for 6–8 weeks with postinfectious GN and is frequently low with idiopathic membranoproliferative GN and most of the systemic causes of MPGN (endocarditis, cryoglobulins, and HCV).

As soon as you see a nephritic picture, the 1st test you do is a complement level. Even if the patient presents with a history of classic postinfectious glomerulonephritis, still measure complement levels first!

Nephritic with Low Complement — Primarily Kidney Presentation

Nephritic/low/kidney:

- Postinfectious GN (PIGN)
- Membranoproliferative GN (MPGN)

Postinfectious GN

Usually, PIGN is caused by group A beta-hemolytic streptococcal infections of the skin or throat (also associated with other infectious causes, especially staph). This entity had been called "post-strep GN" (PSGN).

Symptoms include gross hematuria and/or edema and occur 1–6 weeks after the initial illness (average 10 days post-throat infections, 2–4 weeks after skin infections). The "latency period" is a diagnostic key and is used in differentiating PIGN from IgA nephropathy, wherein the GN coincides with or begins within 3 days of the viral illness (synpharyngitic). Cultures of throat and skin variably grow beta-hemolytic streptococci.

Antistreptococcal antibodies aid in the diagnosis:

- Antistreptolysin O (ASO) titer
- Antideoxyribonuclease B (anti-DNase B) titer
- Antihyaluronidase titer

Know that an ASO titer generally remains elevated for several weeks after a strep infection; the anti-DNase B titer for several months. Complement levels remain low for 6–8 weeks.

PIGN is caused by an antibody-antigen reaction, with the source of the antigen being the infecting agent. Renal biopsy shows immune deposits (IgG, IgM, and complement) in the subendothelial and subepithelial regions (termed "humps") + invasion of the glomerulus with neutrophils. In children, renal biopsies are rarely performed because the diagnosis typically can be made via the clinical history + measurement of complement levels and antistreptococcal antibodies. These infections are rare in adults, though, so an adult with this presentation probably gets a renal biopsy.

PIGN can progress to severe renal failure. Most patients improve with supportive care and treatment of the underlying infection with standard antibiotics. Most children recover completely in 6–8 weeks, but adults may not have complete recovery.

Summary of PIGN: reversible, bloody urine remote to group A streptococcal skin or throat infection (rarely, other infections); low complement for 6–8 weeks; variably positive antistreptococcal antibody titers; subendothelial and subepithelial immune "humps" on renal biopsy; treat the infection; good response in most.

Membranoproliferative GN (MPGN)

MPGN (a biopsy diagnosis) can be idiopathic and cause isolated kidney disease, but more commonly it is associated with systemic diseases, primarily lupus, and HCV-associated cryoglobulinemia. Usually, the MPGN pathology (whether idiopathic or associated with systemic disease) is marked by activation of complement, and about 50% of the time the complement levels are low. While the disease typically presents as a nephritic picture, nephrotic-range proteinuria is not uncommon.

MPGN is one of the diseases that can present either as nephritic/nephrotic or combined nephritic + nephrotic.

QuickQuiz

- What is the definition of nephrotic-range proteinuria?
- What are the systemic complications of nephrotic syndrome?
- What are the complement levels in patients with postinfectious glomerulonephritis?
- Post-strep glomerulonephritis can occur after strep infections at which sites?
- Symptoms of GN due to strep start how long after the original illness?
- What infections are associated with development of MPGN?

If MPGN is diagnosed on kidney biopsy, consider whether MPGN is an immune complex-mediated MPGN or purely complement-mediated MPGN.

Immune complex-mediated MPGN: This form of MPGN results from the deposition of immune complexes in the glomeruli from persistent antigenemia, with antigen-antibody complexes forming as a result of chronic infection (hepatitis C and B with or without cryoglobulins, shunt nephritis, abscess), autoimmune disease (e.g., SLE, Sjögren's), or monoclonal gammopathy (deposition of monoclonal immunoglobulin with or without cryoglobulins). Low C3 and low C4 complement levels are more common in immune complex–mediated MPGN.

Complement-mediated MPGN (due to dysregulation of the alternative pathway): Due to mutation in proteins that regulate the alternate pathway including factors H, I, and B or antibodies against them (antibodies to complement regulating proteins such as H and B and to C3 convertase called C3 nephritic factor) can result in overactivity of alternative complement pathway. Low C3 and normal C4 levels are more common in alternative pathway dysfunction.

The low C3 in PIGN returns to normal after 2–3 months; but in patients with MPGN, it stays low indefinitely. This is useful: If you initially suspected PIGN and C3 stays low > 3 months, suspect MPGN instead, and get a renal biopsy! Treatment is aimed at the underlying disease (e.g., interferon for HCV) if it can be identified. This includes plasmapheresis for cryoglobulinemia. Progression to kidney failure is common.

Hepatitis C, which was recognized as a common cause of immune complex–mediated MPGN in the 1990s, is now considered to be the main viral infection causing MPGN.

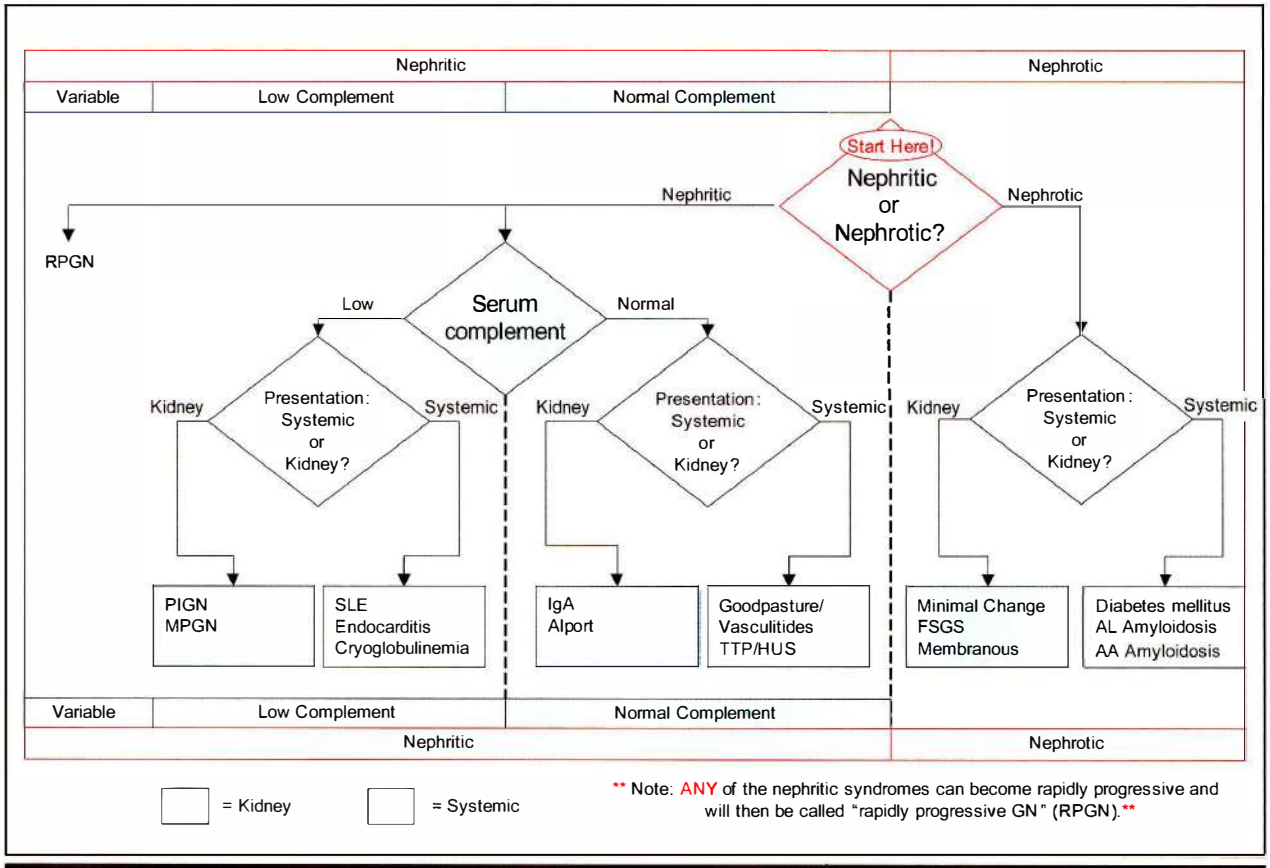


Figure 4-7: A Strategy for Workup of the Glomerular Disorders

Nephritic with Low Complement — Systemic Presentation

Nephritic/low/systemic:

- Systemic lupus erythematosus (SLE). Know also that SLE can produce almost any type of glomerular disease (nephritic or nephrotic).
- Endocarditis.
- Cryoglobulinemia in this situation is usually due to HCV, myeloma, or Waldenström macroglobulinemia.

Lupus Nephritis

Glomerular disease in SLE is divided into 6 patterns of glomerular injury:

- Class I: normal/minimal mesangial
- Class II: mesangial
- Class III: focal proliferative
- Class IV: diffuse proliferative
- Class V: membranous
- Class VI: end-stage/sclerosis

Clinically, the most important categories are class III/IV (which present similarly and are treated identically) and class V (see page 4-47 Membranous Nephropathy). Class III/IV lupus nephritis typically presents with decreased renal function (can be chronic, subacute, or acute) and nephritic syndrome (active sediment, low-grade proteinuria). Complements are usually low, ANA and anti-dsDNA titers are elevated. Commonly, patients have other clinical symptoms of lupus at the time of renal disease diagnosis, but occasionally renal disease is the first/only presenting symptom. The standard now is all lupus patients with an active urine sediment, regardless of GFR, are candidates for renal biopsy.

Table 4-12: Summary Table of Glomerulonephritides — Nephritic Syndrome (1 of 2)

Classification / Complement Level		Name	Presentation	Urine	Notes	Treatment
NEPHRITIC SYNDROME Primarily kidney presentation	Low	PIGN	Post-strep (skin or throat)	Red cells Proteinuria (1–3 g/d) +/– Red cell casts +/– White cell casts	Latent period between infection and symptoms. Complements return to normal after a short period. Check for antibodies of antecedent strep infection.	Treat the infection and supportive care.
		MPGN			Complements stay low > 3 months. Primary MPGN = rare, usually assoc w/ HCV	No good Rx; steroids; frequent renal failure
	Normal	IgA (Mesangial proliferative)	Classic presentation: gross hematuria with viral illness (no latent period)		Best prognosis for pts with intermittent hematuria, may progress in pts with proteinuria	If proteinuria or reduced GFR: ACEIs or ARBs, Steroids
		Alport	GN, deafness, congenital eye disease		X-linked recessive most common	ACEIs or ARBs
		ANCA + renal-limited vasculitis	Rapidly progressive GN, HTN		Nonspecific presentation	High-dose steroids with cytotoxics
NEPHRITIC SYNDROME Systemic presentation	Low	Immune complex GN	SLE Endocarditis Cryoglobulinemia/ HCV/MPGN HBV		MPGN pathology common	Treat the cause.
	Normal		Vasculitis: (micro-scopic polyangiitis, granulomatous polyangiitis) TTP/HUS		Symptoms depend on type of vasculitis	High-dose steroids with cytotoxics TTP: + Plasma-pheresis
NEPHRITIC SYNDROME RPGN	Variable	1) Anti-GBM 2) Immune complex 3) Pauci-im-mune (usually + ANCA)	Acute, rapidly pro-gressive, renal failure +/– signs of systemic disease (depending on cause)		Requires urgent renal biopsy that documents glomerular crescents and demonstrates type of antibodies; check ANCA and anti-GBM ab; consider ANA, anti-dsDNA, cryoglobulins, anti-strepto-coccal Ab	High-dose methylprednisone → prednisone + cytotoxics +/– plasmapheresis

Quick Quiz

- When does the GN due to IgA nephropathy present, relative to an inciting viral illness?

Lupus nephritis should be treated aggressively with either mycophenolate mofetil or cyclophosphamide, in conjunction with steroids. Without treatment, lupus nephritis leads to end-stage kidney disease. Relapses are common.

Nephritic with Normal Complement — Primarily Kidney Presentation

Nephritic/normal/ kidney:

- IgA nephropathy
- Alport syndrome
- ANCA + renal-limited glomerulonephritis

IgA Nephropathy

IgA nephropathy is called "mesangial proliferative GN" or Berger disease (do not confuse with Buerger disease—thromboangiitis obliterans). Worldwide, this is the most common GN; it is more common in Asians and males.

IgA nephropathy has a wide range of presentations, from gross hematuria coincident with or immediately following a URI, to microscopic hematuria with proteinuria and progressive disease, to nephrotic syndrome or RPGN (page 4-45). The hematuria seen in IgA nephropathy commonly occurs either during a viral illness or just after exercise. There is no latent period between infection and appearance of GN, as with PIGN. This is an important distinguishing feature!

The antibody-antigen interaction in this disease causes immune complex deposition of IgA and C3 in the mesangial matrix and skin. Although C3 is deposited, there are usually normal serum complement levels.

IgA nephropathy is more progressive in patients with proteinuria and is relatively benign in those with isolated hematuria. The only way to make this diagnosis is with

Table 4-13: Summary Table of Glomerulonephritides — Nephrotic Syndrome (2 of 2)

Classification	Name	Causes	Urine	Notes	Treatment
NEPHROTIC SYNDROME Primarily kidney presentation	Minimal change disease	Sudden onset of severe nephrotic syndrome. Can be associated with Hodgkin's; use of NSAIDs, lithium	>3 g/d proteinuria Oval fat droplets Edema Hyperlipidemia Complications: DVT bacterial infections	10–15% of nephrotic syndrome in adults Only abnormal finding on bx: loss of foot processes on electron microscopy	Steroids +/– cytotoxics
	FSGS	Primary (idiopathic) causes most common esp. in African-Americans Secondary causes: heroin use, HIV/AIDS, reflux nephropathy, obesity		Pts who respond to steroids have best prognosis	Steroids Cyclosporine ACEIs or ARBs
	Membraneous	Most common cause is idiopathic. Secondary causes: NSAIDs, chronic HBV, solid tumors, SLE		Idiopathic may be associated with antibodies to the PL2receptor	Mild cases: no treatment Treat underlying disease Steroids +/– cytotoxics ACEIs or ARBs
NEPHROTIC SYNDROME Systemic presentation	Diabetes	Diabetic with nephrotic -range proteinuria		Most common secondary cause of nephrotic syndrome; eye disease usually precedes kidney disease.	ACEIs or ARBs +/– low-protein diet; control of blood glucose, BP, and lipids
	AA amyloidosis AL amyloidosis	Injection drug use Multiple myeloma		Look for other clues to myeloma: hypercalcemia, anemia, obtain SPEP and UPEP and measure serum free light chains	Treat underlying disease.

Glomerular diseases associated with low complement levels: Postinfectious GN, lupus nephritis (SLE), cryoglobulinemia, MPGN (hepatitis C and B), infective endocarditis

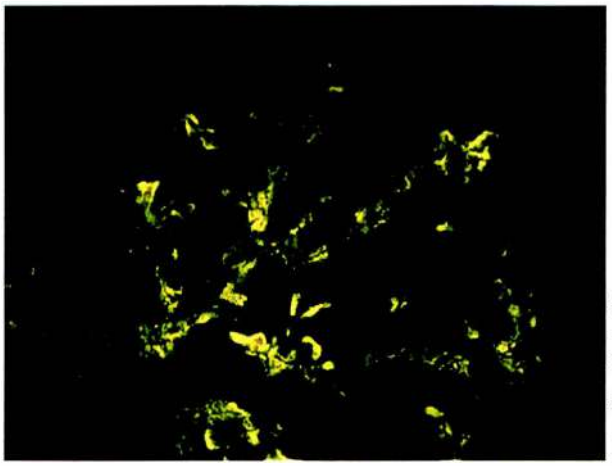


Image 4-5: Immunofluorescent microscopy in IgA nephropathy

renal biopsy, which is performed in patients with a more severe presentation. Biopsy shows deposits of IgA and complement in the mesangium and in the glomerular capillaries on immunofluorescence staining. Light microscopy shows isolated proliferation in the mesangium (with crescent formation if the disease is severe), Image 4-5.

Other diseases may deposit IgA in the mesangium but are not classified as "IgA nephropathy," such as lupus nephritis and Henoch-Schönlein purpura. Clinical presentation in these illnesses differentiates the disease from basic IgA nephropathy. Some illnesses are associated with IgA deposition but without obvious glomerular injury, such as HIV/AIDS, celiac disease, and end-stage liver disease. These presentations are called "secondary IgA nephropathy."

Prognosis for IgA nephropathy is tied to serum creatinine, blood pressure, and amount of proteinuria. Prognosis is good if these values are normal, but it is much worse if any of these are abnormally elevated.

50% of patients with proteinuria have inexorably progressive renal disease.

Observe patients who maintain normal renal function with no proteinuria. Use ACEIs or ARBs for proteinuria (> 0.5 g/d) and progressive disease; use corticosteroid therapy when there is persistent proteinuria (> 1 g/d) despite 6 months on an ACEI/ARB. Statins and fish oil have also been used to modulate the risks of atherosclerosis and also to prevent progression, but their true role is not defined.

Hereditary Nephritis (Alport Syndrome)

Alport's is a hereditary (usually X-linked) syndrome with chronic glomerulonephritis +/– nerve deafness and congenital eye problems involving lenses, retinas, and corneas. These patients have a defect in the alpha-3 subunit of Type IV collagen. Renal biopsy confirms the diagnosis in patients with suspected disease. The hallmark finding is a split lamina densa (part of the GBM) visible on electron microscopy. Genetic testing is also being done. Treatment includes ACEIs or ARBs. Patients with Alport's who get a kidney transplant can develop anti-GBM disease in the transplanted kidney, because their immune system has not previously been exposed to normal Type IV collagen.

ANCA + Renal-limited Glomerulonephritis

This disorder presents as one cause of rapidly progressive glomerulonephritis (discussed below) with the only manifestations being the deterioration of renal function over days to weeks, hypertension, a nephritic urine, and antineutrophil cytoplasmic antibodies. Renal biopsy is necessary to confirm the diagnosis, which requires aggressive initial therapy with high-dose corticosteroids and cyclophosphamide.

Nephritic with Normal Complement — Systemic Presentation

Nephritic/normal/systemic:

- Anti-GBM disease (Goodpasture's)
- Polyangiitis ANCA + glomerulonephritis: granulomatosis with polyangiitis (previously Wegener's), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
- Henoch-Schönlein purpura (IgA vasculitis)
- TTP/HUS

Goodpasture Syndrome: Anti-GBM Antibody Disease

Anti-GBM disease is a broad term that encompasses an acute GN with evidence of anti-GBM antibodies in the serum +/– pulmonary hemorrhage.

When pulmonary hemorrhage is present (common; occurs in 70% of patients), the disease is called Goodpasture's. Otherwise, it's called anti-GBM disease.

Younger male patients are more likely to present with Goodpasture's and older females with idiopathic anti-GBM disease. Despite previous classifications of anti-GBM diseases, this disease is not a vasculitis. Patients present with an active urine sediment and hemoptysis with dyspnea if they have Goodpasture's. If fever or weight loss is present with a GN, consider the vasculitides (discussed next).

In anti-GBM diseases, antibodies that attack the glomerular (and sometimes pulmonary) basement membrane(s) are formed in response to an unknown stimulus. Goodpasture's typically presents as an RPGN (discussed below).

Renal biopsy makes the diagnosis by revealing anti-GBM IgG deposited in a linear fashion along the GBM. Anti-GBM antibodies can be measured in the serum, and, when present, make the diagnosis. Sensitivity of the serum antibody test is not 100%, so when these antibodies are absent, renal biopsy should be performed. The biggest challenge is differentiating granulomatosis with polyangiitis (previously Wegener's) or

Quick Quiz

- What are the findings on renal biopsy in patients with IgA nephropathy?
- What is the difference between Goodpasture syndrome and anti-GBM disease?
- How are anti-GBM diseases diagnosed?
- RPGN has what hallmark finding on renal biopsy?
- What are the 3 categories of RPGN, based on underlying mechanisms?
- What is the empiric treatment for RPGN?

other forms of vasculitis from Goodpasture's. These disorders are more likely to be c-ANCA-positive or have other serologic markers.

Treatment of Goodpasture syndrome is plasmapheresis (to remove the antibodies) with immunomodulation (steroids + cyclophosphamide). Prognosis depends on the extent of renal failure at presentation.

Vasculitides

The main vasculitides that commonly involve an acute GN include:

ANCA + glomerulonephritides: These are discussed in Rheumatology, Book 3, and Pulmonary Medicine, Book 2.

- Granulomatosis with polyangiitis (previously Wegener's)
- Microscopic polyangiitis
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
- Henoch-Schönlein purpura (HSP)

HSP is seen mostly in children but can occur in adults. Kidney or skin biopsy findings in HSP are identical to the findings in IgA nephropathy, but HSP also affects the skin, GI tract, and joints. Patients may have abdominal and joint pains, erythema, lower extremity purpura, and hematuria.

Although these entities are vasculitic, complement levels are usually normal.

TTP / HUS

TTP and hemolytic uremic syndrome are discussed in Hematology, Book 4.

Rapidly Progressive GN

The most aggressive syndrome of AGN is rapidly progressive GN (RPGN). This term refers to any form of acute GN that progresses rapidly (days to weeks) and is associated histopathologically with the hallmark glomerular crescents (extracapillary proliferation) inside Bowman's capsule. Hence, you can have RPGN with high or low complement, or RPGN that presents with systemic disease or as a primary kidney disorder.

Always consider RPGN if a patient presents with severe and progressive renal failure of recent onset with a nephritic urine. Once RPGN is diagnosed, you need to quickly determine and treat the underlying disease, usually by renal biopsy.

In RPGN, creatinine is typically > 3 mg/dL. The urine has protein, red cells, and sometimes RBC casts. Other complaints by the patient are dependent on the cause of the RPGN. There are 3 major pathogenic causes of RPGN:

- **Type 1** is due to anti-GBM antibodies (Goodpasture's).
- **Type 2** is due to immune complex deposition (IgA deposits; ANA in lupus; cryoglobulins; antibodies against an infectious agent, such as streptococci).
- **Type 3** has no evidence of immune deposits (termed "**pauci-immune**"); many of these cases are ANCA+ (anti-MPO+ or anti-PR3+) and are diagnosed as renal-limited granulomatosis with polyangiitis or microscopic polyangiitis. (See Rheumatology, Book 3, for a discussion of types of ANCAs as anti-myeloperoxidase and anti-proteinase 3 antibodies.)

Evaluation of the patient with RPGN should attempt to make a rapid histopathologic diagnosis and measure ANCA titers:

- If there is pulmonary hemorrhage, a linear staining of IgG along the GBM on kidney biopsy, and a high titer of serum anti-GBM antibodies, the disease is Goodpasture syndrome. Again, +anti-GBM antibodies but no pulmonary hemorrhage is just called "anti-GBM disease."
- If patient has ENT manifestations (sinusitis, epistaxis), pulmonary infiltrates/hemoptysis, negative immune florescence on kidney biopsy, and is c-ANCA positive—think granulomatosis with polyangiitis (previously Wegener's).
- If patient has a history of asthma/atopy with peripheral eosinophilia and is p-ANCA+, this is most likely eosinophilic granulomatosis with polyangiitis (Churg-Strauss).
- If there are no systemic features, immunofluorescence is negative on renal biopsy, and ANCA is positive, the patient has pauci-immune GN (otherwise known as renal limited-ANCA vasculitis).
- If RPGN is caused by lupus nephritis, cryoglobulinemia, or PIGN, the patient is hypocomplementemic with characteristic findings on renal biopsy and serologic testing to establish the underlying cause.

Treat RPGN empirically with high-dose methylprednisolone, then prednisone + cyclophosphamide +/– plasmapheresis (if pulmonary hemorrhage). Once the biopsy and other diagnostic results are available, definitive treatment can be given based on underlying disease (e.g., cyclophosphamide is sometimes given to SLE and

granulomatosis with polyangiitis; and plasmapheresis to Goodpasture's and cryoglobulinemia).

Summary of RPGN: rapidly progressive renal failure with nephritic urine sediment; 3 categories; renal biopsy shows crescents; think Goodpasture's, lupus, granulomatosis with polyangiitis, and immune complex disease; treat empirically with steroids and cyclophosphamide, then focus on treating underlying disease; plasmapheresis for anti-GBM and cryoglobulinemia.

NEPHROTIC SYNDROME

Overview

The following glomerulonephritides cause nephrotic-range proteinuria.

Nephrotic syndrome, regardless of cause, is associated with an increased risk of infections and a hypercoagulable state—because of the urinary loss of immunoglobulins and antithrombin III.

Nephrotic — Primarily Kidney Presentation

Nephrotic/kidney:

- Minimal change disease
- Focal segmental glomerulosclerosis (FSGS)
- Membranous nephropathy

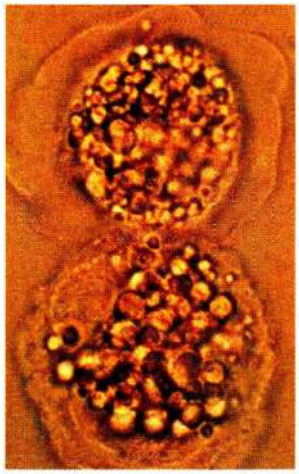
Minimal Change Disease (MCD)

Most common cause of primary nephrotic syndrome in children. MCD accounts for 10–15% of nephrotic syndromes in adults. Pathologic cause seems to be related to T-cell dysfunction, resulting in fusion of the foot processes in the glomerular capillary walls. This makes for a leaky membrane and significant proteinuria.

The vast majority of MCD is idiopathic, but it has been associated with several drugs and diseases.

Especially know the following associations:

- Drugs (NSAIDs, rarely other drugs)
- Lymphoma (both Hodgkin's and NHL)



Courtesy of Sriram S. Nanigian, MD

Image 4-6: Oval fat droplets on light microscopy

Patients present with anasarca or severe peripheral edema that develops over several weeks and without HTN. Adults may have renal failure that usually improves with treatment.

Urine sediment may show oval fat bodies (Image 4-6) that also appear as "Maltese crosses" under polarized light.

MCD diagnosis is made by renal biopsy, which shows no change in histology on light microscopy and absence of immune deposits on immunofluorescence. Electron microscopy shows fusion of epithelial foot processes, though this finding may be seen in any disorder that causes nephrotic syndrome.

Diagnose all adults with nephrotic syndrome with renal biopsy. Treat MCD initially with steroids. Adults are more likely to be either steroid-dependent or resistant and require cyclophosphamide or cyclosporine. Children are typically treated empirically with corticosteroids, with renal biopsy performed only if the expected response to steroids does not occur.

Summary: nephrotic-range proteinuria, children, NSAIDs, lymphoma, atopy, risk of infections and DVT, loss of foot processes, oval fat bodies, steroids, generally very good prognosis.

Focal Segmental Glomerulosclerosis (FSGS)

FSGS has become the most common cause of idiopathic nephrotic syndrome in African-Americans and is the most common glomerular process causing end-stage kidney disease in the U.S. While FSGS is most often a primary disease, it may be familial or secondary. Therefore, consider FSGS if there is a history of HIV/AIDS, heroin use, obesity, sickle cell disease, or chronic vesicoureteral reflux. Collapsing FSGS is the most common cause of nephrotic syndrome in patients with HIV and is the cause of "HIV-associated nephropathy." It is important to distinguish between primary FSGS and the secondary causes (e.g., heroin) because the primary disease frequently responds to steroids—secondary disease, less so.

FSGS is similar to minimal change disease in that there is diffuse foot process fusion; however, there is additional sclerosis limited to segments of the glomeruli (especially juxtamedullary). Unlike minimal change disease, these patients often present hypertensive as well as nephrotic. 50% have a reduction in kidney function at diagnosis.

These patients have slowly progressive renal failure. Those not responding to treatment require dialysis within ~ 5–10 years.

Initial treatment of primary FSGS includes ACEIs/ARBs and high-dose steroids for extended periods in order to induce remission. Patients without remission have a poorer prognosis. Long-term treatment can improve the prognosis and keep up to 70% of patients disease-free.

Treat secondary FSGS with ACEIs or ARBs and therapy directed at the underlying illness. Initiate anti-retroviral therapy in all patients with HIV-associated nephropathy, regardless of CD4 count, as treatment can lead to regression of the renal disease. Always think about tenofovir nephrotoxicity in patients with HIV.

Severe proteinuria and reduction in GFR at diagnosis are associated with worse prognosis.

Summary: nephrotic-range proteinuria, fusion of foot processes and focal sclerosis, African-Americans, young

- What drugs and diseases are associated with minimal change disease?
- "Maltese crosses" under polarized light are seen in the urine sediment of patients with what process? (No—not *Babesia*; this is nephrology, not ID.)
- FSGS is found in what patient groups?
- Solid tumors are associated with which glomerular disease?
- Which RTA is associated with diabetic nephropathy?
- What is the classic finding seen on renal biopsy in a patient with diabetic nephropathy?

hypertensive, AIDS, heroin, obesity. Treat primary disease with long-term steroids.

Membranous Nephropathy (MN)

Idiopathic (primary) membranous nephropathy is a common cause of non-diabetic nephrotic disease in adults, especially in Caucasian males > 40 years of age. Secondary causes include:

- Chronic infections (especially chronic HBV)
- Several drugs (NSAIDs, penicillamine, and gold)
- Underlying solid tumors (tumors are usually obvious, but if not, do age-appropriate malignancy screening)
- Autoimmune thyroiditis and SLE (consider this cause if membranous presents in a young female)

Patients with membranous nephropathy present with a gradually worsening nephrotic syndrome, and 50% of patients have red cells in the urinary sediment (without RBC casts). Most patients have normal blood pressure and renal function at diagnosis.

Renal biopsies should be done in all cases of nephrotic syndrome when the underlying cause is not obvious (e.g., diabetes). Renal biopsy shows GBM subepithelial IgG and C3 deposits on immunofluorescence. Electron microscopy shows subepithelial deposits on the GBM with loss of overlying foot processes. The GBM is also expanded because new matrix is laid down between the subepithelial deposits.

Serologic detection of antibodies to the M-type phospholipase A2 receptor (anti-PLA2R) in the majority of adult patients with idiopathic MN is likely to become available as a diagnostic screening test.

Patients spontaneously improve (up to 30% after 5 years), improve completely or somewhat with treatment, or progress to dialysis (14% at 5 years). Patients with more severe proteinuria and/or reduced GFR have a worse prognosis, as do men > 50 years old. Secondary MN often improves with treatment of the underlying disease or discontinuation of any offending drugs.

For patients with secondary MN, treat the underlying cause. Because some patients with idiopathic MN can have spontaneous remission, not all patients need to be treated immediately. Aggressively treat only those who have persistent high-grade proteinuria (> 4 g/d) despite at least 6 months of conservative management with ACE or ARB and hypertension control. Optimal therapy appears to be corticosteroids plus a cytotoxic agent (cyclophosphamide or chlorambucil).

Membranous nephropathy has the highest prevalence of renal vein thrombosis compared with other causes of nephrotic syndrome.

If a patient with known MN complains of flank pain, hematuria, and high LDH → think about renal infarction secondary to renal vein thrombosis.

Summary: Nephrotic-range proteinuria, HBV, gold, penicillamine, solid tumors, SLE. Prognosis is worse in men and older patients. If severe and secondary causes are excluded, treat with corticosteroids plus a cytotoxic agent.

Nephrotic — Systemic Presentation

Nephrotic/systemic:

- Diabetes mellitus
- Amyloidosis and multiple myeloma
- SLE (covered in Rheumatology, Book 3)
- HIV

Diabetic Nephropathy

Diabetic nephropathy is the most common systemic cause of nephrotic syndrome in adults. It may be associated with hyporeninemic hypoaldosteronism and Type 4 RTA. The risk of nephropathy is the same, regardless of whether patients have Type 1 or 2 diabetes; and, in most cases, retinopathy precedes nephropathy (less rigorous association for T2DM).

The risk of developing nephropathy is multifactorial and is based on:

- age at diagnosis,
- genetics,
- race (increased risk in African-Americans, Hispanics, and the Pima Native American tribe),
- blood pressure,
- glomerular filtration rate (hyperfiltration in the first 5 years after diagnosis = higher risk),
- glycemic control,
- weight (obesity = increased risk),
- smoking, and
- oral contraceptive use.

Renal biopsy classically shows expansion of the mesangium, thickening of the GBM, and sclerosis of the glomeruli (termed the Kimmelstiel-Wilson lesion).

Diabetic nephropathy occurs in 2 phases. In the silent or preclinical phase, the 1st measurable change in renal function is microalbuminuria, which is albumin insufficient in quantity to be detected on routine dipstick (30–300 mg/24 hr). It can be detected by measuring the random urine albumin:creatinine ratio. More than 30 mg albumin/g creatinine represents microalbuminuria. Test all diabetics yearly for albuminuria using the spot albumin:creatinine ratio and, if elevated, treat with an ACEI or ARB even if normotensive.

The clinical phase (overt diabetic nephropathy) typically is associated with proteinuria (> 300 mg/d and often nephrotic-range), hypertension, and progressive loss of kidney function.

Control of hypertension (to < 140/90 with an ACEI or ARB) and glycemia (HbA1c target < 7) definitely slows the rate of progression. ACEI/ARB use has been shown in randomized controlled trials to reduce progression from microalbuminuria to overt proteinuria, and to delay loss of renal function in patients with overt proteinuria in both Types 1 and 2 DM. However, never use ACEIs and ARBs together, as combination use is associated with several adverse outcomes, including hypotension, renal failure, and hyperkalemia.

While the American Diabetes Association added a recommendation to reduce protein intake in diabetics with chronic kidney disease (< 0.8–1.0 g/kg body weight/d in early disease and < 0.8 g/kg/d in late disease), the use of low-protein diet in chronic kidney disease is controversial. Weight reduction and treatment of hyperlipidemia also seem to decrease risk.

Expert recommendations conclude that patients who have proteinuria in the setting of diabetes and retinopathy do not need to undergo kidney biopsy for diagnosis of a declining GFR. Diabetics without eye disease, however, should have a renal biopsy to exclude other glomerular causes of nephrotic syndrome. If dysmorphic red cells are present, the patient probably should have a renal biopsy.

Know: As renal function decreases, insulin requirements decrease (2° to decreased metabolism by the kidneys).

Amyloidosis and Multiple Myeloma

Multiple myeloma can cause the following problems with renal involvement:

- **Cast nephropathy** (myeloma kidney) is the most common renal involvement in which immunoglobulins (Bence Jones proteins) precipitate in the tubules leading to acute renal failure. A clue to myeloma cast nephropathy is negative dipstick protein but positive proteinuria on lab measurement because the dipstick reacts to albumin but not the non-albumin light chains.
- **Hypercalcemia** can cause acute renal failure.
- **Primary "AL" amyloidosis** is a multisystem disease that can include nephrotic syndrome and renal failure (Congo-red stain shows deposits with apple-green birefringence). Associated with multiple myeloma.
- **Monoclonal Ig deposition disease** (MIDD), in which monoclonal immunoglobulin light chains or heavy chains are deposited in the glomerular basement membranes. Pathologically MIDD can resemble diabetic nephropathy, with nodular glomerulosclerosis.
- **Secondary "AA" amyloidosis** is seen in chronic inflammatory states, such as those seen in rheumatoid arthritis and familial Mediterranean fever (FMF). Amyloid nephropathy can also be caused by recurrent skin and soft tissue infections such as those caused by chronic injection drug use. Other clues to amyloidosis include carpal tunnel syndrome and new-onset heart failure associated with nephrotic syndrome.

Treatment of Nephrotic Syndrome

General principles: Treatment of nephrotic syndrome depends on the underlying disease. Control of glomerular pressure is vital in any glomerular disease; increased intraglomerular pressure hastens disease progression. ACEIs or ARBs are best in decreasing intraglomerular pressure. They have been typically prescribed along with a low-protein diet—but benefit of the diet is uncertain. Diuretics usually are needed because edema can be severe, but be careful—patients with nephrotic syndrome generally have difficulty maintaining intravascular volume; salt restriction and diuretics can precipitate prerenal failure. Note that glucocorticoids +/– cytotoxics are used in most nephrotic syndromes—except those caused by amyloid and diabetes. Anticoagulation is used if there is a significant risk of thrombosis, particularly in severe hypoalbuminemia in membranous glomerulopathy. Be aware of the significant increased rate of infections and vaccinate accordingly.

ONCE MORE

Again: Hypocomplementemia always occurs in PIGN and frequently in MPGN (primary or due to HCV). Low complement is also a feature in cryoglobulinemic GN, flares of SLE (which can cause several forms of glomerulonephritis), and bacterial endocarditis.

Hypocomplementemia never occurs in the nephrotic syndromes (minimal change disease, FSGS, membranous nephropathy, diabetic nephropathy, amyloid nephropathy).

And again: Nephritic urine sediment is described as "active" (red cell casts and dysmorphic hematuria > 5 rbc/hpf) and is usually seen in IgA nephropathy (mesangial proliferative), early PIGN, MPGN, SLE, endocarditis, and cryoglobulinemia. RBC casts are not seen in the nephrotic syndromes: minimal change, FSGS, membranous nephropathy, diabetic nephropathy, and amyloid nephropathy.

Quick Quiz

- What is the definition of microalbuminuria?
- When are glucocorticoids not used to treat nephrotic syndrome?
- What is the definition of chronic kidney disease?

And again, urine sediment in renal disease:

- **Prerenal failure**: bland U/A; occasionally granular and/or hyaline casts.
- **Postrenal**: frequently is bland, may have blood; WBC casts if due to infection; sterile pyuria if due to papillary necrosis; never red cell casts.
- **Intrinsic renal**: ATN = dirty brown granular casts.

Glomerulonephritides: nephritic (hematuria with RBC casts and sometimes pyuria with WBC casts) and nephrotic (fat bodies). Interstitial nephritis: eosinophils, RBCs, WBCs, and WBC casts.

Remember: Use steroids in most nephrotic syndromes—except those caused by amyloidosis and diabetes. Many causes of nephritic syndrome require steroids with cytotoxics, especially RPGN.

OTHER DRUG-INDUCED NEPHROPATHIES

NSAIDs inhibit prostaglandin (PG) production. Dilation of the afferent arteriole and maintenance of glomerular perfusion pressure require prostaglandins, particularly in patients with either true or effective reductions in renal perfusion; NSAIDs block this effect, which can lead to acute prerenal failure in patients with low effective circulating volume (low cardiac output, hypovolemia).

NSAIDs cause hyperkalemia by blocking PG-mediated renin release from the juxtaglomerular apparatus (low renin > low aldosterone > decreased renal potassium excretion).

NSAIDs also can cause an acute or a chronic interstitial nephritis, with nephrotic-range proteinuria (common) and papillary necrosis (rare).

Chronic injection drug users are at risk for several types of kidney problems:

- Acute bacterial endocarditis causes either focal or progressive glomerulonephritis by immune complex deposition in the kidney (associated with low complements).
- Endocarditis is associated with septic emboli that may result in renal infarction and hematuria.
- A chronically progressive focal sclerosis is occasionally seen in injection drug users.
- Injection drug users are at risk for HIV infection and subsequent HIV-associated nephropathy caused by FSGS.

KIDNEY INJURY IN CANCER

To summarize cancer and AKI, here is a hodgepodge of facts that you should know.

AKI in cancer can be grouped into several categories:

- **Direct infiltration** by lymphoma, leukemia, or myeloma.
- **Obstruction**, particularly from pelvic and abdominal tumors; intratubular uric acid obstruction due to tumor lysis syndrome, methotrexate crystallization.
- **Glomerular disease**: minimal change disease Hodgkin disease), membranous GN (solid tumors), amyloidosis (multiple myeloma).
- **Chemotherapy drug toxicity**, including: mitomycin C-induced hemolytic uremic syndrome; cisplatin-induced tubular injury; bevacizumab-induced thrombotic microangiopathy, ifosfamide causing ATN.
- **Hypercalcemia** of malignancy can lead to acute renal failure.

Patients with very high WBCs (AML, ALL) and lymphoma with high-tumor burden being treated with antimetabolites are at high risk for tumor lysis syndrome (acute urate nephropathy). Give prophylaxis with aggressive IV fluid hydration (hypotonic or isotonic saline) and allopurinol or rasburicase. Alkalinization of the urine is no longer recommended; bicarbonate should be given only in the setting of metabolic acidosis. A new allopurinol alternative is rasburicase. Rasburicase is an enzyme that catalyzes the oxidation of uric acid and is highly effective for both prevention and treatment of hyperuricemia. Know that rasburicase is contraindicated in patients with G6PD deficiency. Watch for hyperphosphatemia and hyperkalemia, common in tumor lysis syndrome. See Hematology, Book 4.

CHRONIC KIDNEY DISEASE

OVERVIEW

Current practice guidelines have changed the term "chronic renal failure" to chronic kidney disease (CKD). CKD is defined as any of the following:

- Kidney damage > 3 months, with or without decreased GFR, with either pathological abnormalities or markers of kidney damage
- GFR < 60 mL/min/1.73m^2 > 3 months, with or without kidney damage

CKD is divided into stages:

- **Stage 1** = normal GFR
- **Stage 2** = GFR 60–89 mL/min/1.73m^2 body surface area
- **Stage 3** = GFR 30–59
- **Stage 4** = GFR 15–29
- **Stage 5** = GFR < 15 or on dialysis

These stages provide management guidelines for the expected complications of anemia, bone disease, hypertension, salt and water retention, and uremia. The kidney disease outcomes quality initiative guidelines (KDOQI) provide the best evidence-based guidelines for most complications associated with CKD. Anemia, from decreased erythropoietin, is normochromic, normocytic, and responds to erythropoietin-stimulating agents. Peripheral sensory neuropathy and "restless leg syndrome" may occur.

Patients with CKD have an increased risk of heart disease because of their underlying conditions—and because CKD, alone, is an independent risk factor—although we do not know exactly all the factors involved. Heart disease is the number one cause of death.

CKD: MINERAL AND BONE DISORDER

Kidney disease results in abnormalities in calcium and phosphate homeostasis, which results in a spectrum of adverse consequences. The term chronic kidney disease-mineral bone disorders (CKD-MBD) was adapted to reflect these abnormalities.

As GFR declines, the kidneys become less able to excrete phosphorus in the urine. Serum phosphorous levels remain normal until ~ stage 3 CKD, after which phosphorus accumulates in the blood. Phosphorous retention:

- Stimulates release of parathyroid hormone
- Is further associated with hypocalcemia-induced PTH release via 2 mechanisms:
  - Calcium and phosphorus complex together and deposit in the vasculature and tissues.
  - Low GFR inhibits production of the active metabolite of vitamin D, 1,25-$(OH)_2$-D.

Know that hyperphosphatemia is associated with an increased risk of death and heart disease, even in patients without CKD—but especially in those with stages 3–5 CKD.

As the phosphorous levels accumulate, our traditional strategy has been to prescribe calcium-based phosphate binders to prevent the development of secondary hyperparathyroidism and renal osteodystrophy. What we now know is that these calcium-based binders can actually cause the calcium levels to increase, and the resultant hypercalcemia then inhibits PTH release. This is not a good thing.

Bone needs to turn over some—not too much (as occurs with hyperparathyroidism), but not too little either (this situation is called "adynamic bone"). When we treat renal patients for their increasing phosphorous, we can interrupt the fine balance of required bone turnover. If we do not treat their secondary hyperparathyroidism, the bone turns over too much; if we overtreat it, the bone turns over too little. Phosphate binders are either calcium-based ($CaCO_3$ or Ca acetate) or noncalcium-based, such as sevelamer (Renagel®) and lanthanum (Fosrenol®).

To summarize, decreased GFR (stage 3 CKD and higher) causes:

- Increased PO_4
- Normal/low-normal Ca
- Increased intact PTH (iPTH)
- Low 1,25-$(OH)_2$-D --→ secondary HPTH and vascular calcification. (It is necessary to assure that all these patients also have adequate 25-OH-vitamin D levels.)

The development of the noncalcium-based phosphate binders, along with regular measurement of iPTH levels, have greatly improved the management of mineral metabolism in CKD patients. Ideal management is to control phosphorus with diet and binder, which leads to normalization of phosphorous, increased Ca, and decreased iPTH. If PTH is not adequately corrected, addition of 1,25-$(OH)_2$-D (calcitriol) is necessary. However, the PTH should not be lowered all the way to the normal range, as low-turnover (adynamic) bone disease can result.

Renal Osteodystrophy

Renal osteodystrophy refers to the skeletal complications associated with CKD. This may result in bone pain or fracture. Patients with CKD can have 3 types of bone disorders:

1) **Osteitis fibrosa cystica** due to secondary hyperparathyroidism (high bone-turnover disorder)
2) **Adynamic bone** disease due to over-suppression of parathyroid hormone release (low bone-turnover disorder)
3) **Osteomalacia** (low bone-turnover disorder associated with unmineralized bone)

Review of secondary hyperparathyroidism: Labs = ↑ PO_4, ↓ 1,25-$(OH)_2$-D, ↑↑ iPTH, calcium normal/low-normal.

Clinical findings: asymptomatic, but may develop bone pain and have increased risk of fractures. Radiographs classically show subperiosteal bone resorption especially in the distal clavicle and the phalanges.

Treat this by following intact PTH (iPTH) levels and maintaining serum calcium and phosphorous levels in the recommended range (see below) using phosphate binders, 1,25-$(OH)_2$-D or one of the available vitamin D analogs (paricalcitol, doxercalciferol), +/– calcimimetics (cinacalcet). Calcimimetics are new drugs that increase parathyroid receptor sensitivity to calcium and reduce PTH, but can also decrease serum calcium levels.

Which phosphate binder to choose is based on the patient's serum calcium level. We used to treat to keep the calcium-phosphorous product below a specific number, but newer recommendations stress that the product is not as important as the iPTH level. The goal with treatment is to normalize phosphorus without creating adynamic bone.

Quick Quiz

- What is the effect of hyperphosphatemia in patients with CKD?
- What bone disorders are associated with CKD?
- How is adynamic bone disease different from secondary hyperparathyroidism?
- Which phosphate binders should be used in the hypercalcemic patient?
- What are the signs/symptoms of uremia?
- How is normochromic-normocytic anemia in CKD treated? What is the target hemoglobin (read all 3 paragraphs!)?

Current recommendations for stages 3–5 CKD not on dialysis:

- Start with calcium-based binders when the iPTH level starts to increase above "normal," if the serum calcium is 8.5–9.5 mg/dL.
- Monitor the serum calcium and iPTH. Change to a noncalcium-based binder if the serum calcium increases > 9.5 mg/dL or the iPTH is < 100 pg/dL.
- Give doses to target normal serum phosphorous and calcium levels.

Dialysis patients:

- Aim for an iPTH as near normal as possible.
- Give phosphate binders to keep phosphorous 3.5–5.5 mg/dL and calcium 8.4–9.5 mg/dL.
- Make sure hypocalcemic patients are not vitamin D deficient.

Adynamic Bone Disease

Review of adynamic bone disease: Labs = ↑/nl PO_4, ↓ 1,25-$(OH)_2$-D, ↓ iPTH, and calcium normal or high.

Adynamic bone disease is an important type of bone disease in CKD patients on dialysis. It is a low bone-turnover state accompanied by reduced bone formation. The cause is oversuppression of PTH by phosphorous binders and concomitant prescription of vitamin D analogs. Think of it as a sequela of overtreatment of CKD's secondary hyperparathyroidism. And for this reason, iPTH levels in CKD patients have to be closely followed so as not to undertreat or overtreat.

Most patients with adynamic bone disease are asymptomatic, but they can have fractures and hypercalcemia (especially if on analogs and calcium-based binders). Diagnose by observing an intact PTH level of < 100 pg/mL in a patient with CKD. Alkaline phosphatase levels are not elevated. Treat by reducing the amount of vitamin D analog and calcium-based phosphate binders (or substituting them with noncalcium-based binders).

Osteomalacia

Osteomalacia is uncommon in CKD now, and historically was due to the use of aluminum-containing phosphate binders that caused aluminum toxicity. Osteomalacia may still occur due to vitamin D deficiency.

UREMIA IN CKD

Uremia is a constellation of signs and symptoms associated with a GFR < 15 mL/min. Uremic signs and symptoms can include anorexia, nausea/vomiting, pericardial and pleural effusions, hemorrhagic pericarditis, platelet dysfunction and bleeding, pruritus, sensory neuropathies, and central nervous system dysfunction (confusion, difficulty concentrating, encephalopathy, coma). (Uremia does not cause any liver dysfunction.)

ENDOCRINE PROBLEMS IN CKD

CKD also can cause decreased glucose tolerance, decreased gonadal hormone production (with impotence or amenorrhea/infertility), and a low T_3 with a normal TSH.

ANEMIA IN CKD

Anemia of chronic kidney disease is a diagnosis of exclusion. These patients should be evaluated for other causes of anemia, especially iron deficiency, because this is very common in this population. If iron stores are adequate and other causes have been worked up, the anemia can be attributed to CKD.

The normochromic-normocytic anemia in CKD responds dramatically to recombinant erythropoietin (first rule out iron deficiency). The 2012 KDIGO (kidney disease improving global outcomes) guidelines suggest that ESAs not be started among adult nondialysis CKD patients with Hgb concentrations ≥ 10 g/dL. For nondialysis CKD patient with Hgb < 10 g/dL, the decision to start ESAs should be individualized based upon the rate of fall in Hgb concentration, prior response to iron therapy, risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms. Among dialysis patients, KDIGO suggests initiating ESAs when the Hgb concentration is below 10 g/dL.

Before starting treatment with ESAs, ensure there are plenty of iron stores on board (Fe saturation is greater than 20% and ferritin levels are > 100, and replenish with either oral or intravenous iron if stores are low).

While earlier guidelines for ESA treatment in CKD targeted a hemoglobin range of 11–12 g/dL, clinical trials that incorporate ESAs have shown no improvement in outcome and an increased morbidity and mortality if the hemoglobin is corrected to normal (> 13). Now, nephrologists recommend that initiation of an ESA should be based on the clinical status of the patient and not on an absolute hemoglobin level. Currently, ESA should be considered for patients with

symptomatic anemia attributable to erythropoietin deficiency when the hemoglobin level is less than 10 g/dL.

There also is some suggestion from recent studies indicating that ESA may increase the risk of tumor growth, and thus these agents should be used with caution in patients with active malignancy.

TREATMENT OF CKD

Progression of CKD is slowed by ACEIs or ARBs (target BP = < 130/80) and possibly by reduced protein intake (controversial). ACEIs and ARBs decrease intraglomerular pressure, which decreases progression. Recent data suggest that angiotensin II turns on TNF-β, which stimulates fibrosis, and this also may be suppressed by ACEIs/ARBs.

Aggressive management of comorbidities may also decrease progression, so treat metabolic acidosis and hyperlipidemia and counsel to stop smoking. As the disease worsens, avoid nephrotoxins—especially contrast dye, NSAIDs, and aminoglycosides.

GOUT IN CKD

Gout can occur in CKD. Still treat with colchicine or NSAIDs, although you must strictly monitor the dosages of these meds in reduced kidney function. Allopurinol decreases the production of uric acid, and chronic usage is often necessary. (Probenecid works by increasing renal excretion of uric acid. It is not effective and contraindicated in CKD.) For gout affecting a single joint, an intraarticular steroid injection is the preferred treatment.

DIALYSIS

Dialysis—when to start? Answer: When the CKD patient has advancing uremia. This usually means any uremic symptoms in a patient with a CrCl < 15 mL/min. Starting at a specific BUN or creatinine value is of no proven benefit.

Hemodialysis: A forearm AV fistula lasts the longest but should be created several months before dialysis; otherwise, a tunneled dialysis catheter or arteriovenous graft is needed. Refer patients when they develop Stage IV CKD (GFR < 30 mL/min/1.73m^2).

Know that the most common cause of death in dialysis patients is cardiovascular disease. Next is infection. The most common cause of admission is thrombosis/infection of the vascular access.

Dialysis patients have anemia, high triglycerides, and a low HDL. They usually have a metabolic acidosis just before and a respiratory alkalosis just after dialysis.

Maintaining adequate nutrition in these patients is one of the key factors in reducing morbidity and mortality. Vitamin supplements are indicated, especially water-soluble and folate. Water-soluble vitamins are vitamins that are not stored in fat; they must be replenished each day. The main water-soluble vitamins are B-complex and vitamin C.

Continuous ambulatory peritoneal dialysis (CAPD): With CAPD, you do not need an AV fistula or sophisticated machinery, but pay close attention to nutritional status—a high-protein intake is necessary. Fluid shifts are more gradual, so CAPD causes less strain on the heart.

The patient infuses 2–3 L of hypertonic dextrose solution into the peritoneal cavity (subsequently drained by gravity) 4–6 times per day. Many patients receive their peritoneal dialysis (PD) exchanges at night using an automated cycler, in a process called continuous cycler peritoneal dialysis (CCPD). Peritoneal dialysis requires a tunneled peritoneal dialysis catheter placed in the abdomen.

For CAPD, the main complication is peritonitis, usually caused by gram-positive skin flora (commonly *S. epidermidis* or *S. aureus*), and next most commonly, gram-negative organisms. Empiric intraperitoneal therapy with agents effective against both these classes of organisms should be initiated in suspected peritonitis while cultures are pending. Peritonitis should be suspected when the cell count of peritoneal fluid shows > 100 cells with > 50% PMNs. Other CAPD problems include hernias, hydrothorax, high protein loss (12 g/d), and loss of water-soluble vitamins (especially folic acid).

Decreased renal function increases the half-lives of many drugs, which may actually facilitate administration.

DRUG METABOLISM IN CKD

Vancomycin is completely excreted by the kidney; therefore, dosing intervals are markedly prolonged (dose required only once every few days and titrated based on serum levels of vancomycin). On the other hand, aminoglycosides can be completely removed during dialysis, and therefore need to be re-dosed after treatment.

Some drugs require dosing reductions as renal function deteriorates. They are:

- Digoxin
- Glyburide
- Procainamide
- Colchicine
- Low-molecular-weight heparin
- Gabapentin

Many antibiotics have some clearance during dialysis; therefore, they should be re-dosed after the session and may require supplemental doses. The common ones include:

- Most beta-lactams
- Daptomycin
- Metronidazole
- Ciprofloxacin
- Levofloxacin

- When is dialysis initiated in a CKD patient?
- What is the most common cause of death in the dialysis patient?
- What organisms are associated with peritonitis in the patient on CAPD?
- What is the risk of gadolinium use in the patient with CKD?
- Which immunomodulators are used in renal transplant patients?

IMAGING IN CKD

Avoid gadolinium contrast in patients with CKD stages 4 and 5.

Know that gadolinium, a contrast material used in MRIs, can cause nephrogenic systemic fibrosis (NSF) in patients with advanced CKD (all forms, regardless of whether on dialysis or what type of dialysis). Some data suggest that NSF is gadolinium dose-dependent and that it also may be associated with erythropoietin use. Avoid gadolinium in patients with stage 4 or 5 CKD.

Disease presents as a thickening of the skin with symmetrical plaques, papules, or nodules. Skin may have redness and induration. Usually it starts distally and moves proximally. Sometimes systemic symptoms are associated: organ fibrosis, scleral yellowing, and tissue calcification.

Presentation may be concerning for development of an autoimmune disease. Know that sclerodactyly can occur, but livedo reticularis is not associated with NSF. Definitive diagnosis is made with deep punch biopsies of involved skin. Lab tests generally focus on excluding autoimmune disease. NSF is not associated with eosinophilia, abnormal thyroid function tests, CPK elevation, antinuclear antibodies, antiphospholipid antibodies, or rheumatoid factor.

Course is progressive, sometimes fulminant. If renal recovery occurs, commonly the NSF remits---otherwise, there is no treatment.

Intravenous iodinated contrast, such as that utilized for CT studies and angiograms (including cardiac catheterization) can cause contrast-induced nephropathy. Important risk factors for the development of contrast-induced nephropathy include chronic kidney disease, advanced age, diabetes mellitus, and heart failure. The only strategy proven to prevent contrast nephropathy is isotonic intravenous fluids (either isotonic saline or isotonic sodium bicarbonate fluid). N-acetylcysteine (Mucomyst®) is sometimes used, but evidence for its efficacy is mixed.

The diagnosis of NSF is based upon histopathologic examination of a biopsy (deep incisional or punch biopsy) of an involved site.

RENAL TRANSPLANT

Anytime renal function deteriorates in a patient with a kidney transplant, think in the usual terms: Is it prerenal, postrenal, or intrinsic renal? Delayed graft function due to ischemic ATN is the most common cause of intrinsic renal disease immediately post-transplant. Immediate failure of the transplant (called "hyperacute rejection") also can be due to preformed donor antibodies that acutely cause damage to the kidney, even at surgical implantation (kidney becomes discolored and mottled). In almost all transplant centers, early renal dysfunction is evaluated by renal biopsy.

If the kidney functions well after transplant but deteriorates within the first 3 months, again consider whether the problem is prerenal, postrenal, or intrinsic renal. Intrinsic renal causes are the most problematic and include rejection, drug-induced toxicity, infection (CMV or BK virus), and recurrence of disease for which the kidney was transplanted (primary FSGS can recur almost immediately).

Unless evidence is overwhelming for intrinsic renal causes (e.g., return of active urine sediment), start workup by checking levels of immunosuppressant drugs: cyclosporine, tacrolimus, sirolimus. Screen for CMV and BK virus and obtain renal ultrasound. If these are normal or the patient's renal function is not improving, renal biopsy is indicated.

Cyclosporine and tacrolimus are calcineurin inhibitors (CNIs) with similar mechanisms of action. They decrease T-cell proliferation (but not function!) without affecting the bone marrow. Sirolimus is an mTOR kinase inhibitor currently used at some institutions, also with antiproliferative properties. It is always used with cyclosporine initially. All 3 drugs cause dose-related nephrotoxicity and carry FDA boxed warnings for increased risk of death from infections. Side effects of cyclosporine include tremors, hepato/CNS toxicity, and gum hypertrophy. Tacrolimus is more diabetogenic. Sirolimus is associated with wound dehiscence/impaired healing, and development of lymphoma and hyperlipidemia. All are metabolized by the cytochrome P-450 system. Blood levels of CNIs are increased by erythromycin, ketoconazole, voriconazole, and diltiazem—and decreased by phenytoin, caspofungin, carbamazepine, rifampin, and phenobarbital.

Mycophenolate mofetil (MMF) is another immunosuppressive routinely used in most centers and has largely replaced a similar, older agent, azathioprine. Its main side effects are GI with some BM suppression, and it may increase risk for lymphoproliferative disorders. Know that allopurinol increases serum levels of azathioprine but not MMF.

Immunosuppression: Most patients are on "triple therapy" with CNI (or sirolimus), MMF, and a corticosteroid, although many variations of treatment exist. Steroid-free regimens have become increasingly common.

Urinary tract infections, pneumonia, and sepsis are common events after renal transplant. Patients are given

primary prophylaxis against *Pneumocystis* for 1 year post-transplant and against CMV for 3 months. Renal transplant patients are also more likely to get post-transfusion hepatitis, aseptic necrosis of femoral heads, and cataracts. Primary renal disease can recur with FSGS, MPGN, IgA nephropathy, and even diabetes. The main cause of death after kidney transplant is cardiovascular disease.

Both dialysis and renal transplant reverse the platelet dysfunction, renal osteodystrophy, and sensory/cognitive dysfunction of CKD. Only transplant can reverse late manifestations of small vessel calcification and motor neuropathy in CKD.

HEREDITARY KIDNEY DISEASES

ALPORT SYNDROME

Alport syndrome = hereditary nephritis (also discussed under normal complement nephritic syndromes on page 4-44). Alport syndrome can be either X-linked (most cases), autosomal recessive (15%), or autosomal dominant (5%) with variable expression. For X-linked disease, men are affected much more seriously than women. For AD and AR disease, severity is the same in men and women.

Alport syndrome results from a mutation in genes encoding type IV collagen, affecting the basement membrane (the same target area the Goodpasture's anti-GBM antibodies attack) in the glomerulus, cochlea, and the lens. Hearing loss is common. The female X-linked carriers have microscopic hematuria only. The affected males usually have renal failure by the time they are adults.

Consider Alport syndrome in any patient with persistent microscopic hematuria (onset at birth) that worsens after an infection (i.e., include this in the differential diagnosis of PIGN and IgA nephropathy). Also, especially consider Alport syndrome in a woman with microscopic hematuria when there is a family history of males dying of kidney problems. Diagnose with a kidney biopsy in both men and women. Thinning of the basement membrane occurs in both Alport syndrome and the related, though benign condition, "thin basement membrane" disease, which can present with asymptomatic microscopic hematuria.

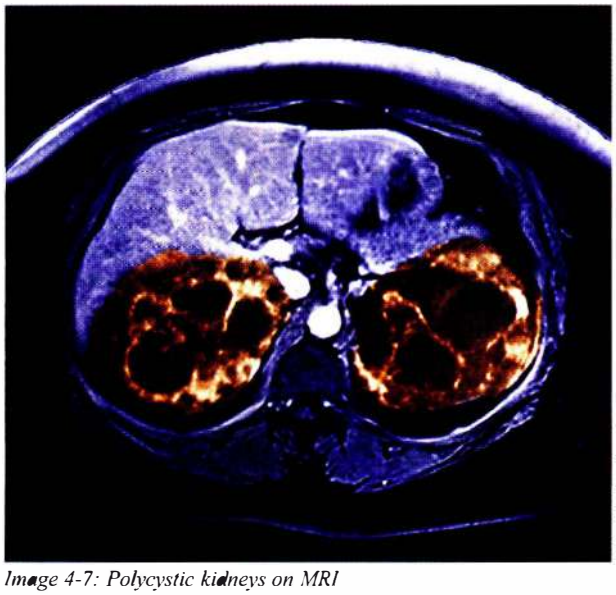


Image 4-7: Polycystic kidneys on MRI

Disease is treated with an ACEI or ARB, because no other therapy has proven effective in a randomized controlled trial. Renal failure is treated with transplantation.

POLYCYSTIC KIDNEY

Autosomal dominant polycystic kidney disease (PCKD) is the most common genetic disease of the kidney. It is usually associated with a mutation on the short arm of chromosome 16. There is a locus near the defective gene that, when found, suggests a tendency for the disease. Patients get cysts of the kidneys, liver, and pancreas as well as associated recurrent hematuria (Image 4-7).

Onset of polycystic kidney disease occurs at ~ age 20. Gross or microscopic hematuria is the most common presenting symptom. Patients also can present with flank pain, chronic kidney disease, hypertension, and cyst infections. Progressive renal failure and HTN are the norm. Associated liver cysts cause hepatomegaly but rarely liver dysfunction. Cerebral aneurysms occur in a very small percent (1–5%).

Screening for aneurysms is recommended only if the patient with PCKD has 1 or more relatives with a history of subarachnoid hemorrhage or a known aneurysm. Some experts also recommend that a patient with PCKD be screened if she has an occupation that places her own life or the lives of others at risk should she lose consciousness.

The diagnosis is generally established when polycystic kidneys are identified by imaging (U/S or CT) during evaluation for hematuria. Renal U/S is also used for screening patients > 18 years of age with a family history of PCKD. Genetic testing is available when the diagnosis is in question.

MEDULLARY DISEASE

There are 2 main inherited medullary kidney diseases:

1) **Medullary sponge disease** (diagnosed by IVP), which is rarely clinically significant but is associated with high PTH, hypercalciuria, and renal stone disease.
2) **Medullary cystic disease**, which can cause renal failure and presents in childhood. This is one of the few chronic kidney diseases in which there usually is a normal urinalysis.

RENAL CYSTS

Renal cysts are very common: 50% of people > 50 years old have them. They are considered benign if "simple" on U/S and the patient is asymptomatic. "Simple" cysts have well-defined margins, dense (compressed)

QuickQuiz

- What are the presenting symptoms of polycystic kidney disease?
- When is a renal cyst considered benign?
- Which antiretroviral drug is associated with renal stones?
- Name the common causes of calcium stones.
- Which bacteria are associated with staghorn calculi?
- Name one of the most important general recommendations for patients with kidney stones, regardless of the type of stones.

surrounding tissues, and no solid component. Otherwise, cyst aspiration or surgical exploration is indicated to rule out cancer. Also see polycystic kidney disease above.

RENAL STONES

Renal stones: 2/3 of renal stones are either calcium phosphate or calcium oxalate; the other 1/3 are struvite or uric acid. Struvite is a phosphate stone with a mixture of cations: calcium/ammonium/magnesium phosphate (Image 4-8 and Image 4-9). Do not forget that patients with HIV/AIDS on indinavir as part of an antiretroviral regimen can get indinavir stones.

Workup following initial stone passage usually includes:

- Chemical analysis of the stone
- Calcium, iPTH (exclude hyperparathyroidism)
- Electrolytes and urine pH (exclude Type 1 distal RTA)
- U/A with C+S (exclude stone-forming urinary pathogens; clue = urine pH > 7.5)
- Abdominal plain films to detect radio-opaque (calcium, cysteine, struvite) vs. radiolucent (uric) stones
- Renal imaging (helical CT is the gold standard; rarely use IVP; in patients with impaired renal function, begin with ultrasound imaging of the kidney)

When it is a 1st stone in a low-risk patient (no illnesses and negative family history) and the stone is not retrieved, limited evaluation is appropriate: serum chemistry including calcium. If serum calcium is elevated x2, work up for primary hyperparathyroidism. All these patients are told to increase oral fluids enough to produce 2 L/d of urine.

For recurrent stones, perform 24-hour urine collection for the following: volume, cystine, calcium, Na, urea, uric acid, citrate, oxalate, and creatinine. If there are signs of acute ureteral obstruction with infection, the patient must be hospitalized because sepsis and papillary necrosis may result.

There are several factors that inhibit or promote stone formation. Citrate is the major inhibitor of calcium stones, but magnesium and pyrophosphate are also inhibitors. Concentrated urine and/or excretion of excessive amounts of stone-forming products cause precipitation and stone formation. Finally, certain products may act as a nidus for stone formation.

Calcium stone causes: hypercalciuria, uric acid, hypocitraturia, hyperoxaluria, and medullary sponge disease. Citrate chelates calcium, thereby preventing stones. Acidosis causes hypocitraturia and also leaches calcium from the bones, resulting in hypercalciuria. Although the calcium stones are usually a combination, they are often grouped into calcium phosphate and calcium oxalate stones.

Hypercalciuria can be caused by hypervitaminosis D, distal (Type 1) RTA, sarcoidosis, and hyperparathyroidism. 1/2 of the patients have "idiopathic" hypercalciuria, now known to be caused by increased calcium absorption from the gut, secondary to an increased renal production of $1,25\text{-}(OH)_2\text{-}D$.

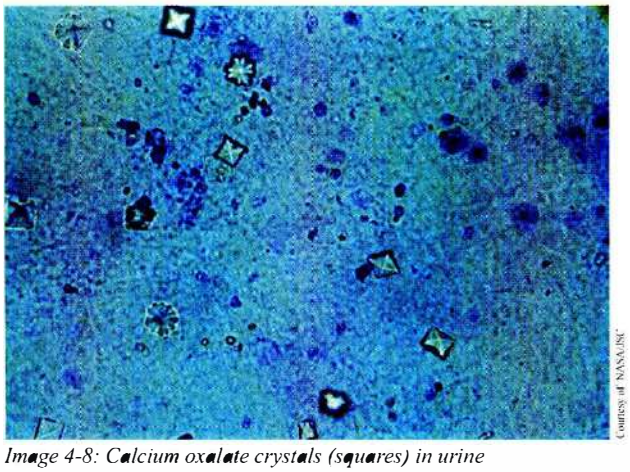


Image 4-8: Calcium oxalate crystals (squares) in urine

Image 4-9: Struvite crystals (coffin lids)

Calcium phosphate stones are more common in patients with I° hyperparathyroidism, acetazolamide, and distal (Type 1) RTA. Distal RTA causes stones by 1) causing an increase in $CaPO_4$ withdrawal from bones (remember that phosphorus is one of the body's main acid buffers!), and 2) producing an alkaline urine that allows this increased $CaPO_4$ to precipitate.

High urinary oxalate is the most important factor in **calcium oxalate** stone formation. Vitamin C is an oxalate precursor and can cause stones if taken in large amounts. Steatorrhea also causes oxaluria; free fatty acids in the bowel chelate the calcium, allowing the oxalate to be absorbed and then excreted in the urine. Uricosuria is a predisposing factor for oxalate stones because the uric acid crystal is similar to calcium oxalate and can act as a nidus for stone formation.

Treat calcium stones by pushing fluids, giving thiazide diuretics for hypercalciuria (decrease urinary calcium), decreasing dietary protein and sodium, giving potassium citrate, and treating high uric acid. Note: Do not decrease dietary calcium intake; this only increases oxaluria!

Struvite (calcium/ammonium/magnesium phosphate) stones grow quickly and often cause staghorn calculi. Think infection when you see staghorn calculi. The ammonium needed to make these stones forms only when urease breaks down the urea. The most common urease producers are *Proteus* and *Klebsiella*. Treatment consists of removal of the stones/calculi; acidification of the urine (this is the only other stone, besides calcium phosphate, made more likely by alkaline urine); and antibiotics. If all of the stones cannot be surgically removed, patients require indefinite antibiotics.

Cystine stones are due to cystinuria. Cystine is undersaturated in the normal urine, but homozygous patients with cystinuria excrete large amounts (autosomal recessive genetics). Look for clear, hexagonal crystals in the urine. Cystine is insoluble. It is usually best to treat by increasing fluids and by alkalinizing the urine—to keep urine cystine concentration normal! Penicillamine forms soluble complexes with cystine but is not well tolerated. Heterozygotes do not form stones.

Uric acid stones are generally seen in patients who chronically excrete acidic urine. You also see them in those who have high serum uric acid. Myeloproliferative syndromes, chemotherapy, and Lesch-Nyhan syndrome can cause such hyperuricosuria in which there is stone formation even at normal urine pH. Treat with urinary alkalinization +/– allopurinol (allopurinol should be used only in patients with documented hyperuricosuria). Give allopurinol before treatment of high-cellular tumors.

Treatment options for acute ureteral obstruction include:

- Allow passage (if < 5 mm).
- Remove via ureterorenoscope (middle and distal stones).
- Remove via percutaneous nephrostolithotomy (staghorn and other large stones).
- Remove via percutaneous ultrasonic lithotripsy (continues to be associated with high complication rate).

Know that urinary alkalinization is done for all stone-formers, except in struvite and calcium phosphate stones. Push fluids so the patient produces about 2 L/day of urine, regardless of the type of stones. Also, remember the difference between cystine and citrate: Cystine is an amino acid that precipitates into stones, while citrate chelates calcium in the urine, thereby preventing stones.

APPENDIX A

You hear a lot about the Henderson-Hasselbalch equation. Did you know that it is derived from the bicarbonate buffer equation:

$$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2 \qquad \text{[eq 4]}$$

H_2CO_3 is carbonic acid. HCO_3^- is bicarbonate. CO_2 is carbon dioxide. In the serum, these 3 molecules exist in equilibrium with one another.

From the law of mass action is derived the dissociation constant for carbonic acid K_{Ai}:

$K_{Ai} = (H^+ \times HCO_3^-) / H_2CO_3$; and since CO_2 is in equilibrium with H_2CO_3, an equilibrium constant is added to K_{Ai}, and we get:

$$K_A = (H^+ \times HCO_3^-) / CO_2 = H^+ \times (HCO_3^- / CO_2)$$

Taking logarithms:

$$\log K_A = \log H^+ + \log (HCO_3^- / CO_2)$$

so:

$$-\log H^+ = -\log K_A + \log (HCO_3^- / CO_2)$$

Noting that dissolved CO_2 is a function of the partial pressure of CO_2 in blood, $CO_2 = 0.03\ P_aCO_2$; and that $pH = \log [1/H^+] = -\log [H^+]$, we get the Henderson-Hasselbalch equation:

$$pH = pK + \log (HCO_3^- / [0.03 \times P_aCO_2]) \qquad \text{[eq 5]}$$

FOR FURTHER READING

[Guidelines in blue]

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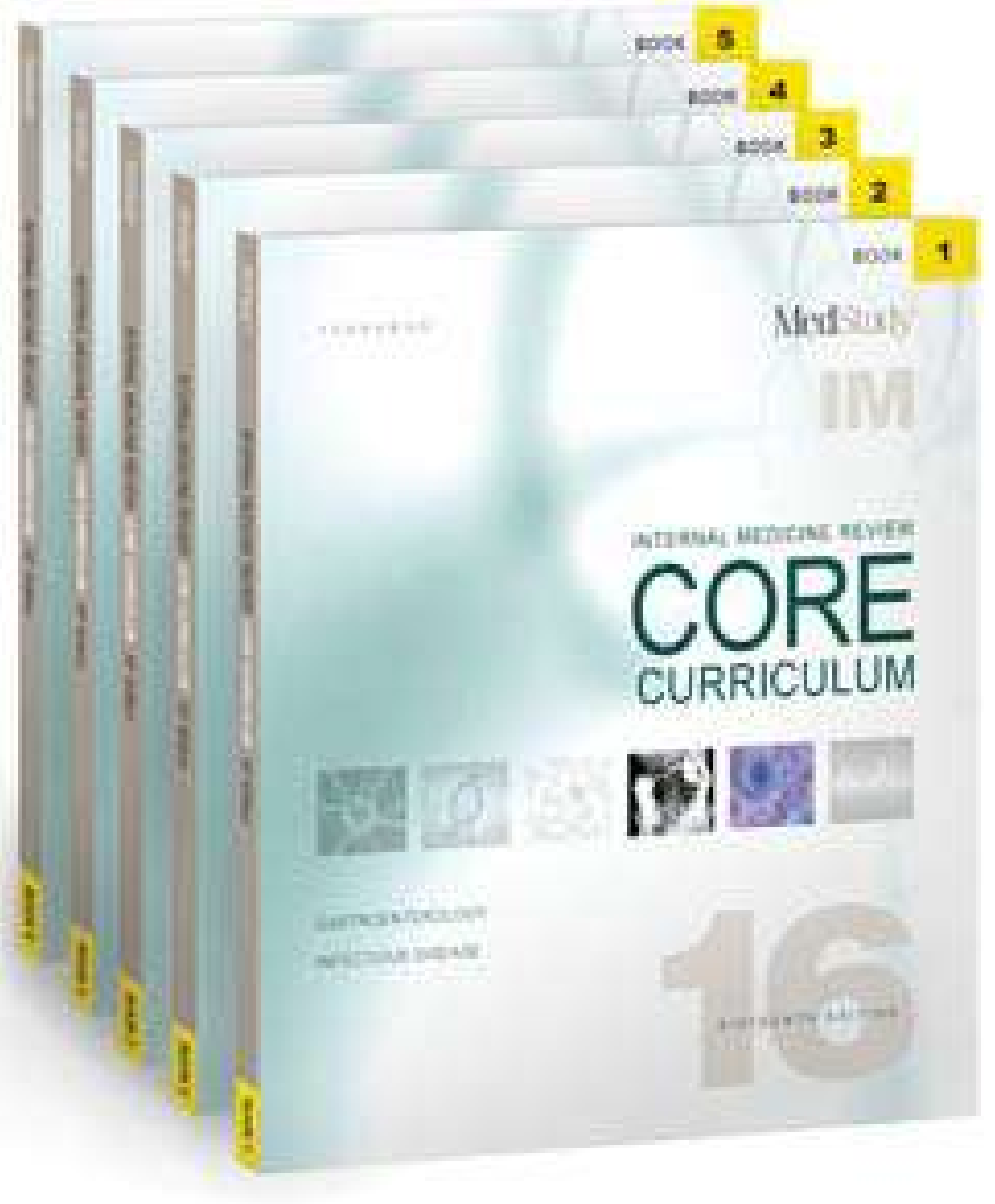
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PROCEDURES, LABS, PHYSICAL EXAM

CHEST X-RAYS

Know all the following chest x-ray findings!

Chest x-ray is an effective means of quickly determining significant increases in both overall heart size and (sometimes) heart chamber sizes. A cardiothoracic ratio > 50% indicates an enlarged cardiac silhouette, suggesting either cardiomegaly or a pericardial effusion. This is the ratio comparing the most rightward and leftward borders of the heart seen on a posteroanterior (PA) chest x-ray, divided by the transverse chest diameter (measured from the inside rib margin at the widest point above the costophrenic angles on the same x-ray). This ratio is valid only for an upright, nonrotated film on full inspiration (diaphragm fully contracted) with a well-visualized cardiac outline and when there is no abdominal compression on the diaphragm, such as that caused by ascites or pregnancy.

On the PA film, the left ventricle causes the bulge in the left-lower side of the cardiac shadow; the right atrium (RA) causes the outline on the right; and the area of the cardiac "waistline"—between the aortic knob and the left ventricle (LV)—is formed by the main pulmonary artery and the left atrial (LA) appendage (Image 5-1).

On the lateral view, any increase in the mass of the left ventricle extends the cardiac shadow posteriorly and lower—closer to the diaphragm. Any increase in the mass of the right ventricle fills in the lower part of the anterior clear space behind the sternum (Image 5-2).

Coarctation of the aorta (COA) is indicated by absence of a normal aortic arch. Instead, look for the "3" sign, which is created by a prominent, left subclavian artery, the coarctation, and poststenotic dilation of the descending aorta. The barium swallow can show a "reversed 3," due to the impressions of the arterial structures on the esophagus. Adults also show intercostal rib notching due to collateral flow through tortuous intercostal arteries.

Heart failure (HF) is indicated by cardiomegaly, pulmonary vascular redistribution (with visibly thickened upper lobe pulmonary veins), Kerley B lines, and pleural effusions (usually right > left).

An **anomalous pulmonary vein** that drains into the inferior vena cava can create a "scimitar sign" on chest x-ray. This is a curvilinear opacity in the right lower lung field due to associated lung hypoplasia.

Aortic abnormalities that you may see include tortuosity and calcification. An aortic aneurysm is sometimes easily visible on the lateral film. An aortic dissection can show up as mediastinal widening on the PA projection.

Pericardial effusion is suggested by a "water bottle" or a "water balloon" shape to the heart, sometimes with significant enlargement of the cardiac silhouette (Image 5-3).

Shunt vascularity (enlarged, sharply defined pulmonary vasculature) is visible with significant ventricular septal defect (VSD), atrial septal defect (ASD), or other left-to-right shunts.

Areas of **calcifications** on chest x-ray:

- Aortic: Think dissection if you see a separation between calcification and the aortic border, especially if the mediastinum appears wide.
- Myocardial: typically from an apical aneurysm.
- Valvular: commonly aortic.
- Annular (ring-shaped): mitral annular calcification; if it is a perfect ring then a prosthetic valve is likely (especially if surgical clips are also present).
- Pericardial: Think constrictive pericarditis; or think TB if the clinical history suggests significant exposure (Image 5-4).

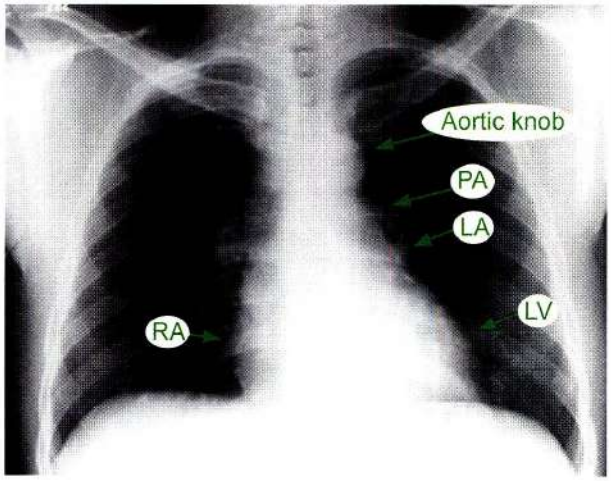


Image 5-1: Normal posteroanterior chest x-ray

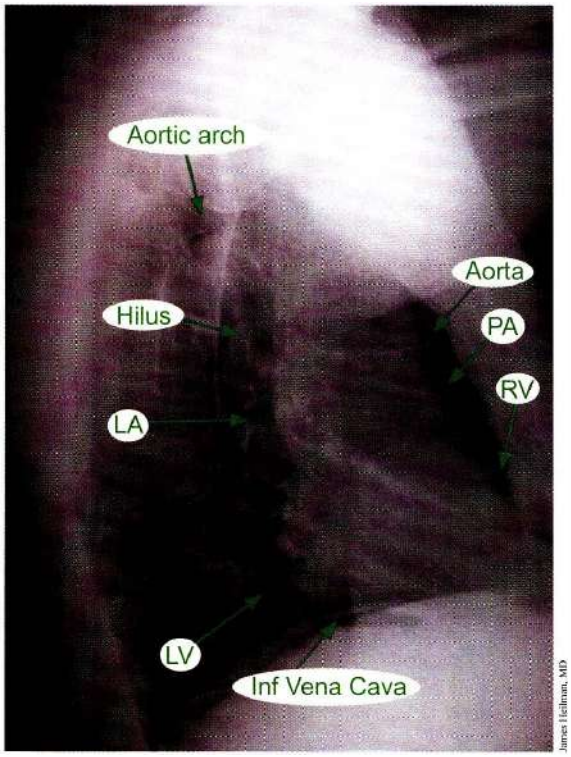


Image 5-2: Normal lateral chest x-ray

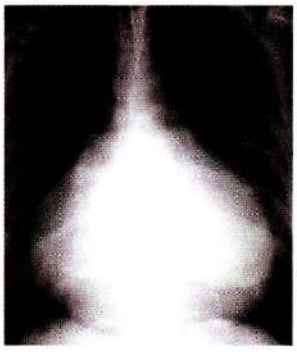


Image 5-3: "Water bottle" heart

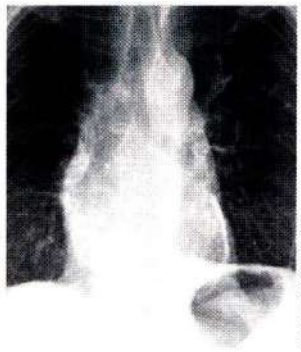


Image 5-4: Pericardial calcification

Know that a single lead in the apex of the right ventricle (RV) indicates the presence of an electronic ventricular pacemaker or implanted defibrillator—with the defibrillator lead being larger and wider than that of a pacemaker, 2 leads indicate an atrioventricular (AV) sequential (dual-chamber) pacemaker, and 3 leads indicate a biventricular pacemaker. If there is no atrial lead, the patient likely has chronic atrial fibrillation.

ECHO

Echocardiography is an ultrasound modality used to image the heart. It utilizes M-mode, 2D, and 3D for structural imaging and Doppler for assessing blood flow rate and direction.

Best use of echo is for the following scenarios:

- Left ventricular structure and systolic function
- Right ventricular structure and systolic function
- Valvular heart disease
- Congenital heart disease
- Myocardial infarction (including post-MI complications)
- Cardiomyopathy (both loss of ejection fraction and hypertrophy of myocardium)
- Pericardial disease
- Cardiac masses (tumor, thrombus, and vegetation)
- Diseases of the aorta and pulmonary artery
- Estimation of pulmonary pressure
- Diastolic function
- Cardiac sources of emboli

Transesophageal echocardiogram (TEE) is an echo performed with an esophageal probe. It offers higher-resolution images compared to transthoracic imaging and is especially useful for evaluating:

- Valvular structure and function
- Left atrium (including left atrial appendage)
- Cardiac masses
- Intracardiac shunts
- Endocarditis
- Aortic dissection

A bubble study (performed by injecting hand-agitated saline and air into the venous system) is used to evaluate intracardiac shunts. Doppler echocardiography measures the velocity and direction of the blood flow. Doppler echo determines mean gradients, peak velocities, and valve area.

So, Doppler is useful in determining the severity of valvular stenosis or regurgitation, as well as in evaluating left ventricular diastolic function, left ventricular outflow tract gradients, and intracardiac shunts. It is also helpful in estimating pulmonary artery (PA) pressure. To estimate pressure by using peak Doppler velocity measured on echo: Pressure gradient (mmHg) = 4 x V^2 (measured velocity). For example, if the velocity across the tricuspid valve is 5 m/sec, then the PA pressure = 4 x (5 x 5) + right atrial pressure. So, if the right atrial pressure in this example is 10 mmHg, then the PA pressure = 110 mmHg (which is extremely high).

CARDIAC STRESS TESTS

Overview

The increased demand for myocardial oxygen with exercise is the key factor in the use of exercise testing as a diagnostic tool for coronary artery disease ([CAD]; a.k.a. coronary heart disease). Stress tests have an integral role in both the detection of CAD (diagnostic tool) and in stratification of risk (prognostic tool). To appropriately utilize stress tests, a patient's pretest probability of CAD must be taken into account. (A positive test in a low-risk patient is more likely to be a false positive, and a negative test in a high-risk patient is more likely to be a false negative.) Diagnostic testing is most valuable when pretest probability for CAD is intermediate.

There are 2 general types of cardiac stress tests done:

1) Exercise tolerance test ([ETT]; basic treadmill or stationary bicycle testing without imaging)
2) Stress imaging testing—"stress" is induced with:
   - exercise (treadmill or bicycle), or
   - pharmacologic stress (either dobutamine or a vasodilator)

   The associated imaging is done with:
   - Echocardiography (a.k.a. "stress echo")
   - Myocardial perfusion imaging (MPI)

Exercise Tolerance Test (Without Imaging)

Exercise tolerance test (ETT), using either a treadmill or stationary bicycle, is the cornerstone of diagnostic testing for ischemia and functional capacity and for determining prognosis (including post-MI).

Despite an overall low sensitivity and specificity (men: sensitivity = 68%, specificity = 77%; women: sensitivity = 61%, specificity = 70%), the sensitivity and specificity increase with higher pretest probability of CAD. ETT has a number of advantages, including: the ability to test functional capacity, safety, widespread availability, and relatively low cost.

QuickQuiz

- On a lateral view CXR, extension of the heart border posteriorly and inferiorly indicates enlargement of which ventricle?
- On a lateral view CXR, extension of the cardiac shadow of the lower part of the anterior clear space behind the sternum indicates enlargement of which ventricle?
- What conditions is a TEE useful for evaluating?
- What are absolute indications for terminating an ETT?
- When are stress imaging studies done instead of an ETT?

The patient typically exercises on a treadmill using standard exercise protocols, such as the Bruce protocol (see Table 5-6 on page 5-12). The level of maximal exercise achieved on the ETT is measured in metabolic equivalents (METS).

ETT should not be performed in 2 groups:

1) Patients unable to exercise sufficiently (must achieve 85% of age-predicted maximum heart rate)
2) Patients with baseline ECG abnormalities that can interfere with interpretation of the stress test (e.g., left ventricular hypertrophy [LVH], left bundle-branch block [LBBB], Wolff-Parkinson-White [WPW], ventricular pacing, and resting ST depression), or taking digoxin

Know the following information related to ETTs:

Definition of a positive ETT: flat or down-sloping ST-segment depression > 1 mm and 80 ms after the J-point in 3 consecutive beats.

Unlike ST elevation, ST depression does not correlate with the anatomic location of myocardial ischemia. Isolated ST depression in inferior leads is far less specific than ST depression in lateral leads (V4–V6).

ST elevation during an ETT in 3 contiguous leads without Q waves of prior MI is an unusual finding that is suggestive of marked ischemia (can be seen also with coronary artery spasm).

Absolute indications for termination of an ETT:

- ST elevation > 1 mm in leads without Q waves from prior MI and excluding aVR, aVL, and V1
- Decrease in systolic BP > 10 mmHg when accompanied by any other evidence of ischemia or hypoperfusion
- Moderate-to-severe angina
- CNS symptoms (ataxia, dizziness, near syncope)
- Signs of poor perfusion (cyanosis/pallor)
- Sustained 2nd or 3rd degree AV block
- Technical difficulties in monitoring ECG/BP
- Patient requests to stop
- Serious arrhythmia (e.g., sustained ventricular tachycardia)

Achieving target heart rate alone is not a reason to discontinue the ETT, and the individual should be encouraged to go as long as tolerated until required to stop for some reason (e.g., dyspnea, fatigue, exhaustion, or one of the absolute indications for termination).

Excellent exercise tolerance (> 10 METS) is associated with a good prognosis independent of the degree of coronary artery disease.

Absolute contraindications to ETT:

- Acute MI within 2 days
- Unstable angina not previously stabilized by medical therapy
- Uncontrolled arrhythmias causing symptoms or hemodynamic compromise
- Symptomatic severe aortic stenosis
- Uncontrolled symptomatic heart failure
- Acute pulmonary embolus or infarction
- Acute myocarditis or pericarditis
- Acute aortic dissection

Stress Imaging Tests

Overview

The stress imaging studies are the stress echo and myocardial perfusion imaging (MPI). The choice of which one to use is often based on operator experience at the facility.

Stress imaging studies are used as the initial diagnostic method when a patient is not a candidate for ETT due to inability to exercise adequately or when there are ECG changes at rest that can interfere with interpretation of the ETT. They also are preferred in patients with prior revascularization.

Stress imaging studies have greater sensitivity and specificity than the regular ETT. They are used when measurement of ejection fraction or myocardial viability is desired in addition to identifying coronary artery disease.

Stressing the Heart for Imaging Studies

The "stress" portion of these tests can be performed with exercise or pharmacologic agents.

With **exercise**, imaging studies are done just like an ETT and require the same ability to meet 85% of age-predicted maximum heart rate. Exercise is preferable because it provides additional functional and prognostic information. Exercise is not used in patients with pacemakers or left bundle-branch block (LBBB) because it can cause false-positive left ventricular anteroseptal perfusion defects. The pharmacologic agents used for cardiac imaging studies are dobutamine or vasodilators.

Dobutamine is both inotropic + chronotropic and causes the heart to act similarly as it would with exercise. As with exercise, a target heart rate must be achieved with dobutamine. Also, as with exercise, dobutamine is not used in patients with pacemakers. Dobutamine stress echo is fine for LBBB (but not dobutamine MPI with LBBB). Dobutamine is the agent used for patients who not only are unable to exercise but who also have a contraindication to vasodilators (e.g., bronchospasm, severe carotid artery stenosis).

Vasodilation: Adenosine, dipyridamole, and regadenoson are the main coronary vasodilators used in the pharmacologic MPI stress tests. Vasodilators do not stress the heart by increasing heart rate as is done with exercise or dobutamine. These vasodilators work in this setting by dilating and increasing blood flow in normal cardiac vessels while doing little to change the flow in stenotic vessels. The dilated normal vessels steal flow from the stenotic vessels, causing perfusion defects in scans (and ST segment changes in ECGs). Vasodilators are not used in patients with history of bronchospasm.

Regadenoson is a more selective A2A receptor activator, has less bronchospasm effect, and allows for a faster stress test. Even so, for the Boards and per current guidelines, dobutamine is still the pharmacologic agent of choice for patients with a history of bronchospasm.

Stress Echo and Stress MPI Indications

Unlike ETT, exercise stress echo and stress MPI can be used in patients:

- with resting ECG ST changes,
- with WPW syndrome, or
- on digoxin therapy.

Note that it is a common misconception that these patients require chemical stress, but this is definitely not true! If they can exercise, these patients have a class I indication for a stress echo with exercise or MPI with exercise (i.e., these patients need the imaging, not the chemical stress).

Note: MPI with vasodilators (but not exercise or dobutamine!) is the test of choice for patients with paced ventricular rhythm.

Stress Echo

The stress echo is a widely used test for myocardial ischemia by the detection of stress-induced wall motion abnormalities. Stress echo is less sensitive but more specific than MPI for the detection of coronary artery disease.

Use exercise or, if unable to exercise, use dobutamine to achieve target heart rate. Then take echo images to evaluate changes in wall motion, systolic wall thickening, and systolic ejection fraction with stress. Abnormal wall motion or failure of the wall to thicken (contract) appropriately suggests ischemia of that region of the myocardium.

In addition to new regional wall motion abnormalities, criteria for abnormal stress echo are left ventricular cavity dilation and decline in global left ventricular systolic function with stress (suggestive of multivessel disease). Stress echo is less expensive than MPI.

Vasodilators are not used for stress echo.

Myocardial Perfusion Imaging

Myocardial perfusion imaging (MPI) uses radioisotopes with single-photon emission computed tomography (SPECT). The most commonly used agents are technetium-99m (^{99m}Tc)–labeled substances (commonly sestamibi or tetrofosmin). Thallium-201 (^{201}TI) is less commonly used.

These tracers distribute in heart tissue in proportion to blood flow; this distribution is recorded by a gamma camera. Perfusion is compared visually between the resting and stressed states. Preserved myocardial perfusion at rest but decreased during stress is suggestive of ischemia ("reversible defect"), while matched reduction in perfusion between the rest and stress images is suggestive of a myocardial infarction ("fixed defect"). Other high-risk markers include transient ischemic LV dilation (TID), reduced post-stress LV ejection fraction, and increased lung or right ventricular uptake, all of which are suggestive of multivessel disease.

MPI is often done with ECG-synchronized "gated" technique, where multiple images are combined and smoothed for better resolution. This allows for assessment of wall motion and ventricular size and function (estimates ejection fraction).

Again, target heart rate must be achieved with exercise or dobutamine for an adequate test; however, achievement of target heart rate is not needed with vasodilator stress. So, dobutamine is used only in cases where the vasodilator is contraindicated (as it would be in patients with bronchospasm—see above).

Other imaging modalities that can be used for MPI (other than SPECT imaging) include cardiac positron emission tomography (PET) and cardiac MRI, both of which are also used to assess for myocardial ischemia and viability.

Myocardial perfusion imaging (MPI) is more expensive than stress echo, and it involves radiation exposure.

Cardiac Stress Tests — Picking the Correct Test

To determine the correct stress test, go through the following scenarios. These are summarized in Table 5-1.

An exercise stress test (i.e., ETT, exercise echo, exercise MPI) is always preferred if the patient has no limitations to exercise (exceptions are LBBB or paced rhythm). If the resting ECG is normal, proceed with ETT—no imaging is needed. If the resting ECG is abnormal (with exception of LBBB and paced rhythm), perform exercise testing with echo or MPI.

Quick Quiz

- When are exercise stress echo and MPI indicated instead of ETT?
- Which stress imaging tests are used in patients with LBBB? With paced ventricular rhythm?
- Which patients may benefit from CPX?

A pharmacologic stress test is done if the patient cannot do more than moderate exercise, is unable to increase the heart rate (e.g., pacemaker) or has LBBB.

Follow these indications when choosing the proper agent:

- If the patient simply is unable to walk and has no other issues, use pharmacologic stress test.
- If the patient has bronchospasm or severe carotid artery stenosis, use dobutamine.
- If the patient has severe HTN or prior ventricular tachycardia (VT), use a vasodilator (adenosine, dipyridamole, or regadenoson), not dobutamine.
- If the patient has a paced ventricular rhythm, use a vasodilator with MPI; again, not dobutamine.

One more time: Do not use adenosine or dipyridamole in someone with asthma or severe carotid stenosis and do not use dobutamine in someone with a history of VT, uncontrolled HTN, or a paced ventricular rhythm.

CARDIOPULMONARY EXERCISE TESTING

Cardiopulmonary exercise testing (CPX) is a special exercise test that measures ventilation and concentrations of oxygen and carbon dioxide during progressive exercise (stationary bicycle/treadmill) and is the gold standard aerobic exercise test. CPX provides the most accurate and reproducible measurement of cardiorespiratory fitness, severity of impairment, and response to intervention. CPX is well established for evaluating patients with systolic heart failure (HF), undergoing a pretransplant assessment, and for patients with unexplained exertional dyspnea.

Table 5-1: Determining Best Cardiac Stress Test

ECG Findings	Able to Exercise?	
	Able	Not Able
Resting ECG normal	ETT*	Dobutamine echo Dobutamine MPI Vasodilator MPI
> 1 mm resting ST depression, WPW, LVH, digoxin	Exercise echo* Exercise MPI*	Dobutamine echo Dobutamine MPI Vasodilator MPI
LBBB	N/A	Vasodilator MPI* Dobutamine echo
Pacemaker	N/A	Vasodilator MPI

* = preferred. Vasodilators = adenosine, dipyridamole, regadenoson.
Vasodilator used if patient has previous V-tach or severe HTN.
Vasodilator not used if patient has asthma or severe carotid stenosis; instead, use dobutamine.

CARDIAC SCANS / CATHS

Contrast Cardiac Catheterization

Coronary angiography is the gold standard for the diagnosis of coronary artery disease (CAD); ventriculograms and aortic root angiography can be done at the same time as the coronary angiogram.

Not only can contrast cardiac catheterization assess coronary anatomy through contrast ventriculography, it also can assess ejection fraction, wall motion abnormalities, ventricular dilatation, degree of mitral regurgitation, and the presence of a ventricular aneurysm. Cardiac catheterization is an invasive procedure with ~ 1% risk of serious complications (death, MI, stroke, arrhythmia, renal failure, bleeding).

These studies all involve arterial access, radiation, and contrast exposure.

Cardiac CT

Cardiac CT is a newer, noninvasive modality for imaging the heart. Cardiac CT includes:

- Coronary computed tomographic angiography (CTA)
- Coronary artery calcium (CAC) scoring
- Assessment of ventricular structure and systolic function

CTA requires IV contrast (check Cr!); also, the heart rate must be < 60 bpm and regular, and patients must be able to hold their breath.

CTA is a reasonable diagnostic test for symptomatic patients who are at intermediate risk for CAD after initial risk stratification, including patients with equivocal stress test results. It should not be used in asymptomatic patients or in symptomatic patients with very low or high probability for CAD. The negative predictive value of CTA is very high; that is, a negative CTA is very helpful in excluding significant coronary artery disease. Usefulness is reduced in patients with pronounced coronary calcification.

CTA is an excellent test for evaluation of patients with congenital coronary anomalies.

CAC (coronary artery calcium) scanning detects atherosclerosis and, unlike CTA, does not require IV contrast. CAC is used for further risk stratification in asymptomatic, intermediate-risk patients. A CAC score of zero is considered low risk for CAD, and > 400 indicates an elevated (~ 3-fold) risk for CAD.

A noncontrasted chest CT (which differs from a dedicated cardiac CT) is highly effective in assessing for pericardial thickening if constriction is a concern.

Keep in mind that all forms of cardiac CT involve radiation exposure.

Cardiac MRI

Static and dynamic cardiac MRI (CMRI) allows high-resolution imaging of ventricular function, valvular motion, and myocardial perfusion.

CMRI is useful to assess cardiac structure and function, valvular heart disease, coronary takeoff, the great vessels, pericardial disease, cardiac masses, myocarditis, and infiltrative diseases.

CMRI also can be used to assess for myocardial ischemia and post-MI tissue viability.

Cardiac MRI involves the use of gadolinium, which should be avoided in patients with advanced renal failure due to the risk of nephrogenic systemic fibrosis.

PULMONARY ARTERY CATHETERIZATION

Pulmonary artery catheterization (PAC) can be used to assess right and left filling pressures, cardiac output, RV and PA pressures, and systemic and pulmonary vascular resistance. This is useful to determine a patient's volume status, causes of shock, and existence of pericardial disease.

The pulmonary capillary wedge pressure (PCWP) is the dampened LA pressure that reflects left ventricular end-diastolic pressure (LVEDP) in most cases. This reflects LVED volume. Know this entire topic!

Normal pressures (mmHg):

- RA < 7, RV = 30/7, PCWP < 12.
- Jugular venous distension in the upright patient indicates an elevated RA pressure > 7 cm H_2O (5 mmHg).
- PCWP increases with LV systolic and diastolic failure, mitral stenosis, aortic and mitral insufficiency, tamponade, and constrictive pericarditis. Consider LV failure if the PCWP is > 15–18; PCWP 15–25 causes dyspnea on exertion (DOE); and PCWP 25–35 causes dyspnea at rest, orthopnea, and interstitial edema. Pressure > 35 (acutely) causes frank pulmonary edema.

Note: The RA pressure and PCWP also increase with decreased compliance of the ventricle (as in LVH and right ventricular hypertrophy [RVH]).

A few PAC scenarios are shown in Table 5-2:

1) Normal: Notice in the examples that the diastolic PA pressure is typically very close to PCWP (usual difference < 5) except in #6, in which there is pulmonary hypertension!
2) Diastolic pressure in all 4 chambers is equalized in both pericardial tamponade and constrictive pericarditis. See the Pericardial Diseases discussion for the tests that differentiate between these disorders (page 5-55).
3) If the cardiac output and PCWP are decreased and the RA pressure is elevated in the setting of an acute inferior MI, the cause is RV infarction with secondary right-sided failure. The RV has decompensated and is unable to fill the left side of the heart. Treatment is to give fluid until the blood pressure returns to normal. This sounds like stressing an already stressed RV—and it is—but there is a net positive effect when BP and, hence, coronary artery blood flow are returned to normal and heart rate is reduced. Think of this in a hypotensive patient with an inferior infarction and raised jugular venous pressure (JVP). Do not give preload-reducing agents such as nitroglycerin because cardiac output depends on adequate preload in the setting of an RV infarct.
4) If the cardiac output is low, PCWP high, and RA pressure high, the patient has biventricular failure with cardiogenic shock. Treatment is to give diuretics, preload and afterload reducers, and inotropes. In a typical case, a patient gets nitroprusside, nitroglycerin, milrinone, or dobutamine.
5) Mitral stenosis (or LV failure) with 2° RV failure.
6) Pulmonary hypertension.

Also know that septic shock is mainly due to a low systemic vascular resistance. These patients have low BP, systemic vascular resistance (SVR), and PCWP—and a high CO.

CARDIAC BIOPSY

Endomyocardial biopsy is used to evaluate the cause of a cardiomyopathy or myocarditis in patients where the diagnosis is uncertain and would change management, or if the patient is not responding to therapy. Monitoring cardiac transplant rejection is the major indication for endomyocardial biopsy. It also can be considered in patients with rapidly progressive heart failure or worsening ventricular dysfunction that persists despite appropriate medical therapy, and in patients suspected of having myocarditis (particularly giant cell myocarditis) or a myocardial infiltrative process (particularly amyloidosis).

Table 5-2: Pulmonary Artery Catheterization Scenarios

	RA Press	PA Press	PCWP	BP
1 (normal)	0–5	(13–28)/ (3–13)	3–11	110/70
2	18	32/18	19	70/50
3	15	21/11	10	70/50
4	18	30/20	20	70/50
5	18	90/32	30	110/70
6	18	90/32	10	110/70

QuickQuiz

- When is PCWP increased?
- When is diastolic pressure equal in all 4 chambers?
- Name 1 indication for doing endomyocardial biopsy.
- True or false? Pulsus paradoxus can be seen in cardiac tamponade.
- What is pulsus bisferiens? What does it indicate?
- What does pulsus alternans indicate?
- True or false? Sustained handgrip increases the murmur of mitral valve prolapse, but decreases the murmur of HCM.

The sensitivity of endomyocardial biopsy in many conditions that affect the heart focally is relatively low, so a "negative" biopsy is not as helpful as a "positive" one.

PHYSICAL EXAM

Note

Know this physical exam topic perfectly! You should know normal findings as well! Consider this whole topic highlighted!

Pulses

Pulsus paradoxus (decreased pulse amplitude with inspiration seen as absence of Korotkoff sounds during inspiration) can be observed clinically by auscultating the BP and listening for an exaggeration of the normal inspiratory decrease in systolic BP (> 10 mmHg). It is present with:

- cardiac tamponade (especially),
- constrictive pericarditis,
- asthma, and
- tension pneumothorax.

Note: Korotkoff sounds are those heard during blood pressure determination with a cuff.

The paradox is that, when severe, you can hear a heartbeat but not feel a pulse during inspiration.

Pulsus bisferiens (bifid with 2 systolic peaks per cardiac cycle) is seen with aortic regurgitation (with or without stenosis!) and hypertrophic cardiomyopathy (HCM, page 5-48).

Pulsus alternans (varying pulse pressure with a regular pulse rate) is seen with severely depressed systolic function of any cause that leads to decreased stroke volume.

Pulsus parvus et tardus (parvus—low amplitude, tardus—slow upswing) = aortic stenosis.

Brachiofemoral delay, the femoral pulse occurring after the brachial pulse, is present in coarctation of the aorta.

Pulse asymmetry occurs in aortic dissection, with good upper-extremity pulses and diminished or absent lower-extremity pulses, or the asymmetry occurs between the left and right extremities.

Peripheral arterial disease ([PAD]; previously called peripheral vascular disease [PVD]) can cause decreased or absent peripheral pulses; a bruit may be heard over the more proximal artery (such as the femoral artery) as well.

Heart Sounds and Murmurs

Heart sounds and murmurs: Again, know this topic! Know the differentiating maneuvers in Table 5-3 and the heart sounds tables in the Valvular Heart Disease discussion (Table 5-10 and Table 5-11 on page 5-34 and page 5-35). Learn these topics so you can determine how one abnormal finding (e.g., a particular heart sound) suggests certain findings on ECG and chest x-ray.

Murmurs

All valve murmurs increase in intensity when blood flow increases across the valve. Standing and the strain phase of Valsalva decrease right and left cardiac filling and cause the sound of most murmurs to decrease, but these actions increase the intensity of the murmurs of mitral valve prolapse (MVP) and hypertrophic cardiomyopathy (HCM). Squatting and lying down (or passive straight-leg raises if already supine) increase cardiac volume. This increased volume and afterload also increases intensity of all murmurs except, again, MVP (page 5-36) and and HCM (page 5-48).

Sustained handgrip (20–30 seconds) boosts systemic vascular resistance and left ventricular volume, and therefore decreases the murmurs of HCM and aortic stenosis (AS). It prolongs the murmur of MVP due to earlier prolapse of the valve; thus, it helps differentiate between HCM and MVP. Typically, use handgrip to differentiate between AS (murmur decreases) and MVP (murmur increases in duration).

Right-sided murmurs and heart sounds are louder during inspiration and any maneuvers that increase venous return, such as passive leg raising and abdominal compression. Left-sided murmurs and heart sounds are louder during expiration. The only semi-exception to this rule is a right-sided ejection click due to pulmonic stenosis; this disappears with inspiration. (On a chest x-ray, pulmonic stenosis can appear as an enlarged pulmonary artery.)

Heart Sounds

S_1 is caused by the closing of the mitral and tricuspid valves. S_1 intensity is decreased when there is

a prolonged PR interval, mitral regurgitation, acute aortic regurgitation (increased LV pressures cause early valve closure), or with a severely calcified mitral valve.

S_1 intensity is increased (i.e., the mitral valve slams shut) by a short PR interval, mitral stenosis, or hyperdynamic ventricular function.

S_2 is caused by the closing of the aortic (A_2) and pulmonic (P_2) valves at the end of systole. P_2 usually occurs just after A_2; this physiologic split is increased with inspiration, because the increased volume of blood in the right ventricle prolongs RV systole and delays closure of the pulmonic valve. It generally disappears on expiration.

A persistently (or widely) split S_2 can vary with respiration but does not disappear on expiration. A widely split S_2 that varies with inspiration (but never completely disappears) can be due to pulmonic stenosis, acute pulmonary embolism, ectopic or pacemaker beats originating in the left ventricle, or right bundle-branch block (RBBB)—all of which cause delayed or prolonged contraction of the right ventricle. A widely split S_2 can also be caused by early closure of the aortic valve, as in mitral regurgitation. Pulmonic stenosis is especially likely if the patient has an ejection click that disappears with inspiration.

You hear a fixed split S_2 when there is an atrial septal defect. The patient presents with a fixed, split-second heart sound, a systolic ejection murmur (SEM), and has pulmonary vascular congestion on the chest x-ray. You can also hear a fixed split S_2 with RV failure when the stroke volume is unable to increase with inspiration.

A delay of aortic closure (A_2) causes a paradoxically split S_2, with P_2 occurring before A_2. In this case you hear increased splitting with expiration instead of

Table 5-3: Maneuvers to Differentiate Murmurs

Maneuver	Result
Passive straight-leg raise (to 45 degrees, listen after 15 sec)	Increases venous return
Valsalva (hold for 20 sec, listen just before end)	Decreases venous return
Standing (squat for > 30 sec then quickly stand; listen during first 15 sec after standing)	Decreases venous return
Transient arterial occlusion (bp cuff on both arms, inflated > 20 mm above systolic pressure)	Increases systemic vascular resistance
Handgrip (isomeric; listen at end of 1 min max grip)	Increases systemic vascular resistance
Squatting	Increases venous return and increases systemic vascular resistance, but preload effect is stronger than afterload effect
Maneuvers for increasing/decreasing specific systolic murmurs	
For HCM use	**Result**
Standing (from squat)	95% get increased murmur
Valsalva (if cannot do squat-to-stand)	65% get increased murmur
Passive straight-leg raise	85% get decreased murmur
Handgrip	85% get decreased murmur
For MVP use	**Result**
Standing and Valsalva	Click-murmur moves earlier
Transient arterial occlusion	In 80%, click-murmur moves later
Handgrip	In 70%, click-murmur moves later
For VSD use	**Result**
Standing and Valsalva	Murmur decreased
Transient arterial occlusion	80% get increased murmur
Handgrip	70% get increased murmur
For AS use	**Result**
Transient arterial occlusion	Murmur decreased
Handgrip	Murmur decreased

QuickQuiz

- When is a persistently split S_2 heard?
- What causes a paradoxically split S_2?
- When is an S_3 important?
- When are large *v* waves seen on the left side? Right side?
- When is rapid *x* and *y* descent seen?
- When are large, right-sided *a* waves seen?
- When are large, left-sided *a* waves seen?
- When are "cannon" *a* waves seen?
- When does a slow *y* descent occur?

inspiration. This delay is commonly caused by LBBB and ectopic or pacemaker beats originating in the right ventricle. Advanced HCM is another cause.

S_3 just follows S_2 and indicates the end of rapid ventricular filling (sounds like lub-dub-huh); this is the first part of diastole, when the first 70% of ventricular filling occurs as the ventricle relaxes. The sound is thought to be due to the tensing of the chordae tendineae. You often hear it in normal children and in persons with high cardiac output, such as pregnant women, but it is typically an abnormal finding in patients > 40 years of age. In these patients, it can be from any condition that increases early LV filling rate or volume, such as acute ventricular decompensation or severe aortic or mitral regurgitation. S_3 in a patient with known left ventricular dysfunction is a poor prognostic indicator—in general, as well as for surgery. Both S_3 and S_4 are best heard in left lateral decubitus position using the bell.

S_4 is heard just before S_1 at the end of diastole (sounds like huh-lub-dub). The S_4 sound is caused by ventricular filling during atrial contraction, and you hear it in patients with decreased ventricular compliance. Increased stiffness of the ventricles causes forceful atrial contraction and causes S_4. You may hear S_4 in ischemic heart disease, aortic stenosis, hypertrophic cardiomyopathy, diabetic cardiomyopathy, and hypertensive heart disease with concentric hypertrophy. You do not hear an S_4 during atrial fibrillation because the sound requires atrial contraction. S_4 also is not audible in mitral stenosis, where there is obstruction of the ventricular inflow.

Venous Waveforms

Venous waveforms: Jugular venous pressure and waveforms are typically examined on the right side of the neck (Figure 5-1). [Know these!] See Table 5-4.

- Large, right-sided *v* waves are seen in ventricular septal rupture and tricuspid regurgitation.
- With severe mitral regurgitation, there are tall, left-sided *v* waves from the regurgitation during systole. Note that left-sided waves are not seen on the JVP but on Swan-Ganz monitoring.
- Rapid *x* and *y* descents are seen with constrictive pericarditis, whereas only a rapid *x* descent is seen in tamponade (loss of the *y* descent).
- Large, right-sided *a* waves are seen in tricuspid stenosis (TS), severe pulmonic stenosis, and severe noncompliant RVH.
- Large, left-sided *a* waves are seen with mitral stenosis (MS).
- "Cannon" *a* waves occur in complete heart block, ventricular tachycardia, or asynchronous ventricular pacing and all conditions with AV dissociation (times when the atrium is contracting against a closed tricuspid valve).
- Slow *y* descent is from delayed atrial emptying as in tricuspid stenosis.

Also see Table 5-10 on page 5-34 for a review of the valve disorders.

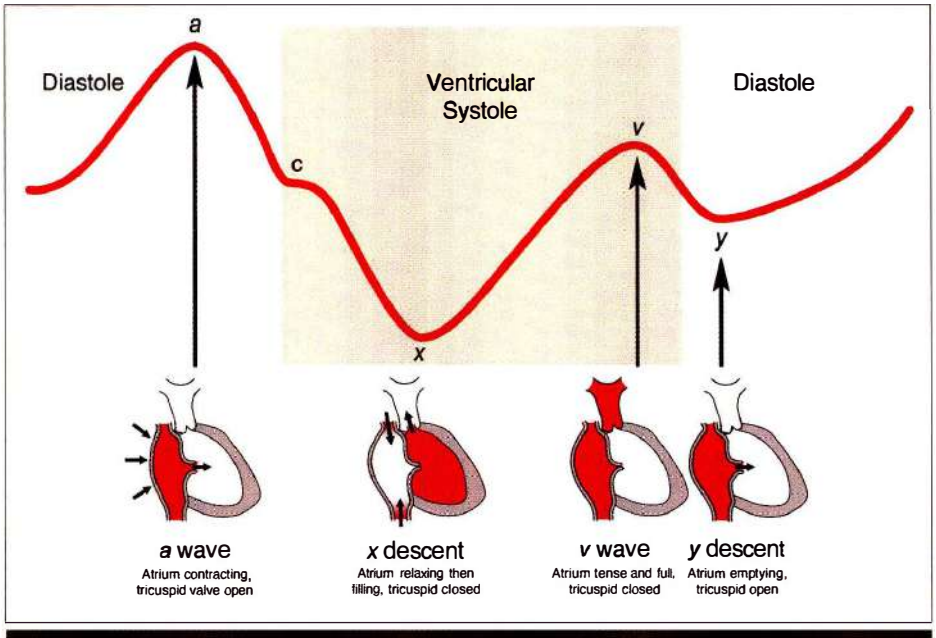


Figure 5-1: Jugular Venous Pulse

Table 5-4: Venous Waveforms in a Clinical Setting

Condition	Neck Vein Appearance	Other Diagnostic Features
Pulmonary HTN	Elevated *a* and *v* waves	Other physical exam findings of pulmonary HTN
Tricuspid regurgitation	Large *v* waves	TR murmur, pulsatile liver
Constrictive pericarditis	Rapid *x* and *y* descents	Kussmaul sign, pericardial knock
Tamponade	Rapid *x* descent	Pulsus paradoxus, hypotension
Tricuspid stenosis	Slow *y* descent	TS murmur
Restrictive cardiomyopathy	Rapid *x* and *y* descents	Low-voltage ECG, echo, myocardial biopsy
Tension pneumothorax	Distended neck veins	Dyspnea, unilateral absent breath sounds, deviated trachea, chest x-ray
Superior vena cava syndrome	Unilateral distended neck veins	Facial edema and cyanosis, diagnosis of cancer
AV dissociation	Irregular cannon *a* waves	ECG
RV infarction	Elevated *a* and *v* wave	Acute inferior MI, Kussmaul sign
ASD	Large *v* waves and rapid *y* descent	Fixed split S_2, echo

HYPERTENSION

Suspect secondary causes of hypertension (HTN) in patients who develop HTN before age 30 years, who have drug-resistant HTN, or who develop uncontrolled HTN that was previously well controlled.

Systolic abdominal bruits (without a diastolic bruit) suggest renal vascular hypertension. Bilateral renal artery stenosis (RAS) can lead to severe exacerbation of hypertension and decline in renal function with initiation of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs). Noninvasive tests to diagnose RAS include duplex ultrasonography, CTA (in individuals with normal renal function), and magnetic resonance angiography (MRA). When clinical suspicion is high and results of noninvasive tests are inconclusive, catheter angiography is recommended to diagnose RAS.

Think of primary hyperaldosteronism in a hypertensive patient with hypokalemia and low renin.

Think of pheochromocytoma in a hypertensive with recurrent and intermittent episodes of severe hypertension, frequently accompanied by palpitations and severe apprehension.

Much more on hypertension in Nephrology, Book 2.

CARDIAC MEDICATIONS

Refer to Table 5-5 for an overview and comparison of commonly used cardiac medications. Pay attention to those that prolong survival!

CARDIAC ISCHEMIA

OVERVIEW

Angina is chest pain caused by a "supply-demand" mismatch between coronary perfusion and cardiac workload. It is typically classified as either stable or unstable (pain at rest, new onset or increased frequency).

Obstructive atherosclerotic coronary artery lesions (supply problem) are the most common cause of stable angina (Image 5-5). Plaque rupture or erosion with superimposed thrombus is the most common underlying process triggering acute coronary syndrome (ACS).

There are many causes of increased demand (e.g., tachycardia, fever, and thyrotoxicosis) and many other causes of a decreased supply (e.g., hypotension, coronary vasospasm, anemia, and hypoxia). Coronary blood flow can be impaired in conditions such as severe aortic valve disease with left ventricular hypertrophy (LVH), hypertension, idiopathic dilated cardiomyopathy, and hypertrophic cardiomyopathy, even in the absence of epicardial CAD.

Note: Only ~ 20% of patients actually have classic angina at the moment of ischemic ST changes. Silent myocardial ischemia is painless but just as harmful as angina-associated ischemia. Silent ischemia is seen frequently in diabetic patients as well as those with prior ischemic events. Silent ischemia, myocardial infarctions, and thrombotic strokes tend to occur in a circadian pattern, with the highest incidence in the early morning hours.

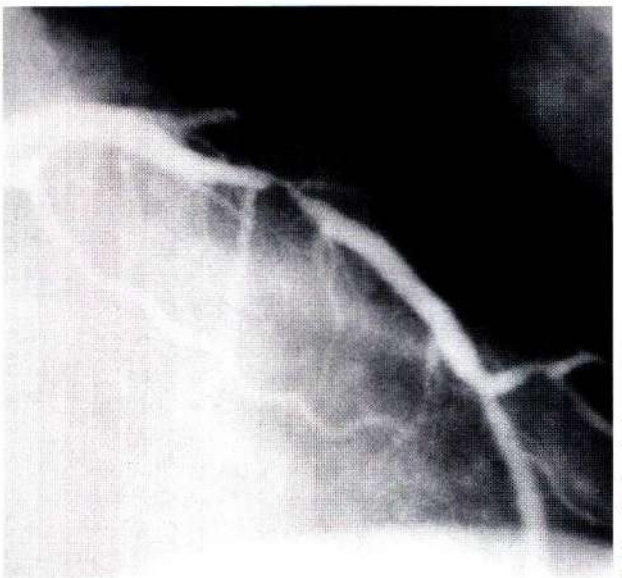
The distinction between stable and unstable angina is a key factor in determining management/diagnostic strategies. Short- and long-term risk (death and MI) in patients with acute coronary syndrome is much higher

Quick Quiz

- True or false? A systolic abdominal bruit without a diastolic bruit suggests renal vascular hypertension.
- What time of day does the highest incidence of spontaneous ischemic cardiac events occur?

than in patients with stable angina, and therefore patients with ACS warrant emergent medical attention, inpatient management, and, much more commonly, revascularization. (See Acute Coronary Syndrome on page 5-14.) Stable angina, on the other hand, is generally evaluated in the outpatient setting and symptoms are often managed medically.

The most important, easily determinable prognostic factor in patients with coronary artery disease is the degree of LV dysfunction. (If severe, it can be a reflection of multi-vessel or left main/left main-equivalent disease.)



Hank Morgan/Photo Researchers, Inc.

Image 5-5: Angiogram showing narrowing in coronary artery.

Table 5-5: Common Cardiac Medications

Medication	Negative Inotrope	Negative Chrono-trope	Negative Dromo-trope	Vaso-dilator	Anti-anginal	Prolong Survival Post-MI	Prolong Survival in HF	Indications
Digoxin	N	+	+	N	N	N	N	Systolic HF, arrhythmias
Beta-blockers	+++	+++	+++	N	Y	Y	Y	HTN, angina, HF, arrhyth-mias
Carvedilol	++	+++	+++	Y	Y	Y	Y	HTN, angina, HF, arrhyth-mias
Nifedipine	++	N	N	Y	Y	N	N	HTN, angina
Amlodipine	+	N	N	Y	Y	N	Y (in DCM)	HTN, angina, DCM
Diltiazem	++	++	++	Y	Y	N	N	HTN, angina, arrhythmias
Verapamil	+++	+++	+++	Y	Y	N	N	HTN, angina, arrhythmias
Nitrates	N	N	N	Y	Y	N	Y (with hydralazine)	Angina, HF
ACEIs	N	N	N	Y	N	Y	Y	HTN, HF
ARBs	N	N	N	Y	N	Y	Y	HTN, HF
Hydralazine	N	N	N	Y	N	N	Y (with nitrates)	HTN, HF
Spironolac-tone	N	N	N	N	N	N	Y	HTN, HF
Eplerenone	N	N	N	N	N	Y (w/HF)	Y (p MI)	HF post MI

Table 5-6: Bruce Protocol

Stage	Min	% Grade	MPH	METs
1	3	10	1.7	4.7
2	6	12	2.5	7.0
3	9	14	3.4	10.1
4	12	16	4.2	12.9
5	15	18	5.0	15.0

The exercise tolerance test is an excellent, objective way to determine the severity of angina and to determine prognosis. Patients who are able to go to stage 4 of Bruce protocol (Table 5-6) have a nearly 100% 5-year survival, while those who cannot get past stage 1 have only a 50% 5-year survival! Note that coronary angiography is not required for the determination of either of these prognostic factors!

Spasms of the coronary arteries usually show up as transient ST-segment elevation if they occur during stress testing.

What causes resting ST-segment elevation? Acute MI, pericarditis, LV aneurysm, LBBB, ventricular pacing, LVH, and benign early repolarization.

Hibernating myocardium is chronically underperfused myocardium. There is no irreversible myocyte injury. When perfusion is restored to normal, contractility should return to normal.

Reperfusion injury occurs when a severely ischemic myocardium is reperfused after ~ 1 hour, causing further irreversible microvascular damage and damage to the myocardial cells.

Stunned myocardium is also the result of acute ischemia. From the time perfusion is restored, it can take 7–10 days for the ventricular function to return to normal.

Treatment of all angina: Modify risk factors and correct aggravating factors such as anemia, hypertension, smoking, drug abuse, and noncompliance. (Good luck!)

ANTI-ANGINAL DRUGS

Beta-blockers and **nitrates** are the staples of medical treatment, but **calcium channel blockers** can also help. Nifedipine and amlodipine decrease angina by both coronary artery vasodilation and peripheral vasodilation (decreases workload). The main anti-anginal effect of diltiazem and verapamil is due to their negative chronotropic effect.

ASA decreases mortality and MI occurrence in unstable (and probably stable) angina. Use clopidogrel (Plavix®) in patients who cannot tolerate or are allergic to ASA or who have an indication to take this in addition to ASA.

Ranolazine (Ranexa®) may also have a role in some patients with persistent angina on maximal standard therapy, or as a substitute for beta-blockers. It is thought to work by inhibiting the late sodium current in cardiac myocytes, thereby reducing sodium and calcium overload that follows ischemia. This improves myocardial relaxation and reduces left ventricular diastolic stiffness, which in turn enhances myocardial contractility and perfusion.

More on anti-anginal drugs:

- Nitrates, beta-blockers, and calcium channel blockers all decrease myocardial O_2 demand, and all decrease afterload.
- Nitrates decrease preload more than afterload and also dilate coronary vessels. Acute preload reduction is why nitrates can cause severe decompensation in patients with an acute right ventricular MI. (Remember, do not give nitrates during acute RV infarct.) Patients on nitrates get a sympathetic reflex increase in heart rate (HR). Nitrates are degraded in the liver. Tolerance develops rapidly with nitrates (tachyphylaxis), but you can avoid tolerance by having a 6-hour "nitrate-free window" once a day; i.e., between midnight and 6 a.m. Development of tolerance is less likely with mononitrates than with dinitrates.
- Beta-blockers decrease myocardial O_2 demand by decreasing HR, blood pressure (BP), and contractility. Beta-blockers complement nitrates well because they decrease the reflex tachycardia.
- Calcium antagonists: The combined vasodilatory and antihypertensive effects make them ideal for patients with angina/ischemia and hypertension. See Table 5-5. Verapamil and diltiazem should be used cautiously, if at all, in patients with systolic heart failure due to the negative inotropic effects. Short-acting nifedipine is contraindicated due to steep drops in BP and reflex tachycardia.
- There is a high probability of coronary thrombus formation with unstable angina, so always use either IV heparin or subcutaneous low-molecular-weight heparin (LMWH) if there are no contraindications.

The following are now recommended concomitantly with heparin and for follow-up medical therapy for unstable angina:

- Aspirin daily for life
- Clopidogrel x 1 month and ideally up to a year (particularly if a stent is placed)

EVALUATION OF CHRONIC STABLE ANGINA

Note

The following is drawn from the 2012 ACC/AHA guidelines. First and foremost is the involvement by an informed patient: Choices about diagnostic and therapeutic options should be made through a process of shared decision making involving the patient and physician, with the physician explaining information about risks, benefits, and costs to the patient.

Quick Quiz

- What does ST-segment elevation suggest on an exercise ECG stress test?
- What are causes of resting ST-segment elevation?
- Explain the similarities and differences between hibernating myocardium, reperfusion injury, and stunned myocardium.
- What are the main drugs used to treat angina?
- Which patient might ranolazine (Ranexa®) benefit?
- Which anti-anginal drugs decrease myocardial oxygen demand?
- Which anti-anginal drugs decrease afterload?
- Which anti-anginal drugs decrease preload?
- What anti-anginal drug do you not give to a patient with RV infarct? Why?
- Why should you determine the probability of CAD in a person with intermittent chest pain?
- For which patient with chronic stable angina do you do an echocardiogram? Why?
- A patient undergoing a workup for chronic stable angina is determined to be at high risk for death. What is the next step?

Evaluation of a patient with chest pain is a 3-step process:

1) Determine the probability of CAD.
2) Noninvasive testing for diagnosis and risk stratification.
3) Additional workup based on estimated risk.

1. History and Physical Exam: Determine Probability of CAD

First assess the probability of coronary artery disease (CAD). Factors used in the assessment include type of chest pain (typical, atypical, nonanginal), age, gender, risk factors (particularly diabetes mellitus, smoking, and hypertension), and ECG abnormalities (Q waves and ST abnormalities). This step is very important because it determines pretest probability for the rest of the tests, which improves the positive and negative predictive values of these tests.

After other causes of chest pain are ruled out, determine the following:

- Typical vs. atypical chest pain is determined by assessing quality, location, and duration of the chest pain. Also, what precipitates or relieves the pain?
- Cardiovascular risk factors: especially DM, HTN, smoking, hyperlipidemia, family history of CAD, and postmenopausal status in women. History of substance abuse must be obtained. Cocaine can accelerate atherosclerosis, enhance platelet aggregation, cause vasospasm, and increase myocardial oxygen demand.
- The following comorbid conditions can precipitate symptoms in the presence of coronary obstruction or, when severe, cause angina in the absence of coronary obstruction by:
  - Increasing cardiac demand: hyperthyroidism, cocaine use, severe uncontrolled HTN, significant valvular disorder, aortic stenosis, or HCM
  - Decreasing myocardial oxygen supply: anemia, hypoxemia, and increased blood viscosity

From the above, determine if the patient has high, intermediate, or low probability of CAD. Low probability needs no further testing. Those with intermediate or high probability of CAD should undergo "risk stratification" with further testing (discussed next).

2. Noninvasive Tests for Chronic Stable Angina: Diagnosis and Risk Stratification

ECG: especially for checking ST-T wave changes that suggest ischemia, Q waves, and LVH. Other findings (e.g., RBBB, LBBB, atrial fibrillation, bifascicular block) are not specific indicators of CAD.

Chest x-ray is done only if there are signs of heart failure (HF), valvular disorders, or pericardial disease.

Exercise testing is the most important test in risk stratification. See Table 5-1 on page 5-5 to review how to pick the best stress test for your patient. And remember, for those who can exercise, do exercise testing for all with stable angina.

Exercise capacity is one of the stronger indicators of long-term risk. For this reason, it is preferable to perform exercise stress if the patient is able to achieve maximal workload. In addition, exercise can provide a higher physiological stress than would be achieved by pharmacological testing.

Assess LV systolic function (generally with echo) only in patients with prior MI, pathological Q waves, symptoms or signs suggestive of heart failure, arrhythmias, or heart murmur.

If the test results won't change management (severe comorbid conditions that preclude possibility of revascularization or patient does not want revascularization), do not order.

3. Determination of Further Workup in Chronic Stable Angina

Based on stress test results, determine the probability of death or MI and stratify patient into a high-risk (> 3%/year), intermediate-risk (1–3%/year), or low-risk group (< 1%/year). Patients with high risk should be referred for coronary angiogram. Patients with low or intermediate risk should be treated with medical

therapy to improve symptoms and function, and further workup can be deferred if symptoms can be controlled with medical therapy.

Low-risk patient: low-risk Duke treadmill score (≥ 5) indicating good exercise capacity with no signs of significant ischemia, normal stress echo, or normal or small myocardial perfusion defect.

High-risk patient: high-risk Duke treadmill score (≤ –10), inducible wall motion abnormalities > 2 segments on stress echo, stress induced perfusion abnormalities ≥ 10% of myocardium on MPI, or severely reduced left ventricle (LV) systolic function.

If a patient has an **intermediate-risk** treadmill score (score between –10 and +5), stress imaging should be considered to further assess risk. Again, stress testing is not as useful for low-risk (false positives) and high-risk patients (false negatives).

TREATMENT OF CHRONIC STABLE ANGINA

Objectives of treatment of chronic stable angina include reduction of premature cardiovascular death, prevention of complications including MI and heart failure, complete or near complete elimination of symptoms, and improvement of functional capacity and quality of life.

Medical therapy to prevent MI and death:

- Antiplatelet therapy: aspirin (clopidogrel if aspirin is contraindicated)
- High-dose statin
- Beta-blockers (if left ventricular ejection fraction [LVEF] < 40% or prior MI)
- ACE inhibitors (if LVEF < 40%, DM, HTN, or CKD)

Medical therapy for relief of symptoms:

- Beta-blockers as initial therapy.
- Prescribe calcium channel blockers or long-acting nitrates when beta-blockers cannot be used, or in combination with beta-blockers when beta-blockers are not sufficient.
- Ranolazine in combination with beta-blockers.

High-risk patients and patients with low or intermediate risk who remain significantly symptomatic should be referred for coronary angiogram to define coronary anatomy.

Compilation of all recommendations:

- Diet: Limit saturated fats (to < 7% of total calories), eliminate trans fats, and limit cholesterol intake (to < 200 mg/d).
- Physical activity: 30–60 min/d of moderate-intensity aerobic activity for 5–7 d/wk.
- Stepwise strategy smoking cessation (ask, advise, assess, assist, arrange, avoid), avoidance of exposure to environmental tobacco smoke.
- Weight loss.
- Blood pressure management (goal < 140/90): ACEI/ARB and/or add thiazide diuretics or calcium channel blockers if needed to obtain goal BP.
- Influenza vaccine annually.
- Statin in all patients (if no contraindications/ adverse effects).
- Antiplatelet therapy: aspirin 75–162 mg/d indefinitely; clopidogrel when aspirin is contraindicated.
- Beta-blockers: started and continued for 3 years in all patients with normal LV function. Continue indefinitely if LVEF < 40%. Use carvedilol, metoprolol succinate, or bisoprolol in all patients with LVEF < 40%, unless contraindicated.
- ACEIs in all patients who also have hypertension, diabetes mellitus, LVEF < 40%, or chronic kidney disease, unless contraindicated (ARB if ACEI intolerant).

CARDIOVASCULAR DISEASE (CVD) PREVENTION IN WOMEN

A 2011 update of the AHA Guidelines for CVD Prevention in Women warns that:

- Hormone therapy should not be used as primary or secondary prevention.
- Antioxidants (i.e., vitamin C, E, beta-carotene) should not be used as primary or secondary prevention.
- Folic acid or vitamin B_6 should not be used.
- Garlic, coenzyme Q10, selenium, or chromium should not be used.
- Do not use aspirin in healthy women < 65 years of age for primary prevention of MI. (Aspirin is okay for those ≥ 65.)

ACUTE CORONARY SYNDROME

CLASSIFICATION OF ACS

This is another area from which many exam questions are drawn. [Know this well!]

Acute coronary syndrome (ACS) is generally caused by atherosclerotic plaque rupture, fissuring, erosion, or a combination with superimposed intracoronary thrombosis; results in acute ischemia; and is associated with an increased risk of cardiac death and myocardial infarction. Acute coronary syndrome is composed of 2 types:

1) Unstable angina (UA) or non-ST elevation
2) ST elevation

UA/non-ST elevation ACS includes unstable angina (UA) or non-ST elevation MIs (NSTEMIs). You will see these terms combined as UA/NSTEMI.

Quick Quiz

- Would you recommend aspirin in a healthy woman < 65 years old for primary prevention of MI?
- What are the 2 major categories of ACS?
- Name 1 group of patients that is more likely to present with MI without chest pain.
- How are troponin I and T used? How long do they stay elevated after an MI?

ST elevation ACS is ST elevation MIs (STEMIs).

Rarely, ACS can be due to occlusion by coronary emboli, congenital abnormalities, coronary spasm, and a wide variety of systemic inflammatory diseases.

Terms "Q wave" and "non-Q wave MI" are no longer used.

Patients with NSTEMIs have a smaller size of infarcted area and decreased early mortality compared to those with STEMIs, but a higher risk for persistent angina, reinfarction, and death within several months! This is due to the diffuse coronary disease more commonly seen in NSTEMI patients.

So, although NSTEMIs have a lower early mortality, they have a higher 6-month mortality compared to STEMIs. Also, know that patients with NSTEMIs are more likely than those with STEMIs to have had a prior MI or angina!

Differential diagnosis of prolonged chest pain includes: ACS (MI), aortic dissection, pericarditis, esophageal or biliary tract problems, pneumothorax, pulmonary embolism, pleuritic pain related to pneumonia, musculoskeletal inflammation, and psychogenic causes.

NOTES

15% of acute myocardial infarctions (AMIs) are asymptomatic.

MI without chest pain or with atypical chest pain is more common in the following:

- Elderly (about 2/3 of these patients > 75 years of age)
- Diabetics
- Women
- Those with prior CAD

Mitral regurgitation due to papillary muscle dysfunction is seen more commonly with inferior MIs.

Ventricular septal defect (VSD) from septal rupture is seen more commonly with anterior and inferior MIs.

Arrhythmias in the first 48 hours after MIs are due to acute ischemia (or are reperfusion-related) and do not imply a need for long-term antiarrhythmic therapy.

Inferior vs. anterior MI: Inferior MIs are associated with more stable arrhythmias, such as junctional escape and Mobitz 1, instead of the poorer prognosis with Mobitz 2 and bundle-branch blocks (BBBs), which are more often seen in anterior MIs. Even when Mobitz 2 or complete heart block is seen in an inferior MI, it is usually temporary. Also, the amount of infarcted myocardium is typically larger with anterior MIs. Unfortunately, septal rupture can occur in either type. (See Complications of Myocardial Infarction on page 5-22.)

MARKERS FOR AMI

Serum markers that increase in response to acute myocardial necrosis include troponins, creatine kinase myocardial bands (CKMBs), and myoglobin (Table 5-7).

[Know all of the following!]

Assays to detect components of cardiac muscle, troponin I and troponin T (cTnI and cTnT), are now the gold standard for the detection of myocardial necrosis. The level of either of these also has been shown to have prognostic implications in the setting of an acute MI. The 2 troponin assays are equally useful, and local preferences dictate which one is used.

Troponins first become elevated at 4 hours following an MI and peak at about 44 hours after the event. They can remain elevated for 10–14 days after an MI, which can muddy the picture in those suspected of having a recurrent MI—use myoglobin and/or CKMB instead (see below). On the other hand, because they do stay elevated so long, troponins are beneficial in the workup of those who present more than 24–48 hours after onset of symptoms.

Be aware that troponins can also be elevated in chronic renal failure, myopericarditis, HF, sepsis, pulmonary embolism, and cardiac trauma. In addition, troponins can be elevated with RV strain causing microvascular dysfunction. Although troponins are sensitive markers for acute myocardial infarctions (AMI), they are not highly specific; therefore, they are good for excluding AMI but not as good for confirming one. Sensitive but not specific.

CK and its isozyme **CKMB** have been the traditional markers of choice for myocardial necrosis. CK is a nonspecific marker of muscle injury (both skeletal and

Table 5-7: Acute Myocardial Infarction Markers

Marker	Initial Elevation	Peak Elevation	Return to Normal
Myoglobin	1–4 hr	6–7 hr	24 hr
Troponin I (rule of 4s!)	4 hr	44 hr	10–14 d
CKMB	3–12 hr	24 hr	2–3 d
CKMB isoform	2–6 hr	18 hr	2 d

myocardial), while CKMB is specific to myocardium. These become detectable at 3–12 hours following an MI event and peak at 24 hours. CKMB typically returns to normal range after 48–72 hours, earlier than the troponins.

Both CK and CKMB can be elevated due to non-MI causes, such as in rhabdomyolysis. The CKMB:total CK ratio can be useful to distinguish between cardiac and noncardiac sources of CK elevation—although this is not fully reliable in very severe cases of muscle injury.

Myoglobin is a very sensitive, but nonspecific, test for acute myocardial necrosis. It rises very rapidly, so a negative myoglobin in the first few hours is useful in ruling out an infarction (high negative predictive value). Because it is excreted quickly in the urine, myoglobin is also the quickest to return to normal—within 24 hours—so it can be potentially useful to help evaluate recurrent chest pain soon after an MI, when troponins and CKMB are still elevated. Because of its low specificity, it is not frequently used in clinical practice.

The most sensitive and specific markers now used are a combination of troponin I or T and CKMB.

With both the troponins and CKs, the overall trend is important and gives added information beyond a single elevated value ("trending enzymes"). An individual whose enzymes continue to rise is a very different patient from someone whose enzymes peaked earlier in the day, even in the absence of symptoms!

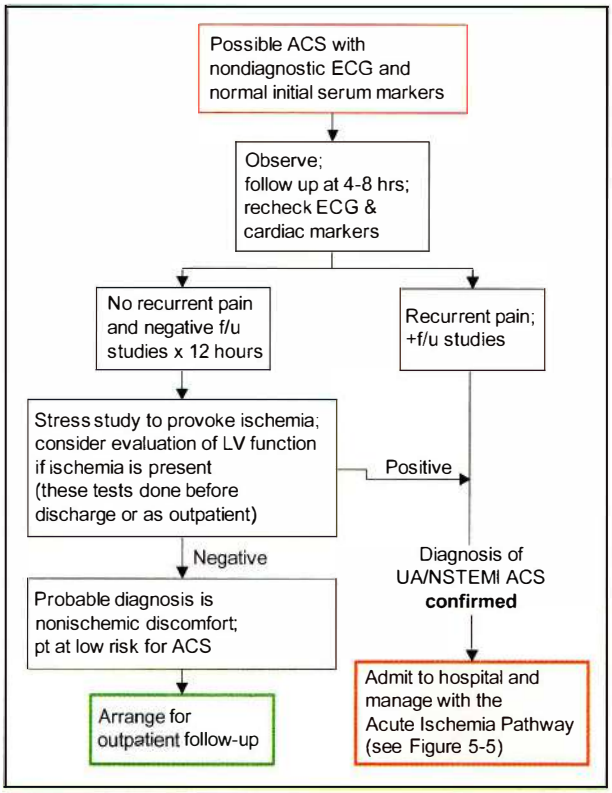


Figure 5-2: Diagnostic Pathway for Possible ACS

TREATMENT OF ACS

Overview

In general, the sequence to addressing acute coronary syndrome is to first take proper care of the patient prior to arrival in the emergency department. Once the patient arrives, do an assessment, do an ECG, and draw labs. Based on these results, determine if the patient with suggestive symptoms is actually having an ACS.

Figure 5-2 diagrams this process of determining if the patient has ACS.

Figure 5-3 diagrams the process of managing UA/NSTEMI ACS vs. ST-elevated ACS.

If the patient has definite ACS, pursue 1 of the following protocols:

- Acute Ischemia Treatment Pathway—UA/NSTEMI (Figure 5-4)
- Acute MI Treatment Pathway with STEMI or New LBBB (Figure 5-5 on page 5-21)

Now, let's go through these steps in more depth.

Prehospital Management

2013 ACC/AHA guidelines for chest pain:

- Call 911 and transport to hospital by ambulance (rather than friends/relatives): EMS can diagnose STEMI earlier with prehospital ECG and preferentially transport to PCI-capable hospital (shorter reperfusion times and lower mortality), and can treat cardiac arrest en route.
- Give nonenteric coated ASA (162–325 mg) as bite and chew x 1.
- Nitroglycerin (tablets or spray): If the drug is available, give only 1 dose, then:
  - Unimproved or worsening—give no more; call 911.
  - Improved—can repeat to max of 3 doses (at 3–5-minute intervals).

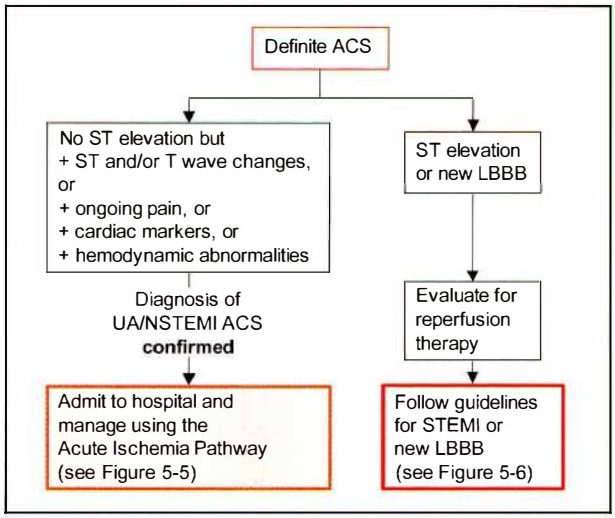


Figure 5-3: Initial Tx Pathway for Definite ACS

Quick Quiz

- What are the prehospital guidelines for chest pain?
- What are the major things you should do in early risk stratification of a patient who presents with ACS in the emergency department?
- Based on early risk stratification of ACS, to what 3 groups can a patient be assigned?

  - Note: If the patient has taken a phosphodiesterase-5 inhibitor (e.g., sildenafil or vardenafil) within 24 hours (48 hours for tadalafil), do not give nitroglycerin due to the risk of severe hypotension!
- ECG in the field by EMS.
- Be prepared to recognize and manage ventricular arrhythmias.

Evaluation of Patients with Symptoms Suggestive of ACS

Early evaluation: For patients who present to the emergency department with symptoms suggestive of ACS, immediately (within 10 minutes) get an ECG, draw blood for cardiac markers, give aspirin if not contraindicated, and conduct a directed history and physical examination.

High-risk features include all of the following:

- Ongoing chest pain for longer than 20 minutes
- Reversible ST-segment changes of at least 0.5 mm
- Elevated cardiac enzymes
- Signs of LV dysfunction

What happens next depends on the ECG:

- If the ECG is abnormal: Follow guidelines (see below).
- If the ECG is nondiagnostic: Repeat the ECG q 15–30 minutes or do continuous monitoring.

Note: An acute MI involving the left circumflex can still present as a nondiagnostic (or normal) 12-lead ECG; consider obtaining V7–V9 leads.

Based on this early assessment, assign patients to 1 of the following 3 groups in the ACC/AHA protocol:

1) Noncardiac chest pain or chronic stable angina: Treat accordingly.
2) Possible ACS with nondiagnostic ECG and normal initial serum markers (Figure 5-2): Observe at least 12 hours following symptom onset. If there is no recurrence of symptoms, a 2nd set of markers is negative, and an ECG is unchanged, perform further risk stratification with an appropriate stress test. Patients who have a negative or low-risk stress test can be discharged to home and followed as outpatients (green box in Figure 5-2). If the observed patients have recurrent symptoms, subsequent positive cardiac

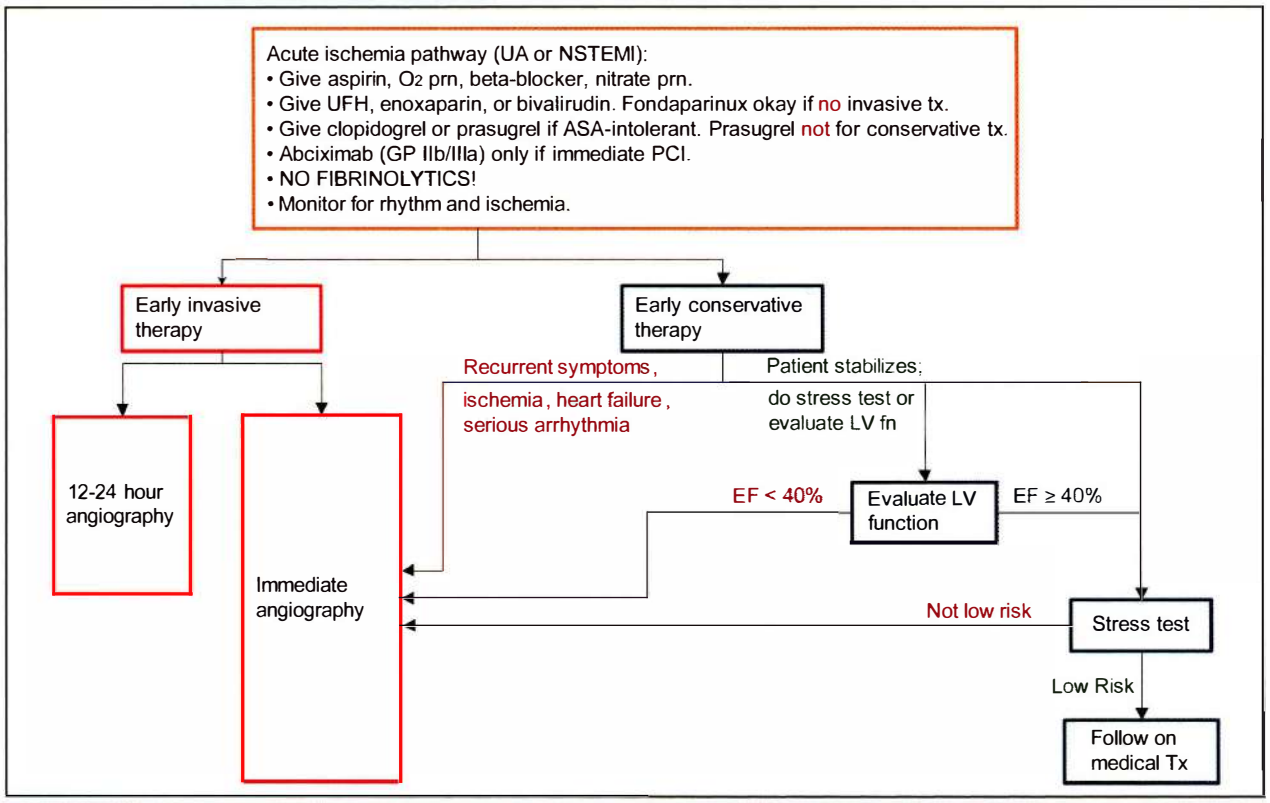


Figure 5-4: Acute Ischemia Treatment Pathway — UA or NSTEMI

markers, ECG changes, or a positive stress study, admit and manage according to the acute ischemia pathway (Figure 5-4).

3) Definitive ACS: immediately determine whether there is ST-segment elevation or new LBBB (Figure 5-3):
   - Patients without ST-segment elevation or new LBBB should be admitted and treated according to the acute ischemia protocol.
   - Patients with ST-segment elevation or new LBBB should be considered for emergent reperfusion therapy.

We will discuss each of these scenarios shortly, but first let's talk about general measures considered for all patients with ACS.

ACS: GENERAL MEASURES

ECG, NTG, Morphine, Beta-Blockers, ACEIs, Atropine

General anti-ischemic measures for all patients with ACS include:

- Continuous ECG monitoring
- Aspirin
- Sublingual nitroglycerin (NTG) spray x 3 prn for pain and IV NTG for continued ischemia or hypertension
- Morphine if pain is not relieved by NTG
- Oral beta-blocker and an ACEI if the patient is still hypertensive or has evidence of LV dysfunction (EF < 40%)

Supplemental oxygen should be administered to patients with UA/NSTEMI with an arterial saturation < 90%, respiratory distress, or other high-risk features for hypoxemia. (Pulse oximetry is useful for continuous measurement of S_aO_2.) It is reasonable to consider supplemental oxygen during the first 6 hours of any ACS; however, supplemental oxygen can increase coronary vascular resistance!

Note: Beta-blockers reduce myocardial O_2 consumption. Also, by blocking the often-excessive sympathetic activity, they reduce the load on the heart and decrease the likelihood of arrhythmias. Oral use is preferred.

Contraindications to beta-blockers include bradycardia, hypotension, 2nd or 3rd degree AV block, pulmonary edema, and asthma. Caution should be used in giving beta-blockers to patients with signs of acute heart failure. (See Beta-Blockers on page 5-52).

Non-dihydropyridine calcium channel blockers (verapamil or diltiazem) can be given if beta-blockers are contraindicated and the patient continues to have ischemia and hypertension but no LV dysfunction.

Atropine is indicated for the temporary management of acute sinus bradycardia with signs of low cardiac output while preparing for temporary pacing. Bradycardia associated with MI (usually inferior MI) may be temporary, and atropine alone may be sufficient.

Anticoagulant / Antiplatelet Therapy in ACS

Overview

Intense antiplatelet and parenteral anticoagulant therapy with multiple agents is a major treatment recommendation for ACS.

Parenteral Anticoagulants

The parenteral anticoagulants are unfractionated heparin (UFH), enoxaparin, fondaparinux, and bivalirudin. One of these agents is recommended for most patients with ACS:

- UFH is preferred if coronary artery bypass graft (CABG) is anticipated within 24 hours (or coronary angiography, although this is not as absolute).
- Enoxaparin is commonly used; however, keep in mind that the dose should be adjusted in the patient with renal impairment.
- Fondaparinux can be considered if the patient has increased risk of bleeding, especially if a conservative (noninvasive) strategy is chosen for the patient. It is not used if percutaneous coronary intervention (PCI) is expected (due to increased risk of catheter thrombosis and increased coronary complications). If it is in use, and invasive angiography/PCI is planned, switch to another agent, such as UFH or bivalirudin.

Antiplatelet Therapy

Aspirin

Administer aspirin at a dose of 162 or 325 mg immediately to all patients with ACS, and continue indefinitely unless there are contraindications.

Thienopyridines — Platelet $P2Y_{12}$ Receptor Blockade

Thienopyridines include clopidogrel (Plavix®), and prasugrel (Effient®). Their effect is additive to aspirin. These drugs block the ADP receptor $P2Y_{12}$ on platelets. Ticlopidine is no longer routinely used due to its side effect profile.

Interaction between proton pump inhibitors (PPIs) and thienopyridines was thought to be a problem, but latest studies do not prove a cause and effect relationship. PPIs are not contraindicated with thienopyridines, but consider the risks/benefits if using concomitantly.

Clopidogrel requires a liver enzyme (CYP2C19) to become active. Overall, 2–14% are poor metabolizers: 2–5% of African-Americans and Caucasians and up to 20% of Asians. There are genetic tests that can check for this issue. In 2010, clopidogrel (Plavix®) received an FDA boxed warning about poor metabolizers and the tests available, but genetic testing is not recommended in any current guideline.

Prasugrel is a thienopyridine that has a faster onset of action and is effective in clopidogrel-resistant patients. It has significantly more antiplatelet activity and therefore

Quick Quiz

- What anti-ischemic measures are done initially for all patients with ACS?
- Which patients should receive a platelet GP IIb/IIIa inhibitor?
- Of those with ACS, what group gets considered for fibrinolytic therapy and what group definitely does not?
- Under what conditions is angiography/PCI considered for those with UA/NSTEMI?

lower cardiovascular events—but also higher rates of significant bleeding and is contraindicated in the elderly.

Clopidogrel and prasugrel can be used interchangeably for all proven ACS scenarios except if CABG is imminent (operative bleeding complications).

Nonthienopyridines — Platelet $P2Y_{12}$ Receptor Blockade

Ticagrelor (Brilinta®), a nonthienopyridine, is a recently approved reversible oral antagonist of the platelet $P2Y_{12}$ receptor with a rapid onset of action. Similarly to prasugrel, it is more effective than clopidogrel with no difference in overall bleeding. It can be used as an alternative to clopidogrel/prasugrel.

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein (GP) IIb/IIIa inhibitors act on the final common pathway of platelet aggregation—where fibrin binds platelets together by connecting to the GP IIb/IIIa receptor. The most studied drug is abciximab. Others are eptifibatide, tirofiban, and lamifiban. Only the IV forms are effective. GP IIb/IIIa inhibitors are considered for high-risk ACS patients (elevated troponin, hemodynamic instability, dynamic ECG changes); however, since introduction of dual oral antiplatelet therapy they are used less commonly.

Fibrinolytic Therapy in ACS

Do not give fibrinolytic therapy to patients with UA/NSTEMI because it increases mortality. Do give fibrinolytic therapy to those ACS patients with STEMI or new LBBB if immediate PCI is not available and if there are no contraindications (discussed later).

Antiarrhythmic Drugs in ACS

Give lidocaine only if the patient has ventricular fibrillation/tachycardia. Prophylactic lidocaine is harmful. Lidocaine has an increased half-life in patients with heart failure (HF) and those on propranolol. Amiodarone is the current drug of choice for ventricular tachycardia and ventricular fibrillation.

ACS: MANAGEMENT OF UA / NSTEMI — THE ACUTE ISCHEMIA PATHWAY

Early Invasive vs. Conservative Therapy

Note: The 2012 update of the ACC/AHA UA/NSTEMI treatment guidelines have 2 areas of focus (Figure 5-4 on page 5-17):

1) Antithrombotic therapy with multiple agents
2) Aggressive use of early cardiac catheterization in those with moderate-to-high risk

Regarding UA/NSTEMI treatment:

- Use antiplatelet therapy, such as clopidogrel, prasugrel, or ticagrelor for at least 1 year after receiving a drug-eluting (DES) or bare-metal stent (BMS) and at least 1 month without a stent (for up to a year).
- Note: If a patient needs surgery, do not stop clopidogrel, prasugrel, or ticagrelor until at least 6 months and preferably 1 year after DES placement. Similarly, do not stop these agents until at least 30 days after BMS placement. Withholding clopidogrel, prasugrel, or ticagrelor and performing surgery prior to these time frames has an increased risk of death and in-stent thrombosis.
- Intense lipid and BP control is recommended.
- Stop all nonsteroidal antiinflammatory drugs (NSAIDs)—except ASA—during hospitalization.

Okay, you have determined the patient is having ACS and have initiated treatment according to the general measures on the prvious page. You've drawn labs and done the ECG, which reveals no acute ST changes. The labs come back, and you determine that the patient has NSTEMI (cardiac markers abnormal) or UA (markers normal).

You have 2 options:

1) Early invasive therapy (angiography)
2) Early conservative therapy

Early Invasive Therapy in UA / NSTEMI

Urgent invasive therapy for UA/NSTEMI indications:

- HF or hemodynamic instability
- Recurrent or refractory angina
- Life-threatening arrhythmias

Invasive therapy for UA/NSTEMI within 24–48 hours indications:

- Elevated cTnI or cTnT
- Dynamic ST changes
- Diabetes
- GFR < 60 mL/min
- EF < 40%
- Early post-MI angina
- PCI within the previous 6 months
- Prior MI

- Prior CABG
- Intermediate/high-risk patients (either by clinical judgment or using a scoring system such as the TIMI risk score)

All UA/NSTEMI patients selected for early invasive therapy get the following medical therapy:

- Parenteral anticoagulant:
  - UFH, enoxaparin, or bivalirudin. Do not give fondaparinux due to increased rate of catheter thrombus formation.
- Antiplatelet therapy:
  - ASA plus either clopidogrel, prasugrel, or ticagrelor (dual therapy). Note: Do not use prasugrel for patients with prior history of stroke/transient ischemic attack ([TIA]; use clopidogrel in these cases).
  - GP IIb/IIIa inhibitor can be given if the patient is high risk.

Remember: UA/NSTEMI patients do not receive fibrinolytic therapy.

Early Conservative Therapy in UA / NSTEMI

Patients with UA/NSTEMI who respond to intense medical therapy, have none of the high-risk features listed under invasive therapy above, and do well on post-ACS stress testing are at low risk for immediate and 1-year mortality—and can be followed without invasive evaluation.

Conservative therapy for UA/NSTEMI patients:

- Parenteral anticoagulant:
  - UFH, enoxaparin, or fondaparinux for 48 hours. Fondaparinux is especially useful if there is risk of bleeding.
- Antiplatelet therapy:
  - ASA with either clopidogrel or ticagrelor. Always give dual antiplatelet therapy.
  - Prasugrel or IIb/IIIa inhibitors are not given for conservative therapy.

This is basically the same anticoagulant/antiplatelet treatment as those getting UA/NSTEMI early invasive therapy, except that IIb/IIIa inhibitors and prasugrel are not used and fondaparinux is now a reasonable option.

Again, remember that UA/NSTEMI patients do not receive fibrinolytic therapy.

Long-Term Antiplatelet Therapy after UA / NSTEMI

Without a stent:

- ASA 75–162 mg/d for life
- Clopidogrel or ticagrelor x 1 month to 1 year

Bare-metal stent (BMS):

- ASA 162–325 mg/d x 1 month, then 75–162 mg/d for life
- Clopidogrel, prasugrel, or ticagrelor x 1 month to 1 year

Drug-eluting stent (DES):

- ASA 162–325 mg/d for 3–6 months, then 75–162 mg/d for life.
- Clopidogrel, prasugrel, or ticagrelor for at least 1 year. Consider continuing for longer than a year.

Cocaine and Methamphetamine Users with ST Elevation

Give nitroglycerin, calcium channel blockers, and benzodiazepines (not beta-blockers):

- If ST-segments are elevated and there is no immediate improvement with treatment, proceed with coronary angiogram or fibrinolytics if cath lab is not available.
- If chest pain resolves with treatment, troponin is not elevated, and there are no ST-T abnormalities, patient does not need stress test.
- Avoid beta-blockers.

ACS: MANAGEMENT WITH STEMI OR NEW LEFT BUNDLE-BRANCH BLOCK

Note

The management of acute coronary syndrome (ACS) for those with ST elevation MI (STEMI) is the same as for those with a new left bundle-branch block (LBBB) (Figure 5-5). Also know that STEMI includes those with a posterior infarct (ST depression in V1, V2 and tall Rs in V1, V2). General measures are discussed above.

The following are additions to the general measures for all ACS patients discussed on page 5-18.

STEMI (or new LBBB) patients get the following medical therapy:

- Parenteral anticoagulant:
  - UFH, enoxaparin, or bivalirudin. Give UFH or bivalirudin if going to cath lab within 24 hours (which ideally should be nearly everybody).
- Antiplatelet therapy:
  - ASA plus clopidogrel, prasugrel, or ticagrelor (in emergency department)
  - IIb/IIIa inhibitors as early as possible when patients are going to the cath lab for PCI

Immediate Reperfusion Therapies

Overview

Consider emergent reperfusion (primary PCI or fibrinolytic therapy) in all patients who present within 12 hours of the onset of symptoms with a STEMI or a new (or presumed new) LBBB.

Quick Quiz

- What are the reperfusion therapies you give to (or consider for) those with STEMI or new LBBB? Who gets what?
- In what conditions has PCI been shown to be better than fibrinolytic therapy?
- In what conditions has PCI been shown to be especially indicated?
- What are the absolute and relative contraindications to fibrinolytic therapy?

Primary PCI

Primary percutaneous coronary intervention (PCI) is urgent reperfusion therapy typically using a stent (bare-metal or drug-eluting). BMSs should be used in patients with high bleeding risk, inability to comply with 1 year of dual antiplatelet therapy, or anticipated invasive or surgical procedures in the next year (Image 5-6).

Primary PCI has been shown to be superior to fibrinolytic therapy when used in patients with STEMI, MI with new LBBB, and new true posterior MI. Outcomes are also better than fibrinolytic therapy as long as an experienced practitioner performs the procedure without significant delay, particularly within 12 hours of the onset of symptoms—and within 90 minutes of the arrival of the patient in the emergency department. (Door-to-balloon time is a commonly measured metric for quality of care in STEMI.) Patients with STEMI who present to a hospital without PCI capabilities should be transferred to a PCI-capable hospital with a goal of no more than 120 minutes from first medical contact (FMC) to stent placement.

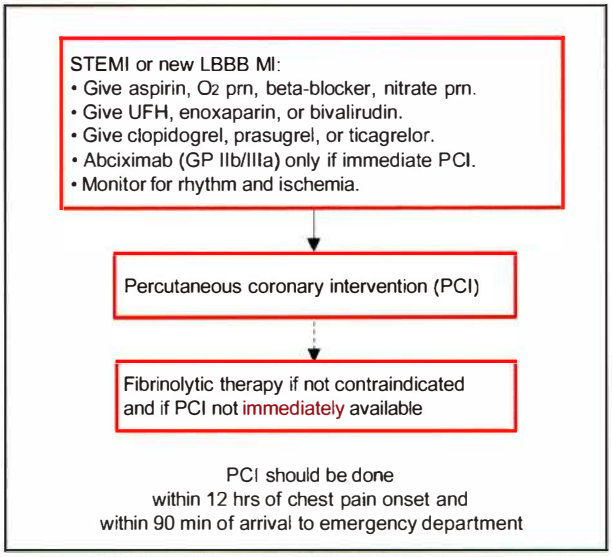


Figure 5-5: Acute MI Treatment Pathway with STEMI or New LBBB

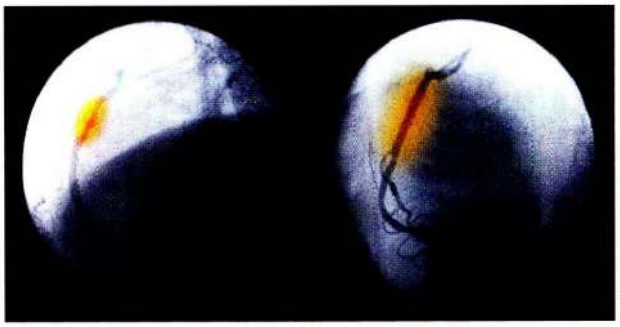


Image 5-6: Angiogram of a blocked coronary artery before and after stent placement

Primary PCI is particularly beneficial in patients with highest risk for mortality (e.g., cardiogenic shock) or acute severe HF following a STEMI or new LBBB MI.

In the patient who presents with completed STEMI (beyond 12 hours of the onset of symptoms), coronary angiogram is indicated if the patient continues to have chest pain or is in heart failure, left ventricular ejection fraction (LVEF) is moderately to severely reduced, there is electrical instability (ventricular tachycardia [VT] or ventricular fibrillation [VF]), or post MI stress test shows significant ischemia.

Fibrinolytic Therapy

If reperfusion therapy is indicated and primary PCI is not available at the first hospital, or FMC-to-device time at a PCI-capable hospital exceeds 120 minutes, initiate fibrinolytic therapy in STEMI patients in the absence of contraindications.

Many studies show that the sooner the patient receives fibrinolytic therapy, the greater the benefit in reduction of mortality, with the most benefit in the first 4 hours and the greatest of all in the first hour. Patients with new bundle-branch block benefit the most, followed by anterior MI, then inferior MI. Start fibrinolytic therapy within 30 minutes of arrival in the emergency department.

Note: Fibrinolytics are used for patients at facilities that do not have the capabilities for urgent PCI. Following treatment with fibrinolytic therapy, high-risk STEMI patients (recurrent ischemia, cardiogenic shock, severe HF, or other high-risk features) should be transferred to a PCI center to undergo coronary angiography and PCI immediately—without waiting to determine whether reperfusion has occurred.

Fibrinolytic agents include the recombinant, tissue-type plasminogen activators (e.g., rt-PA, TNK), anistreplase, streptokinase, and urokinase.

Contraindications to fibrinolytic therapy can be either absolute or relative contraindications.

Absolute contraindications:

- Previous hemorrhagic stroke at any time; other cerebrovascular events within 1 year
- Intracranial neoplasm
- Active internal bleeding
- Suspected aortic dissection

Relative contraindications:

- Persistent BP > 180/110
- Remote nonhemorrhagic CVA (> 1 year)
- Current use of anticoagulants with INR > 2–3; bleeding diathesis
- Recent (2–4 weeks) major trauma or surgical procedure
- Noncompressible vascular puncture
- Previous exposure to streptokinase/anistreplase
- Pregnancy
- Active peptic ulcer

Of the patients with STEMI/new LBBB initially evaluated for fibrinolytic therapy, almost 2/3 do not get fibrinolytic therapy for the reasons listed above or because of advanced age. The risk of intracranial hemorrhage increases with age, to as much as 1% in patients > 75, but age by itself is no longer a contraindication. Many of these patients are still good candidates for primary PCI.

Additional Recommendations from the 2013 ACC / AHA STEMI Guidelines

- Stop all NSAIDs (except ASA), including COX-2s!
- Start oral beta-blocker within 24 hours if no signs of HF, evidence of low-output state, increased risk for cardiogenic shock, PR interval > 0.24 seconds, 2nd or 3rd degree heart block, active asthma, or reactive airway disease.
- Do not give fibrinolytic therapy if immediate PCI is anticipated. In addition, there is no role for partial- or low-dose fibrinolytic therapy.
- Give clopidogrel or ticagrelor (no PCI) + ASA (1 year).
- Place patient on a high-dose statin.
- ACEIs within 24 hours to all with anterior STEMI, HF, EF ≤ 40% (unless contraindicated). Use an angiotensin receptor blocker if ACEI intolerant.
- An aldosterone antagonist (e.g., spironolactone, eplerenone) should be given to those with no contraindications who are already receiving an ACEI and beta-blocker, have an EF ≤ 40%, and have either symptomatic heart failure or diabetes mellitus.
- IV nitroglycerin in the first 24 hours for ongoing chest pain or hypertension.
- Blood sugars must be maintained at < 180 using insulin-based regimens for diabetics while avoiding hypoglycemia.
- Influenza vaccine yearly.

If urgent CABG is planned, aspirin should be withheld, and clopidogrel, prasugrel, and/or ticagrelor should be stopped 24 hours before urgent on-pump CABG. Short-acting intravenous GP IIb/IIIa receptor antagonists (eptifibatide, tirofiban) should be discontinued at least 2–4 hours before urgent CABG; abciximab should be discontinued at least 12 hours before urgent CABG.

Complications of Myocardial Infarction

Left Ventricular Dysfunction

Left ventricular dysfunction after an MI is predictive of a poor prognosis. Pump failure is now the primary cause of in-hospital death from ST elevation MI (STEMI). Patients in cardiogenic shock have historically had mortality rates of > 85%, but studies using PCI or emergent CABG have demonstrated an improvement in these dismal outcomes.

Right Ventricular Infarction Complications

Right ventricular infarction (RVI) frequently accompanies an inferior MI and is almost always due to occlusion of the proximal right coronary artery. Inferior MI complicated by RVI has a significantly worse prognosis than inferior MI alone.

ST-segment elevation in right-sided chest leads (e.g., V3R–V7R) is an indication of infarction of the right ventricle. If a patient with inferior MI presents with hypotension, suspect RVI.

Suspect RVI in all cases of inferior MI, which is typified by the clinical triad of hypotension, clear lung fields, and elevated jugular venous pressure. A Kussmaul sign is frequently present.

If you perform right heart catheterization, an elevated RA pressure of ≥ 10 mmHg with decreased pulmonary capillary wedge pressure (PCWP) and CO are quite specific for right ventricular MI.

Management of RVI is frequently diametrically opposed to that of LV infarction. Avoid nitrates and preload reducing agents. Fluid support is essential. Inotropic support, typically with dobutamine, may be necessary.

Arrhythmias and Blocks

A variety of tachyarrhythmias can occur with myocardial infarction/ischemia.

Atrial fibrillation (A-fib) with hemodynamic instability requires emergent treatment with direct current (DC) synchronized cardioversion. If patients do not require cardioversion, control the ventricular rate in these patients with beta-blockers, diltiazem, or digoxin.

Treat ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) with defibrillation (DC unsynchronized cardioversion).

For sustained VT with a pulse accompanied by hemodynamic instability, treat with DC synchronized cardioversion.

For episodes of sustained VT not associated with hemodynamic instability:

- Amiodarone is the drug of choice. It can be given as a continuous infusion or as boluses every 10–15 minutes. Lidocaine can be an effective alternative agent, and procainamide is also an option.

Quick Quiz

- How does management of RVI differ from LV infarction?
- Which patients with VT after an MI get DC cardioversion?
- What are the medical options for hemodynamically stable MI patients with VT?
- When do the major mechanical complications tend to occur after an MI? How do they present? What is the best initial test to diagnose such a complication?
- When should a patient with STEMI be referred for consideration for an ICD?

- Correct any hypokalemia or hypomagnesemia.
- Routine prophylactic use of lidocaine to prevent VT is no longer recommended.

For patients who develop ventricular tachycardia or ventricular fibrillation after the first 48 hours, the short-term and long-term mortality rates are increased. Such patients should be considered for electrophysiologic study and an implantable cardioverter-defibrillator (ICD).

Note that patients with isolated, premature ventricular contractions, or runs of nonsustained (< 30 seconds) VT, do not need antiarrhythmic therapy on a routine basis. Beta-blockers are effective for ventricular ectopic activity and preventing arrhythmias.

Bradycardia and AV block are more common with inferior MIs than anterior MIs because of the increased vagal tone and AV nodal ischemia associated with an inferior infarct. Remember: Prognosis is related to the size of the infarct, not the presence of AV block itself. The block is often transient and does not require a permanent pacemaker.

AV block accompanying an anterior MI implies destruction of a large amount of myocardium in the interventricular septum, is associated with a high mortality, and frequently requires permanent pacing if the patient survives.

Indications for temporary pacing at the time of an MI include:

- Symptomatic bradyarrhythmias unresponsive to medical treatment
- Asystole or sinus arrest
- Complete (3rd degree) AV block
- Mobitz type 2 second-degree AV block

Mechanical Complications after STEMI

Rupture of a papillary muscle, if it occurs, usually does so 3–7 days after an inferior MI. The patient rapidly develops shock and acute pulmonary edema. You may (or may not) hear a short, early systolic murmur. Echocardiography is indicated in any hemodynamically unstable MI patient and is the diagnostic modality of choice for all of these conditions. The treatment is urgent cardiothoracic surgery.

Ventricular septal defect, if it occurs, generally does so 3–7 days after an anteroseptal MI. Incidence is about 0.3% of MIs (before reperfusion therapy era, incidence was 1–3%). Again, the patient rapidly develops shock. A loud, holosystolic murmur is heard widely over the precordium. Samples from a right heart catheter demonstrate an oxygen saturation step-up from the right atrium to the pulmonary artery of at least 10%. Confirm the diagnosis by echocardiography. Once again, the mortality rate is very high, and the only treatment is urgent cardiothoracic surgery.

Free-wall rupture of the LV commonly occurs 3–7 days after a large, anterior MI, most frequently in elderly hypertensive women. Sudden syncope is typical. The neck veins are grossly engorged from tamponade; pulsus paradoxus, tachycardia, and hypotension make up the triad. Hemodynamic collapse occurs quickly. There have been a few heroic saves with immediate surgery, but rapid death is the usual outcome.

The 2013 ACC/AHA STEMI guidelines recommend diagnosis of mechanical complications after STEMI with transthoracic echocardiography. Arterial pressure monitoring with an indwelling arterial line is appropriate in some patients, particularly those requiring mechanical ventilation. Intraaortic balloon counterpulsation is indicated in patients in cardiogenic shock after STEMI who do not quickly stabilize with pharmacological therapy or with a mechanical complication as a bridge to urgent revascularization and/or surgery.

Implantable Cardioverter-Defibrillators

Implantable cardioverter-defibrillator (ICD) therapy is indicated before discharge in patients who develop sustained ventricular tachycardia/ventricular fibrillation more than 48 hours after STEMI, provided the arrhythmia is not due to transient or reversible ischemia, reinfarction, or metabolic abnormalities.

Studies have shown that ICDs prolong survival in post-MI patients with LVEF < 30–35%, depending on NYHA classification. LVEF is typically reevaluated after 40 days following revascularization to allow stunned or hibernating myocardium to recover. An ICD is particularly indicated if there are baseline episodes of ventricular tachycardia.

CORONARY ARTERY DISEASE

NOTE

We'll talk about the risk factors for coronary artery disease (CAD), screening, and revascularization options.

RISK FACTORS FOR CAD

The primary risk factors for CAD:

- Age
- Male gender
- Family history of early CAD (females < 65, males < 55)
- Smoking
- Hypertension
- DM
- Elevated LDL level

Aerobic exercise and elevated HDL are inversely linked to CAD. HDL is increased by exercise, estrogens, niacin, and small amounts of EtOH. HDL is decreased by smoking and androgens. However, pharmacologic treatment of low HDL is no longer recommended by national guidelines.

SCREENING

Check a "fasting lipid panel" at least every 5 years in healthy persons, starting at age 20. The "fasting lipid panel" includes total cholesterol, LDL, HDL, and triglycerides. Much more on lipids in Endocrinology, Book 4!

LDL is usually a calculated value:

LDL = total cholesterol – HDL – 1/5 of triglycerides

The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults states that all patients with CAD should receive a high-intensity statin, regardless of lipid levels. (A high-intensity statin is defined as one that lowers LDL cholesterol by at least 50% on average. Currently, that includes atorvastatin 40–80 mg and rosuvastatin 20–40 mg. A moderate-intensity statin is one that lowers LDL cholesterol by 30 to < 50%. That includes all other available statins plus the lower doses of atorvastatin and rosuvastatin.)

The 2013 ACC/AHA guidelines identify 4 statin benefit groups:

1) Patients with clinical atherosclerotic cardiovascular disease (ASCVD)—such as CAD or stroke
2) Patients with LDL ≥ 190 mg/dL
3) Patients ages 40–75 with DM and LDL 70–189 mg/dL
4) Patients without clinical ASCVD or DM who are ages 40–75 with LDL 70–189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher

Patients in the above 4 groups should receive a statin medication.

Lipids can be falsely low for up to 2 months after a myocardial infarction or cardiac surgery.

Statins enhance plaque stabilization and can independently improve long-term prognosis.

ACC/AHA guidelines and drug treatment are covered in Endocrinology, Book 4, under Lipoproteins.

Additional factors to consider:

- Advise no smoking.
- Give antihypertensive medications to treat to goal BP.
- Coronary artery calcium scores and other serum markers, such as high-sensitivity CRP, can be used in some patient populations to add to the total risk assessment for coronary artery disease.
- Do not forget to ask about substance abuse, particularly cocaine.

REVASCULARIZATION

The revascularization options are:

- Coronary artery bypass graft (CABG)
- Percutaneous coronary intervention (PCI) with either stents or angioplasty

CABG vs. PCI

The 2012 ACC/AHA guidelines recommend revascularization under the following circumstances:

- CABG to improve survival for all patients with significant, left main CAD (> 50% diameter stenosis).
- CABG to improve survival in patients with significant (> 70% diameter) stenoses in 3 major coronary arteries or in the proximal LAD artery plus 1 other major coronary artery (e.g., proximal circumflex).
- CABG is reasonable to improve survival in patients with significant (> 70% diameter) stenoses in 2 major coronary arteries with severe or extensive myocardial ischemia (i.e., high-risk criteria on stress testing, abnormal intracoronary hemodynamic evaluation, or > 20% perfusion defect by myocardial perfusion stress imaging) or target vessels supplying a large area of viable myocardium.
- CABG is reasonable to improve survival in patients with mild-to-moderate left ventricle (LV) systolic dysfunction (EF 35–50%) and significant (> 70% diameter stenosis) multivessel CAD or proximal LAD coronary artery stenosis, when viable myocardium is present in the region of intended revascularization.
- CABG is recommended to improve survival in patients with complex 3-vessel CAD with suitable anatomy and in those with multivessel CAD and diabetes mellitus, particularly if a left internal mammary artery graft can be anastomosed to the LAD artery.

QuickQuiz

- What are the primary risk factors for CAD?
- What increases HDL?
- Which patient groups definitely should get CABG?
- Which patient groups could get either PCI or CABG?
- In 3-vessel disease, what is the benefit of CABG—survival, symptoms, or both?
- With saphenous vein bypass, what percentage of veins is occluded in 10 years?
- Name 2 drugs used with DESs.

- PCI or CABG to improve symptoms is beneficial in patients with 1 or more significant (> 70% diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite optimal medical therapy.
- PCI or CABG to improve survival for survivors of sudden cardiac arrest with presumed ischemia-mediated ventricular tachycardia caused by significant (> 70% diameter) stenosis in a major coronary artery.
- PCI is reasonable as an alternative to CABG in selected stable patients with significant (> 50% diameter stenosis) unprotected left main CAD with anatomy associated with a low risk of PCI complications and a good, long-term outcome, and clinical characteristics predicting a significantly increased surgical morbidity/mortality.

CABG improves symptoms and survival in:

- Left main, left main-equivalent (2-vessel disease with 1 vessel being proximal LAD), or 3-major coronary artery disease
- Multivessel CAD or proximal LAD disease with LV dysfunction and viable myocardium
- Complex 3-vessel CAD
- Multivessel CAD with DM

With saphenous vein bypass, there is a 50% chance of occlusion in 10 years (about 5% per year), but with internal mammary grafts, 90% are open at 10 years! Think: the word "VEINS" has 5 letters and so 50% open at 10 yrs; "LIM-ARTERY" has 9 letters so 90% open at 10 years! Internal mammary grafts are the standard of care for surgical revascularization of the LAD. Chance of MI is the same after bypass.

CABG vs. PCI: In most of the recent trials, patients have the same survival results, but the need for revascularization is greater in the PCI group. In these trials, survival has been better for diabetics who get an internal mammary-LAD bypass than for those with a PCI. Studies are continually trying to tease out specific patient populations and coronary lesions that benefit from CABG vs. PCI, particularly in the drug-eluting stent era. This is a "moving target" because left main disease can be stented as well now with good results in certain patient groups.

Again: Survival does not improve after bypass unless the patient has:

- 3-vessel disease with significant LV dysfunction, or
- left main or left main-equivalent disease, or
- diabetes.

Stents

Stents are the mainstay of PCI. These are placed in the area of blockage and then expanded, thereby opening the lumen to normal size. Stents do not cause as much dissection of the plaque and are not susceptible to elastic recoil—both of which can occur with angioplasty alone. Stents also have a lower restenosis rate than plain angioplasty. The in-stent restenosis is almost always due to neointimal hyperplasia, but stents also carry a risk of in-stent thrombosis, particularly during the early period after placement. This is why antiplatelet therapy is so important after stent placement, and a bare metal stent requires dual antiplatelet therapy for a minimum of 30 days to prevent in-stent thrombosis.

Drug-eluting stents (DESs) are made with a metallic stent backbone supporting a polymer covering that contains a slow-release drug. These drugs have properties that decrease the neointimal hyperplasia that is the cause of most restenoses. Commonly used DESs contain medications such as sirolimus, paclitaxel, and everolimus. With these agents, the restenosis rate drops dramatically (to 5%) compared to bare-metal stents ([BMSs]; 25%), although there is a slight increase in late stent thrombosis (0.4%). As opposed to BMSs, DESs require prolonged obligatory dual-antiplatelet therapy due to the delay in neointimalization: minimum 1 year as opposed to 30 days with a BMS. There are growing concerns over late stent thrombosis with DES, particularly after antiplatelet agent withdrawal. Also, rare local and systemic hypersensitivity reactions have been reported and can contribute to late stent thrombosis risk. Thus, prolonged antiplatelet therapy may be needed > 1 year.

Other

Balloon angioplasty stretches the plaque and vessel wall to enlarge the lumen. There is a 30–50% chance of restenosis within 6 months. Balloon angioplasty is currently used for vessels too small to allow coronary stenting. It is also used to predilate vessels before stent placement.

Rotational ablation atherectomy (catheter with diamond-grinding chips in it) has a role for heavily calcified lesions.

PERIPHERAL ARTERIAL DISEASE

CAUSES OF PAD AND INTERMITTENT CLAUDICATION

Peripheral arterial disease (PAD), previously called peripheral vascular disease (PVD), has many causes, including the following:

- Arteriosclerosis (arteriosclerosis obliterans—most common cause in middle-aged and older); 2 major risk factors for arteriosclerotic PAD are diabetes (5x greater chance) and smoking. Other modifiable risk factors include hyperhomocysteinemia, hyperlipidemia, and hypertension. Note: Patients with arteriosclerotic PAD are at increased risk of MI and stroke.
- Arteritis (connective tissue disease, Takayasu arteritis).
- Trauma (jackhammer hands).
- Buerger disease (especially smoking males < 30 years old)—also called thromboangiitis obliterans. It involves medium and small arteries and often affects arteries of the wrists (positive Allen test) and hands.
- Entrapment—think especially of thoracic outlet syndrome and popliteal artery entrapment. Suspect popliteal artery entrapment in young men with intermittent claudication of calf or foot arch with walking—but not running!

It is important to differentiate vascular claudication from lumbar spinal stenosis, and know that the latter causes a pseudoclaudication. Lumbar spinal stenosis is relieved only by sitting down (flexing the spine), but not by standing still. It is exacerbated by anything that extends the spine, such as standing or walking (especially downhill). Vascular claudication is relieved by sitting down or standing still. Neither disease causes nocturnal leg cramps. When the distance to onset of claudication or severity abruptly changes, thrombosis *in situ* or an embolic event should be considered.

DIAGNOSIS OF PAD

The resting ankle brachial index (ABI) should be used to establish the lower extremity PAD diagnosis in patients with suspected lower extremity PAD; i.e., those with 1 or more of the following: exertional leg symptoms, nonhealing wounds, age ≥ 65, or ≥ 50 years if history of smoking/diabetes.

ABI classification: noncompressible > 1.40, normal 1.00–1.40, borderline 0.91–0.99, and abnormal (i.e., PAD) < 0.90.

Continuous-wave Doppler ultrasound is useful to diagnose anatomic location and degree of stenosis of PAD.

Exercise tolerance tests (ETTs) are recommended to objectively measure functional limitation of claudication and response to therapy. ETTs with pre-exercise and post-exercise ABI values provide diagnostic data useful in differentiating arterial claudication from nonarterial claudication ("pseudoclaudication").

Magnetic resonance angiography (MRA) of the extremities (with gadolinium enhancement) is useful to diagnose anatomic location and degree of stenosis of PAD. Computed tomographic angiography (CTA) can be considered as a substitute if there are contraindications to MRA.

Contrast angiography provides detailed information about arterial anatomy and is recommended for evaluation of patients with lower extremity PAD when revascularization is contemplated.

Thromboembolism is the usual problem with aneurysms of limb arteries. Aneurysm of the popliteal artery can be diagnosed by U/S or CT scan. In patients with femoral or popliteal aneurysms, U/S (or computed tomography or magnetic resonance) imaging is recommended to exclude contralateral femoral or popliteal aneurysms and abdominal aortic aneurysms (AAAs).

TREATMENT OF PAD

Recommendations:

- Statin in all patients.
- Keep BP < 140/90 or < 130/80 with DM or CKD; beta-blockers are effective and not contraindicated.
- Proper foot care.
- Smoking: Counsel to stop smoking, offer behavioral and pharmacologic Rx (varenicline, bupropion, and nicotine replacement therapy); ask smokers/former smokers about tobacco use at every visit.
- Antiplatelet therapy with aspirin 75–325 mg or clopidogrel 75 mg daily is indicated as well to decrease cardiovascular events (warfarin gives no benefit!).
- Exercise 30–45 minutes at least 3 days/week.
- Cilostazol (Pletal®) 100 mg bid, a phosphodiesterase inhibitor that increases the cAMP in platelets and blood vessels—resulting in a reversible inhibition of platelet aggregation—has been shown to improve symptoms and increase walking distance. Use only if LV function is normal because patients with class III or IV heart failure have increased mortality with any phosphodiesterase inhibitor.
- Pentoxifylline (Trental®) effect is marginal and not well established.

If PAD is due to Buerger disease, stop tobacco use. If Takayasu arteritis is present, treat the disease with steroids.

Other treatment: Many forms of PAD can now be effectively treated with percutaneous intervention (angioplasty and stents)—with low restenosis rates. Surgical bypass can also effectively relieve symptoms and ischemia. In general, proximal (iliac and femoropopliteal) stenosis and short-segment occlusions are best treated endovascularly (e.g., focal aortoiliac occlusive disease), with long lesions and occlusions best treated surgically.

With acute peripheral arterial occlusion, heparin protects the collateral circulation during evaluation by preventing

QuickQuiz

- What are the causes of arteriosclerotic PAD?
- What is Buerger disease?
- What is the difference between claudication and pseudoclaudication?
- What is the first test to establish the diagnosis of lower extremity PAD? What result is considered abnormal?
- What antiplatelet therapy is recommended for patients with PAD?
- What is primary Raynaud syndrome? How is it treated?
- Atherosclerotic disease of the carotid artery provides more risk for which of these: MI, stroke, or TIA?
- When is carotid endarterectomy indicated?

thrombus formation around the new clot. Many arterial emboli to the lower extremities come from the heart, but atheromatous emboli from a diseased aorta can also occur, which can cause renal failure and ischemia of the toes (Image 5-7). Embolectomy/thrombectomy is the treatment of choice.

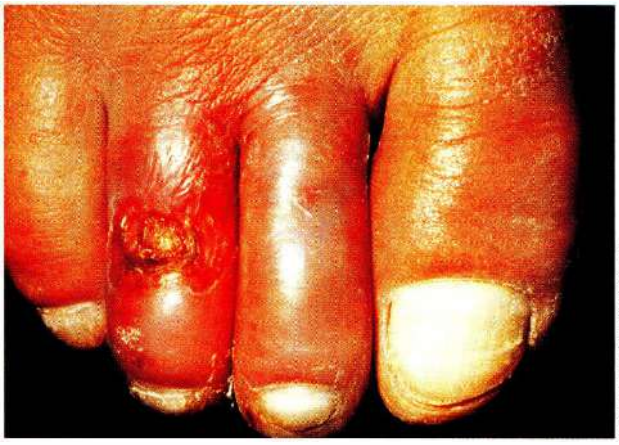


Image 5-7: Thromboangiitis obliterans or Buerger disease symptoms on patient's toes

VASOSPASTIC DISEASE

Vasospastic disorders: Primary Raynaud phenomenon (Raynaud disease) is constriction of small arteries and arterioles when cold, leading to acrocyanosis. It is sometimes associated with livedo reticularis. It involves small arteries and arterioles in the digits and skin (Image 5-8).

Treatment: calcium channel blockers (CCBs), biofeedback, and nitroglycerin if CCBs are ineffective.

Prinzmetal angina is a coronary artery vasospastic disease that can lead to transient, dramatic ST elevation mainly at rest and occasionally with exercise. Think of this diagnosis in a younger individual with transient ST elevation during an episode of pain but normal coronary arteries on cath. Treatment includes nitrates and especially calcium channel blockers.

CAROTID ARTERY DISEASE

CAROTID ARTERY ATHEROSCLEROSIS

Atherosclerosis within the carotid artery occurs most frequently within the common carotid bifurcation and proximal internal carotid artery. Patients with atherosclerotic carotid artery disease are at a higher risk of having an MI than of having a transient ischemic attack (TIA) or stroke!

In asymptomatic patients with known or suspected carotid stenosis, ultrasound is recommended as the initial diagnostic test to detect hemodynamically significant carotid stenosis.

Ultrasound is also recommended to detect carotid stenosis in symptomatic patients (i.e., who develop focal neurological symptoms in left or right internal carotid artery territories). Magnetic resonance angiography (MRA) or computed tomography angiography (CTA) is indicated to detect carotid stenosis when ultrasound cannot be obtained or yields equivocal/nondiagnostic results.

Patients who experience nondisabling ischemic stroke or TIA symptoms within 6 months (symptomatic patients) should undergo carotid endarterectomy (CEA) if: 1) the diameter of the lumen of the ipsilateral internal carotid artery is reduced (> 70% by noninvasive imaging or > 50% by catheter angiography); and 2) the anticipated rate of perioperative stroke/mortality is < 6%. Carotid artery stenting is indicated as an alternative to CEA for these same patients. It has the same indications as CEA but stenting has a higher 30 day postsurgical mortality, so it typically is used for a subset of these patients with a lesion not suitable for surgery, restenosis after previous CEA, or radiation stenosis.

Medical therapy for atherosclerotic carotid disease includes: aspirin, clopidogrel, or low-dose aspirin + extended release dipyridamole; treat blood pressure to goal < 140/90; statins for all; and smokers should quit!

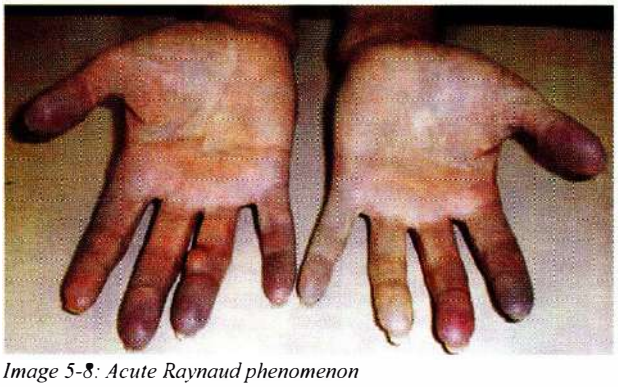


Image 5-8: Acute Raynaud phenomenon

INTERNAL CAROTID ARTERY DISSECTION

Suspect spontaneous dissection of the internal carotid artery (cervical area) in a patient with unilateral headache associated with either TIAs or a dilated pupil. It can also present with only a history of unilateral neck pain in a hypertensive patient. Look for cholesterol emboli on the funduscopic exam. Spontaneous dissection of the internal carotid artery typically resolves with no treatment, with excellent recovery. Occasionally, anticoagulation or a stent is needed.

CEREBRAL EMBOLIC DISEASE

OVERVIEW

The causes of cerebral embolic events of cardiac origin (and the approximate % of events they cause):

- Atrial fibrillation (45%)
- Acute MI (15%)
- Ventricular aneurysm (10%)
- Mechanical valve prosthesis (10%)
- Valvular heart diseases, including endocarditis (10%)
- Other cardiac abnormalities (10%)

"Other" includes patent foramen ovale, which allows an intermittent right-to-left shunt and "paradoxical" emboli, and dilated cardiomyopathy, which allows formation of a mural thrombus.

Noncardiac cause of embolic cerebral events is atherosclerosis, both aortic and carotid (discussed above).

Nonembolic causes of cerebral ischemic attacks or strokes are thrombosis, systemic hypoperfusion, and blood disorders (especially clotting disorders).

TRANSIENT ISCHEMIC ATTACK

The definition of transient ischemic attack (TIA) has changed and is no longer related to duration of symptoms. TIA is now defined as any period of CNS ischemia without infarction. Ischemic stroke is defined as ischemia with infarction. The CNS includes the brain, spinal cord, and retina. More on TIA under Dizziness, Causes of Vertigo in Neurology, Book 5.

Medical treatment of TIA: If there is a history of TIA but no history of cardioembolic stroke, no significant lesion is found, and the patient does not have atrial fibrillation, it is probable that the cause is atherosclerosis; therefore, the patient should be placed on antiplatelet therapy: ASA + dipyridamole, ASA alone, or clopidogrel alone. Ticlopidine is similar to clopidogrel but is not a 1st line drug because of severe neutropenia that occurs in 1%! Unlike with coronary artery disease, the combination of ASA + clopidogrel has not been shown to be beneficial over either agent alone for stroke or TIA prevention.

AORTIC DISEASE

AORTIC ANEURYSMS

Overview

The causes of aortic aneurysms can be broadly categorized as degenerative diseases, inherited or developmental diseases, infections, vasculitis, and trauma. With aortic aneurysms, rupture is the biggest threat. Atheroembolism is another complication of abdominal aortic aneurysm. Signs of atheroembolism, in decreasing order, are: livedo reticularis, then blue toes, then ischemic ulceration. (Remember, though, that most emboli to the lower extremities originate in the heart!) Hypertension from progressive renal insufficiency can occur if abdominal aneurysms are not treated.

Thoracic Aortic Aneurysms

Thoracic aortic aneurysms tend to dissect as well as rupture. Aortic dissection is an intimal tear in the aorta, resulting in a dissecting hematoma, which can cause severe pain and occlusion of the aorta and involved vessels. Systemic hypertension, cystic medial necrosis, bicuspid aortic valve, coarctation of the aorta, and 3rd trimester of pregnancy are predisposing factors. Aortic dissection is a major cause of death in those with Marfan syndrome.

Cystic medial necrosis is the most common pathology in ascending aortic aneurysms, whereas atherosclerosis is most frequently associated with aneurysms of the aortic arch and descending thoracic aorta. The average growth rate of thoracic aneurysms is 0.1–0.2 cm per year.

The **DeBakey** classification of aortic dissection lists 3 types:

Type I: Involves the ascending aorta, aortic arch, and descending aorta

Type II: Proximal in the ascending aorta alone

Type III: Involves the descending aorta alone, commonly just after the subclavian artery

The **Stanford** classification lists 2 types:

Type A: Any dissection involving the ascending aorta

Type B: Limited to the descending aorta only

Stanford Type A combines DeBakey I and II; this makes sense because all type A aortic dissections are managed similarly. Hence, the Stanford classification is more commonly used now.

Proximal dissection can cause aortic regurgitation, hemopericardium with tamponade, and MI due to involvement of a coronary artery (usually the right coronary artery). Dissections typically present with severe anterior chest pain and/or severe interscapular pain.

Diagnosis [Know]: CT and MRI are the diagnostic procedures of choice for possible aortic dissection. Transesophageal echo is a reasonable alternative if the patient is too unstable to go to radiology.

QuickQuiz

- How might spontaneous dissection of the internal carotid artery present clinically? What is its prognosis?
- What are the procedures of choice for diagnosing a dissecting aortic aneurysm?
- At what size is surgery indicated for a thoracic aortic aneurysm?
- At what size is surgery indicated for an abdominal aortic aneurysm?
- Which *Streptococcus*, if found as a cause of endocarditis, warrants a colonoscopy?

Treatment: Decrease elevated blood pressure immediately with beta-blockers and nitroprusside. There is preliminary evidence that Marfan's-related aneurysms should be treated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) to block TGF-signaling. Ascending aortic dissections are at greater risk for complications, so they always require surgery. Descending aortic dissections are mainly treated medically unless evidence of end-organ damage develops (renal insufficiency, GI ischemia, limb compromise), which suggests continuing dissection and the need for emergent surgery.

Thoracic aortic aneurysm: Surgery is indicated at 5.5 cm in the ascending aorta (5 cm if Marfan's) and 6 cm in the descending aorta.

Also, surgery is indicated if the aneurysm is small but enlarging rapidly (> 10 mm in a year), associated with symptoms, compressing surrounding structures, or is of traumatic origin.

Abdominal Aortic Aneurysm

Screening is covered in General Internal Medicine, Book 5, under Preventive Medicine, Screening Exams.

Abdominal aortic aneurysms (AAAs) are more common in men. They tend to rupture rather than dissect. Treat BP and lipids as for patients with CAD, and advise to stop smoking (and recommend smoking cessation interventions).

If asymptomatic, aneurysms 4–5.4 cm should be monitored with ultrasound or CT every 6–12 months. Aneurysms > 5.5 cm or symptomatic (abdominal/back pain + pulsatile mass + hypotension) should undergo surgical repair. AAAs that expand > 0.5 cm in 6 months should undergo surgical repair as well. Put the patient on beta-blockers during the observation period.

Know that acute MI and other CAD-related problems are the cause of 70% of perioperative mortality for AAA repair. Surgical risk is decreased if the patient does not have CAD, so perform a CAD screening with a nuclear stress test if the patient has ≥ 2 CAD risk factors (listed on page 5-24). Use perioperative beta-blockers in patients with CAD undergoing surgical repair of AAA.

Open or endovascular repair of infrarenal AAAs and/or common iliac aneurysms are options in good surgical candidates; however, endovascular repair requires periodic long-term surveillance imaging to monitor endoleak, shrinkage/stability of excluded aneurysm sac, and to determine need for further intervention.

COARCTATION OF THE AORTA

Coarctation of the aorta (COA) is a congenital problem that causes persistent hypertension, sometimes even after surgical correction. Cardiac output responds normally to exercise. Blood pressure is higher in the upper extremities than in the lower. People with COA have a high risk of developing subsequent aortic disease, including aneurysms and dissection, even after correction of the lesion. A bicuspid aortic valve is often seen (~ 50%) in COA patients. See more on COA on page 5-58.

VALVULAR HEART DISEASE

INFECTIVE ENDOCARDITIS

Overview

[Know this section well.]

More on causes and treatments of infective endocarditis (IE) is discussed in Infectious Disease, Book 1. For treatment purposes, endocarditis is classified as:

- Native valve
- Prosthetic valve
- IV drug related
- Culture negative

These can have acute or subacute presentations.

Streptococcus, *Enterococcus*, and *S. epidermidis* are the usual causes of the subacute form, while *S. aureus*, group B *Streptococcus*, and gram-negative organisms cause acute endocarditis.

S. aureus causes 80–90% of staphylococcal IE and is the most common cause of acute IE. Recent data from the International Collaboration on Endocarditis (ICE) suggest that *S. aureus* has become the leading cause of IE worldwide in injection drug users and prosthetic valves and most often presents as an acute disease.

Strep accounts for 60–80% of all endocarditis cases. Viridans streptococci are responsible for 30–65% of native valve endocarditis in adults. *S. bovis* is often associated with a GI malignancy in the elderly as well as polyps and diverticulosis––order colonoscopy in all patients with *S. bovis* endocarditis.

Enterococcal endocarditis is found in older men with genitourinary disease or after instrumentation or surgery.

S. aureus (coagulase-positive), *S. epidermidis* (coagulase-negative), and gram-negative endocarditis are seen in IV drug abusers and patients with prosthetic heart valves. Other risk factors for these types of IE include dialysis, Type 1 diabetes, burn victims, HIV, certain chronic dermatologic conditions, and patients with recent surgical incisions (including median sternotomy for valve replacement).

Right-sided endocarditis and the resulting septic pulmonary emboli can show up as right ventricle (RV) enlargement and multiple lung infiltrates on chest x-ray. Onset of heart failure is a bad sign. When there is right-sided endocarditis, it is almost always due to IV drug abuse (IVDA); however, IVDA-associated left-sided endocarditis occurs even more commonly! (Left-sided endocarditis has a higher incidence, and it has many more causes.)

Occasionally, endocarditis presents only with signs of embolic events, such as black toes or septic emboli to other organs. It can also present as an illness of smoldering, nonspecific symptoms (weight loss, fevers, chills, night sweats, etc.), or heart failure due to valvular insufficiency.

Classic physical exam findings include new regurgitant heart murmurs, Osler nodes (tender nodules on the pads of the digits), Janeway lesions (nontender erythematous/hemorrhagic macular/nodular lesions on the palms or soles), splinter hemorrhages (Image 5-9), and Roth spots.

Blood cultures are positive in right- and left-sided endocarditis with equal frequency (95%). This is because there is a constant level of bacteremia in endocarditis; whereas with most other bacterial causes of fever, the bacteremia precedes the temperature spike.

Diagnosis of endocarditis is by the Duke criteria; echo, including TEE, is frequently used to help make the diagnosis. Diagnosis is covered in Infectious Disease, Book 1.

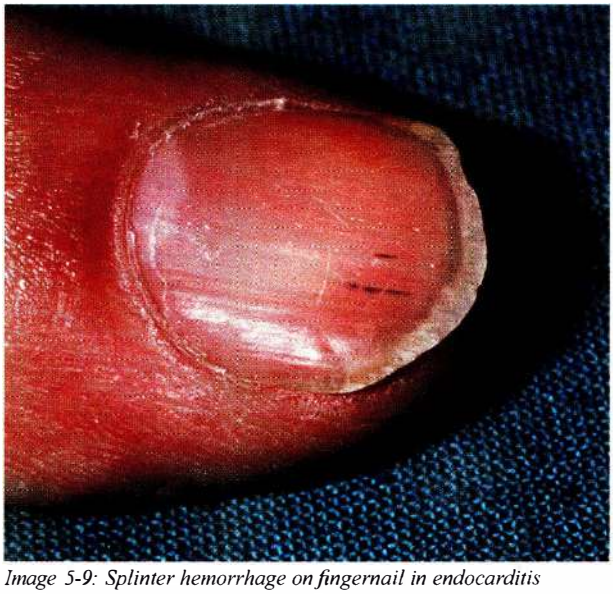


Image 5-9: Splinter hemorrhage on fingernail in endocarditis

Endocarditis occurring within 2 months of prosthetic valve placement means the valve was seeded when the valve was implanted. It is harder to treat (especially if *S. epidermidis*); if there is no response to 1 round of adequate antibiotics, replace the valve.

If it has been > 2 months since the prosthetic valve placement, antibiotic treatment is generally sufficient. The valve must also be replaced if there is evidence of valve ring infection or myocardial penetration or unstable prosthesis. These can appear as a new heart block or a new BBB.

Surgery is indicated in endocarditis for refractory heart failure, usually from acute valve regurgitation, extension of the infection to the myocardium (or perivalvular abscess), failure of medical therapy, or large vegetations with systemic emboli or recurrent emboli on adequate therapy.

For treatment of infective endocarditis, see Infectious Disease, Book 1.

Antibiotic Prophylaxis

Overview

Know the following from the ACC/AHA 2008 Focused Update on Infective Endocarditis.

Significant changes to the bacterial endocarditis prophylaxis prevention guidelines were made because it has become clear that infective endocarditis is more likely to occur from bacteremia caused by brushing teeth than from medical procedures. It appears that medical procedures cause little if any infective endocarditis.

Indications for Prophylaxis

Prophylaxis is no longer indicated for GI/GU surgeries. Prophylaxis prior to dental procedures is now indicated only for patients with specific highest-risk-for-IE cardiac conditions:

- Prosthetic valves
- Previous episode of endocarditis
- Congenital heart disease (CHD)
  - Unrepaired cyanotic CHD
  - Repaired CHD within 6 months of procedure
  - Repaired CHD with residual defects
- Cardiac transplant patients with valve lesions

Prophylaxis is no longer indicated for bicuspid aortic valve, any ASD or VSD (unless unrepaired and cyanotic, or repaired with residual defect), native valvular stenosis or regurgitation, mitral valve prolapse (with or without murmur), coronary artery bypass graft (CABG), or HCM (unless repair occurs within 6 months of procedure).

Quick Quiz

- Which type of ASD requires antibiotic prophylaxis before a dental procedure? Which of these require antibiotic prophylaxis: previous CABG? VSD? Mitral valve prolapse without murmur? Mitral valve prolapse with murmur? Prosthetic valve? Are your answers based on the ACC/AHA 2008 guideline update?
- Following acute rheumatic fever, how many years on average does it take for valvular dysfunction to occur?
- What common clinical symptoms do patients with aortic valve stenosis present with?

Antibiotic Selection for Prophylaxis

[Know the following:]

Dental procedures: All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa require prophylaxis in high-risk patients. See Table 5-8.

GU/GI procedures: Prophylaxis is not indicated in these high-risk patients for any GI or GU procedures.

Respiratory tract procedures, or skin or musculoskeletal tissue infection: The high-risk patient should receive prophylaxis that covers staphylococci and beta-hemolytic streptococci.

RUBELLA

Rubella during pregnancy is a common cause of patent ductus arteriosus (PDA), supravalvular aortic stenosis, branch pulmonary artery stenosis ("peripheral PS"), and other congenital cardiac defects.

RHEUMATIC FEVER

Rheumatic fever is common outside of the U.S., with more than 470,000 cases worldwide. In the U.S., the latest incidence is about 2–14 cases/100,000. In patients with pharyngitis, always swab throats for a strep screen. Joint affliction in rheumatic fever is distinguished from rheumatoid arthritis by the lack of typical joint deformities and a negative rheumatoid factor. The associated carditis typically has no symptoms referable to the heart!

Rheumatic fever occurs more frequently in overcrowded areas. It is the most common cause of mitral stenosis and tricuspid stenosis (Table 5-9 on page 5-32). Symptoms of valvular dysfunction generally occur, on average, 20 years following acute rheumatic fever infection.

SPECIFIC VALVE LESIONS

Note

Refer to Table 5-10 and Table 5-11 on page 5-34 and page 5-35 as you study these valve lesions.

Aortic Stenosis

Aortic stenosis (AS) is generally due to age-related, calcific valve degeneration. Congenital bicuspid aortic valves usually start getting calcified and stenotic between ages 40 and 70 years, while the normal trileaflet aortic valves become stenotic at > 75 years old. A bicuspid aortic valve is the most common congenital valve disorder (1–2%). Less frequently, rheumatic heart disease also can cause AS, generally in the setting of mitral valve disease.

Presenting signs and symptoms include the classic triad of heart failure, angina, and syncope with exercise.

Bedside physical exam with significant AS: The carotid pulse has a decreased amplitude and slowed upstroke (parvus et tardus), and the heart has a sustained apical impulse. Associated heart sounds include:

- A mid-to-late peaking, diamond-shaped systolic ejection murmur at the right upper sternal border (RUSB) or suprasternal notch, which radiates to the neck
- An S_4 gallop
- Often a decreased or absent 2nd heart sound due to decreased mobility of the aortic valve leaflets
- A paradoxical S_2 split with severe AS

Occasionally, an AS murmur is transmitted to the apex, where it can be confused with the systolic murmur of mitral regurgitation (the Gallavardin effect).

Table 5-8: Endocarditis Prophylaxis — Dental Procedures

Situation	Antibiotic	Regimen
Oral prophylaxis	Amoxicillin	2 gm orally
Unable to take oral medications	Ampicillin or Cefazolin* or ceftriaxone	2 gm IM/IV 1 gm IM/IV
Allergic to penicillin	Clindamycin or Cephalexin* or Azithromycin or clarithromycin	600 mg orally 2 gm orally 500 mg orally
Both allergic to penicillin and unable to take oral meds	Clindamycin or Cefazolin* or ceftriaxone	600 mg IM 1 gm IM/IV

*Note: Cephalosporins should not be used if the PCN allergy is an immediate-type hypersensitivity reaction.
Note: Antibiotics (PO or parenteral) are given 30 to 60 minutes before the procedure.

Table 5-9: Modified Jones Criteria for the Diagnosis of Rheumatic Fever

Major	Minor
Carditis	Previous rheumatic fever
Polyarthritis	Arthralgias
Chorea	Fever
Erythema marginatum	Acute phase reactants (high sed rate or WBC)
Subcutaneous nodules	ECG changes: prolonged PR interval

To make the diagnosis: requires 2 major criteria or 1 major and 2 minor criteria and evidence of a preceding group A strep infection (positive strep test or rising or elevated [> 250 Todd units] ASO titers).

The systolic ejection murmur of AS is louder with squatting, whereas the murmur of hypertrophic cardiomyopathy (HCM) decreases.

An ejection click sounds like a guitar string being plucked immediately after S_1. This ejection click is classic and common in bicuspid aortic valve patients but is not heard with age-related calcific AS. Ejection clicks can also be heard in patients with pulmonic stenosis.

With aortic stenosis, a systolic thrill can sometimes be felt over the upper precordium and the suprasternal notch. This thrill is a palpable sensation similar to feeling the purring of a cat.

Doppler echo is very accurate in detecting severe AS.

A left heart cath is typically used in the determination of AS if there is a discrepancy between clinical and echo findings---or to detect concomitant coronary artery disease.

Patients with AS have a high rate of coronary artery disease (CAD): 1/3 in those 40–60 years of age and 2/3 in those > 60.

AS severity by valve area:

- Mild = 1.9–1.5 cm^2
- Moderate = 1.5–1 cm^2
- Severe = ≤ 1 cm^2

Mean gradients are also frequently used:

- Mild = < 25 mmHg
- Moderate = 25–40 mmHg
- Severe = > 40 mmHg

Without surgical intervention, median survival depends on clinical presentation, given by the mnemonic **SASH**:

- **S**urvival in AS:
  - **A**ngina = 5 years
  - **S**yncope = 3 years
  - **H**eart failure = 2 years

Results with surgical treatment are much better, so refer for valve replacement early for all symptomatic patients. It is also indicated for patients with severe asymptomatic AS who develop left ventricle (LV) dysfunction or who need CABG.

Percutaneous methods of valve replacement (known as "transcatheter" valve placement) are currently available for symptomatic patients who are high-risk surgical candidates.

Caution must be used with vasodilators in the treatment of ventricular failure due to AS. Aortic stenosis has the worst prognosis of all valvular lesions, and medical therapy alone is not effective.

Chronic Aortic Regurgitation

Chronic aortic regurgitation (AR) occurs as a result of valve deformity (e.g., bicuspid valve, rheumatic fever, endocarditis, or degenerative valve disease) or an abnormal aortic root (e.g., dilation seen in Marfan syndrome, senile aortic disease, giant cell arteritis, relapsing polychondritis, or syphilis).

Chronic AR causes LV volume overload, which eventually causes LV dilation and a drop in LV systolic function.

Bedside physical exam with chronic AR: Chronic aortic regurgitation has several classic physical findings:

- A decrescendo diastolic high-pitched blowing murmur caused by the regurgitation through the valve. This murmur is loudest at the left sternal border (3rd space) if due to the aortic leaflet, and at the right sternal border (RSB) if due to aortic root disease (because the root is closer to the RSB). The high-pitched blowing sound of this murmur indicates a high flow, whereas mitral stenosis, which also causes a diastolic murmur, causes a low-flow diastolic "rumble."
- Occasionally, you hear an Austin Flint murmur, which does sound similar to the low-flow rumble of mitral stenosis. It is thought to be due to the high-pressure regurgitant jet striking the anterior mitral leaflet and impeding mitral valve inflow by causing early closure. This murmur is not associated with a presystolic accentuation as seen in MS.
- A wide and bounding "Corrigan" pulse 2° to elevated systolic and low diastolic components of BP that causes "water-hammer" arterial pulses.
- There are many other exam findings associated with chronic AR that have eponyms and are all related to pulsations; e.g., Becker sign = visible pulsations of the retinal arteries; de Musset sign = bobbing of the head with the pulse; Müller sign = bobbing of uvula during systole.

Chest x-ray shows an enlarged left ventricle and may show dilation of the ascending aorta. Aortic angiography can be performed at the time of cardiac

Quick Quiz

- When should valve replacement occur for aortic valve stenosis?
- Name 2 conditions that cause chronic aortic regurgitation.
- What is the usual treatment for acute aortic regurgitation?
- When the mitral stenosis is more severe, is the S_2-OS interval smaller or larger?
- Which type of murmur occurs in mitral stenosis?
- Which mitral lesion is associated with hemoptysis?

cath and is the gold standard to diagnose AR—although it is more frequently diagnosed with echo.

Patients with chronic AR should be monitored with echocardiograms to follow chamber size and LV function.

Treat chronic and severe AR with vasodilators. Routine use of vasodilator therapy is no longer recommended for non-severe AR. ACEIs/ARBs are typically used, along with diuretics to treat symptoms. Valve surgery is indicated if the patient is symptomatic or when echocardiogram shows LV end-systolic dimension > 55 mm, LV end-diastolic dimension > 75 mm, or EF < 55% (remember AR: the 55/55 rule!).

Intraaortic balloon pump placement is contraindicated in patients with aortic regurgitation.

Acute Aortic Regurgitation

Native acute AR is normally caused by a flail leaflet due to:

- Endocarditis
- Type A aortic dissection
- Trauma

Prosthetic valve acute AR can be caused by:

- Tissue valve leaflet rupture
- Mechanical valve closure problem (e.g., thrombosis)
- Paravalvular regurgitation due to infection

Patients with acute AR present with severe pulmonary edema and low cardiac output. Because the cardiac output and BP are low, there is no bounding arterial pulse. The diastolic murmur is short because it ends when the ventricular pressure rises to the level of the low aortic pressure. The LV in these patients does not have time to compensate for the LV volume overload.

Patients with significant acute AR and heart failure without a reversible cause almost always need immediate surgery.

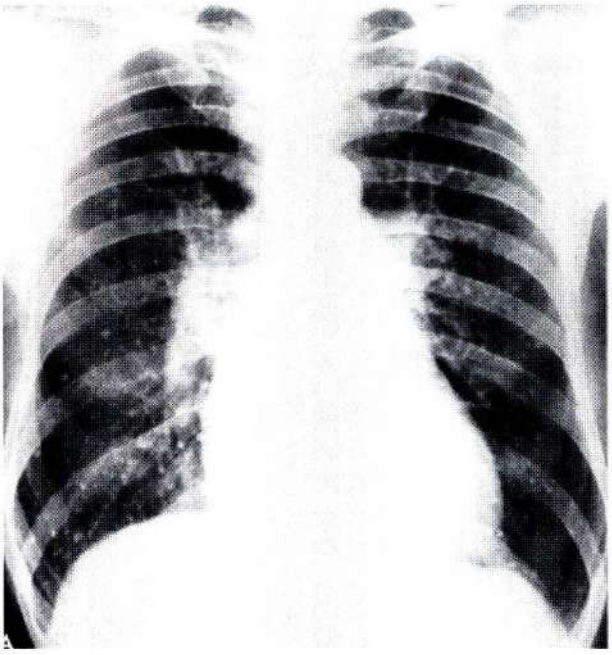


Image 5-10: Mitral stenosis with enlarged left atrium

Mitral Stenosis

Mitral stenosis (MS) is relatively rare in the U.S. It is almost always due to rheumatic fever. Other causes are SLE, rheumatoid arthritis, and severe valve calcification. Atrial fibrillation is common. MS can cause heart failure (HF), but sometimes 2° pulmonary hypertension is the main physical finding.

Bedside physical exam with MS: Patients have a diastolic murmur with a diastolic opening snap (OS) caused by the tensing of the chordae tendineae and stenotic leaflets. The time interval between the second heart sound (S_2) and the OS or the S_2-OS interval is inversely related to the severity of the MS: the more severe the MS, the higher the left atrial (LA) pressure, and thus the earlier the mitral valve is forced open in diastole, the smaller the S_2-OS interval.

As mentioned in heart sounds, the S_1 is accentuated and can also have a snapping quality. The diastolic murmur is often described as a "rumble," which suggests low flow, in contrast to the high-pitched, high-flow diastolic murmur heard in aortic regurgitation.

The chest x-ray shows the following triad:

1) Prominent pulmonary artery revascularization
2) An enlarged left atrium (see straightening of left atrial border in Image 5-10 on page 5-33)
3) Normal-sized LV

The ECG also shows the enlarged left atrium. Do an echo to confirm the diagnosis. Hemoptysis can occur in patients with MS; it is due to rupture of the pulmonary bronchial vessels distended by pulmonary venous hypertension.

Table 5-10: Heart Defects and Associated Sounds (1 of 2)

Valve Defect	Murmurs	Clicks	Change in Heart Sounds	Pulse Waveforms; a/v Waves
Aortic stenosis	S: SEM at RUSB, mid-to-late peaking, diamond shaped	S: Ejection click if congenital or bicuspid	Absent S_2 (occ); S_4; Parodoxically split S_2	Slowed carotid upstroke
Acute aortic regurgitation	D: Short diastolic murmur		S_3 if severe	Thready
Chronic aortic regurgitation	S: Occasional early systole SEM. D: 1) High pitched, decrescendo early to holodiastolic (regurgitation through the valve) 2) Austin Flint: low, rumbling diastolic (regurgitant stream striking the anterior mitral leaflets)		S_3 if severe	"Corrigan pulse"; "Water-hammer pulse"
Mitral stenosis	D: Diastolic rumble	D: Opening snap (only diastolic click!)	S_1 is enhanced, sometimes "snapping." May be silent if severely calcified	Large left *a* waves and *y* descent
MVP with murmur; chronic mitral regurgitation (CMR)	S: MVP: Late SEM follows click. CMR: Pansystolic constant murmur	S: MVP: Mid-systolic click (Click-murmur syndrome)	S_3 if severe; S_4	
Acute mitral regurgitation	S: Pansystolic decrescendo at apex		S_3 if severe	Large left *v* waves
Tricuspid stenosis	D: Diastolic at LSB			Giant right *a* waves
Tricuspid regurgitation	D: Systolic at LLSB			Large right *v* waves
Pulmonic stenosis		S: Ejection click	Persistently/widely split S_2	Large right (jugular) *a* wave
VSD	S: Holosystolic at LLSB			
ASD—ostium secundum	S: SEM at LSB (increased flow across pulmonic valve)		Fixed-split S_2	
ASD—ostium primum	S: SEM at LSB (increased flow across pulmonic valve); also often associated TR or MR murmur		Fixed-split S_2	
Coarctation of the aorta	Midsystolic to continuous murmur (depending on severity) in the upper back			
HCM	S: Harsh midsystolic murmur		S_4	Brisk carotid upstroke that is BIFID in 2/3
PDA	S + D: Continuous "machinery" murmur at LUSB		Paradoxically split S_2	

Note that S_4 is also heard in ischemic heart disease, diabetic cardiomyopathy, and hypertensive heart disease with concentric hypertrophy.
Note: RIght-sided murmurs sound louder on Inspiration; lEft on Expiration; all right-sided valve problems can rarely be caused by carcinoid.
Cannon *a* waves occur in complete heart block and with ventricular pacing.

Table 5-11: Heart Defects and Associated Sounds (2 of 2)

Murmur Louder with:	CXR	Other:	Valve Defect
Squatting*, expiration after PVCs	LVE	Sustained apical impulse; etio: bicuspid valve classic triad is LVF, angina, and syncope with exercise	Aortic stenosis
Squatting*, expiration	LAE	Etio: virtually always rheumatic fever SSx: hemoptysis. Secondary pulmonary HTN	Mitral stenosis
Squatting*, expiration	LVE	Etio: congenital, endocarditis, or dilated aortic root from: Marfan, VSD, arteritis, polychondritis, syphilis	Chronic aortic regurgitation
Squatting*, expiration	Normal	Cardiogenic shock and pul edema Consider aortic dissection	Acute aortic regurgitation
Standing or Valsalva: longer—moves earlier into systole; sustained handgrip, expiration	LAE	Etio of MVP: congenital; ischemia	MVP with murmur; chronic mitral regurgitation (CMR)
Squatting*, expiration	Normal	Etio: endocarditis, MI with papillary muscle ischemia or rupture, chordae tendineae rupture; SSx: pul edema	Acute mitral regurgitation
Inspiration	RVH; enlarged pulmonary artery	Etio: virtually always congenital—rarely caused by rheumatic fever and carcinoid; congenital type usually does not progress	Pulmonic stenosis
Squatting*, inspiration	RAE	TS is rare; Etio: usually rheumatic fever but also congenital and carcinoid synd. with carcinoid, pt. usually also has TR SSx: venous congestion	Tricuspid stenosis
Squatting*, inspiration	RVE	Etio: usually dilation from pul HTN; other: rheumatic fever, endocarditis (IVDA), carcinoid. Liver pulsations, JVD	Tricuspid regurgitation
Handgrip	RVE + LVE	Consider in new MI with new systolic murmur	VSD
	RVE; shunt vascularity	ECG: RAD, RBBB	ASD—ostium secundum
	RVE	ECG: LAD, RBBB	ASD—ostium primum
	Rib notching, loss of aortic notch		Coarctation of the aorta
Standing, Valsalva. Note: Sustained handgrip decreases murmur.	LVE	Apical impulse may have double- or triple-taps	HCM
	Calcification of ductus arteriosis		PDA

*Squatting or lying down; or raising legs if already supine.
... Persistently/widely split S_2 (still varies with inspiration but never goes away) occurs with pulmonic stenosis, PE, RBBB, LV ectopic beats.
... Fixed split S_2 (A_2-P_2 interval remains the same throughout breathing cycle) from ASD.
... Paradoxically split S_2 (P_2 before A_2) is caused by severe HCM, LBBB, RV ectopic beats, AS, and PDA.

Pregnancy: The increased blood volume in pregnancy can cause a precipitous exacerbation of MS. The initial presentation of MS in a pregnant patient may be new-onset atrial fibrillation and pulmonary edema. Heart rate and volume control (beta-blockers and diuretics) are an essential part of treatment. If anticoagulation is necessary, never give warfarin in the 1st trimester; it is teratogenic. Give adjusted-dose heparin instead.

All nonpregnant patients with MS-caused atrial fibrillation should be anticoagulated with warfarin.

Do percutaneous valvotomy in patients with symptomatic MS or asymptomatic MS with pulmonary hypertension (pulmonary artery systolic pressure > 50 mmHg at rest or > 60 mmHg with exercise). Surgical mitral valve replacement is less desirable but frequently is a necessary alternative if valvular anatomy is not favorable for percutaneous valvotomy (especially if there is severe calcification of the valve) or significant (more than mild) mitral regurgitation is present.

Chronic Mitral Regurgitation

Chronic mitral regurgitation (MR) can be due to rheumatic heart disease, mitral valve prolapse (below), annulus dilation from left ventricular dilation, prior episode of endocarditis, and/or ischemic effects on the papillary muscle (from coronary artery disease or MI). Chronic MR presents differently from acute MR. Because the heart has an enlarged left atrium in the chronic form, there is less back pressure to the flow across the incompetent mitral valve, resulting in a constant intensity, holosystolic murmur instead of decrescendo (as in acute MR). Atrial fibrillation frequently develops. In both severe chronic and acute MR, the S_1 is soft or absent and S_2 is widely split. (The aortic valves close early because of decreased volume ejected from the left ventricle.) An S_3 is common in severe MR.

The left ventricular ejection fraction (LVEF) in MR is frequently normal or above normal, because LV outflow now has 2 routes of exit during systole (forward through the aorta and backward through the regurgitant mitral valve). Significant MR should be treated with diuretics and afterload reducing agents (ACEIs/ARBs). Do surgery if the patient is symptomatic or if asymptomatic with:

- LVEF < 65%, and/or
- LV enlargement with left ventricular end-systolic diameter > 40 mm, or
- pulmonary hypertension.

Repair (if possible) is preferable to replacement. Percutaneous valve repair is now available.

Mitral Valve Prolapse

Mitral valve prolapse (MVP) is the most common valvular problem seen in practice (up to 2.4%) and is more common in women. There are different causes of MVP. Most MVPs are considered a normal variant; in these, the chordae tendineae are weakened, causing a billowing of the otherwise normal mitral valve leaflets. On the other hand, myxomatous changes in the mitral valve leaflets (determined by echo) invariably progress to mitral regurgitation. Many symptoms (dyspnea, panic attacks, chest pain, etc.), previously attributed to MVP, have been shown to occur with no greater frequency than in otherwise healthy people.

Bedside physical exam with MVP: These patients have a midsystolic click (followed by a mid-to-late systolic murmur [click-murmur syndrome] if there is associated MR).

The murmur of MVP is like the murmur in hypertrophic cardiomyopathy (HCM) in that decreased preload increases the intensity of the murmur. The click and murmur become louder and move earlier into systole with standing or Valsalva, both of which decrease preload and, hence, LV volume. (An earlier click means a longer murmur.) This gives the clue for how you can tell the difference between an ejection click (aortic or pulmonary stenosis) and the midsystolic click—an ejection click is fixed, whereas the midsystolic click varies in timing with changes in the patient's position. Stand the patient up, and the midsystolic click sounds just like an ejection click. Squatting or supine position increases LV size and causes the click to occur later, thereby shortening the murmur. Dynamic auscultation is required to diagnose MVP clinically.

Acute Mitral Regurgitation

Acute mitral regurgitation (AMR) commonly presents with acute-onset pulmonary edema.

Causes of native valve AMR include:

- Flail leaflet (due to endocarditis, MVP, or trauma)
- Papillary muscle ischemia or rupture (MI, trauma)
- Chordae tendineae rupture (endocarditis, acute rheumatic fever, trauma, spontaneous)

Causes of prosthetic valve AMR include:

- Tissue valve leaflet rupture
- Mechanical valve closure problem (e.g., thrombosis)
- Paravalvular regurgitation due to infection

Bedside physical exam with AMR: Decrescendo systolic murmur at the apex. Echocardiogram shows a hyperactive LV with normal-to-high ejection fraction and a normal-sized left atrium. There are large, left-sided *v* waves on wedge pressure tracing.

Treat with afterload reduction and diurese. Unlike severe AR, intraaortic balloon pump can be helpful for patients in heart failure from AMR. Urgent surgery is often required.

Quick Quiz

- What should you consider in a pregnant woman with new onset of atrial fibrillation and pulmonary edema?
- Describe the murmur sometimes heard with MVP. Does that murmur's intensity decrease or increase with standing? With Valsalva maneuver?
- Carcinoid usually results in what type of tricuspid murmur?
- On physical exam, in patients with tricuspid regurgitation, what large waves are noted on the jugular waveform?
- True or false? Pulmonic stenosis is virtually always acquired.
- Ebstein anomaly is occasionally associated with which structural and electrical abnormalities?

Tricuspid Stenosis

Tricuspid stenosis (TS) is rare. Causes are rheumatic fever (usual), congenital, carcinoid syndrome, and endocarditis. If the cause is carcinoid, the TS is generally found in association with tricuspid regurgitation (TR). Note: Carcinoid can affect either right-sided heart valve and typically implies a hepatic tumor if valvular involvement is present. (The pulmonary vascular bed is generally quite effective in removing the active 5-HIAA products that lead to valve damage.) Patients have systemic venous congestion without pulmonary venous congestion or pulmonary hypertension.

Bedside physical exam with TS: Patients have a diastolic murmur along the left sternal border, which increases with inspiration (as do all right-sided murmurs). They have a giant *a* wave, caused by backflow during atrial contraction against a stenotic tricuspid valve. There may be ascites and lower-extremity edema.

The ECG shows the tall, peaked P waves in II and VI (evidence of the right atrial hypertrophy) but no indications of right ventricular hypertrophy (RVH). Chest x-ray shows an enlarged right atrium.

Treat the underlying disease and perform surgery.

Tricuspid Regurgitation

Tricuspid regurgitation (TR) often is a functional result of RV dilation, which can be caused by end-stage left ventricular failure, pulmonary embolism, or other causes of pulmonary hypertension. TR can also be caused by rheumatic heart disease, endocarditis, carcinoid, and congenital disease—Ebstein anomaly. Endocarditis affecting the tricuspid valve is typically seen in drug abusers, and it is often caused by staph; also consider *Candida*.

Bedside physical exam with TR: Patients have a holosystolic murmur along the lower left sternal border (increases with inspiration) that does not radiate to the axilla. Severe TR can cause a parasternal heave, liver pulsations, venous distention, ascites, and lower extremity edema (signs of RV failure). There are large, jugular *v* waves, reflecting the backflow through the tricuspid valve during ventricular contraction.

Diagnose with echo. Treat the underlying disease. Antibiotic treatment is usually sufficient for endocarditis; the valve rarely needs to be removed, unless the cause is *Candida*. Surgery also can be indicated in circumstances of severe destruction of the valve.

Pulmonic Stenosis

Pulmonic stenosis is virtually always congenital, and it typically does not progress! It is a fairly common congenital valve anomaly in adults. Rarely is it caused by rheumatic heart disease or carcinoid. It may cause RV hypertrophy. Although it generally is not seen along with other abnormalities, it does occur in Noonan syndrome, in which the patient has low-set ears and hairline.

Bedside physical exam with severe pulmonic stenosis: Patients have an ejection click and a prominent jugular *a* wave, which is caused by backflow during atrial contraction against an inadequately emptied right ventricle.

If needed, open the stenotic pulmonic valve with balloon valvuloplasty.

Pulmonic Regurgitation

Pulmonic regurgitation is typically secondary to pulmonary hypertension (e.g., primary, cor pulmonale, mitral stenosis), but it may be due to a primary valve lesion (congenital, rheumatic heart disease, endocarditis, carcinoid). Pulmonary artery pressure is > 60 mmHg in patients with secondary pulmonic regurgitation.

Ebstein Anomaly

With Ebstein anomaly, the tricuspid septal leaflet is positioned lower in the ventricle than normal (apically displaced)—so the RA appears huge and the RV small. Tricuspid regurgitation (TR) murmur is common. It is occasionally seen with atrial septal defect (ASD) and with WPW syndrome.

VALVE SURGERY

In general, valve surgery is indicated for any valve problem if the patient is symptomatic at rest or with low levels of exertion. Even though there is high mortality, valve surgery is better than no surgery in patients with severe valve disease and ventricular failure (since the natural history in these cases is 100% early mortality).

Bioprosthetic valves are less durable (especially in young patients and those on hemodialysis) but do not require anticoagulation. These are indicated in patients with a life expectancy of < 5–10 years and those with contraindications to anticoagulation (chronic bleeding problems, ulcers). They also are often given to women of childbearing age to avoid having to use anticoagulants during pregnancy.

Mechanical valves are used for all others and do require anticoagulation, but they are very durable—typically lifelong in most cases.

Balloon valvuloplasty is the procedure of choice in pulmonic valve stenosis and frequently mitral stenosis—but not aortic stenosis due to a very high short-term restenosis rate (6–12 months).

For mitral regurgitation (MR), if surgery is required, do valve reconstruction whenever possible because it has better outcomes and about half the morbidity of MV replacement. Reconstruction is valve repair and/or annuloplasty with an annuloplasty ring, and is especially likely to be done with MVP, ruptured chordae, flail leaflets, endocarditis, and annular dilation. Valve replacement is usually necessary in MR that is due to rheumatic fever.

Newer "edge-to-edge" percutaneous MV repair, where a device (a clip) is placed across the two leaflets in their mid-part, creating a double-orifice mitral valve, is now being performed; this procedure is ordinarily reserved for patients who are high risk for traditional repair. Similarly, percutaneous aortic valve replacement is now available for patients who are at high risk for surgery.

The major determinants in prognosis after valve surgery include ejection fraction, degree of symptoms, and type of valve surgery (valve repair is better than replacement). Echocardiography is best for checking for prosthetic valvular function. A transesophageal echocardiogram (TEE) is especially useful for checking mitral valve prosthesis. Fluoroscopy is also a useful tool for documenting leaflet motion with mechanical valves if valve dysfunction is suspected.

When anticoagulating mechanical valves, keep the INR 2.0–3.0 for the aortic valve and 2.5–3.5 for the mitral valve. A mechanical mitral valve has a higher risk for a thrombus formation compared to an aortic (hence the higher INR requirement). Therefore, if holding warfarin for a procedure or surgery, then bridging anticoagulation with unfractionated heparin is recommended for mechanical mitral valves.

Final Pearls about Murmurs

[Know:]

- Aortic stenosis: suprasternal notch thrill with systolic murmur, paradoxically split S_2
- Chronic aortic regurgitation: early diastolic, blowing, decrescendo murmur heard best at left sternal border, 3rd intercostal space, with patient leaning forward and exhaling; also, low-pitched late-diastolic rumble (Austin Flint)
- Mitral stenosis: hemoptysis, opening snap, low-pitched diastolic murmur at the apex

Valsalva (one last time): decreases the murmur of aortic stenosis (AS), increases the murmur of hypertrophic cardiomyopathy, and increases the murmur of mitral valve prolapse.

ARRHYTHMIAS

MECHANISMS OF ARRHYTHMIAS

The 3 usual mechanisms of abnormal rhythms are reentry, triggered activity, and automaticity. The reentry is the most common mechanism of arrhythmias, especially AV node reentrant tachycardia (AVNRT), atrial flutter, and most ventricular tachycardias. AVNRT is the most common type of reentrant tachycardia—hence it also is the most common supraventricular tachycardia (SVT). Be able to diagnose all rhythms at a glance (see ECGs on page 5-60).

SICK SINUS SYNDROME

Sick sinus syndrome causes any one (or combination) of sinoatrial node problems, including sinus bradycardia, sinus pauses/sinus arrest, and tachy-brady syndrome (typically baseline sinus bradycardia or sinus pauses with intermittent episodes of rapidly conducting atrial fibrillation/atrial flutter). These patients generally do not need electrophysiologic testing. Because prognosis is good, there are only 2 indications for treatment with a pacemaker:

1) Symptomatic patient
2) Patient with tachy-brady syndrome where treatment of tachyarrhythmias might precipitate or worsen bradycardia

HEART BLOCK

1st degree heart block: PR interval > 200 ms. Can be caused by medications and generally requires no treatment.

2nd degree heart block (Mobitz 1, Wenckebach): gradual prolongation of PR interval until QRS drops; return PR interval shorter than last conducted PR interval. It can occur during periods of high vagal tone during sleep (obstructive sleep apnea) or in endurance athletes. It generally does not require treatment unless it is causing symptoms.

2nd degree heart block (Mobitz 2): abrupt loss of P wave conduction to the ventricle with no evidence of gradual prolongation. Generally, it indicates higher grade AV block, and associated symptoms can necessitate pacemaker placement.

Quick Quiz

- What are the major prognostic factors after valve surgery?
- Describe the abnormal heart sounds found in AS, chronic AR, and MS.
- What is the treatment sequence for atrial flutter?
- What procedure can cure the most common types of atrial flutter with 85–95% success rate?

3rd degree heart block (complete heart block): None of the P waves are conducted to the ventricles, and there is often a regular junction (40–60 bpm) or ventricular (20–40 bpm) escape rhythm.

Permanent pacing is indicated if there is a Mobitz 2 or complete heart block—especially if symptomatic. See Arrhythmias and Blocks, starting on page 5-22, for more detailed pacing criteria post-MI.

To differentiate between AV node block vs. infranodal block: AV node block typically has narrow QRS complexes, has escape focus rate > 40 bpm (typically 40–60 bpm), and is responsive to atropine. Infranodal block (involving the His-Purkinje system) is mostly associated with widening of the QRS complex.

SUPRAVENTRICULAR TACHYCARDIAS

Atrial Flutter

Typical (Type I) atrial flutter, the common form, has a characteristic atrial rate of 300 bpm (240–340)—commonly with a 2:1 AV block. Pay close attention for atrial flutter when any ECG is shown with a heart rate of 150 bpm; atrial flutter waves at 300 bpm with 2:1 AV block gives a heart rate of 150 bpm.

Atrial flutter can be:

- typical counterclockwise rotation around the right atrium, characterized by negative sawtooth flutter waves in II, III, and aVF (with positive deflection in V1); or
- clockwise, characterized by positive flutter waves in ECG leads II, III, and aVF (with prominent negative deflection in V1).

These 2 atrial flutter types share the same right atrial reentrant circuit around the cavo-tricuspid isthmus (circuit running between the inferior vena cava and the tricuspid valve).

Atrial flutter is generally an indication of disease, most often either organic heart disease or pulmonary disease. Flutter is a relatively unstable rhythm and often spontaneously converts to either atrial fibrillation or a normal sinus rhythm.

The normal AV block is 2:1 with a ventricular rate of half the atrial rate. If it is ≥ 3:1, the cause is either medications or can suggest advanced AV conduction system disease. Systemic embolization (most notably TIA/stroke) can occur due to atrial flutter or atrial fibrillation; thus, anticoagulation needs to be considered in both disorders.

Vagal maneuvers or adenosine cannot terminate atrial flutter; however, they can slow the ventricular rate and allow better diagnosis. Rule out pulmonary emboli (often multiple) and thyroid disease—especially if there is no heart or lung history.

The most effective treatment for atrial flutter is synchronized DC (direct current) cardioversion. Always shock if the patient is hemodynamically compromised.

Do not continue DC cardioversion if the patient repeatedly reverts back to atrial flutter.

Antiarrhythmic drugs can be used for nonemergent cardioversion. IV ibutilide is most effective and can be considered a 1st line pharmacologic cardioversion for atrial flutter; however, be aware that it can cause QT prolongation (8%) and *torsades de pointes*. Make sure potassium and magnesium levels are normal prior to administering ibutilide to minimize risks of *torsades*.

Procainamide, flecainide, and propafenone can be used as well. See Antiarrhythmic Therapy on page 5-45.

In patients with atrial flutter and preexcitation syndrome (WPW), avoid digoxin, calcium channel blockers, and beta-blockers. See WPW, page 5-42.

Radiofrequency ablation is a treatment modality that can cure the most common types of atrial flutter (success rate 85–95%), and it is used for persistent or recurrent atrial flutter, although recent studies have suggested it is a reasonable 1st line approach in some circumstances.

Anticoagulate patients with atrial flutter, as you would for atrial fibrillation (see next). Indeed, up to 60% of patients with atrial flutter have had atrial fibrillation in the preceding year.

Atrial Fibrillation

Overview

Atrial fibrillation (A-fib) is the most common sustained arrhythmia. Ventricular rhythm is irregularly irregular with ventricular rate generally in the range of 120–180 bpm in the absence of drug therapy. Many patients with atrial fibrillation have structural heart disease, and it is commonly associated with hypertension, heart failure, valvular heart disease, coronary artery disease, chronic lung disease, and obstructive sleep apnea.

A-fib can be classified as first detected (only 1 diagnosed episode), paroxysmal (≥ 2 episodes, self-terminating, each lasts ≤ 7 days, most < 24 hours), persistent (≥ 2 episodes, each lasts > 7 days), and permanent (> 6–12 months).

The symptoms of A-fib vary widely between patients.

Some patients are asymptomatic and others have severe, functionally disabling symptoms. Complications are embolic events—mainly stroke, and tachycardia-induced cardiomyopathy.

With new-onset A-fib or in A-fib not responsive to the usual treatment, consider hyperthyroidism, untreated or undertreated obstructive sleep apnea, hypomagnesemia, alcoholism/cocaine abuse, excessive caffeine (energy beverages), and nicotine as possible causes.

Treatment of Atrial Fibrillation

Rhythm Control vs. Rate Control

You have 2 choices for the treatment of A-fib:

1) Rhythm control (restoration and maintenance of sinus rhythm)
2) Rate control (control of ventricular response)

There are no significant differences in mortality or morbidity between the 2 treatments. Rate control is the common strategy for asymptomatic or minimally symptomatic patients, while rhythm control is often selected for significantly symptomatic and younger patients. For patients with hemodynamic instability, ongoing myocardial ischemia, symptomatic hypotension, angina or heart failure, emergent/urgent direct-current (DC) cardioversion is recommended.

A-Fib Rhythm Control: DC Cardioversion

DC cardioversion is the most effective method to restore sinus rhythm. Pharmacologic rates of successful cardioversion are lower and depend on the antiarrhythmic drug used and clinical scenario. If possible, DC cardioversion should be carried out under sedation, with appropriate cardiac and hemodynamic monitoring.

Emergent/Urgent DC cardioversion is recommended for patients with hemodynamic instability (angina pectoris, MI, shock, or pulmonary edema), ongoing myocardial ischemia, symptomatic hypotension, angina or heart failure, and WPW syndrome with rapid ventricular rate.

Important points regarding DC cardioversion:

- With slow A-fib, consider inserting a temporary pacemaker before DC cardioversion because the patient could have sinus nodal disease and may have asystole after cardioversion.
- TEE-guided cardioversion is done frequently, especially if the time of onset of the A-fib is unclear. It is fast and cost-effective.
- Just as with atrial flutter, do not continue DC cardioversion if the patient repeatedly goes right back into A-fib shortly after being shocked.

Note: In what other scenarios do you not shock a patient with an abnormal tachycardic atrial rhythm (but stable hemodynamically)? Digitalis intoxication and hypokalemia.

A-Fib Rhythm Control: Pharmacologic Cardioversion

When attempting pharmacologic cardioversion, use these guidelines—again, use is based on duration of symptoms.

- For A-fib > 7 days:
  - 1st line: dofetilide
  - 2nd line: amiodarone or ibutilide
- For A-fib < 7 days:
  - 1st line: dofetilide, flecainide, ibutilide, or propafenone (previously, dronedarone*)
  - 2nd line: amiodarone (Exception: If < 48 hours and poor cardiac function, amiodarone is 1st line.)

*Do not prescribe dronedarone to patients with class IV heart failure or those who have had decompensated heart failure in the past month, especially if LVEF < 35%, because it causes increased mortality in these patients. In addition, dronedarone should not be used in patients who have had pulmonary toxicity on amiodarone or elevated LFTs.

Maintenance Drugs for Rhythm Control

Pharmacological therapy can be useful in patients with recurrent paroxysmal or permanent A-fib to maintain sinus rhythm. Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of A-fib is recommended. Deciding which drug to use is based on the presence of structural heart disease (safety) and, to a lesser degree, on efficacy. Catheter ablation is useful in maintaining sinus rhythm for selected patients with significantly symptomatic, paroxysmal A-fib who have failed treatment with an antiarrhythmic drug and have a normal or mildly dilated left atrium, normal or mildly reduced LV systolic function, and no severe pulmonary disease. Catheter ablation is less useful (however, can be considered) in treatment of patients with symptomatic persistent A-fib.

Selection of antiarrhythmic drugs:

- No or minimal heart disease: flecainide, propafenone, sotalol, and dronedarone; if ineffective, then amiodarone, dofetilide, or catheter ablation.
- Heart failure (EF < 35%): amiodarone or dofetilide (definitely not dronedarone!); if ineffective, then catheter ablation.
- Coronary artery disease: dofetilide or sotalol; if ineffective, then amiodarone or catheter ablation.
- Hypertension:
  - Left ventricular hypertrophy (LVH) present: Use amiodarone; if ineffective, then catheter ablation.
  - LVH not present: Use flecainide, propafenone, or sotalol. If these fail, then go to amiodarone, dofetilide, or catheter ablation.

Quick Quiz

- In what circumstance is immediate DC cardioversion indicated for A-fib?
- What can happen after DC cardioversion to the patient who has A-fib with a slow rate? What intervention prevents this complication?
- According to the 2013 guidelines, what HR is an acceptable target for patients with A-fib and stable ventricular function? For others, how is strict control of heart rate defined?
- For patients undergoing cardiac surgery, what medication should be used to prevent postoperative A-fib?

Use of class IC agents for atrial fibrillation:

The unopposed use of class IC agents (e.g., no concomitant AV nodal blocking agents) can organize atrial fibrillation into atrial flutter conducting to the ventricles much more rapidly. This rapid conduction could degenerate into ventricular tachycardia (VT) or ventricular fibrillation (VF). To avoid this potentially fatal event, always use class IC agents with AV nodal agents such as beta-blockers, non-dihydropyridine calcium channel blockers, or digoxin.

Reminders for rhythm control of atrial fibrillation:

1) Dofetilide and sotalol require hospital monitoring to initiate therapy.
2) Dronedarone cannot be used in the New York Heart Association (NYHA) class IV heart failure (HF) or if HF exacerbation in past 4 weeks.

A-Fib Rate Control

The 2013 update to the ACC/AHA Practice Guideline: Management of Patients with Atrial Fibrillation states that a resting heart rate < 110 bpm is acceptable and is as good as strict control if stable ventricular function (LVEF > 40%) and there are no or acceptable symptoms related to the arrhythmia; though uncontrolled tachycardia may, over time, be associated with a reversible decline in ventricular performance. Strict control of heart rate is considered 80 bpm at rest or 110 bpm during a 6-minute walk.

Use beta-blockers (atenolol, metoprolol) or calcium channel blockers (verapamil, diltiazem) for rate control at rest and with exercise. Digoxin can have a synergistic effect for rate control when combined with these medications.

A-fib with HF: acute setting and no preexcitation—IV beta-blockers (esmolol, metoprolol, or propranolol) to slow ventricular rate or amiodarone to slow ventricular rate and possibly restore sinus rhythm. Calcium channel blockers (verapamil, diltiazem) should be used with caution to slow the ventricular response in patients with hypotension or heart failure because of negative inotropic effects.

IV digoxin or amiodarone is used to control the heart rate acutely in patients with A-fib and HF who do not have an accessory pathway.

If exertional symptoms related to A-fib are present, assess heart rate control during exercise, adjusting pharmacological treatment to keep the rate in physiological range.

Digoxin is useful to control the heart rate at rest in patients with A-fib with HF, LV dysfunction, or for sedentary individuals.

Radiofrequency ablation of the AV node with subsequent permanent pacing is a treatment for patients with refractory A-fib and for those who cannot tolerate the meds needed for rate or rhythm control. This strategy provides definitive rate control but does not cure the underlying atrial fibrillation—hence, patients still require anticoagulation.

In many patients, A-fib originates as abnormal impulses arising in the pulmonary veins. Radiofrequency ablation, or isolation of the pulmonary veins, is becoming increasingly popular in treating recurrent, drug refractory, symptomatic A-fib, although it is not yet established as 1st line therapy.

Postoperative A-Fib

For patients undergoing cardiac surgery, give an oral beta-blocker to prevent postoperative A-fib (unless contraindicated). For those who develop postoperative A-fib, achieve rate control with AV nodal blocking drugs (beta-blockers, calcium channel blockers, or digoxin). Routine postoperative amiodarone is not indicated for the prevention of atrial fibrillation.

Anticoagulation for Atrial Fibrillation Before and After Cardioversion

If it has been < 48 hours since the onset of A-fib, cardiovert most patients without any preceding anticoagulation.

If it has been > 48 hours since the onset of A-fib (or duration of A-fib is unknown) and the patient is stable, you must achieve adequate anticoagulation x3 weeks before you attempt cardioversion. As an alternative to preceding anticoagulation, it is reasonable to perform TEE, and if there is no identifiable thrombus, perform a cardioversion.

After cardioversion: Treat with low-molecular-weight or unfractionated heparin until INR = 2–3 on warfarin. As an alternative to heparin/warfarin, one of the novel oral anticoagulants (NOACs) can be considered.

Chronic Anticoagulation

Antithrombotic therapy to prevent thromboembolism is recommended for all patients with A-fib (irrespective of rate or rhythm control strategy), except for those with lone A-fib (age < 60 years without heart disease and without risk factors) or contraindications. The selection of the antithrombotic agent should be based upon the absolute risk of stroke. Patients with rheumatic mitral stenosis and prior thromboembolism are at highest risk. For patients with non-valvular A-fib (without rheumatic mitral stenosis or prosthetic valves), the **CHADS2** scoring system is often used for risk stratification:

- **C**HF during last year or EF < 35% (any history): 1 point
- **H**TN (prior history): 1 point
- **A**ge ≥ 75: 1 point
- **D**M: 1 point
- Prior **S**troke, TIA, or embolic event: **2** points

Meds based on CHADS2:

- 0 points = ASA alone
- 1 point = oral anticoagulation or ASA
- 2 points or more = oral anticoagulation

Oral anticoagulation can be achieved with vitamin K antagonists or new anticoagulant agents (dabigatran, rivaroxaban, and apixaban). New agents do not require monitoring (INR); however, they cannot be used in patients with prosthetic valves, rheumatic mitral stenosis, renal insufficiency, and advanced liver disease.

Dabigatran is useful as an alternative to warfarin for prevention of stroke and systemic thromboembolism in patients with A-fib and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve, significant valve disease, severe renal failure (Cr clearance 15 mL/min) or advanced liver disease (impaired baseline clotting function).

MAT

Multifocal atrial tachycardia (MAT) is mainly diagnosed by ECG criteria of atrial rate > 100 beats/minute with P waves of at least 3 distinct morphologies.

MAT is usually seen in patients with pulmonary disease and may be a result of theophylline use. MAT can also be caused by very low K^+ and Mg^{+2}.

Therapy is directed at underlying illness. If medications are deemed necessary, calcium channel blockers or amiodarone might be useful. Digoxin is of no use in MAT! It can actually worsen it, in addition to causing digoxin-toxic arrhythmias.

SVT

Supraventricular tachycardia (SVT) refers to narrow QRS complex tachycardias originating above the ventricles. The key step in assessment is recognition of P wave and position of P wave in comparison to QRS.

If no P wave is seen (buried in QRS) or is seen at the end of the QRS (very short R-P interval), the patient has AV node reentrant tachycardia (AVNRT). Representing 60–70% of regular SVT, AVNRT is the most common reentrant tachycardia.

If a P wave is somewhere in ST-segment (short R-P interval) AV reentrant tachycardia ([AVRT]; 20–30% of regular SVT) should be considered.

If a P wave is seen after a T wave (long R-P interval), atrial tachycardia (10% regular SVT) is most likely the diagnosis. In acute management of narrow QRS complex, regular tachycardia treatment options include beta-blockers, adenosine, calcium channel blockers, or carotid sinus massage.

Most SVTs are due to a reentrant mechanism. Again, the most common SVT is AVNRT. Rate is typically 150–250 bpm (although it can be slower or faster). Radiofrequency ablation is highly successful and can be considered equally with medical therapy as 1st line long-term therapy. Situations where ablation is preferred include hemodynamic instability, severe symptoms, failed medical therapy, public safety (pilots and bus drivers), and clear patient preference. If medical therapy is chosen, beta-blockers, calcium channel blockers, or digoxin are 1st line options, followed by antiarrhythmic drugs (typically flecainide or propafenone if there is no structural heart disease).

WPW

Wolff-Parkinson-White ([WPW]; preexcitation syndrome): PR interval is < 0.12 seconds due to a delta wave and symptoms of tachycardia. Total QRS is > 0.12 seconds because of the fusion between the impulse that uses the normal conduction system and that which uses the abnormal (accessory) pathway, which bypasses the AV node. This bypass tract (accessory pathway, AP) conducts faster than the AV node; therefore, a portion of the electrical current reaches the ventricle sooner (the delta wave on the ECG) and preexcites the ventricle—hence the alternative name, "preexcitation syndrome." Occasionally, the accessory pathway is concealed, and the delta wave is not visible. An unusual cause of WPW can involve Ebstein anomaly of the tricuspid valve.

Spectrum of arrhythmias related to WPW includes orthodromic AVRT (narrow QRS complex regular tachycardia, which uses the AV node antegrade and AP retrograde), antidromic AVRT (wide QRS complex regular tachycardia, which uses the AP antegrade and AV node retrograde), and atrial fibrillation (irregularly irregular wide QRS complex tachycardia using antegrade AP conduction).

Treatment of accessory pathways: Many patients have completely asymptomatic AP and no dysrhythmias. Patients with AP and symptoms of tachycardia (called WPW syndrome) can be treated with vagal maneuvers, adenosine, or calcium channel blockers—same as any

Quick Quiz

- How is the CHADS2 score calculated? At what CHADS2 score should you treat with warfarin/NOACs (unless contraindicated)?
- In what patient group is MAT found?
- What is the treatment for acute A-fib in WPW?
- On an ECG, PVCs are often followed by what type of pause?
- Ventricular tachycardia (VT) is defined as ≥ 3 sequential PVCs occurring at what bpm?
- List the ECG criteria consistent with VT.

SVT! (In these cases, the impulses are moving down the normal conduction system and returning via the accessory pathway to complete the circuit.) But never treat acute A-fib in WPW with digoxin, verapamil, or beta-blockers. Although verapamil and digoxin increase the refractory period in the AV node, they can preferentially enhance conduction down the accessory pathway and precipitate ventricular fibrillation (V-fib).

Instead, treat acute A-fib in WPW with IV procainamide, ibutilide, or amiodarone. Shock if there are any signs of hemodynamic deterioration in any WPW tachyarrhythmia; especially watch those with ventricular rate > 285 bpm because they are at greatest risk of V-fib.

WPW syndrome is associated with a low but definitive risk of sudden death, and therefore radiofrequency ablation is the preferred long-term treatment option!

VENTRICULAR ARRHYTHMIAS

PVCs

Premature ventricular contractions (PVCs) often have a compensatory pause; that is, they do not reset the sinoatrial node, and the time between the sinus beats that are on either side of the PVC = 2 basic RR intervals.

Asymptomatic, simple PVCs do not need to be treated if LV function is normal. If you do attempt treatment (beta-blockers are 1st line), the PVCs should decrease by 80% for the treatment to be considered successful—otherwise, stop treatment. (Most patients have spontaneous resolution, or decrease anyway.) Simple PVCs occur beyond the T wave, are uniform, and have constant coupling (reentrant).

Complex PVCs (pairs, triplets) also do not need to be treated if the patient is asymptomatic and has no heart disease!

If a patient has had an MI and has an ejection fraction of < 40%, frequent PVCs (> 10/hour) indicate a high risk of sudden cardiac death—especially if they are sequential.

Ventricular Tachycardia

ECG Findings

Ventricular tachycardia (VT) is defined as 3 or more sequential QRS complexes of ventricular origin at a rate of 100 bpm or faster. Based on duration and association with symptoms, VT can be defined as nonsustained (asymptomatic with duration of less than 30 seconds) or sustained (symptomatic or duration of more than 30 seconds). VT can be monomorphic and polymorphic.

Monomorphic VT is generally regular in rate and appearance. It needs to be differentiated from SVT with aberrant conduction, bundle-branch block, pacing, and QRS changes due to severe hyperkalemia. The majority of patients with monomorphic VT have structural heart disease (particularly ischemic heart disease). Idiopathic VT occurs in otherwise structurally normal hearts and has much better prognosis. The most common idiopathic VT is right ventricular outflow tract (RVOT) VT.

ECG criteria indicative of VT [Know!]:

- AV dissociation
- Fusion and capture beats
- Northwest axis
- Positive or negative concordance in precordial leads
- Absence of rS complex in all precordial leads
- If rS is present, r to S time > 100 msec
- QRS width of > 140 msec with a RBBB
- QRS width > 160 msec with a LBBB

If a patient with a history of structural heart disease develops wide QRS complex regular tachycardia, VT is significantly more likely than SVT.

VT also can be bidirectional, with the complexes alternating in direction; this is usually due to digitalis intoxication but also can be seen post-MI and in a relatively rare genetic condition called catecholaminergic polymorphic ventricular tachycardia (CPVT).

Polymorphic VT generally has irregular ventricular rate and displays polymorphic QRS morphology. QRS complexes appear to twist around an isoelectric axis. Duration of polymorphic VT is typically brief; however, it can be sustained and can degenerate into V-fib. It can occur in patients with prolonged QT interval (*torsades de pointes*) or in patients with normal QT interval (typically in the setting of ischemia/MI).

Treatment

For sustained monomorphic VT, do the following:

- Stable: Give IV amiodarone.
- Hemodynamically compromised: Shock.
- Unstable and refractory to electrical cardioversion: Give IV amiodarone/procainamide.
- VT specifically with acute MI: Most use amiodarone first. IV lidocaine can be useful.

For sustained polymorphic VT, do the same as monomorphic, except:

- IV beta-blockers if ischemia is suspected or cannot be excluded
- IV amiodarone, as long as there is no prolonged QT
- Urgent cath if ischemia is suspected
- Assess for *torsades de pointes* (see below)

Never use verapamil with any wide complex tachycardias in the emergency setting. (30% of those with ventricular tachycardia rapidly deteriorate!)

RVOT VT can be terminated acutely with adenosine, and beta-blockers/calcium channel blockers (CCBs) can be used for long-term management. Remember, you generally do not want to use CCBs for wide-complex tachycardias.

Implantable Cardioverter-Defibrillators

Implantable cardioverter-defibrillators (ICDs) can be used for secondary (after event occurs) or primary prevention.

The following are Class I indications for ICDs from the 2008 ACC/AHA device therapy guidelines and 2012 focused update:

- Patients who are survivors of cardiac arrest due to VF or who have hemodynamically unstable sustained VT after evaluation has excluded any completely reversible causes
- Patients with structural heart disease and spontaneous sustained VT (> 30 sec), whether hemodynamically stable or unstable
- Patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study
- Patients with LVEF ≤ 35% due to prior MI who are at least 40 days post-MI and are in the NYHA functional Class II or III; also, LVEF < 30% and in the NYHA functional Class I
- Patients with nonischemic dilated cardiomyopathy (DCM) who have an LVEF ≤ 35% and who are in the NYHA functional Class II or III
- Patients with nonsustained VT due to prior MI, LVEF ≤ 40%, and inducible VF or sustained VT at electrophysiological study

Torsades de Pointes

Know this topic! *Torsades de pointes* (TdP) is a common type of polymorphic VT. It is associated with prolonged QT interval (congenital or acquired). Acquired forms are most often drug induced.

Drugs that commonly cause TdP are:

- Class Ia antiarrhythmic drugs (quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (sotalol, dofetilide, and amiodarone)
- Haloperidol and tricyclic antidepressants
- Antibiotics (macrolides)
- Antihistamines (astemizole and terfenadine)
- Antifungal agents (ketoconazole)

You also can see TdP in association with very low K^+ or Mg^{+2}. Bradycardia can promote TdP in patients with prolonged QT.

Treat *torsades de pointes* with:

- DC cardioversion for sustained episode.
- Magnesium sulfate 2–4 grams IV over 10–15 minutes.
- Correction of hypokalemia.
- Correction of bradycardia (isoproterenol or pacing).
- Never treat with Class Ia or Class III antiarrhythmic drugs (AADs).

To prevent recurrence of TdP: 1) discontinue any offending medications, 2) prevent bradycardia with isoproterenol or overdrive pacing, 3) supplement potassium and magnesium.

Nonsustained Ventricular Tachycardia

Nonsustained ventricular tachycardia (NSVT) is defined as asymptomatic VT (> 3 sequential PVCs with HR > 100 bpm) lasting for < 30 seconds.

NSVT can indicate increased risk for death in patients with heart disease, particularly ischemic cardiomyopathy. NSVT patients are at risk of sustained VT and sudden death when:

- they have ischemic cardiomyopathy (LVEF < 40%), or
- sustained VT can be induced at electrophysiologic testing (EPT).

These patients benefit from ICD implantation.

Patients with NSVT without structural heart disease have good prognosis, and they do not require further management.

PACEMAKERS

Permanent pacing is indicated for patients with symptomatic bradycardia, sinus node dysfunction (sick sinus syndrome), and AV conduction problems. In the absence of symptoms, permanent pacing should be strongly considered for patients with complete heart block and advanced (i.e., not Wenckebach) type 2 second-degree AV block (particularly associated with wide QRS).

The most common pacemaker (Table 5-12) is **DDD**, which stands for **d**ual-chamber paced, **d**ual-chamber sensed, and **d**ual response to sensing: triggered and inhibited. Most clinicians use DDD, unless the patient is in chronic, slow atrial fibrillation. The DDD is the most physiologic and provides better exercise tolerance.

Quick Quiz

- With what type of tachycardia should you never use verapamil?
- ICDs are recommended for primary prevention in what situations with ischemic and nonischemic cardiomyopathy patients?
- Which antiarrhythmic drugs prolong the QT interval?
- What is the treatment for *torsades de pointes*?
- Under what conditions is permanent pacing recommended?
- How long do you have to wait for an antiarrhythmic to reach steady-state therapeutic levels?

"Pacemaker syndrome" (associated lightheadedness and/or syncope) can occur with single-chamber ventricular pacing and is commonly cured by dual-chamber (DDD) pacers, which restore the atrial "kick."

"Pacemaker-mediated tachycardia" can occur when paced ventricular complexes are sensed by the atrial lead and then trigger subsequent ventricular paced beats; this cycle can continue indefinitely.

ANTIARRHYTHMIC THERAPY

Drugs

Overview

With antiarrhythmic drugs (AADs), always wait 4–5 half-lives before determining whether a drug is effective.

Notes:

- All AADs have a proarrhythmic potential.
- Per the CAST study, there is evidence that Ic anti-arrhythmic drugs decrease survival in patients with ventricular arrhythmias that occur post-MI. The only drug that shows a benefit is a beta-blocker after a Q wave (ST elevation) infarction.
- Mexiletine is effective in most patients who respond to lidocaine.
- Digoxin works by inhibiting membrane ATPase. It increases contractility and slows AV conduction and HR.
- Quinidine increases digitalis levels.

Class I: Sodium channel blockers that slow electrical conduction in the heart.

Ia: Quinidine, procainamide, disopyramide—slow conduction velocity, prolongs action potential duration, and can prolong QT interval.

Ib: Lidocaine, tocainide, mexiletine, phenytoin—shorten action potential duration slightly with no significant QT prolongation.

Ic: Flecainide and propafenone—slow conduction velocity without effect on potential duration or QT interval.

Class II: Beta-blockers—decrease heart rate and blood pressure by blocking impulses that can cause irregular heart rhythm and decreasing hormonal effects (e.g., adrenaline) on the heart.

Class III: Amiodarone, sotalol, and the newer agents, dofetilide (oral Tikosyn®) and dronedarone (Multaq®)—prolong the action potential by potassium channel blockade. These agents can cause QT prolongation. Note: See side effects on dronedarone below.

Class IV: Calcium channel blockers, especially verapamil and diltiazem, slow inward current. They decrease heart rate and blood pressure like class II.

Adenosine and Digoxin

Digoxin is not in the above classes of antiarrhythmics, but it has antiarrhythmic effects and occasionally is used for this. Remember that digoxin is usually reserved for treating severe heart failure.

Adenosine is also not in the above groups. Adenosine slows conduction in the AV node and is used for conversion of SVT (AV node reentry) to normal sinus rhythm. It also induces coronary artery vasodilation and is used in cardiac perfusion imaging. It depresses LV function, but it has such a short half-life, it can even be used in patients with decreased LV function.

Table 5-12: Permanent Pacemakers

The North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group (NBG) Code
First letter = chamber(s) paced—**V/A/D** (ventricle, atrium, or dual [V + A])
Second letter = chamber(s) sensed—**V/A/D/O** (ventricle, atrium, dual [V + A], or none)
Third letter = mode(s) of response—**T/I/D/O** (triggered, inhibited, dual [T + I], or none)
Fourth letter = programmability—**P/M/C/R/O** (programmable rate and output, multiprogrammable, communicating, rate-modulated, or none)
Fifth letter = arrhythmia control—**P/S/D/O** (pacing, shock, dual [P + S], or none)

Notes on Verapamil

Avoid verapamil with:

- Atrial fibrillation or atrial flutter occurring in WPW
- Wide-complex tachycardias
- Beta-blockers—relative contraindication because they are both negative chronotropes and negative inotropes
- Patients with asymptomatic hypertrophic cardiomyopathy (HCM)
- Patients with obstructive HCM in the setting of systemic hypotension or severe dyspnea at rest

Okay to use verapamil:

- To control the ventricular response to A-fib or atrial flutter in an otherwise healthy heart
- MAT
- SVT (2nd choice after adenosine)
- Symptomatic treatment in HCM (but look above regarding avoiding verapamil in HCM)
- Severe, concentric LVH
- Hypertension

Major Side Effects of AADs

[Know!] All AADs are, by their nature, arrhythmogenic. Especially remember the following:

Class Ia:

- Quinidine: prolongs the QRS complex and the QT interval---occasionally leading to *torsades de pointes*, diarrhea, and (rarely) autoimmune thrombocytopenic purpura. Also "cinchonism": hearing loss, tinnitus, and psychosis.
- Procainamide: Prolongs QT and QRS but also causes blood dyscrasias, such as agranulocytosis, neutropenia, and thrombocytopenia, in ~ 0.5%. It also causes drug-induced lupus and must be used with caution in HF patients because it has a mild myocardial depressive effect.
- Disopyramide: prolonged QT, QRS, and *torsades de pointes*. It is also anticholinergic and vagolytic, so it causes urinary retention, constipation, dry mouth, and negative inotropic effects. Because quinidine and disopyramide prolong both the QRS and QT intervals, avoid them in patients with 2nd or 3rd degree heart block. Disopyramide has a negative inotropic effect, so avoid in patients with HF.

Class Ib:

- Lidocaine: seizures.
- Tocainide is now used less often because of an association with aplastic anemia.

Class II: Beta-blockers commonly cause decreased libido and impotence. They must be tapered slowly; stopping a beta-blocker abruptly can precipitate angina.

Class III: All of them can cause prolonged QT, QRS, and *torsades de pointes*.

- Amiodarone is the most effective, but also, due to the extremely high iodine content, it is the most toxic antiarrhythmic drug. It causes corneal deposits in 98% of patients!—also, hyper/hypothyroidism, pulmonary fibrosis, gray skin, and sun sensitivity but not hematologic changes. Pulmonary fibrosis from amiodarone can be severe and is fatal 10% of the time. It ordinarily occurs in the first year of treatment. It tends to occur only in older patients (> 40 years old), and in those with low CO diffusing capacity. (Pulmonary fibrosis is unlikely to develop on a maintenance dosage of < 200 mg/day.) Amiodarone also causes a less common acute form of pulmonary toxicity. Again, amiodarone: hepatic toxicity; extremely long half-life (40–55 days); hyper/hypothyroidism; gray skin.
- Dronedarone: July 2011—dronedarone showed 2x increased mortality in patients with permanent A-fib and class III and IV heart failure. Current recommendation is to not prescribe dronedarone to patients with permanent A-fib.
- Dofetilide: works by blocking the cardiac ion channel carrying the delayed rectifier potassium current (I_{Kr}). It is used to treat highly symptomatic A-fib and can be used in patients with CAD and HF. Dofetilide must be started as an inpatient by approved prescribers and is renally-dosed. It can cause significant QT prolongation requiring dose reduction or discontinuation. Do not use dofetilide with the following medications: cimetidine, verapamil, ketoconazole, trimethoprim, prochlorperazine, megestrol, or any form of hydrochlorothiazide; these agents can increase the activity of the CYP3A4 liver enzyme and increase dofetilide levels.

Digitalis toxicity is more likely to occur in elderly patients and in those with low K^+, low Mg^{+2}, or low pO_2 (low, low, low), and impaired renal function. The toxic levels of digoxin are determined by changes in the ECG, not by blood levels. Most common ECG changes are bradycardia and prolonged PR interval.

Electrophysiologic Testing

Electrophysiologic (EP) studies are most commonly used to identify and characterize SVTs and VTs, often as a precursor to radiofrequency ablation.

Radiofrequency Ablation

Radiofrequency ablation is the treatment of choice for WPW syndrome.

It is also used for the following if the patient prefers it to standard drug therapy or the condition is not responsive to meds:

- AVNRT
- Atrial tachycardia

Quick Quiz

- When is it okay to use verapamil; when is it not okay?
- Which antiarrhythmic drug can cause lupus?
- Name the side effects associated with amiodarone.
- What determines a toxic level of digoxin?
- For what conditions is the treatment of choice radiofrequency ablation, guided by EP studies?
- What is the most common cause of syncope?
- Explain how you approach the diagnostic workup in a patient with probable neurocardiogenic (vasovagal) syncope.
- What are the tests used to work up high-risk patients with syncope?

- Atrial flutter
- Idiopathic VT

It has also been used to treat atrial fibrillation by ablating a focal source of A-fib or by destroying the AV node and placing a ventricular pacemaker.

SYNCOPE

Syncope is sudden transient loss of consciousness with associated loss of postural tone and spontaneous recovery. It is important to differentiate syncope from other types of loss of consciousness. Classifications of syncope:

Neurally mediated (reflex) syncope symptoms include dizziness, lightheadedness, and fatigue, with prodromal features such as diaphoresis, pallor, palpitations, nausea, hyperventilation, and yawning. Myoclonic jerks can occur when the patient is unconscious, and it needs to be distinguished from seizure activity. Several subtypes:

- Vasovagal syncope, as in the common faint, is the most common cause of syncope. It is triggered by intense emotion, pain, prolonged standing, alcohol, or heat exposure. Vasovagal episodes are typically preceded by a prodrome that includes nausea, vomiting, flushing, hot flashes, and diaphoresis. Extremely elderly patients may not have a classic prodrome.
- Situational reflex syncope is triggered by cough, micturition, etc. These triggers provoke reflex vasodilation and bradycardia leading to syncope.
- Carotid sinus hypersensitivity may be responsible for up to 40% of falls in the elderly and is diagnosed with a pause > 3 seconds during carotid sinus massage (CSM). Absolute contraindications to CSM include MI within 3 months and TIA/CVA within 3 months. Relative contraindications to CSM include previous VT/VF or carotid bruit.

Arrhythmia: Bradycardia, SVT, or VT.

Orthostatic hypotension: Syncope due to orthostatic hypotension 2° autonomic dysfunction causes symptoms with no increase in the patient's heart rate with standing or during the vertical phase of tilt-table testing.

Typically, try nonpharmacologic therapy first (e.g., support hose and increased salt); but treatment can also include midodrine (ProAmatine®). Midodrine is a prodrug for desglymidodrine, an alpha agonist that stimulates the alpha-adrenergic receptors of both arteriolar and venous vessels. Fludrocortisone, a mineralocorticoid agonist that promotes retention of sodium and water, also can be used but can cause supine hypertension.

Organic heart disease: Anatomic causes include depressed EF (causing VT/VF), AS, HCM, atrial myxoma, PE, pulmonary hypertension (HTN), and ischemia.

Medications: Check the patient's history for new medications. Common medications associated with syncope include cardiovascular, neurologic, antiparkinsonian, and antidepressants. A classic cause of drug-related syncope includes medications for BPH (prazosin, terazosin, and tamsulosin).

A thorough history, physical exam, supine and upright blood pressure, and ECG are an essential part of the initial evaluation followed by additional testing in selected subgroups (carotid sinus massage, echocardiogram). If the diagnosis is certain, treatment is initiated. If the diagnosis remains uncertain, stratify the patient to determine whether the patient is at increased risk of death (typically patients with severe structural heart disease, clinical, or ECG features suggesting arrhythmic syncope).

High-risk patients should be admitted for further workup, which can include coronary angiogram and EP study. Low-risk patients, particularly with only 1 episode of syncope, usually do not require further evaluation.

If the history is typical, and this is the first episode in a young patient with no suspected heart disease, the patient can be reassured and sent home.

Initial measures aimed at reducing events include avoidance of precipitating factors and also avoiding volume depletion. Patients should also be taught to sit or lie down at the onset of symptoms and to initiate physical isometric maneuvers (leg crossing and hand grip). Value of pharmacologic agents (beta-blockers, fludrocortisone, midodrine) is less certain. Frequent episodes, despite initial management, require evaluation with continuous ambulatory electrocardiography (patients with severe cardioinhibitory response during syncope could benefit from pacemaker placement). Patients in high-risk occupations should be investigated with the first episode of syncope.

CARDIOMYOPATHIES

There are 3 main types of nonischemic cardiomyopathy: hypertrophic, restrictive, and dilated.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is the most common of the genetic cardiovascular diseases (autosomal dominant pattern of inheritance; [Image 5-11]). It is characterized by a thickened but not dilated left ventricle in the absence of other cardiac or systemic conditions (HTN, aortic valve stenosis). HCM is the most common cause of sudden death in young age (age < 35), including competitive athletes.

Patients with HCM typically present with heart failure, chest pain (typical or atypical), or syncope. They can be asymptomatic and recognized because of abnormal physical exam (murmur).

Bedside with HCM: The patient typically has a harsh, crescendo-decrescendo systolic murmur, typically in the left 3rd space, which increases with Valsalva and decreases with sustained handgrip. There is a carotid pulse that has a brisk upstroke, but, because outflow obstruction occurs late in systole, it is bifid in 2/3 of HCM patients. The briskness of the upstroke further distinguishes it from aortic stenosis. Palpation at the apex can surprise you with a double- or triple-tap impulse. A mitral regurgitation murmur can also be heard from systolic anterior motion (SAM) of the mitral valve due to a suction-like effect of the outflow obstruction.

The ECG with HCM is abnormal in more than 90% of patients. Most common abnormalities include LVH, ST-T changes with sometimes marked T wave inversion in the lateral precordial leads, and Q waves in inferior and lateral leads.

Diagnosis is commonly made with echocardiogram, although recently cardiac MRI has emerged as a new diagnostic modality. There is no single classic morphologic form, and virtually all possible patterns of hypertrophy have been described. Some patients have dynamic obstruction related to SAM of the mitral valve.

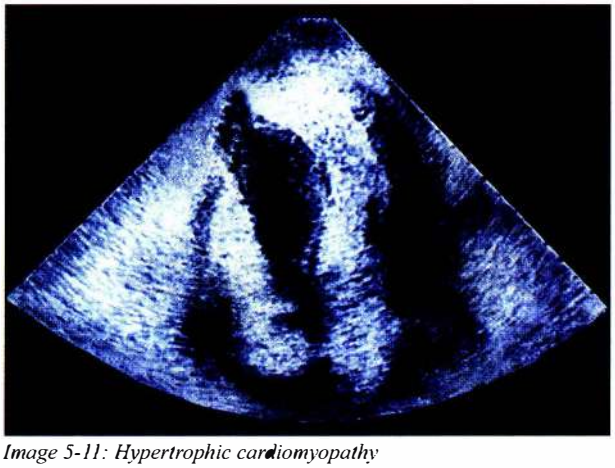


Image 5-11: Hypertrophic cardiomyopathy

Approximately 1/4 of patients with HCM have a resting gradient (greater than 30 mmHg).

A majority of patients with HCM have normal life expectancy with little or no disability; however, subgroups of patients are at risk for complications, including sudden death, progressive heart failure, and atrial fibrillation.

Risk factors for sudden death in HCM (and possible role for ICDs):

- Septal thickness > 30 mm
- Personal history of syncope
- Family history of sudden death in 1st degree family member
- NSVT on Holter monitor
- Failure to augment systolic BP on exercise tolerance testing (< 10 mmHg increase at peak exercise)

Treatment for HCM

Treatment for HCM:

- **Beta-blockers** (obstructive and nonobstructive HCM) and verapamil (obstructive HCM) improve diastolic filling by slowing heart rate.
- **Disopyramide** with beta-blockers for obstructive HCM when other drugs fail to achieve symptom control.
- **IV phenylephrine** (or other pure vasoconstrictor) is recommended for treating acute hypotension in HCM patients who do not respond to IV fluids.
- **ICD placement** is recommended for HCM patients with prior documented cardiac arrest, ventricular fibrillation, or hemodynamically significant VT. ICD is also reasonable to place if sudden cardiac death (SCD) in ≥ 1 first-degree relative(s), LV wall thickness ≥ 30 mm, or ≥ 1 recent unexplained syncopal episode(s).
- **Septal reduction therapy** via intracoronary injection of ethanol to cause a controlled septal infarction can reduce the obstruction in eligible patients with severe drug refractory symptoms and left ventricular outflow tract (LVOT) obstruction. Diuretics with beta-blockers to reduce filling pressures in hypertrophic cardiomyopathy (HCM) patients with severe heart failure, and then only with extreme caution!
- **Septal myectomy** is preferred treatment for patients with severe drug refractory heart failure (HF) symptoms (NYHA III and IV).

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy must be differentiated from constrictive pericarditis (page 5-55) because the signs and symptoms can be similar. Although constrictive pericarditis is often quickly treated with good results, restrictive cardiomyopathy is not reversible.

Arrhythmias, such as atrial fibrillation, occur early in the course of these diseases. Constrictive pericarditis is a pericardial problem; restrictive cardiomyopathy is a myocardial problem.

QuickQuiz

- What are the risk factors for sudden death in patients with HCM?
- What are the 3 main medications used in the treatment of HCM?
- What are some causes of restrictive cardiomyopathy?
- List some of the etiologies of DCM.
- In the 2013 ACC/AHA, what are the newly defined 2 major subdivisions of heart failure?

Causes of restrictive cardiomyopathy include amyloidosis, sarcoidosis, hemochromatosis, and lipid storage diseases. On 2D echocardiogram, the myocardium may be thickened with a granularity, which suggests an infiltrative process.

Thoracotomy is occasionally done to ensure that you do not miss a treatable constrictive pericarditis; these are treated with pericardiectomy.

Treat mild-to-moderate restrictive cardiomyopathy with diuretics.

DILATED AND NONISCHEMIC CARDIOMYOPATHIES

Patients with dilated cardiomyopathy (DCM) have ventricular dilation and depressed myocardial contractility in the absence of abnormal loading conditions such as hypertension or valvular disease. African-Americans have nearly a 3-fold risk for developing DCM when compared to Caucasians.

The prognosis of patients with symptomatic HF and DCM is poor, with 50% mortality at 5 years.

Etiologies of DCM:

- Familial cardiomyopathies (e.g., noncompaction)
- Idiopathic (probably viral—most common)
- Obesity
- Diabetes
- Hyperthyroidism
- Acromegaly
- Alcohol
- Cocaine
- Cancer chemotherapy (especially anthracyclines)
- Ephedra
- Cobalt
- Anabolic steroids
- Chloroquine
- Clozapine
- Amphetamines
- Methylphenidate
- Catecholamines
- Organic solvents ("glue sniffers" heart)
- Late hemochromatosis

Think Chagas disease in patients from Central and South American countries.

In contrast, nonischemic cardiomyopathies include cardiomyopathies due to volume or pressure overload, such as hypertension or valvular heart disease.

In pregnant women, a peripartum cardiomyopathy can occur anytime from the beginning of the last trimester through the first 6 months postpartum.

Heart failure due to dilated cardiomyopathy is treated similarly to other causes of HF (see below).

HEART FAILURE

OVERVIEW

Heart failure (HF) is defined as a complex clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. Left ventricular ejection fraction (LVEF) is considered important in classification of patients with HF.

The lifetime risk of developing HF is 20% for Americans ≥ 40 years of age. African-American males have the highest risk for HF, and the highest 5-year mortality rate (Atherosclerosis Risk in Communities [ARIC] Study-—ongoing).

The 2013 ACC/AHA definitions:

- Heart failure with reduced ejection fraction (HFrEF): EF ≤ 40%, systolic HF
- Heart failure with preserved ejection fraction (HFpEF): EF ≥ 50%, diastolic HF

Cardiac output is well maintained in mild HF, usually at the expense of increased left ventricular end-diastolic volume (LVEDV) and increased heart rate.

Numerous adaptations occur in response to heart failure in the peripheral circulation, kidney, skeletal muscle, and other organs. The changes contribute to the overall clinical manifestations and ultimately become maladaptive.

In response to exercise, LVEDV and plasma norepinephrine rise more than in controls, but the resulting cardiac output increase does not rise in proportion to O_2 consumption—so the patient has dyspnea on exertion and is easily fatigued. The adrenergic system and the renin-angiotensin-aldosterone system play a major role in progression of heart failure and maladaptive mechanisms.

LOW-OUTPUT HF

NYHA Classification

NYHA (New York Heart Association) classification of heart failure (classes and definitions) is a functional classification based on how much the patient is limited during physical activity. In clinical use, it is being superseded by the ACC/AHA classification (next). NYHA classification:

Class I: Cardiac disease but no limitation in physical activity.

Class II: Slight limitation of normal physical activity (fatigue, palpitations, dyspnea, and/or angina).

Class III: Marked limitation of physical activity. Slight activity causes symptoms.

Class IV: Symptoms may be present at rest. Unable to carry on any physical activity without discomfort.

ACC / AHA Staging

The 2013 ACC/AHA staging system for HF shows heart failure as more of a progressive disorder and has goals of therapy for each stage (A through D). Know the definition, goal of therapy, and medications for each stage of HF.

Stage A HF patients are at high risk for heart failure but have no structural heart disease/symptoms of HF and include those with hypertension (HTN), atherosclerotic disease, diabetes, obesity, and metabolic syndrome. Stage A also includes any asymptomatic patient using cardiotoxins (such as anthracycline) or with a family history of cardiomyopathy.

So yes, you read this right: Just having HTN means you have Stage A heart failure!

Goals for Stage A therapy are to treat the disorder (HTN, lipid disorder) and control/avoid other conditions that can lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents (excess alcohol/illicit drug use). Regular physical activity to improve functional status is recommended in all HF patients.

Stage A drugs include ACEIs/ARBs/statins in appropriate patients.

Stage B HF patients have structural heart disease but without signs or symptoms of heart failure. This stage includes patients who have a history of a previous MI and those with LV remodeling from left ventricular hypertrophy (LVH) or low LVEF, and those with asymptomatic valvular heart disease.

Goals of Stage B therapy are to prevent HF symptoms and prevent further cardiac remodeling.

Stage B drugs are: ACEIs/ARBs, beta-blockers, and statins if history of MI/ACS. Use ICD if indicated, and revascularization or vascular surgery as appropriate.

Stage C HF patients have structural heart disease with prior or current symptoms of heart failure. These are patients with structural heart disease as described above in Stage B, and who additionally have signs and symptoms of HF (e.g., dyspnea, fatigue, and decreased exercise tolerance).

Goals for Stage C therapy are control symptoms, patient education, improved health-related quality of life, and prevention of hospitalization and mortality.

Stage C drugs are:

- loop diuretics for all volume overload NYHA II–IV patients, hydralazine/isosorbide dinitrate for symptomatic African-American NYHA III–IV patients, aldosterone antagonist for NYHA II–IV patients (Cr > 30 mL/min and K < 5 mEq/dL), and
- statins and beta-blockers as used in Stage B (i.e., if MI/ACS), and ACEIs/ARBs as used in Stage A.

Use ICD and/or cardiac resynchronization therapy (CRT) if indicated, and revascularization or vascular surgery as appropriate.

Stage D HF patients have marked symptoms at rest and frequent hospitalizations despite maximal medical therapy.

Goals for Stage D therapy are to control symptoms, improve health-related quality of life, reduce hospital readmissions, and establish patient's end-of-life goals.

Stage D drugs are the same as those for Stage C.

Options for Stage D patients also include consideration of "extraordinary measures," including heart transplant, chronic inotropes, temporary or permanent mechanical circulatory support (ventricular assist devices), and experimental surgery or experimental drugs; and palliative care, hospice, and ICD deactivation.

Until definitive therapy (coronary revascularization, mechanical circulatory support, or heart transplantation) is performed or acute precipitating problem resolves, patients with cardiogenic shock should receive temporary IV inotropic support to maintain systemic perfusion and preserve end-organ performance.

The most common causes of HF with reduced EF (HFrEF) are:

- coronary artery disease (40%—although recent data pushes this to near 60% of etiologies),
- dilated cardiomyopathy (30%),
- valvular disease (15%), and
- hypertension (10%).

HF is the most common diagnosis in hospitalized elderly patients. Only 50% of patients with HF die from actual pump failure; ~ 40% die from arrhythmias!

Quick Quiz

- Define Stage A through Stage D heart failure (ACC/AHA classification). What are the goals of therapy for each of these stages?
- What is the sequence of drugs used to treat HF based on ACC/AHA stages?
- What are the most common causes of low-output HF?
- What factors are associated with poor prognosis in HF?
- What is the sequence of events that worsens HF?

Determining Prognosis in HF

In severe HF, a worse prognosis is associated with:

- Lower ejection fraction
- Low sodium
- CKD
- Anemia
- Elevated troponin
- High brain natriuretic peptide (BNP)
- Increased width of QRS
- Persistent sinus tachycardia
- Poor functional capacity (NYHA III and IV)
- High norepinephrine and catecholamine levels

Exercise training in patients with stable chronic HF is associated with an 11% reduction in combined all-cause death or hospitalization (2009 HF-ACTION Trial).

The Seattle Heart Failure Model and/or The Heart Failure Survival Score can provide a reasonable "ballpark" estimate of HF prognosis based on standard clinical data.

Mechanism of HF

Heart failure with reduced ejection fraction (HFrEF) results in decreased cardiac output. This in turn causes an increased A-a O_2 difference and decreased renal perfusion. The decreased cardiac output can be due to systolic dysfunction, diastolic dysfunction, or both. Note that diastolic dysfunction can occur with normal cardiac output (see below). After a certain point, decreased cardiac output from any type of HF causes decreased renal perfusion. This stimulates the release of renin, which allows the conversion of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II in the lungs. Angiotensin II then stimulates the secretion of aldosterone, which then causes retention of Na^+ and water, causing a greatly increased filling pressure (moving the Starling curve to the right).

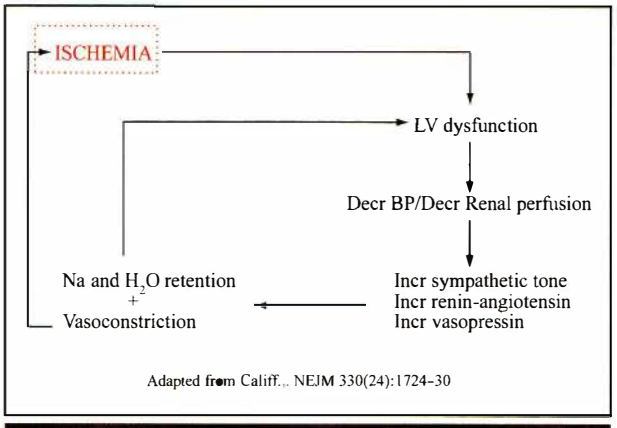


Figure 5-6: Spiral of Worsening HF

Let's see if we have all of that: Low CO → low renal perfusion → high renin → high angiotensin I → high angiotensin II → high aldosterone → retention of Na^+ → retention of water → high filling pressure → exacerbation of HF (Figure 5-6). The increased heart rate in HF is due to both an increased sympathetic tone and an increased level of catecholamines in an attempt to compensate for reduced stroke volume. The higher the catecholamine pool, the worse the prognosis.

ADH is released from the hypothalamus but has a minor effect.

Atrial (or A-type) natriuretic peptide (ANP) and brain natriuretic peptide ([BNP]; also called B-type natriuretic peptide) are released from the heart myocytes; the release is stimulated by stretching of the atrium (ANP and BNP) and the ventricle (BNP). ANP and BNP increase excretion of sodium and water, cause vasodilation, and inhibit the effects of aldosterone. These peptides are released in an attempt to offset the effects of renin angiotensin and ADH but cannot antagonize them adequately.

In severe heart failure, the BNP increases 20–100-fold. High levels of these peptides (especially BNP) actually correlate directly with a poor prognosis in HF. BNP is also elevated in restrictive cardiomyopathy but not constrictive pericarditis and is used to differentiate between these disorders.

About 50% of HFs are caused by diastolic dysfunction (more recently termed "heart failure with preserved EF"; HFpEF) rather than systolic dysfunction. Myocardial ischemia, severe concentric LVH, HCM, and diabetic cardiomyopathy cause diastolic dysfunction, at least initially. With diastolic dysfunction, the CO is often normal; HF develops from increased filling pressure (from decreased relaxation due to increased stiffness). So the problem is not that the ventricle is not squeezing enough, but rather that it is not relaxing enough. This is reflected in elevated left and right end-diastolic pressure (LVEDP and RVEDP), tachycardia, and an S_4.

Treatment for HF

General Measures

See above for treatment according to ACC/AHA stage. We will now discuss the individual drugs and how they affect/improve survival in heart failure.

(Note: In our discussion, the term class refers to NYHA classification; the term stage refers to the ACC/AHA classification.)

Current pharmacologic management of low-output heart failure is aimed at reducing ventricular preload and afterload as well as diminishing, inhibiting, and/or antagonizing neurohormonal vasoconstrictor activation, rather than directly increasing cardiac contractility as in the past.

The optimal treatment of heart failure aggressively addresses the major risk factors including hypertension, diabetes, obesity, metabolic syndrome, hyperlipidemia, and coronary artery disease (CAD). Therapies that promote regression of LVH or reverse remodeling of the dilated heart should be used; these include inhibitors of catecholamines and the renin-angiotensin-aldosterone pathway.

ACE Inhibitors and ARBs

Angiotensin-converting enzyme inhibitors ([ACEIs]; captopril, enalapril, lisinopril, benazepril, fosinopril, quinapril, ramipril) are 1st line therapy. They are indicated in patients with HFrEF and current or prior symptoms to reduce morbidity and mortality. They decrease systemic vascular resistance, pulmonary capillary wedge pressure, right atrial pressure, and end-diastolic and end-systolic dimensions; and they improve cardiac performance, as evidenced by increased cardiac output and stroke volume, and by improved fractional shortening, as determined by echocardiography. Hence, they decrease tachycardia due to HF. ACEIs block formation of angiotensin II. They also decrease the incidence of ventricular arrhythmia and prolong survival. In addition, they reverse the remodeling in the myocytes, which causes progression of heart failure.

Angiotensin II receptor blockers (ARBs) block the effect of angiotensin II at the cell wall. ARBs are given in place of ACEIs (if ACEI intolerant) and are equally effective (commonly grouped as "ACEI/ARB").

ARBs cause less cough than ACEIs and are often given when patients develop refractory cough on ACEIs. Cough is caused by excessive bradykinin.

Monitor patients on ACEIs/ARBs for renal impairment and hyperkalemia.

Commonly used ARBs:

- Candesartan (Atacand®)*
- Valsartan (Diovan®)*
- Irbesartan (Avapro®)
- Olmesartan (Benicar®)
- Eprosartan (Teveten®)
- Losartan (Cozaar®)
- Telmisartan (Micardis®)

*Randomized controlled trial data show mortality benefit in heart failure.

Beta-Blockers

Beta-blockers are now part of standard heart failure treatment. In HF, the sympathetic nervous system is overstimulated. This raises norepinephrine levels, which can cause cardiac remodeling, lead to arrhythmias, and increase mortality risk. Mortality is clearly improved by carvedilol (~ 65% relative risk reduction), metoprolol succinate, and bisoprolol (~ 35%). They are indicated in patients with HFrEF and current or prior symptoms to reduce morbidity and mortality.

Previously, it was taught that starting these drugs while patients are decompensated is contraindicated. Current guidelines recommend initiation of beta blockade at any stage of heart failure, once adequate diuresis has been achieved and intravenous diuretics have been discontinued. Carvedilol (Coreg®) is a nonselective beta-blocker that also has some alpha-blocker effect. Use in conjunction with ACE inhibitors in Class I–IV heart failure.

Diuretics

Give diuretics if needed for volume control (i.e., decrease edema and pulmonary congestion) during Stage C therapy. Remember: Therapy now begins with ACEIs/ARBs and beta-blockers before patients even have symptoms.

Diuretics are effective in both heart failure with reduced or preserved EF for symptom control (volume overload). All but the aldosterone antagonist diuretics have no mortality benefit, unlike ACEIs/ARBs and beta-blockers.

Treat heart failure (HF) patients admitted with significant fluid overload promptly with IV loop diuretics. In those already receiving outpatient loop diuretics, the initial IV dose should be > their chronic oral daily dose and be given as either intermittent boluses or continuous infusion. Adjust diuretic dose for symptom relief, to reduce volume, and avoid hypotension.

If a loop diuretic given twice daily in doses equivalent to furosemide 100–200 mg/d is inadequate, a thiazide diuretic or metolazone can be added, which results in a synergistic effect. This combination can result in severe hypokalemia, so close monitoring is necessary.

Aldosterone antagonists (aka mineralocorticoid antagonists) reduce morbidity and prolong survival in NYHA II–IV and with reduced EF < 35%:

- Spironolactone showed a 30% decrease in mortality at 24 months when given to patients with Class IV HF or Class III having had Class IV in the previous 6 months (1999 RALES trial).

QuickQuiz

- When are beta-blockers started in the treatment of HF?
- With what type of HF do aldosterone antagonists prolong survival?
- True or false? Digoxin can be beneficial in HFrEF patients to decrease hospitalizations for HF.
- In what population is hydralazine + isosorbide dinitrate beneficial?
- Which patients with chronic HF should receive anticoagulation?

- Eplerenone showed a 15% decrease in mortality at 16 months in patients with recent MI and EF < 40% and evidence of HF or diabetes mellitus (2003 EPHESUS trial). Monitor patients closely for hyperkalemia.
- NYHA II patients should have prior HF hospitalization and elevated plasma natriuretic peptides before being placed on aldosterone antagonists.

More notes on diuretics:

- **Thiazides** mainly block Na^+ and Cl^- resorption in the distal convoluted tubule and, to a minor extent, block Na^+ resorption in the proximal tubule. Examples are hydrochlorothiazide and metolazone (Zaroxolyn®).
- **Spironolactone** competitively inhibits aldosterone (so, is K^+ sparing) and is being used increasingly in the management of chronic heart failure. **Eplerenone** is similar to spironolactone but more selective for the mineralocorticoid receptor.
- **Furosemide** (Lasix®), **bumetanide** (Bumex®), **torsemide** (Demadex®), and **ethacrynic acid** are the loop diuretics. They block Na^+ resorption in the ascending limb of the loop of Henle. Bumetanide may also have some action on the proximal tubule.
- **Indapamide** (Lozol®, Lozide®) has an unknown mechanism of action. It has an antihypertensive effect occurring far below the antidiuretic effect. Probably has renal and extrarenal effects.
- **Triamterene** has an unknown mechanism of action.

With azotemia, do not use spironolactone or triamterene because these can cause hyperkalemia; thiazides are not effective, but furosemide usually is. Much more on this in Nephrology, Book 2.

Digoxin

Digoxin can be beneficial in HF with reduced EF to decrease hospitalizations for HF. It is started after the above therapies are established and the patient is still symptomatic. In HF, digoxin appears to reset the baroreceptors and dampen the renin-angiotensin effects; it has very little inotropic effect. It also is used to control the ventricular rate in a patient with HF and atrial fibrillation. Digoxin has no mortality benefit. See Table 5-13 for Drugs that Increase Digoxin Level.

Nitrates

Nitrates are occasionally used next (good venodilator, moderate arterial dilator)—remember the nightly 6-hour nitrate-free window to prevent tolerance (discussed under Anti-Anginal Drugs on page 5-12).

With ventricular failure, patients can have increased systemic (peripheral) vascular resistance (SVR) with a normal or low BP, and they still benefit from an arteriolar vasodilator.

Hydralazine and Isosorbide Dinitrate

Hydralazine is an afterload reducer (arterial vasodilator); it also increases heart rate. Hydralazine is frequently used with nitrates to get the added benefit of decreased preload.

The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality in African-Americans with NYHA III–IV HFrEF, as adjunctive therapy to ACEIs (or ARBs) and beta-blockers (2004 A-HeFT). The combination can also be helpful in patients with current or prior symptomatic HFrEF who cannot be given ACEIs/ARBs (drug intolerance, hypotension, renal insufficiency).

Anticoagulation

For patients with chronic HF and permanent, persistent, or paroxysmal atrial fibrillation plus an additional risk factor for cardioembolic stroke (Hx HTN, DM, previous stroke/TIA, or age ≥ 75) give individualized anticoagulation (warfarin, dabigatran, apixaban, or rivaroxaban).

Table 5-13: Drugs that Increase Digoxin Level

Alprazolam
Amiodarone
Abx: Macrolides and tetracycline
Cyclosporine
Diphenoxylate or propantheline (decrease bowel motility)
Indomethacin
Itraconazole (antifungal)
Omeprazole
Propafenone (class Ic antiarrhythmic)
Quinine
Spironolactone

Clinical practice guidelines also recommend anticoagulation in heart failure patients with a cardioembolic source (history of systemic or pulmonary embolism, or a mobile left ventricular thrombus). In the absence of above mentioned indications, anticoagulation is not recommended in patients with HFrEF.

Decompensated HF patients admitted to hospital should receive VTE prophylaxis.

Other Therapy

The 2013 ACC/AHA guideline update for the Management of Heart Failure recommends implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death and to reduce total mortality in patients with HF (nonischemic dilated cardiomyopathy or ischemic heart disease) who are at least 40 days post-MI and who have an EF ≤ 35% and NYHA II/III symptoms on optimal medical therapy, or who are post-MI with EF ≤ 30% and NYHA I symptoms on optimal medical therapy. ICD candidates must also have an expected survival > 1 year. See Implantable Cardioverter-Defibrillators on page 5-44 for Class I indications for ICD therapy.

Ventricular dyssynchrony is caused by electrical disturbances that cause the heart to pump blood in an inefficient way. It is suggested by severe HF (NYHA III/IV), severely decreased ejection fraction (LVEF ≤ 35%), and QRS exhibiting LBBB configuration with QRS duration ≥ 120 ms.

Cardiac resynchronization therapy (CRT) involves pacing the right and left ventricles and is recommended for patients with EF ≤ 35%, sinus rhythm, LBBB with a QRS duration of ≥ 150 ms, and is NYHA II/III, or patients who are ambulatory with NYHA IV symptoms despite optimal medical therapy. (Per 2012 ACC/AHA update of device therapy guidelines.)

Emergency Treatment for Severe Heart Failure

[Know:] With severe ventricular failure, patients may require short-term treatment with inotropes (dopamine, dobutamine, and milrinone).

Dobutamine is another inotropic agent that can be used for severe ventricular failure. It does not have the vasoconstrictor activity of dopamine and actually has some vasodilatory effects.

Dopamine:

- At < 2 μg/kg/min dopamine stimulates the dopaminergic receptors and causes mesenteric dilation.
- At 2–5 μg/kg/min, it has a predominantly beta-agonist effect (positive inotropy) and increases renal perfusion.
- At > 10 μg/kg/min, it mainly has an alpha-agonist effect and causes vasoconstriction. Generally never use > 10 μg/kg/min!

Milrinone (Primacor®) is an inotropic/vasodilator agent with phosphodiesterase inhibitor activity (peak III cAMP—an isoenzyme of cAMP). It is also indicated for short-term IV treatment of HF. It does not cause thrombocytopenia (unlike amrinone), and it is not associated with tachycardia.

Rarely used: Prazosin and minoxidil are also afterload reducers but are associated with rapid development of tolerance and fluid retention. Nitroprusside is not used much now because of tolerance and toxicity problems.

Mechanical circulatory support (MCS) is beneficial in selected patients with Stage D HFrEF in whom definitive management (cardiac transplantation) or cardiac recovery is anticipated or planned. Nondurable MCS (percutaneous and extracorporeal ventricular assist devices) are reasonable as a "bridge" to recovery/decision in carefully selected HFrEF patients who have acute, profound hemodynamic compromise. Durable MCS can be used to prolong survival for carefully selected HFrEF patients.

Revascularization (CABG or PCI) is indicated for patients on optimal medical therapy with angina and suitable anatomy, especially left main stenosis (> 50%) or left main equivalent disease. For end-stage HF, cardiac transplant is the best option. There is a 65% 5-year survival and a 55% 10-year survival!

Harmful for HFrEF patients:

- Definitely avoid or withdraw most antiarrhythmics, calcium blockers (except amlodipine), NSAIDs, and thiazolidinediones.
- Long-term use of positive inotropic drugs is potentially harmful, except as palliation for patients with end-stage disease (Stage D) who cannot be stabilized with optimal medical therapy.

HIGH-OUTPUT HF

"High-output" ventricular failure is seen with peripheral shunting (large AV fistulas, severe hepatic hemangiomatosis, and Paget disease!) and low-systemic vascular resistance, as seen in gram-negative sepsis. You can also see it in patients with hyperthyroidism, beriberi, carcinoid, or anemia. Remember, though, these patients often have a normal cardiac output at the time of diagnosis—because of the worsening ventricular failure!

RIGHT VENTRICULAR FAILURE

"The most common cause of right heart failure is left heart failure!" is what you heard on rounds. And, indeed, right ventricular failure (RVF) is mainly caused by pulmonary hypertension (1° or 2°)—typically secondary to left ventricular failure (LVF). RVF is also seen with large RV infarctions and cor pulmonale. Remember: If the patient has signs of RVF (JVD and liver congestion), but pressures are the same in all chambers in diastole, think external compression (constriction or effusion).

Quick Quiz

- CRT is indicated for which HF patients?
- Know all drugs used for emergency treatment of severe HF!
- What does dopamine do at low doses (< 2 µg/kg/min)? At doses of 2–5 µg/kg/min?
- True or false? MCS is beneficial in selected patients with stage D HFrEF in whom definitive management (cardiac transplantation) or cardiac recovery is anticipated or planned.
- With what diseases does high-output heart failure occur?
- What is the treatment for acute pulmonary edema?
- What are some causes of non-constrictive pericarditis? What ECG changes can you see?

Orthopnea: As LVF progresses, orthopnea usually worsens, but it may then actually improve temporarily as RV function worsens due to the pulmonary hypertension.

Paroxysmal nocturnal dyspnea does not improve with sitting up, as orthopnea does.

PULMONARY EDEMA

Immediate treatment for acute pulmonary edema:

- Patient should be sitting with legs dangling, if possible, to decrease venous return.
- Give 100% O_2, morphine (to decrease anxiety and decrease vasoconstriction).
- Give furosemide (causes venodilation even before the diuresis).
- IV nitroglycerin or nitroprusside can be used if systolic BP is > 100.
- Strongly consider the use of dobutamine if systolic BP < 90.
- Aminophylline is rarely used to increase respiratory muscle function.

PERICARDIAL DISEASES

NON-CONSTRICTIVE PERICARDITIS

90% of non-constrictive pericarditis is idiopathic and probably viral in origin; often, there is a preceding URI or gastroenteritis.

Causes of non-constrictive pericarditis:

- Idiopathic (90%), probably viral
- Tuberculosis
- Connective tissue diseases
- Sepsis
- Renal failure (uremic)
- Cancer
- Postradiation
- Hypothyroidism
- MI (Dressler syndrome)
- Open heart surgery (postpericardiotomy syndrome)
- Certain drugs, especially procainamide and hydralazine

Suspect TB as the cause if the patient is at high risk, or if the symptoms of pericarditis do not resolve after 2 weeks of treatment.

Both Dressler syndrome and postpericardiotomy syndrome are autoimmune processes that occur several weeks after the precipitating event. Even if the history is very suggestive, you must consider the following entities and exclude them to make the diagnosis: MI, pulmonary embolus, and endocarditis. Other causes include uremia and connective tissue disease.

Patients with pericarditis commonly present with very severe chest pain, sometimes pleuritic, which (classically) improves when leaning forward. The pain is retro-sternal and left precordial, and referred to the neck, arms, or left shoulder. Typically, the patient has some fever and tachycardia. A pericardial friction rub, which does not always occur and can be evanescent, is diagnostic for pericarditis.

The ECG may show diffuse concave-up ST elevation (vs. localized, concave-down ST elevation in an acute MI) and, occasionally, depressed PR segments, especially in lead II. ECG changes occur in 4 stages:

- Stage 1: diffuse ST elevation segments with upward concavity with PR depression
- Stage 2: normalization of ST segments after several days
- Stage 3: inverted T waves
- Stage 4: weeks or months after onset of acute pericarditis, ECG returns to normal

Pericarditis can cause transient increases in troponin (secondary to associated myocarditis). Treat pericarditis by stopping any possible causative drugs and giving NSAIDs. Do not treat idiopathic pericarditis with steroids because there can be a relapse when they are stopped. Treatment with colchicine has been shown to reduce recurrence.

CONSTRICTIVE PERICARDITIS

It occurs when resorption of pericardial effusion is followed by obliteration of the pericardial cavity with scarring. Constrictive pericarditis must be differentiated from restrictive cardiomyopathy (page 5-48) because the signs and symptoms can be similar.

(Again: Although constrictive pericarditis is often quickly treated with good results, restrictive cardiomyopathy is not reversible.)

Constrictive pericarditis may follow:

- Viral or idiopathic pericarditis
- Traumatic hemopericardium
- Tuberculosis
- Cardiac surgery
- Mediastinal irradiation
- Purulent infection
- Histoplasmosis
- Rheumatoid arthritis
- SLE
- Neoplastic disease (especially breast cancer, lung cancer, and lymphoma)
- Chronic renal failure with uremia treated by chronic dialysis

In constrictive pericarditis, ventricular filling is normal during early diastole but reduces abruptly when the elastic limit of the pericardium is reached.

Constrictive pericarditis is characterized by rapid, early, diastolic filling of the LV, causing a loud presystolic knock just after S_2. Pulsus paradoxus can occur but is usually mild.

There are 2 clinical hallmarks of constrictive pericarditis:

- Kussmaul sign: When, because the heart is encased in a "shell," the negative pressure during inspiration is transferred to the venous inflow tract, resulting in a lack of the normal decrease in jugular venous distention (JVD) during inspiration. When severe, JVD can increase even during inspiration.
- Large, right-sided *x* and *y* descents. This is seen as a brisk collapse of the jugular veins during diastole.

Constrictive pericarditis can cause calcification of the pericardium (~ 50%). You can see this best on the lateral chest x-ray because it is typically found over the right ventricle, but you also can see it on the PA view and on CT. A lateral chest x-ray that shows calcification over the right ventricle is pathognomic for constrictive pericarditis.

CT and MRI are best for measuring thickness of pericardium, but echo is also used. A pericardial thickness of > 5 mm is suggestive of, but not sufficient for, diagnosis. The pericardium can be of normal thickness in ~ 20–25% of cases of constrictive pericarditis.

In both tamponade and constrictive pericarditis, cardiac cath shows the same pressure during diastole in all 4 chambers. You can often make the differentiation between tamponade and constrictive pericarditis at the bedside using these hallmark signs (see tamponade below). Constrictive pericarditis must be treated with an open thoracotomy and pericardiectomy. Unfortunately, this resolves the problem only 50% of the time!

Brain natriuretic peptide (BNP) plasma levels are being used to differentiate between constrictive pericarditis and restrictive cardiomyopathy. BNP increases with heart failure. With restrictive cardiomyopathy, there is a component of HF, and BNP levels are markedly elevated (e.g., 8x max normal). With constrictive pericarditis, there is little or no actual HF, and BNP levels are typically just above normal.

RECURRENT PERICARDITIS

Recurrent pericarditis is a condition in which the only disabling problem is the associated chest pain. It does not progress to constrictive pericarditis. It is only rarely associated with arrhythmias. Treat with NSAIDs, colchicine, and glucocorticoids. Pericardiectomy often does not have good results and is tried only after medical treatment options have been exhausted.

PERICARDIAL EFFUSION

Pericardial effusion is generally diagnosed with an echocardiogram, but CT and MRI are the most accurate, especially if the resultant tamponade is due to localized pockets of effusion. Surgical drainage is preferable in traumatic hemopericardium, post-surgical effusion, and when bacteria or TB is suspected as the cause of tamponade. On the other hand, pericardiocentesis rarely helps in diagnosis but is often used to treat viral, idiopathic, neoplastic, hypothyroid, and renal failure-related tamponade. Pericardial window biopsy can help diagnose TB. Sometimes, you need an endomyocardial biopsy to differentiate constrictive vs. restrictive etiology. If pericardiocentesis fluid is diagnostic in acute pericardial effusion in an otherwise normal person, it is normally due to a neoplasm! (Read the previous sentence again—it's a little tricky.)

Tamponade [Know!] is a critical cardiovascular compromise caused by a pericardial effusion. There is obstruction to the inflow of blood to the ventricles. The most common causes are trauma, cancer, uremia, and acute pericarditis. When there is rupture of the free wall of the heart, as in trauma or post-MI, tamponade develops quickly; otherwise, it generally develops slowly.

The 3 hallmarks of acute tamponade:

1) Hypotension and muffled heart sounds
2) Pulsus paradoxus (systolic BP drops > 10 mmHg during inspiration)
3) Jugular venous distention with no collapse during diastole (i.e., an attenuated *y* descent)

Tamponade causes soft, distant heart sounds. Compare and know the difference between this and constrictive pericarditis (above).

Quick Quiz

- What are the 2 clinical hallmarks of constrictive pericarditis?
- When is the measured diastolic pressure of all 4 chambers equal?
- How is BNP used to differentiate constrictive pericarditis from restrictive cardiomyopathy?
- What treatments can be helpful in recurrent pericarditis?
- Name the 3 hallmarks of cardiac tamponade.
- What is the most common congenital abnormality found initially in adults?
- True or false? Ostium secundum ASD often has right axis deviation and/or RBBB on ECG.
- When should surgery be performed for a secundum ASD?
- What type of cyanosis would you expect to see in someone with a PDA?
- What is the most common congenital defect in children?

CONGENITAL HEART DISEASE

NOTE

Most adult patients with congenital heart disease are asymptomatic! Know that the magnitude of any shunt does not depend on the total blood flow rate, but is commonlyly a constant ratio of pulmonic to systemic flow (Qp/Qs).

ASD

Ostium Secundum ASD

Secundum atrial septal defect comprises 70% of all atrial septal defects (ASD). It is the most common form of congenital heart disease found initially in adults (F > M), excluding a bicuspid aortic valve. With a large secundum ASD, there is a systolic ejection murmur at the left sternal border (2° to increased flow across the pulmonic valve), occasionally a diastolic murmur (from increased flow across the tricuspid valve), and a fixed split S_2. The left-to-right shunt causes diastolic overloading of the right ventricle and increased pulmonary blood flow with inspiration and expiration.

ECG shows right axis deviation and/or right bundle-branch block (RBBB). Chest x-ray shows an enlarged RV with shunt vasculature. Notice all of the right-sided stuff with ASD—makes sense because ASD causes a volume load on the right side of the heart. Patients can develop 2° atrial fibrillation.

Standard treatment had been open surgical closure, but now most secundum ASDs are closed percutaneously. If there is a > 2:1 left-to-right (pulmonary/systemic) shunt, a surgical closure is done, even if the patient is asymptomatic. In this case, the ASD would eventually cause an increase in pulmonary vascular resistance and associated complications.

Generally, severe, fixed pulmonary hypertension is considered a contraindication to surgical repair of the ASD.

Ostium Primum ASD

This form of ASD is seen most commonly in Down syndrome. Patients with ostium primum atrial septal defect may have a loud pansystolic murmur 2° to mitral and/or tricuspid regurgitation. The regurgitation is due to the ostium being low on the septum, interfering with the function of the AV valves or left mitral valve. ECG has left axis and RBBB.

Surgery for any type of ASD essentially cures the problem. Functional Class III/IV patients can revert to functional Class I with excellent survival! Eisenmenger syndrome is a contraindication to ASD surgery.

Sinus Venosus ASD

Sinus venosus ASD is associated with anomalous pulmonary venous return because it occurs high on the septum. It is a cause of 10% of ASDs.

PDA

Adult patients with patent ductus arteriosus (PDA) are usually asymptomatic; females > males. PDAs are typically discovered early by detection of the distinct murmur. Endarteritis can occur in PDA.

PDA causes a continuous, "machinery" murmur at the LUSB. As pulmonary pressures rise, the murmur becomes less continuous. Differential cyanosis (e.g., clubbed toes, normal fingers) with pulmonary hypertension is possible.

Chest x-ray shows calcification of the ductus arteriosus in adults.

If the patient develops pulmonary hypertension, consider Eisenmenger syndrome (see page 5-58).

Surgical or percutaneous closure in symptomatic patients has excellent results. Elderly patients also benefit from surgery.

PULMONARY STENOSIS

Balloon valvuloplasty is the procedure of choice for treating pulmonary stenosis. It has favorable long-term clinical and hemodynamic results.

VSD

Ventricular septal defects (VSDs) are the most common congenital defect in children. They are uncommon in adults because most have either closed spontaneously or have been surgically closed in childhood. 80% of small VSDs close spontaneously in the first 10 years of life. Large VSDs usually require surgery (although even 10% of these eventually close spontaneously). A loud holosystolic murmur is heard at the left lower sternal border.

COARCTATION OF THE AORTA

Know that a bicuspid aortic valve occurs in ~ 50% of patients with coarctation of the aorta (COA)! Other associated anomalies include mitral valve problems, left ventricular myocardium problems, and membranes in the left atrium. Notice that all of the heart problems associated with coarctation of the aorta are left-sided! The classic physical findings are either a delayed femoral/brachial pulse (feeling the brachial and femoral pulses, there is a distinct delay in femoral pulse) or an absent femoral pulse. Patients can have upper-body hypertension and can get hypertensive aneurysmal dilatation and rupture of the circle of Willis. Look for rib notching on chest x-ray due to the collateral vessels getting very large and eroding the ribs. Turner syndrome is associated with coarctation of the aorta and a bicuspid aortic valve.

ANOMALOUS CORONARY ARTERY

Pre-mortem detection is extremely difficult and requires a high index of suspicion. This can present as exertional chest pain or exertional syncope in a young, otherwise healthy individual. Syncope after exercise can occur in "normal" people, but syncope during exercise is never normal.

With anomalous coronary artery, there is an abnormal course of 1 of the 2 coronary arteries between the 2 great vessels, the pulmonary artery and aorta. At rest, there is plenty of room for the vessel to pass without compromise; however, in extreme exercise, the cardiac output can increase 4–8-fold. This expands the elastic pulmonary artery and aorta, resulting in compression of the coronary artery as it courses between the great vessels. This compression creates coronary ischemia and arrhythmias.

SUDDEN DEATH IN EXERCISING YOUNG PEOPLE

The most common cause of death in exercising young people is HCM (36%). Next most common are coronary anomalies (17%)—although this is a more likely cause in the 30–40-year-old group.

Also consider primary pulmonary hypertension as the cause in young women.

Etiologies of sudden death in exercising young people:

- HCM (36%)
- Coronary anomalies (17%)
- Possible HCM (8.2%)
- Myocarditis (5.9%)
- Arrhythmogenic RV cardiomyopathy (4.3%)
- Ion channelopathies including long QT syndrome ([LQTS]; 3.6%)

OTHER

Marfan syndrome causes decreased strength of the aorta (with aortic regurgitation and dissection) and mitral regurgitation. Rubella causes congenital pulmonic stenosis, PDA, and multiple pulmonary artery stenoses. Cystic fibrosis can eventually cause pulmonary hypertension.

PULMONARY HEART DISEASE

COPD AND SLEEP APNEA

The most common causes of pulmonary heart disease are COPD and sleep apnea syndrome. These two are covered extensively in Pulmonary Medicine, Book 2, so we will cover the other causes here.

EISENMENGER SYNDROME

Eisenmenger syndrome occurs in patients with a large, intracardiac shunt when the pulmonary vascular resistance becomes greater than systemic vascular resistance—so, the shunt becomes right-to-left instead of the more normal left-to-right. It is a result of severe pulmonary hypertension, which can develop early (or late) in patients with large, cardiac, left-to-right shunts of virtually any type: VSDs, PDAs, and ASDs. Cyanosis is common. Heart-lung transplant is the only effective treatment for Eisenmenger syndrome.

CHRONIC THROMBOEMBOLIC OBSTRUCTION

Chronic thromboembolic obstruction mainly occurs as a result of impaired fibrinolytic resolution of acute thromboembolism, leading to organization, incomplete recanalization, and chronic obstruction of the pulmonary vascular bed. Most patients treated for acute pulmonary thromboembolism do not develop chronic pulmonary hypertension. Chronic thromboembolic obstruction is also the result of other causes of secondary pulmonary hypertension such as large left-to-right shunts and chronic LVF.

Progression of this disease probably results from the pulmonary arteriolar changes (instead of more PEs); these are similar to the changes that develop with large septal defects. The resultant increased pulmonary vascular resistance causes RVF. Surgical removal of the thromboembolic material results in significant

Quick Quiz

- What are the 2 most common causes of sudden death in an exercising young person? What third cause do you consider in young women?
- What is the only effective treatment for Eisenmenger syndrome?
- What are the 2 cardiac-related absolute contraindications to pregnancy?
- True or false? Warfarin is not contraindicated in pregnancy.
- Know how to very quickly determine the axis of an ECG. Brand Figure 5-7 into your brain!

improvement. Vena cava filters may be used in patients with deep vein thrombosis (DVT). Anticoagulate.

PULMONARY ARTERIAL HYPERTENSION

Note that the terms for this disease are changing. Previously it was called idiopathic pulmonary hypertension (IPH), and before that, primary pulmonary hypertension. The World Health Organization has reorganized causes of pulmonary hypertension into 5 groups of which IPH is now part of Group 1: Pulmonary arterial hypertension (PAH).

PAH includes the "sporadic idiopathic pulmonary hypertension" that commonly occurs in young women, is refractory, and results in death within 5–10 years.

Treatment: Calcium channel blockers (in patients who are "reactive" to vasodilator testing) and sildenafil (Viagra®, Revatio®) are helpful. Endothelin antagonists and prostacyclins can also be of use. Heart-lung transplant is occasionally used.

It is important to differentiate between 1° and 2° because surgery may help 2° PAH. A heart catheterization rules out secondary causes such as right-to-left shunt and chronic LVF. A perfusion lung scan rules out PE. Pulmonary capillary wedge pressure (PCWP) is, of course, increased only in the pulmonary hypertension caused by, or concurrent with, LVF.

PREGNANCY AND THE HEART

Pregnancy: Absolute contraindications to pregnancy include PAH and Eisenmenger syndrome (particularly deadly if cyanosis is present); both are discussed above. In secundum ASD, aortic stenosis, and dilated cardiomyopathy, the patient must be closely watched. In aortic stenosis and dilated cardiomyopathy, patients are typically kept at bed rest. Secundum ASD patients are normally not at risk for cardiac decompensation, unless they develop atrial fibrillation.

Warfarin is contraindicated in pregnancy due to its teratogenic effects. It is absolutely contraindicated in the 1st trimester; although, to be safe, most physicians do not give it at all during pregnancy. Heparin, LMWH, digoxin, quinidine, propranolol, calcium channel blockers, and DC cardioversion are not contraindicated. Although heparin is not contraindicated, it does cause increased morbidity and mortality in mother and child.

A maternal rubella infection during pregnancy is a common cause of supravalvular aortic stenosis, pulmonic stenosis, and other congenital cardiac defects.

HCM among asymptomatic women is not a contraindication for pregnancy. In women with HCM who are asymptomatic or whose symptoms are controlled with beta-blockers, the beta-blockers should be continued during pregnancy with increased surveillance for fetal bradycardia, cretinism, or intrauterine growth retardation. In women with HCM and resting or provocable LVOT obstruction (≥ 50 mmHg) and/or cardiac symptoms not controlled by medical therapy alone, pregnancy is associated with increased risk; refer these patients to a high-risk obstetrician.

Most pregnant women experience some pedal edema. Flow murmurs and S_3 gallops are also common, and the jugular venous pressure increases. Remember to rule out both mitral stenosis and secundum ASD in the pregnant patient presenting with new-onset atrial fibrillation and pulmonary edema.

THE ELECTROCARDIOGRAM

THE 12-LEAD ECG

First, we will briefly go over the basics of ECGs. Refer to Figure 5-7 as we go through this.

A lead tracing is positive if the wave of depolarization spreads toward the positive pole of that lead, and it is negative if it spreads away from the positive pole. The tracing is zero if the wave spreads at a 90° angle to it. For instance, if II is zero, look for the maximum projection to be at aVL (either + or –).

With the 12-lead ECG, the wave of depolarization is recorded on both the frontal and horizontal planes and gives a 3-dimensional representation of the heart. The projection of the electrical activity of the heart onto the frontal plane is recorded by the frontal leads I, II, III, aVR, aVL, and aVF. On the horizontal plane, it is recorded via electrodes placed in the V1-6 position. Occasionally, a V3R and V4R (placed same as V3 and V4, except on the right side of the chest) are used to better monitor the right side of the heart (e.g., right-sided ischemia). Depolarization moving toward the lead causes a positive deflection (P wave and QRS), as does repolarization moving away from the lead (T wave).

The frontal leads give inferior-superior-left-right information. For example, II, III, and aVF cover the inferior area. ST variations/Q waves occur in these leads with inferior ischemia and infarction.

The horizontal leads relay anterior-posterior-lateral information. Think of V1 as looking at the right side of the heart while V6 looks at the left side. The QRS in V1 is positive when the right ventricle (RV) is depolarizing (and negative when the LV is depolarizing), whereas the QRS in V6 is positive when the LV is depolarizing.

AXIS DEVIATIONS

The normal mean QRS axis is between –30° and +100°. > +100° is right axis deviation (RAD), whereas < –30° is left axis deviation (LAD). A quick, fairly accurate method to determine this is to just look at I and aVF. If both are prominent, you can quickly tell in which quadrant the mean vector lies. Visualize the following:

- Both (+) = normal
- I (+) and aVF (–) = check for LAD
- Both (–) = extreme right or left axis
- I (–) and aVF (+) = check for RAD

Left axis deviation (LAD) is usually due to left anterior hemiblock and, therefore, is a marker for CAD—as are all fascicular blocks.

Right axis deviation (RAD) is often a normal finding in children and young adults. Other causes include left posterior hemiblock (LPHB), RVH, and acute or chronic RV overload syndromes such as pulmonary hypertension/embolism, and pulmonic stenosis. If an adult is incidentally found to have RAD, do further workup.

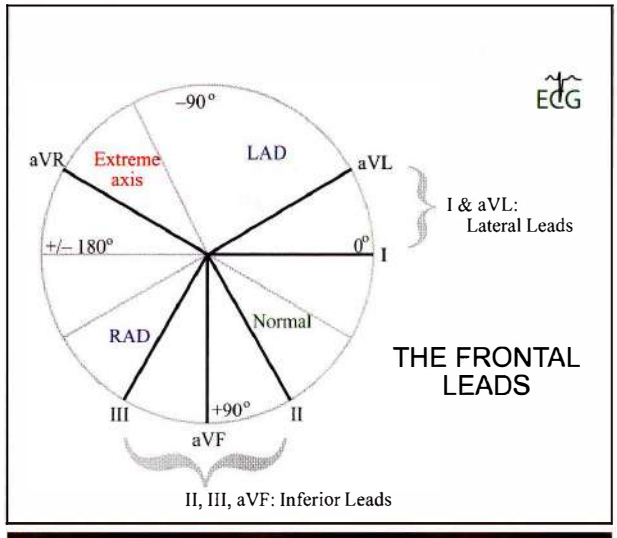


Figure 5-7: Axis Determination Diagram

RATES AND INTERVALS

The ECG is recorded on paper with a 1 mm² graph, with a thicker line every 5 mm. Because the paper moves at 25 mm/s, each thicker line is 1/5 of a second—or 0.2 sec (200 ms), and each mm represents 0.04 sec (40 ms). The interval covering 5 thicker lines (or "big squares") is 1 second.

There are a couple of quick ways to determine the heart rate. I'll discuss the RR interval, but any prominent wave of the standard QRS may be used to determine the interval. Using a calculator, a quick and accurate method for determining heart rate is 1,500/RR interval in mm. So, if the beat interval is 28 mm, the rate is 1,500/28 = 54 bpm. A less accurate, but easier, method is to divide 300 by the number of "big squares" in the RR interval. If the beat interval is 28 mm, this is not quite 6 big squares. You divide 300 by 6 and get 50, but you know the heart rate is actually a little faster because the interval is not quite 6 big squares. A derivative of this is the method taught in Dubin's book, *Rapid Interpretation of EKG's*, in which you memorize 2 sets of triplicates: 300–150–100 and 75–60–50. These match to the heart rates corresponding to RR intervals of 1, 2, 3, 4, 5, and 6 big squares.

Normal rate is 60–100 bpm. Sinus tachycardia is defined as a sinus rhythm of > 100 bpm; sinus bradycardia is < 60 bpm. So, an RR interval < 3 big squares indicates tachycardia; > 5 big squares indicates bradycardia.

Quick Quiz

- What are the causes of left axis deviation?
- What are the causes of right axis deviation?
- Does RAD always warrant additional workup in an adult?
- Name the causes of prolonged QT intervals. Yes, all of them that are listed in the text!
- What are the P wave findings for RAH? For LAH?

INTERVALS

PR INTERVAL

The PR interval indicates the time between atrial and ventricular depolarization. Normal duration is 3–5 small squares (120–200 ms). Longer than 200 ms (1 big square) is the definition of 1° AV block.

Shorter than 120 ms (3 small squares) may indicate WPW (delta wave), junctional rhythm (with retrograde P wave—see next), or left atrial overload (widened P wave—see next).

QRS DURATION

QRS duration is normally < 100 ms (i.e., 1/2 a big square). QRS > 120 ms may be caused by bundle-branch block, ventricular beat/rhythm/ventricular pacemaker, drugs such as tricyclics, and WPW. 100–120 ms is often due to an incomplete BBB.

QT INTERVAL

The QT interval corrected for rate is normally 340–470 ms depending on gender and age. $QT_c = QT/(RR)^{0.5}$; that is, the QT interval (in ms or sec) divided by a conversion factor that, although dimensionless, is derived from the square root of the beat interval in seconds. Again: The RR interval in this calculation must be in seconds. (Consider the difference in dividing by the square root of 0.7 vs. the square root of 700!) When scanning ECGs, a rule of thumb is: The QT interval normally is ~ 40% of the RR interval—do the calculation for QT_c if it appears shorter or longer.

With prolonged QT_c, there is a tendency to develop *torsades de pointes*.

Prolonged QT_c has many causes:

- Tricyclic overdose
- Hypocalcemia
- Hypomagnesemia
- Hypokalemia
- Starvation
- CNS insult
- Hypothermia
- Type Ia and III antiarrhythmics (Ia = quinidine, procainamide; III = amiodarone, sotalol)

More recently discovered causes of prolonged QT_c are:

- Non-sedating antihistamines such as astemizole and terfenadine (since pulled from the market)—their QT prolongation tendency can be increased by erythromycins, some "azoles" such as ketoconazole, and hepatic dysfunction.
- Drugs such as methadone, phenothiazines, amiodarone, sotalol.
- Liquid protein diet.

Short QT_c can be caused by hypercalcemia and digitalis.

WAVEFORMS AND SEGMENTS

P WAVE

The P wave results from the depolarization of the atrium. The normal P wave is < 2 mm in height and < 120 ms (3 small squares) in duration, and the normal axis is –50 to +60 degrees. (Where else have you seen 120 ms? The normal PR interval is 120–200 ms.) See Figure 5-8.

Most information from the P wave can be derived from II, aVR, and V1. As the wave of depolarization spreads from the SA node high in the right atrium and through the right and then left atrial myocardium, the mean vector is downward and to the patient's left—so the normal P wave is positive in II and negative in aVR.

A retrograde P wave is negative in II and positive in aVR—indicating an ectopic focus originating in the inferior part of the atrium or at the AV junction, resulting in a wave of depolarization traveling toward aVR (picture this!). A retrograde P wave from the AV junction often causes a tracing with a short PR interval.

Because atrial depolarization traverses from the patient's right to left, the left/initial side of the P wave represents the right atrium, while the right/terminal side of the P wave represents the left atrium (mid-P wave is both).

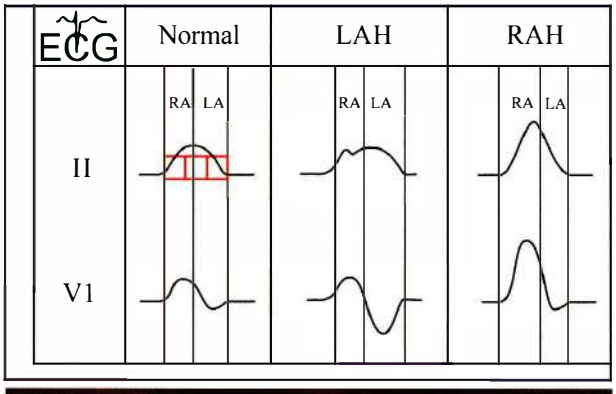


Figure 5-8: P Wave in Atrial Enlargement

The normal P wave is positive in lead II and positive or biphasic in V1; when biphasic, the P wave is positive on the left side and a little negative on the right side. This is because the wave of depolarization through the atrium is toward V1 in the right atrium (left side of P wave) and somewhat away from V1 in the left atrium (right side of P wave).

With right atrial preponderance, (enlargement, hypertrophy, overload), the right atrial (initial) portion of the P wave is widened, and therefore overlaps onto the left atrial portion of the P wave. The P wave width stays normal (< 120 ms), but look for an increased P wave amplitude in II (also III and aVF, but just look at II) and in V1 (the positive portion). Actually, the P wave being "peaked" in II is more important than it being tall.

Decreased P wave amplitude is seen in severe hyperkalemia.

With left atrial overload, the right side of the P wave is enlarged, resulting in a wide P wave with a shortened or absent PR interval (i.e., < 120 ms). Other typical findings are a widened notched P wave in II and an enlargement of the negative portion of the P wave in V1. The most sensitive ECG finding for left atrial enlargement is a negative P wave in V1, with a duration of > 40 ms (1 small square). On the other hand, the most specific ECG finding is a notched P wave (usually in II) with an interpeak distance of > 40 ms.

COPD: Because of the hyperexpanded lungs, the heart assumes a more vertical position, and there is resultant RAD of the P wave. A +90° P wave axis is highly suggestive of COPD. The pulmonary hypertension may result in right atrial preponderance with associated P wave changes (see previous discussion).

T WAVE

The T wave is ordinarily in the same direction as the QRS, indicating that repolarization is actually occurring in the opposite direction of depolarization.

Peaked T waves are sometimes associated with the following:

- Hyperkalemia
- Hyperacute MI
- Intracerebral hemorrhage
- In septal leads (V1-2) in evolving post-MI

Focal-flipped T waves may accompany:

- Ischemia
- V1-2 with RBBB, RVH, and RV HTN
- V1-2 with LVH
- Lateral leads (I, aVL, V6) with LBBB
- The precordial leads with LVH with "strain"

Diffuse flipped T waves may accompany:

- Pericarditis
- Diffuse ischemia; post-resuscitation
- Metabolic abnormality
- Intracerebral hemorrhage

U WAVE

The U wave occurs just after the T wave. It is commonly small and is best seen in V2-3. If seen, it is usually a < 1 mm, rounded deflection in the same direction as the T wave. If the U wave is prominent, there is an increased tendency for *torsades de pointes*. Prominent U waves are present with hypokalemia, bradycardia, digitalis, and amiodarone.

Negative U waves are considered significant—even if the rest of the ECG is normal! Causes are ischemia, HTN, AV valve disease, and RVH. Negative U waves occur in up to 60% of patients with an anterior MI, up to 30% of patients with an inferior MI, and up to 30% of angina patients.

ST SEGMENT

There are 3 main causes of ST-segment elevation: acute MI, Prinzmetal angina, and pericarditis. It may also be present with early repolarization variant, intracerebral hemorrhage, hypertrophic cardiomyopathy, LVH, LBBB, cocaine abuse, myocarditis, and hypothermia.

ST-segment depression occurs with:

- Subendocardial ischemia (especially if downsloping or flat), such as seen in classic angina.
- ST depression in V1-2 with an acute posterior MI.
- Reciprocal depression in V1-2 with some inferior wall MIs—especially those with lateral or posterior extension. There may also be reciprocal ST depression in inferior leads with some anterior/septal MIs.
- LVH with LV strain (ST depression with flipped T waves in precordial leads).
- Isolated RV infarction, when there is ST elevation in V1 and ST depression in V2.
- RVH that may cause RAD and ST-segment depression preceding a flipped T wave in V1.
- Digitalis toxicity.
- Hypokalemia.

QRS COMPLEX

In QRS complex, depolarization of the ventricles occurs simultaneously after the depolarization of the interventricular septum. The normal mean vector of depolarization of the interventricular septum points from the patient's left to the right across the septum. You see this as a small initial deflection, which is positive in V1 (R wave) and negative in V6 (Q wave) (Figure 5-9).

The left ventricle is normally much more massive than the right ventricle; therefore, the mean QRS vector (reflecting depolarization of the ventricles) is strongly to the patient's left. You see a large negative deflection in V1 and positive deflection in V6. On the frontal plane,

Quick Quiz

- When are peaked T waves seen?
- When are focal-flipped T waves seen?
- U waves indicate a predisposition to what serious condition?
- What is the significance of a negative U wave?
- What are the common causes of U waves?
- Name the 3 main causes of ST-segment elevation.
- What are the causes of ST-segment depression?
- What are the ECG criteria for LVH? RVH?
- In LBBB, the left side of the septum depends on what to depolarize?

as mentioned above, the mean vector is between –30 and +100 degrees.

The normal duration of the QRS is < 100 ms.

QRS changes seen with ventricular hypertrophy and conduction disturbances are discussed next.

VENTRICULAR HYPERTROPHY

LVH

LVH (left ventricular hypertrophy) causes a prolongation of activation of the myocardium. It is thought that relative coronary insufficiency (increased muscle mass > increase in size of the capillary bed) may be a factor in this prolonged activation. Another factor may be the overgrowth of the muscle mass relative to the Purkinje system.

This prolongation of activation, in addition to moving the mean QRS axis more posterior, superior, and to the left, also results in a reversal of repolarization, which now proceeds from the endocardium to epicardium, and is reflected by a flipped T wave in the septal leads (V1-2).

LVH causes an exaggeration of the negative deflection in V1 and the positive deflection in V6. There are several accepted ECG criteria for LVH, including: SV1 + (RV5 or RV6) > 35 mm or (RV5 or RV6) > 25–35 mm. This is read "the S in V1 + the R in V5 is > 35 mm," etc. (Figure 5-9).

The diagnosis of LVH is strengthened by an intrinsicoid deflection of > 50 ms (1.25 small squares). This is the time from the beginning of the QRS complex to the peak of the R wave. For greater ease of use, intrinsicoid deflection is often called the "R peak time." Note: When you notice an obvious intrinsicoid deflection, make sure

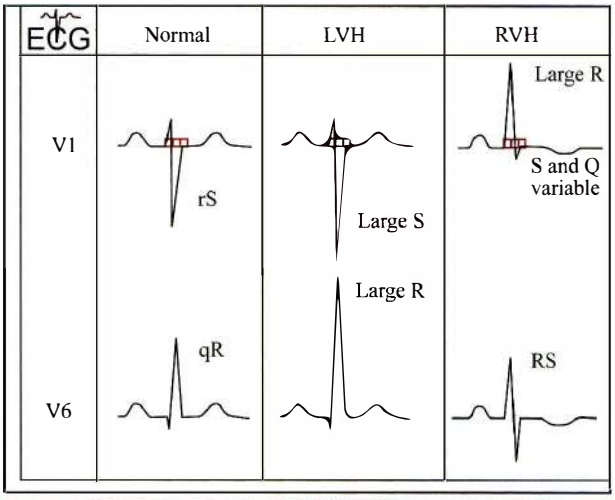


Figure 5-9: Ventricular Hypertrophy

to check the PR interval—you might be looking at a delta wave in WPW!

Although the specificity of the various ECG criteria for LVH is quite high at ~ 95%, the sensitivity is low and varies from 25% for the above criteria to 50% for a complicated point system. Note that if the prevalence of LVH in a population is 5%, there are many more false negatives and many more false positives than true positives, making this fairly useless as a screening test. (Go and work this out using the Bayesian 4-square! Population 10,000; sensitivity = 25%; specificity = 95%; find all the other numbers. Answer: TP = 125, FP = 475, FN = 375, TN = 9,025; PPV = 21% [not good!]; NPV = 96%. Statistics are covered in General Internal Medicine, Book 5.)

When there is left axis deviation, the ECG criteria for LVH change! Use: SIII > 15 mm (Rosenbaum).

A left ventricular "strain" pattern may be present with LVH. LV strain is precordial ST-segment depression and flipped T waves seen in a patient with ECG criteria for LVH.

RVH

Because RVH (right ventricular hypertrophy) is such an abnormal condition, with the mass of the right ventricle increasing to the point of shifting the mean QRS vector to a right axis, the specificity for RVH is very high when ECG criteria are met—although, as with LVH criteria, the sensitivity is low.

ECG criteria for RVH are right axis deviation and, again, because of repolarization changes, ST-segment depression and a flipped T wave in V1, sometimes in V2. The ST-segment depression and flipped T wave generally indicate RV stress/hypertension (Figure 5-9).

Pulmonary embolism (PE): Note that with acute, severe pulmonary embolism (acute cor pulmonale), ECG changes are reflective of acute RV strain with RV and RA dilation +/– ischemia. There is often a RBBB,

sometimes RAD, and usually clockwise rotation. Because these are all nonspecific findings, and because of the changing nature of this event, the most important factors that increase sensitivity of the ECG in the setting of possible PE is a prior ECG tracing for comparison and serial tracings after admission. S1Q3T3 pattern (S wave in lead I, Q wave in lead III, and an inverted T wave in lead III) is an indication of RV strain and is a specific, but not sensitive, indication for acute PE.

CONDUCTION DISTURBANCES

AV BLOCKS

Atrioventricular (AV) blocks are due to conduction disturbances at the AV node. Know the 3 degrees and their patterns.

1st degree AV block prolongs the PR interval by > 200 ms (1 big square).

2st degree AV block results in 2 main patterns:

- Mobitz 1, Wenckebach phenomenon: progressive prolongation of the PR interval until there is a dropped QRS (ventricular beat).
- Mobitz 2: Normal PR intervals, but periodically there is a dropped QRS. 2:1 AV block is 2 P waves for each QRS, 3:1 is # of P waves for each QRS, etc. Mobitz 2 almost always has a wide QRS complex (if narrow, typically Mobitz 1).

3rd degree AV block: No depolarizations are conducted through the AV node. The P wave and QRS have independent regular rhythms (AV dissociation). If the QRS complex has a normal width (< 100 ms), there is a junctional ectopic pacemaker. Junctional pacing rate is 40–60 bpm, whereas ventricular pacing is 20–40 bpm. Note: The AV node has no pacemaker activity. Junctional pacing originates from the myocardial tissue at the AV junction. (It may be near the AV node, but it is not a part of the AV node!)

BUNDLE-BRANCH BLOCK

Overview

Just a little after the AV node, the fast conduction pathway, known as the bundle of His, splits in two. These 2 fast conduction pathways travel down the interventricular septum, and one then goes to the right ventricle, while the other one—functionally if not anatomically—splits again and proceeds to the anterior and posterior sections of the left ventricle. If conduction in one of these pathways is blocked, the depolarization downstream to that pathway is delayed because the myocardial tissue in that area can then be depolarized only via the depolarization wave from much more slowly conducting adjacent myocardial tissue. Refer to Figure 5-10.

LBBB

Left bundle-branch block (LBBB): The QRS is prolonged with a duration of 120–180 ms (3–4.5 small squares). Because the left ventricle depolarization is now transmyocardial, it is depolarized over a longer period, resulting in an RR' (notched or slurred) in the lateral leads (I, aVL, and V6), and there is a corresponding SS' (also called QS) in V1. 1/2 of patients have a normal axis, 1/2 have LAD (–30° to –90°).

The T wave vector and sometimes the ST segment are opposite in direction to the mean QRS vector in LBBB. Therefore, as illustrated in Figure 5-10, you see negative T waves following the positive RR' in I, aVL, and V6—and positive T waves following the negative QRS in V1-3.

Important note: In LBBB, the left side of the septum depends on myocardial conduction to depolarize; hence, conduction is slow over the left side and depolarization progresses from right to left, causing an rS or QS in V1. This right-to-left depolarization of the septum overcomes the expression of any septal Q waves with an MI—including the inferior leads. So, just as new septal Q waves do not appear in a patient with LBBB and an acute MI, MI-related septal Q waves disappear if LBBB develops because of the MI. Therefore, LBBB makes it impossible to use the ECG as an evaluation tool in a patient you suspect of having an MI.

Criteria for LBBB:

- QRS = 120–180 ms (3–4.5 small squares).
- The left ventricle is depolarized, later resulting in an RR' (slurred or notched) in V6 and an SS' (QS) in V1.
- The T wave is often opposite the mean QRS vector in anteroseptal and lateral leads.

Incomplete LBBB fulfills the above criteria, except QRS < 120 ms.

RBBB

Right bundle-branch block (RBBB): The direction of septal depolarization is normal—left to right, but

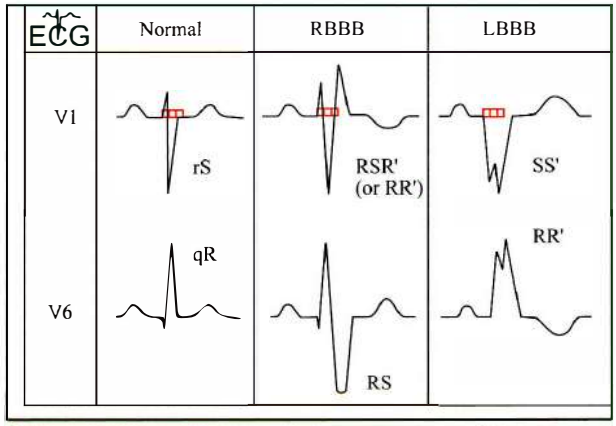


Figure 5-10: Bundle-Branch Block

Quick Quiz

- What do you see on an ECG in LBBB? RBBB?
- What is so serious about a recent MI and the development of a bifascicular block?
- What is the difference between an ectopic beat and an escape beat?

the right ventricle is depolarized over a longer period, resulting in an RR' or RSR' ("rabbit ears") in V1 and an S wave in V6. Visualize how the RSR' in V1 is formed: The initial R wave is due to normal left-to-right septal depolarization, the S is depolarization of the left ventricle, and the final R' is due to the delayed depolarization of the right ventricle. In V6, the S wave is due to delayed depolarization of the right ventricle.

The T wave is usually negative in V1, sometimes in V2.

Criteria for RBBB:

- QRS > 120 ms (3 small squares).
- Depolarization of the right ventricle is delayed, resulting in an RSR' ("rabbit ears") or RR' in V1 and often a slurred S wave in V5-6.
- Flipped T waves in V1, sometimes V2.

Incomplete RBBB fulfills the above criteria, except QRS < 120 ms.

LAFB

Left anterior fascicular block (LAFB) or left anterior hemiblock (LAHB). QRS duration is 100–120 ms. Septal activation is in a left-to-right (normal) and inferior direction. This inferior septal depolarization is sometimes reflected in a Q wave in the lateral leads (I and aVL). Because the last part of the heart to depolarize is the left posterobasal to anterolateral wall, the mean frontal QRS vector has a left-facing axis (-45° to 0°). This also causes lead I to record a large R wave and the inferior leads to record a large S wave. Left axis deviation (LAD) more negative than -45° with a normal QRS duration is nearly always due to LAFB. Actually, LAFB is the component that causes the LAD in 1/2 of patients with LBBB.

Criteria for LAFB:

- Left axis deviation (LAD) -45° to –90°, with a large S wave in the inferior leads (II, III, and aVF) and a dominant R wave in I
- Absence of other causes of LAD (incomplete or complete LBBB)
- Poor R wave progression across the precordium

LPFB

Left posterior fascicular block (LPFB) or left posterior hemiblock (LPHB): This problem is rare, and the ECG pattern is rather nonspecific because you can also see it in patients with RVH, lateral infarction, and emphysema. You can be sure that it is a LPFB only if it is a recent change—all else being the same. The septal depolarization is left to right but directed superiorly, causing a small Q wave in the inferior leads. Because final depolarization in the heart is in the inferior and posterior walls with the vector pointing inferior and to the right, there are large R waves in the inferior leads (II, III, aVF) and large abnormal S waves in the lateral limb leads (I, aVL). This also results in a mean QRS axis of +80° to +140°. The T wave is normal.

Criteria for LPFB:

- Small Q and large R (qR) waves in II, III, and aVF
- Small R wave in I, followed by a large S wave in I, aVL
- Rightward axis (+80° to +140°)

Bifascicular Block

Bifascicular block has 3 presentations:

1) Complete LBBB
2) RBBB + LAFB
3) RBBB + LPFB

The last is the least common. Anterior MI and calcific aortic stenosis are associated with bifascicular block. Remember that acute MI + a new bifascicular block indicate a high risk for progression to complete heart block.

WIDE QRS

Wide-complex QRS may be caused by BBB, ventricular origin of the complex, and/or aberrant conduction. More on this is discussed next and under the previous Arrhythmia topic on page 5-38.

ARRHYTHMIAS

ECTOPIC vs. PACEMAKER

An ectopic beat occurs from an ectopic (abnormal) focus earlier than the expected next beat. It may originate in the atria, AV junction, or the ventricle.

Throughout the heart are foci of cells with pacemaker capability, which can take over if there is a delay in depolarization, such as when the SA node ceases to function normally or there is a severe conduction disturbance. Atrial, non-SA node pacemaker activity has an inherent rate of 60–80 bpm. AV junction (not AV node!) pacemaker rate is 40–60 bpm. Ventricular pacemaker rate is 20-40 bpm (idioventricular rhythm).

Note that ectopic beats are different from escape/pacemaker beats. Ectopic beats are early. Escape beats are at the rate of inherent pacemaker activity.

ATRIAL ARRHYTHMIAS

Atrial fibrillation:

- No P waves: "irregularly irregular" rhythm
- Clinically: varying pulse pressure and no a waves

Atrial fibrillation is the result of multiple ectopic foci firing continuously or disorganized atrial activity. It is thought to be due to a micro-reentry mechanism. No P waves are seen, although there is loud, chaotic atrial "noise" throughout the tracing.

Atrial flutter (Type I):

- High atrial rate: characteristic rate ~ 300 bpm (range 240–340), typically with a 2:1 AV block
- Sawtooth formation
- Whole number ratio of flutter waves to QRS complexes

Atrial flutter is due to a wave of depolarization repeatedly going around and around the atrium—usually with an anatomic obstacle, such as an AV valve, in the pathway. This results in the "sawtooth"-appearing P wave with an atrial rate of ~ 300 bpm (but it varies between 240 and 340 bpm). There is commonly a 2:1 or 3:1 AV block with a resulting ventricular rate of 150 or 100, respectively.

There is also a Type II atrial flutter with a much higher atrial rate: 340–440 bpm.

Wandering pacemaker is exactly what the name implies. The pacing impulse migrates from one atrial pacemaker focus to another. It is a benign condition seen mostly in young people—especially athletes. The varying focus is reflected by varying shapes of the P wave.

Multifocal atrial tachycardia (MAT) is similar to wandering pacemaker, except that MAT occurs at a higher rate with more chaotic switching between pacemakers. MAT is associated with COPD, hypoxia, digitalis, theophylline, severe hypokalemia, and hypomagnesemia. Atrial rate is 100–130 bpm. The rhythm is "irregularly irregular."

Sinus pauses result in a long TP interval. An ectopic escape beat (different P wave) may precede the resumption of the rhythm. If an atrial pacemaker takes over the rhythm, the rate is usually 60–80 bpm. If a junctional pacemaker focus takes over the rhythm, this is termed a "junctional (escape) rhythm." With a junctional rhythm, there is a change in the P wave—it may not be visible or it may be a retrograde P wave very close to the QRS (short PR interval). Junctional rate is normally 40–60 bpm.

VENTRICULAR ECTOPIC BEATS AND HEART BLOCK

Premature ventricular contraction (PVC):

- The QRS complex occurs earlier than expected (premature), is wider than normal, and has a higher amplitude than normal.
- P wave is obscured in the QRS complex.
- T wave is inverted.
- The next RR interval is longer than normal. This is called a full compensatory pause. The SA node is not reset by the ventricular depolarization—hence, the P waves march out normally.

A ventricular escape beat may occur if the sinus pause is long enough, and no atrial or junctional pacemakers kick in.

Complete (3rd degree) heart block has an atrial beat marching independently of a junctional or ventricular escape beat. Remember junctional = narrow, 40–60 bpm. Ventricular = wide, 20–40 bpm. Medication and certain illnesses can affect these rates.

Study tip: Now is a good time to review ventricular tachycardias vs. aberrant conduction. See the discussion on page 5-43.

MYOCARDIAL INFARCTION

COMMON FINDINGS

[Know this section!] Common findings in myocardial infarction: Within the first minute or so of acute ischemia, the T waves flip. After 1–2 minutes, they become positive and peaked (hyperacute). Then injury to the cells occurs, causing the ST segment to elevate. Q waves are associated with cell death. These associations of ECG changes with the actual pathophysiologic processes are somewhat artificial, but clinically useful.

Again:

1) T wave changes (ischemia), then
2) ST-segment changes (injury), and then
3) Development of Q waves (cell death)

LOCATION OF MI vs. ECG CHANGES

Left ventricle:

- Septal MI = changes in V1-2
- Anterior MI = V3-4
- Anteroseptal MI = V1-4
- Lateral MI = I, aVL, V5, V6
- Anterolateral = I, aVL, V3-6 (if V1-6 = extensive anterolateral MI)
- Inferior MI = II, III, aVF
- Apical MI = II, III, aVL and any of V1-4

QuickQuiz

- What are the ECG findings with A-fib?
- What are the ECG findings with MAT?
- What are the ECG findings with a PVC?
- Describe the sequence of ECG changes with the different phases of an MI.
- What ECG changes occur with a septal MI? Anterior? Lateral? Know all these!
- What conditions can cause diffuse inverted T waves?
- What conditions can cause a prolonged QT?
- What type of MI is AV node dysfunction associated with? What about bifascicular block?
- What conditions cause resting ST elevation?

- Posterior MI = tall R in V1-2; ST depression in V1-2
- High lateral MI = I, aVL

Right ventricle:

- RV infarction is best determined by placement of the right precordial leads. ST elevation in V4R to V6R is fairly sensitive and specific for RV infarction (~ 90% each). It is diagnostic of RV infarction if the ST elevation is greater in V4R than in V1-3.
- With the standard ECG, suspect an RV infarction if, with an inferior infarction, there is also ST-segment elevation in V1-2. Also be suspicious in the instance where you see ST-segment elevation in V1, along with ST-segment depression in V2!

NOTES

With acute inferior MI, there may be reciprocal ST depression in septal leads (V1-2). With an anterior/septal MI, there may be reciprocal ST depression in the inferior leads.

The trick for reading the ECG with a suspected acute posterior MI is to hold the ECG upside-down and backwards, while holding it up to a light to see the tracing. Study V1-2. A posterior MI assumes the morphology of other MIs with this trick. (R waves look like Q waves and ST depression appears to be ST elevation.)

Posterior MI is often associated with inferior- and lateral-wall MIs. So, if you see either of these, look closely for signs of a posterior MI.

Signs of acute infarct and ischemia signs may be obscured by LBBB, WPW, HCM, and ventricular pacemakers.

REMEMBER ...

These ECG changes [Know!]:

- Diffuse, inverted T waves: ischemia, pericarditis, drugs, metabolic abnormality, and CNS insult (intracerebral hemorrhage).
- Prolonged QT: drug effect (quinidine, sotalol, dofetilide), hypocalcemia, hypomagnesemia, and CNS insult. This is a precursor to *torsades de pointes*.
- Peaked T waves: hyperkalemia. (If severe, ECG looks like a sine wave.)
- Large U waves are associated with hypokalemia, bradycardia, and digitalis toxicity.
- A low-voltage ECG tracing is associated with pericardial effusion, hypothyroidism, obesity, and COPD.
- AV node dysfunction is associated with an inferior MI and with digitalis and verapamil toxicity.
- Bifascicular block, in contrast, is associated more with anteroseptal MI and calcific aortic stenosis.
- What causes ST-segment elevation during a stress test? Stress-induced coronary artery spasms.
- What causes resting ST elevation?
  - Acute MI
  - Post-MI wall motion abnormalities in the infarcted areas
  - Spontaneous spasm of the coronary artery
  - Pericarditis

ANALYSIS

Analyzing the ECG:

First, check the rate and rhythm. Next, check the intervals—especially the PR, QRS, and QT. Then, check waveforms.

The ECGs on the following pages give you a little practice.

Figure 5-11 provides a memory aid for ECG interpretation. This memory aid is copied below each ECG on the following pages.

Table 5-14 and Table 5-15 summarize the information in the ECG section of the text.

Study tip: To the top left of each ECG is the presenting information. The bottom-left notes are the main findings. So do not look at the bottom information until you have done your reading of the ECG!

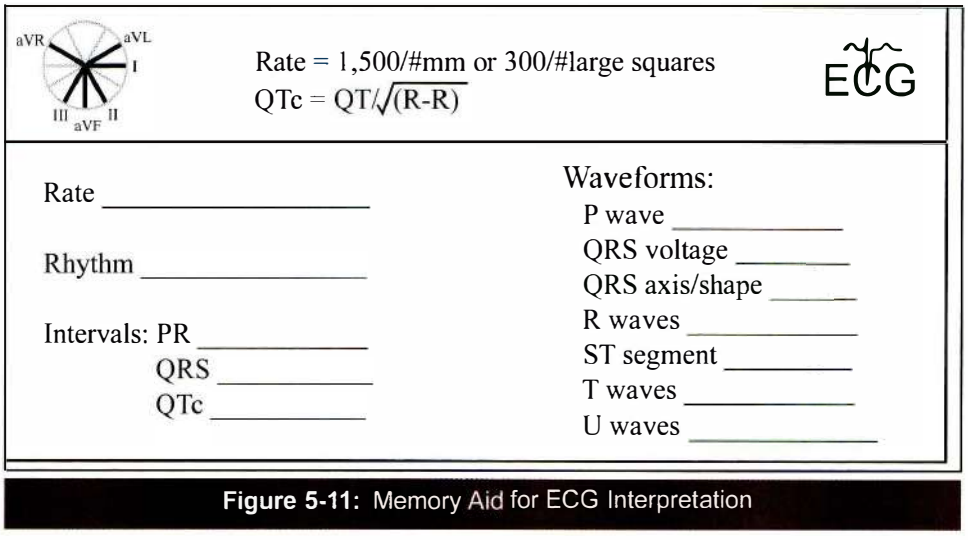


Figure 5-11: Memory Aid for ECG Interpretation

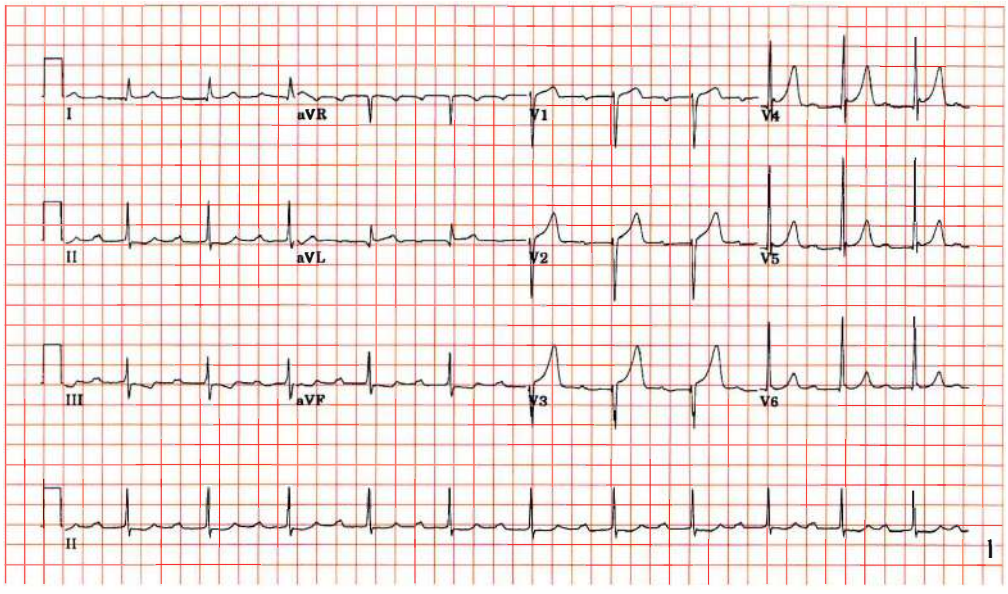
Table 5-14: ECG Summary Table (1 of 2)

		Normal	Abnormal	Common Causes
Heart Rate	1) HR	60–100 bpm	< 60 bpm	Sinus bradycardia, sick sinus syndrome, beta-blockers, junctional or ventricular rhythm
			> 100 bpm	Sinus tach, A-fib with rapid V response, V-tach, SVT
			= 150 bpm	Rule out atrial flutter with 2:1 AV Block.
Heart Rhythm	2) Rhythm	NSR	Many	Multiple (see text)
Intervals and Durations	3) PR	120–200 ms	< 120 ms	Shorter than 120 ms (3 small squares) may indicate: WPW (delta wave) Junctional rhythm (with retrograde P wave) Left atrial overload
			> 200 ms	1st degree AV block
	4) QRS	< 100 ms	> 100 ms	Think WPW if the PR interval is shortened Ventricular ectopy or pacemaker Aberrant conduction (BBB) Drugs; tricyclic overdose (also causes long QT)
	5) QT_c	340–450 ms (men) 340–470 ms (women)	> 450 ms (men) > 470 ms (women)	Hypocalcemia lengthens ST segment Hypokalemia (often w/large U waves) Type Ia (quinidine) and III (amiodarone) antiarrhythmics Tricyclic overdose (also causes long QRS) Intracranial bleed (also causes inverted Ts)
			< 340 ms	Hypercalemia Digitalis effects (which also often causes a scooping of the ST segment)

Table 5-15: ECG Summary Table (2 of 2)

Waves and Segments	Abnormal	Common Causes
6) P wave	> 2 mm, > 120 ms	Tall, peaked P waves in II suggest right atrial overload Biphasic in V1 and broad and notched in II suggest left atrial overload
	Decreased	Severe hyperkalemia
7) Q waves	In ant or inf leads	Acute: More severe MI
8) QRS voltage	High	LVH (SV1 + RV5 > 35 or RV6 > 25–35)
	Low	1) Pericardial effusion 2) Tamponade 3) Emphysema 4) Obesity 5) Amyloid
9) QRS axis	Right: > +110 Left: < –30	Right axis may be seen in: 1) Normal in children and young adults 2) LPFP (+80 to +140) 3) RVH 4) RV overload (pul HTN, PE) Left axis may be seen in: LAFB and LBBB
10) R wave		1) Intrinsicoid deflection > 50 ms with some LVH 2) Delta wave with WPW; V1 shows RR' or RSR' with RBBB 3) Large R in I with LBBB and LAFB 4) Large R in inferior leads with LPFB 5) R in V1, V2 with posterior MI 6) Six causes of Tall R wave in V1: RVH, RBBB, WPW with delta wave, Posterior Infarct, Duchenne's muscular dystrophy, Dextrocardia
11) S wave		1) S wave in V6 with RBBB 2) Large S waves in inferior leads with LAFB 3) Large abnormal S waves in lateral leads (I, aVL) with LPFB
12) ST segment	Elevation	1) Diffuse: acute pericarditis or myocarditis 2) Localized means MI, transmural ischemia, or wall motion disorder: Area involved: 1) Septal = changes in V1-2 2) Anterior MI = V3-4 3) Anteroseptal MI = V1-4 4) Anterolateral = I, aVL, V3-6 (if V1-6 also, then = extensive anterolateral MI) 5) Lateral MI = I, aVL, V5, V6 6) Inferior MI = II, III, aVF
	Depression	1) Subendocardial ischemia (esp if downsloping or flat) such as seen in classic angina 2) ST depression V1-2 with acute posterior MI 3) Reciprocal depression V1-2 with some inferior wall MIs—esp. those w/ lateral posterior extension; also, conversely, reciprocal ST depression in INFERIOR leads with some ANTERIOR MIs 4) Dig toxicity 5) LVH 6) hypokalemia 7) LV strain (ST depression with flipped precordial T waves) 8) RVH with RAD and ST depression preceding a flipped T wave in V1
13) T wave	Tall, peaked	1) Hyperacute MI (usually with ST elevation and sometimes Q waves) These are followed in time by a more prolonged T wave inversion 2) Hyperkalemia (early sign—followed in time by widened QRS and decr. P wave, prolonged QRS, and AV conduction problems) 3) Intracerebral hemorrhage 4) Common in V1-2 with evolving posterior MI
	Inverted	1) Post hyperacute MI (see above) 2) Severe ischemia (may have prolonged QT) 3) Post resuscitation 4) Pericarditis 5) Intracranial bleed can cause deep inverted T waves (along with prolonged QT) 6) In lateral leads (I, aVL, V6) with LBBB 7) In septal leads (V1-2) with RBBB and LVH 8) In V1 with some RVH (suggests RV hypertension)
14) U wave	> 1 mm, positive (nl)	1) Indicates increased susceptibility to *torsades de pointes* 2) Drugs: Type Ia (usu w/prolonged QT) 3) Hypokalemia: (usu w/prolonged QT)
	Negative	1) HTN 2) AV valve disease 3) Major ischemia 4) RVH 5) Up to 60% of patients with an anterior MI 6) Up to 30% of patients with an inferior MI 7) Up to 30% of angina patients

Case 1: A 57-year-old man with previous myocardial infarction and chronic hypertension on digoxin, beta blockers, and ACEI.



Note 1st degree AV block with P-R of 340 ms. Left ventricular hypertrophy. Probable early repolarization—the sharp S wave in V4-5 enhances the likehood of the ST segment being due to repolarization. Possible inferior ischemia.

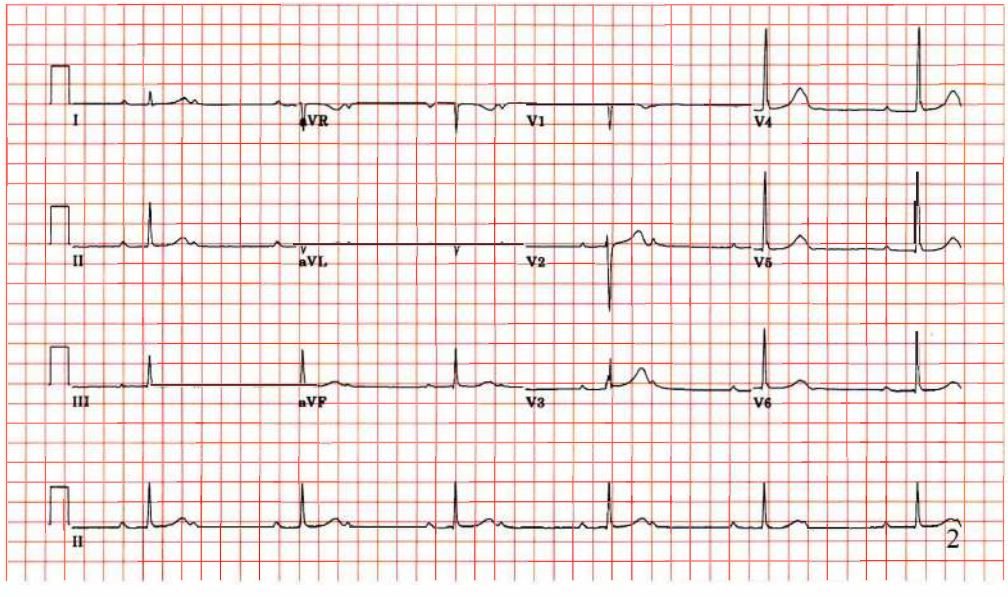
Rate _____

Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 2: A 36-year-old man with history of cocaine abuse and "slow heart rate" since his teens.



Note sinus rhythm with Mobitz type 2 second-degree 2:1 AV block. This initially looks like Mobitz 2, but there is a subtle increase in the PR interval and this also has a narrow QRS complex (Mobitz 2 usually has a wide complex).

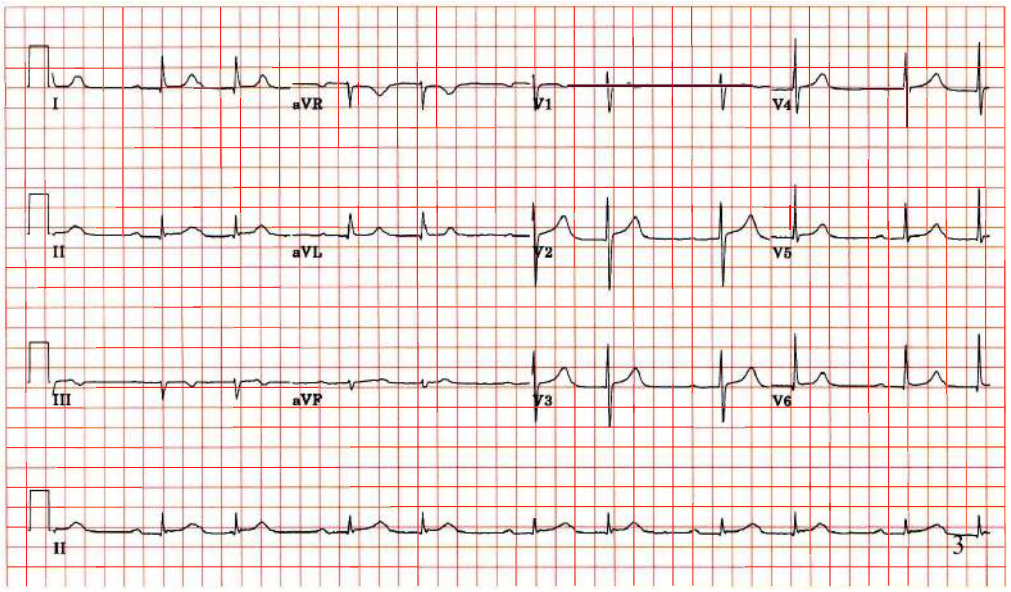
Rate _____

Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 3: A 76-year-old man with chronic heart failure.



Note second-degree Mobitz type I (Wenckebach) 3:2 AV block. The first P wave is visible, the second is just peeking out of the previous T wave, and the third is fused with the previous T wave. Possible COPD.

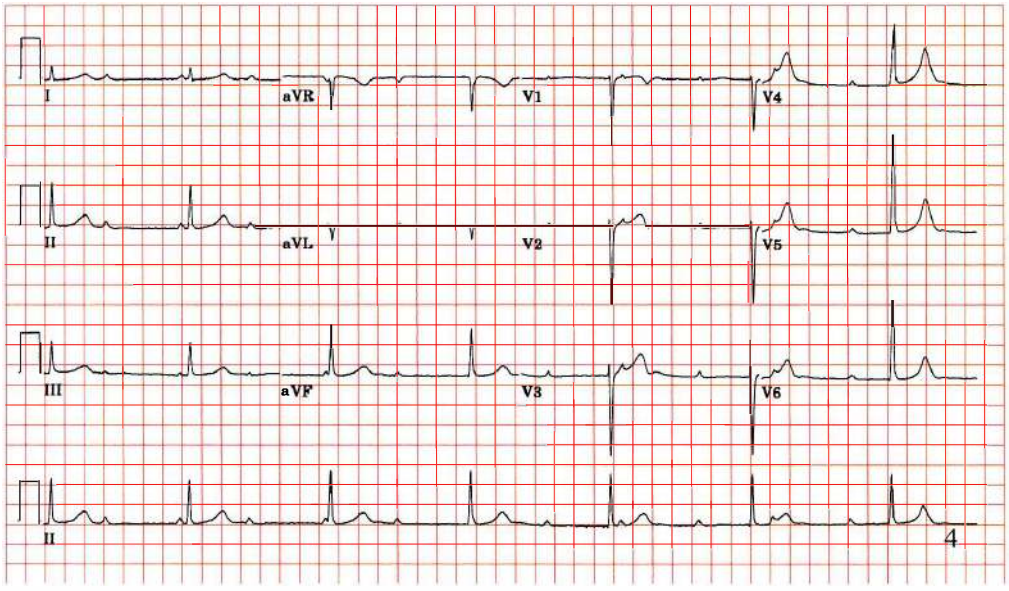
Rate _____

Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 4: A 36-year-old man with history of drug abuse and "slow heart rate" since he was young.



Note sinus rhythm with complete, 3rd degree AV block.

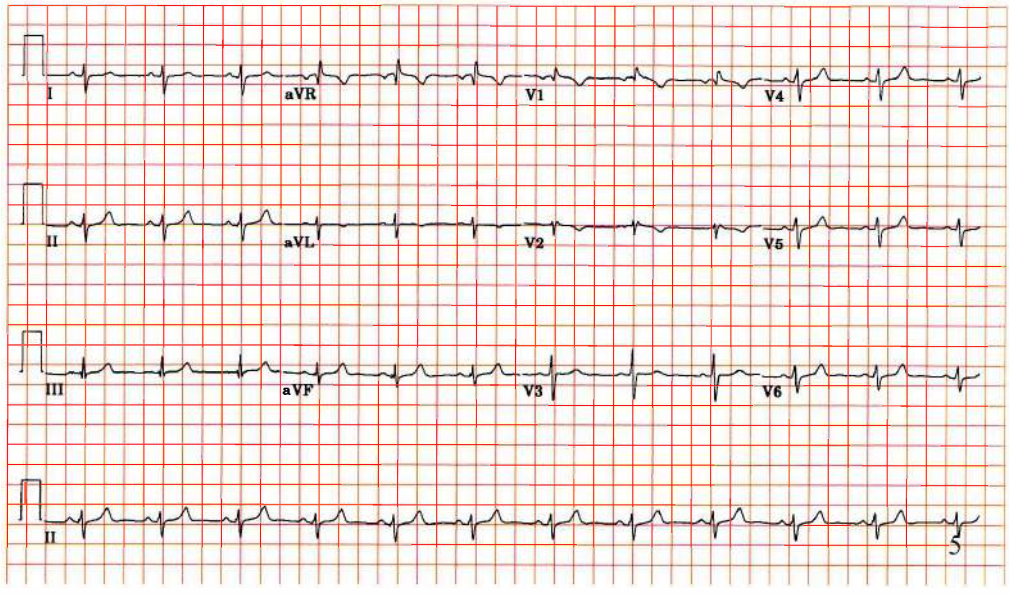
Rate _____

Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 5: A 54-year-old woman with history of chronic smoking.



Rate _____

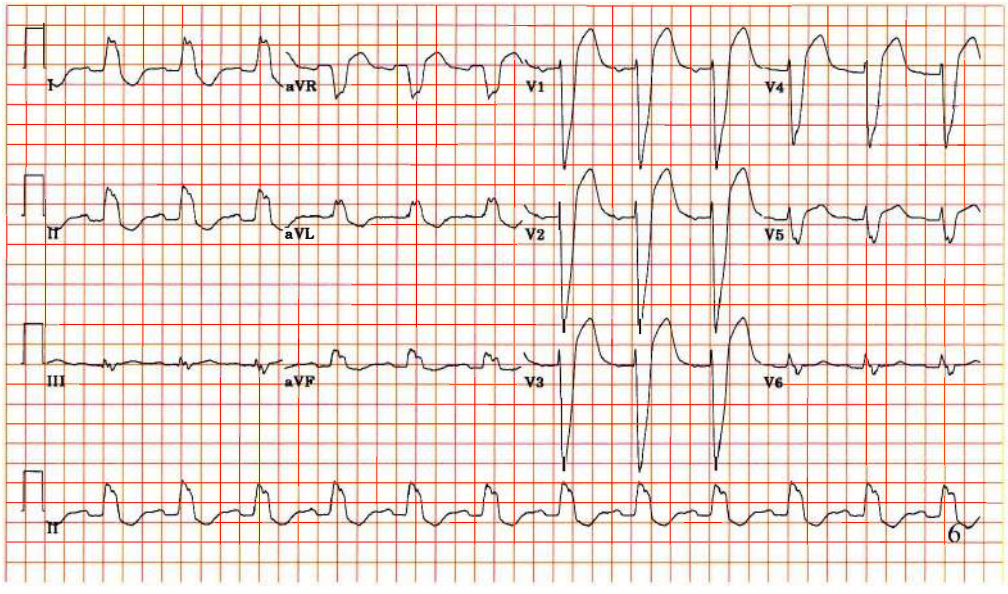
Rhythm _____

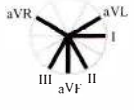
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note sinus rhythm with right axis deviation and incomplete RBBB consistent with pulmonary disease pattern.

Case 6: A 77-year-old man with a history of chronic congestive heart failure.





Rate _____

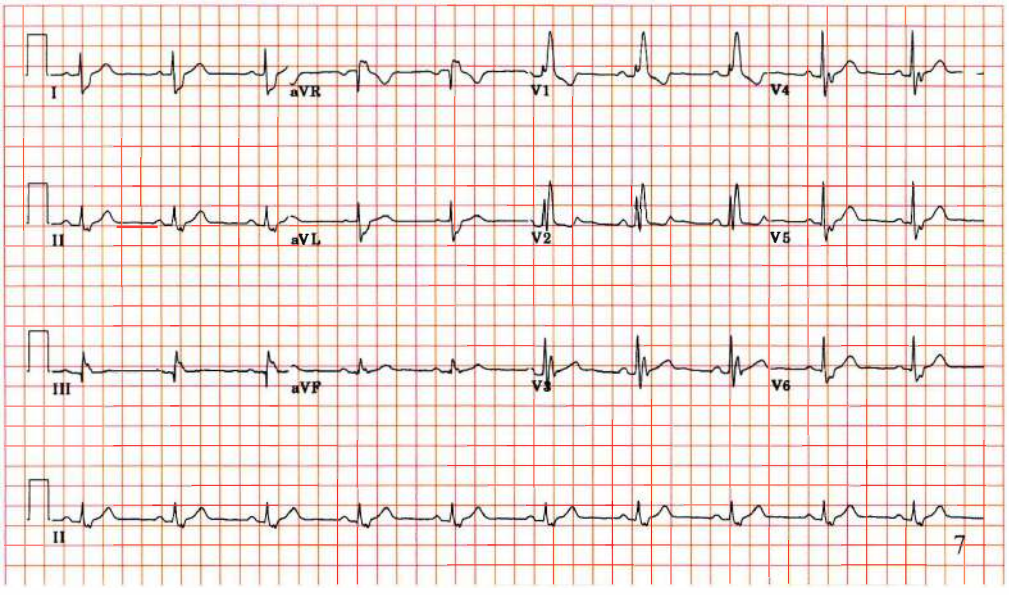
Rhythm _____

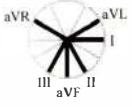
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note sinus rhythm with complete LBBB and left atrial enlargement. This LBBB is a little atypical, but notice the large slurred S in the anteroseptal leads and the T wave opposite the mean QRS in the anterolateral leads. Also notice the terminal portion of the QRS in V1-3 is slurred—also consistent with LBBB.

Case 7: A 67-year-old man with a history of a cardiac murmur and prior repair of a congenital heart defect.





Rate _____

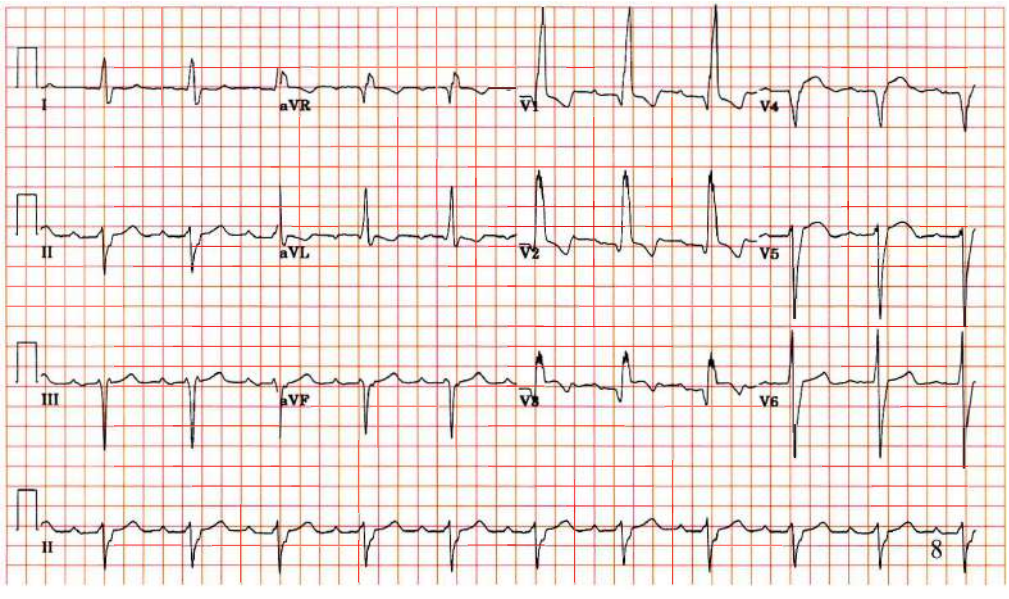
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note sinus rhythm with RBBB.

Case 8: A 77-year-old man with a history of myocardial infarction and recurrent syncope.



Rate _____

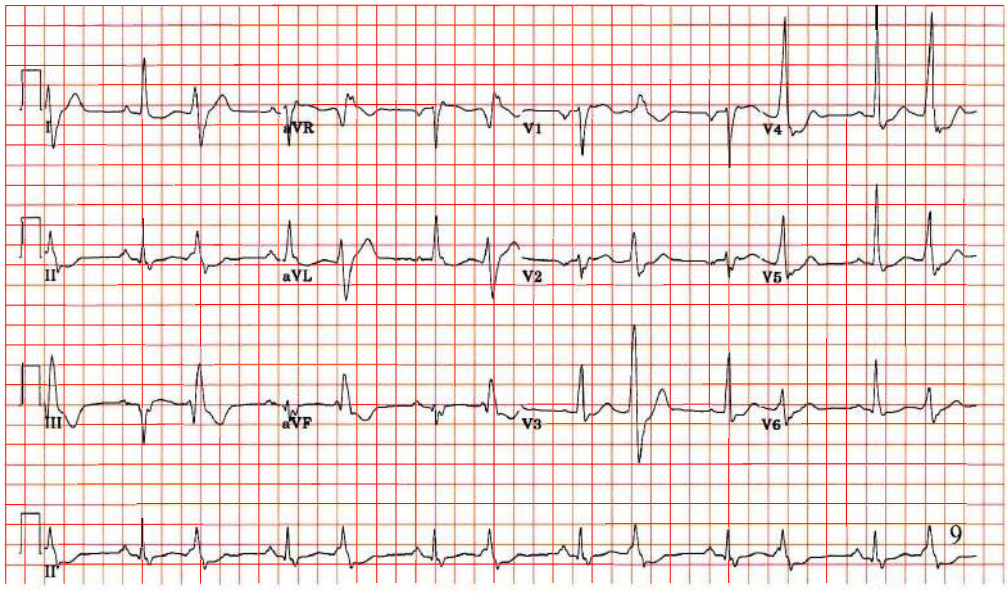
Rhythm _____

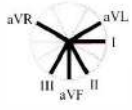
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note sinus rhythm, 1st degree AV block, RBBB and left anterior fascicular block (bifascicular block). Note also Q waves from V1 to V4 consistent with anteroseptal infarct.

Case 9: A 65-year-old man with recurrent palpitations.





Rate _____

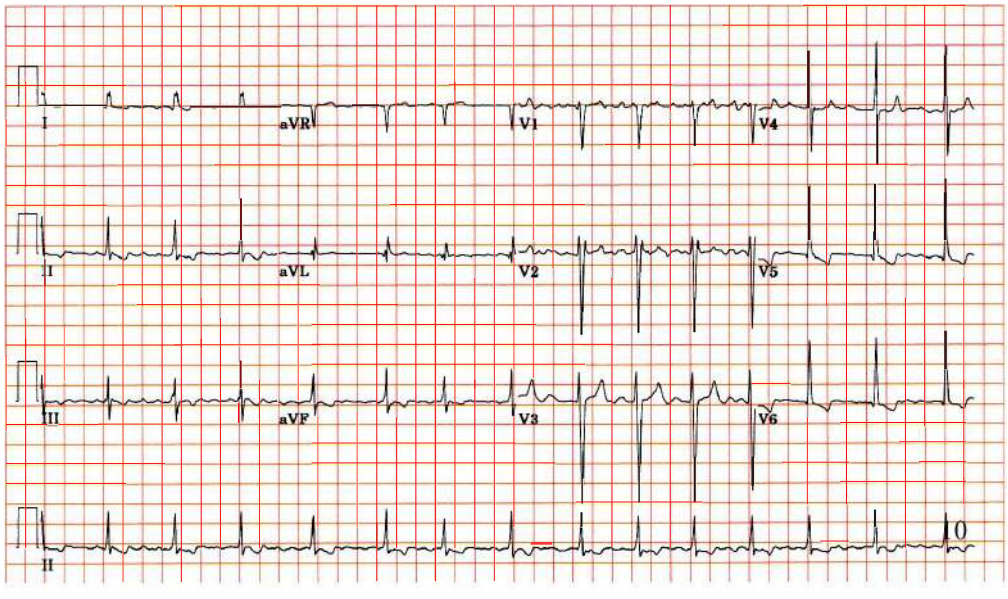
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note sinus rhythm with frequent ventricular premature beats in bigeminy. Note the full compensatory pause after the PVC.

Case 10: A 45-year-old man with a history of rheumatic fever as a child and cardiac murmurs.



Rate _____

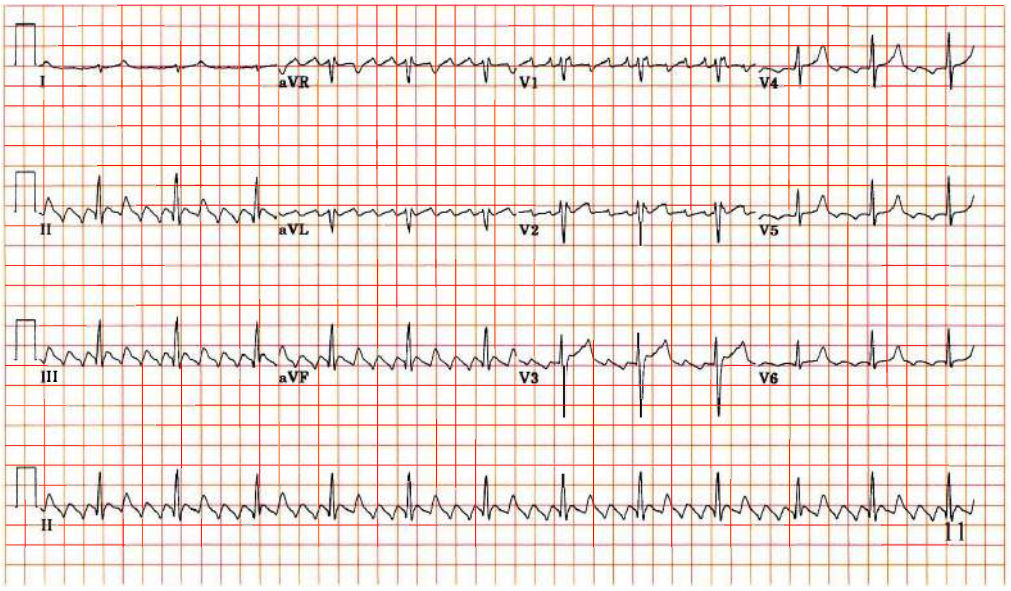
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note atrial fibrillation and flipped Ts in the inferior-lateral leads.

Case 11: A 44-year-old man with a history of 2-pack-per-day smoking for 15 years.



Rate _____

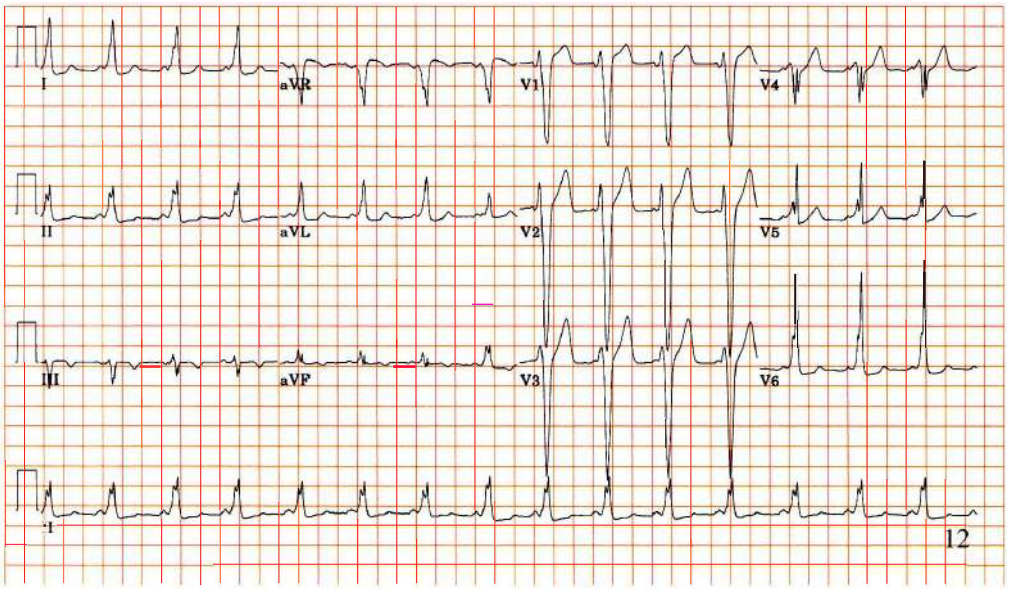
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note atrial flutter with 4:1 block, vertical axis, and incomplete RBBB.

Case 12: A 34-year-old man with history of palpitations since childhood.



Rate _____

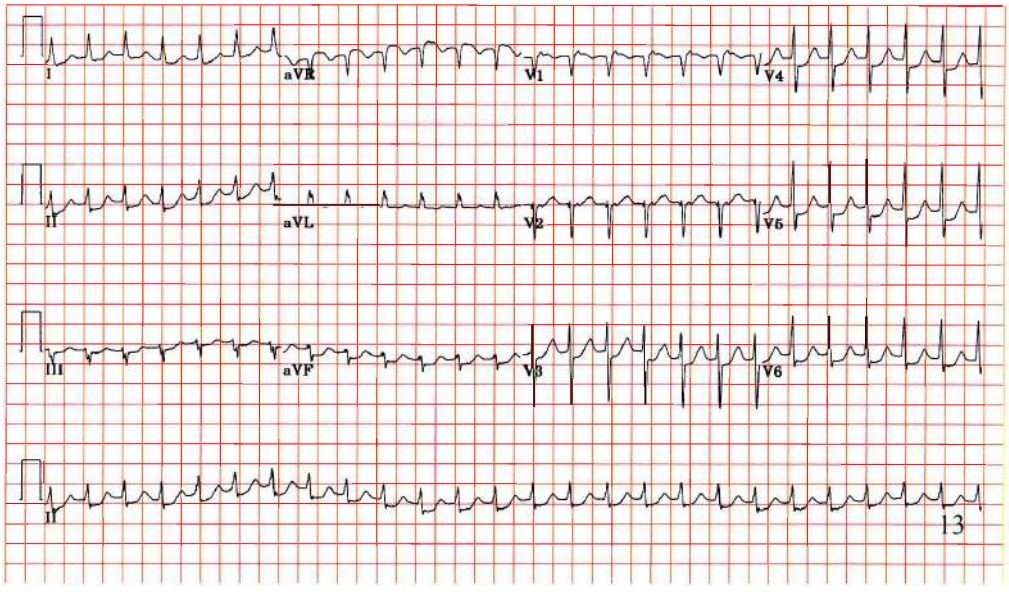
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note sinus rhythm, short P-R interval, and delta wave consistent with Wolff-Parkinson-White syndrome. This is one of those ECGs on which you may mistake the delta wave for prolonged intrinsicoid deflection (as seen with LBBB and LVH) until you check the PR interval and find it is short!

Case 13: A 74-year-old woman with recent episodes of light headedness and palpitations.



Note narrow QRS tachycardia with retrograde P waves evident in precordial leads V1 and V2 consistent with AV node reentrant tachycardia at a rate of approximately 150 bpm. Also pronounced ST-segment depression in the inferio-lateral leads—it is likely that the rapid rate is a factor in the ischemia.

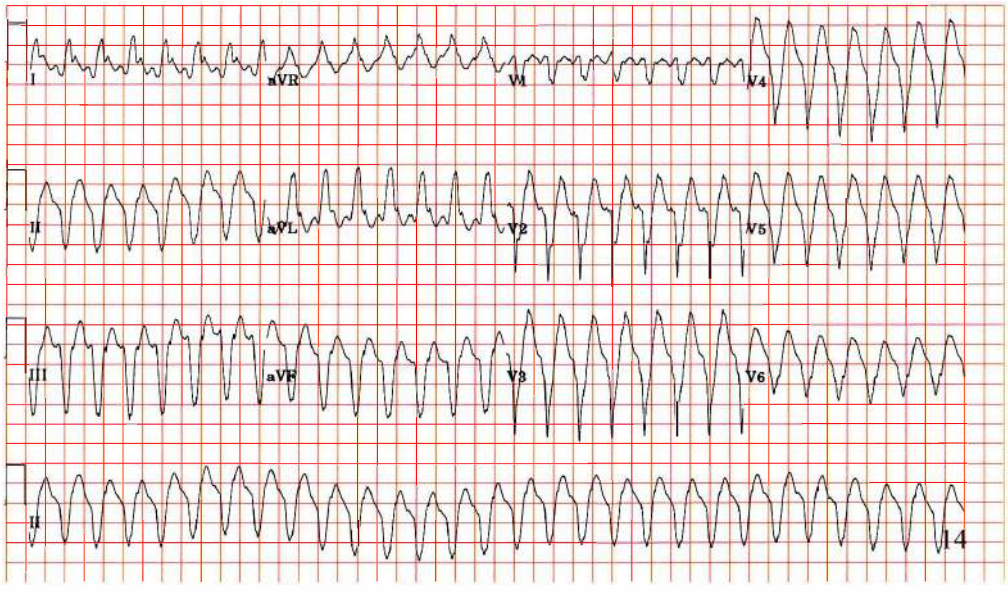
Rate _____

Rhythm _____

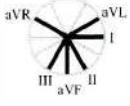
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 14: A 71-year-old man with history of previous myocardial infarction and coronary artery bypass surgery admitted for chest pains and syncope.



Note the wide QRS tachycardia with negative concordance in the precordial leads consistent with ventricular tachycardia. Negative concordance is the QS pattern throughout the precordial leads; there is no hint of R wave progression.



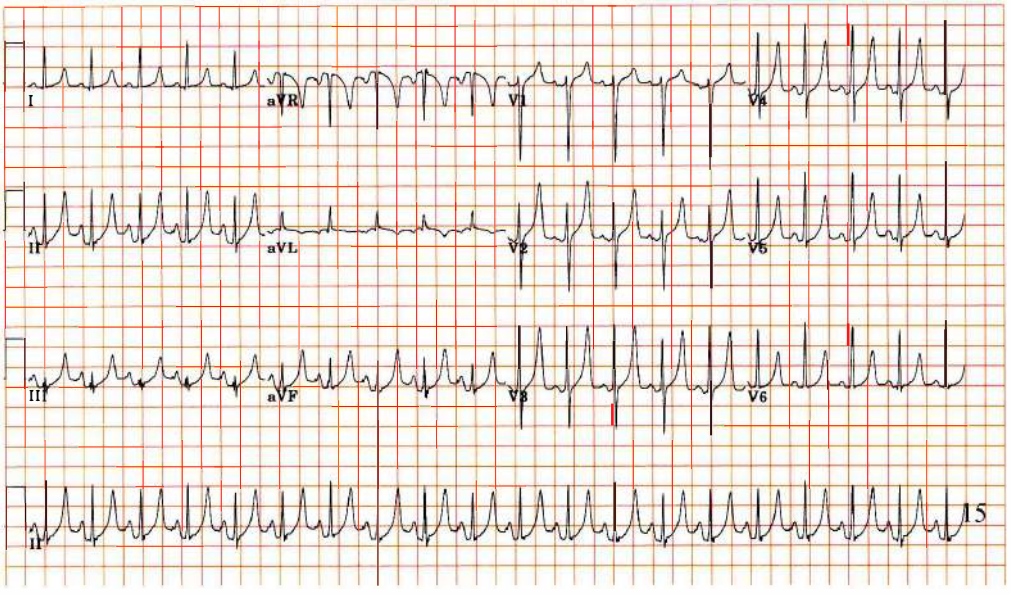
Rate _____

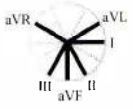
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 15: A 47-year-old man with Type 1 diabetes and chronic renal insufficiency admitted with diabetic ketoacidosis and serum potassium of 7.





Rate _____

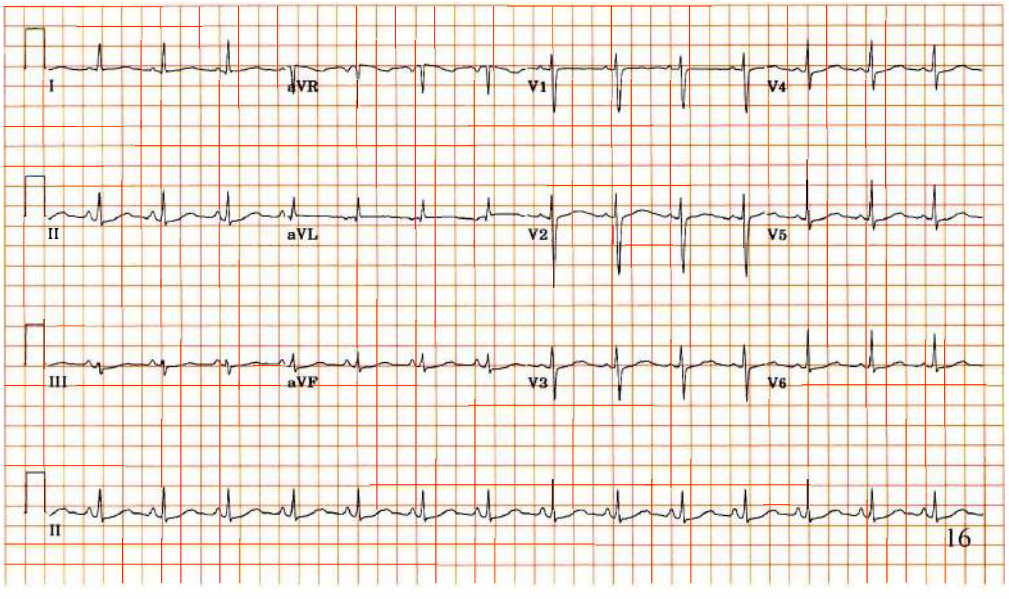
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note tall and peaked T waves. LVH by voltage criteria consistent with hyperkalemia.

Case 16: A 39-year-old woman successfully resuscitated from ventricular fibrillation with no evidence of acute myocardial infarction.



Rate _____

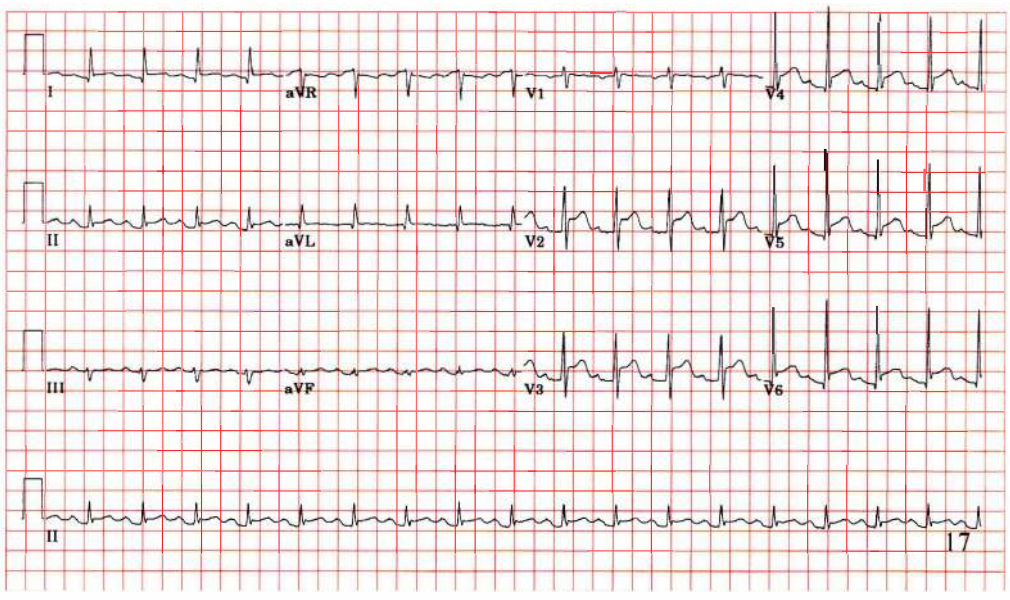
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note prolonged QT of 530 and a QTc of 640 ms. When measuring the QT interval, you must look at all the leads and choose the longest QT interval—in this case, use lead V2.

Case 17: A 65-year-old man admitted for pleuritic chest pains 1 week following a bout of flu-like symptoms.



Rate _____

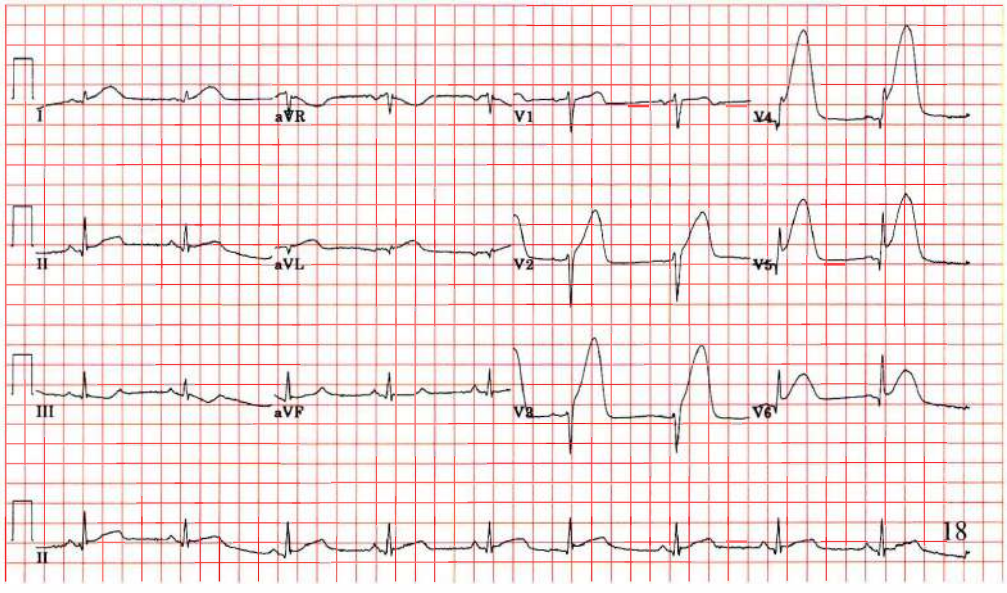
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note diffuse ST-segment elevations consistent with pericarditis. There is PR segment depression best seen in II also often seen with pericarditis. Also note the concave up ST-segment elevation more consistent with pericarditis than MI.

Case 18: A 65-year-old man admitted with a 2-hour episode of severe retrosternal chest pains and shortness of breath.



Rate _____

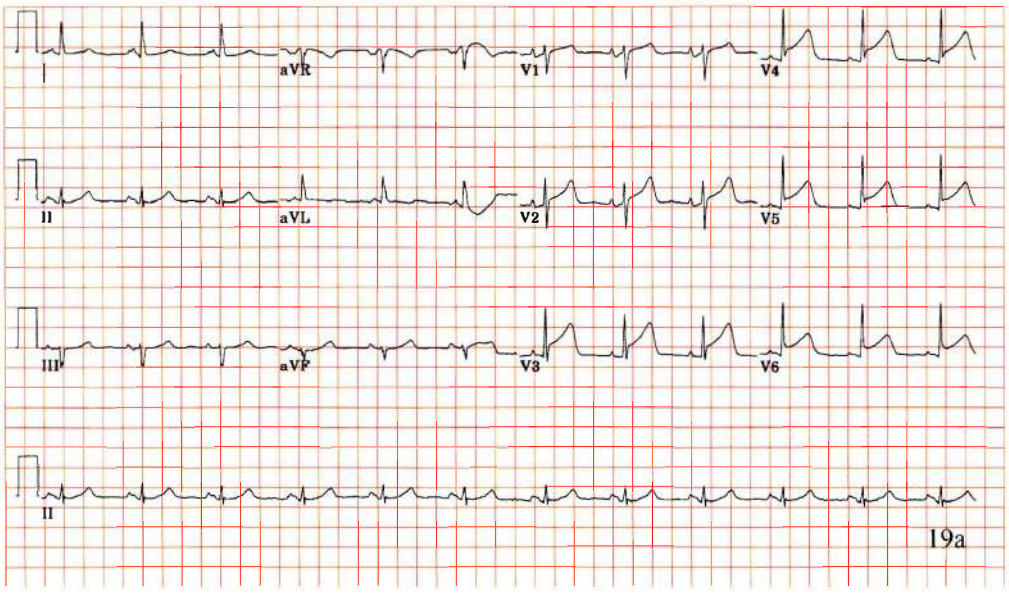
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

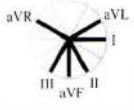
Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note marked ST-segment elevation in precordial leads consistent with acute extensive anterolateral infarction. Associated T waves are hyperacute.

Case 19a: An 80-year-old woman is seen in the emergency department 3 hours after waking up with severe retrosternal pressure and lightheadedness.



Note ST-segment elevations in the precordial leads consistent with acute anterolateral STEMI. Even though the ST segment is mildly concave up, the lack of an S wave in V4-5 makes early repolarization unlikely—as does the presenting complaint!



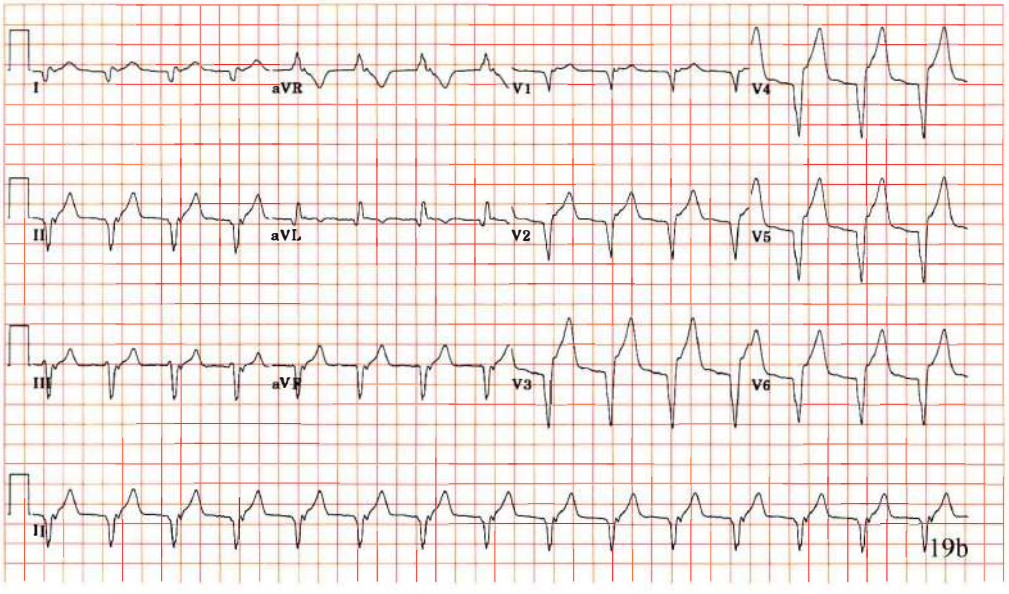
Rate _____

Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 19b: 20 minutes following infusion of a thrombolytic, a repeat ECG is performed.



Shows accelerated idioventricular rhythm (reperfusion arrhythmia) or "slow" ventricular tachycardia at 90 bpm. Note change in QRS duration and axis shift with retrograde P waves—showing a V-A association (i.e., the ventricle is resetting the atrium!).

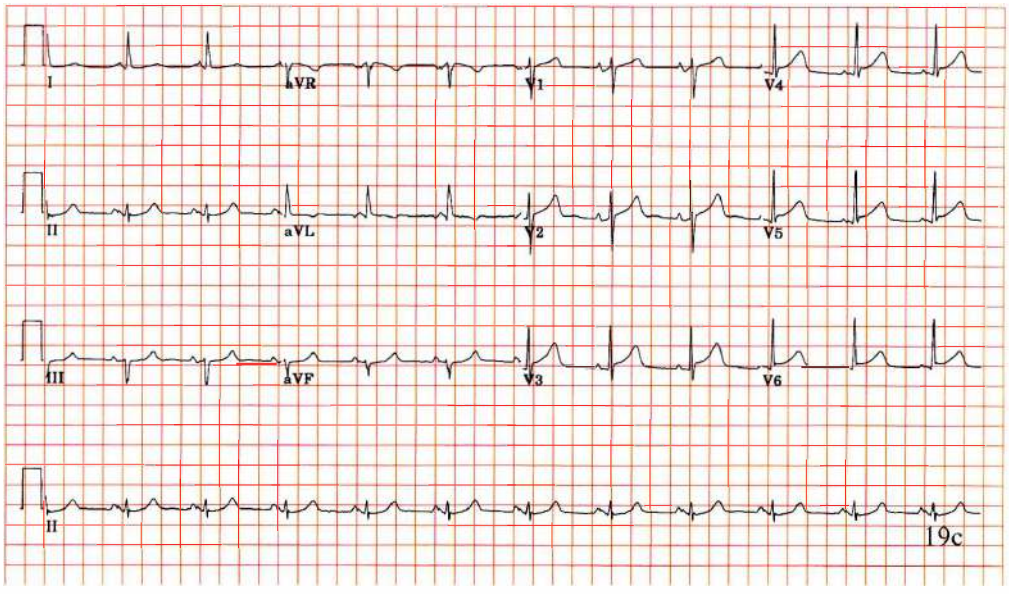
Rate _____

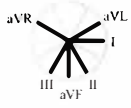
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 19c: 90 minutes after thrombolysis the patient is pain free.





Rate _____

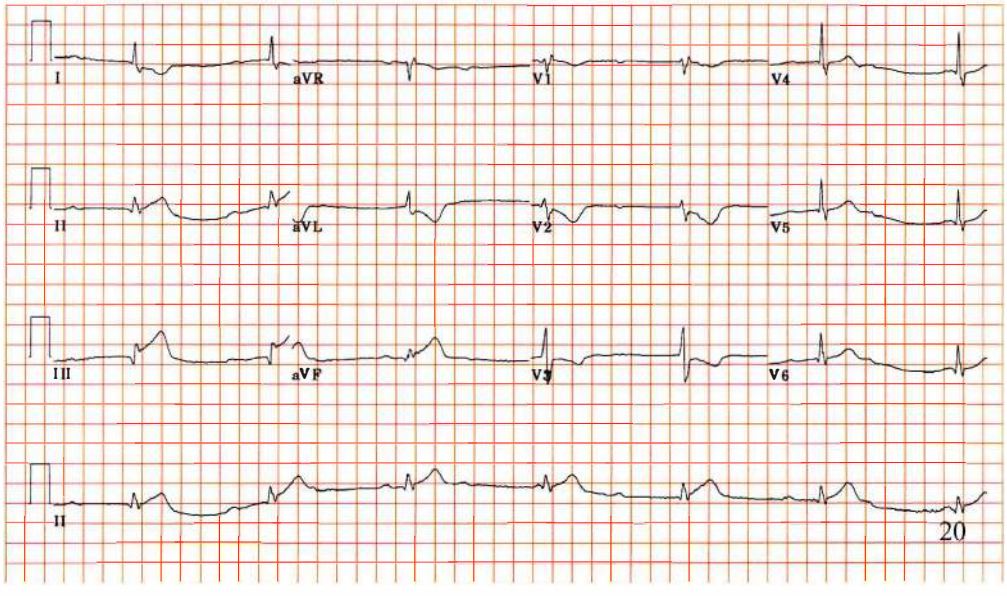
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

A repeat ECG shows significant resolution of the precordial ST-segment elevations.

Case 20: A 65-year-old man with severe epigastric pains, nausea, and vomiting of 2-hour duration.



Rate _____

Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note acute inferior infarction with reciprocal ST segment changes in the right precordial leads and complete AV block shown by AV dissociation with an atrial rate of 75 and a ventricular rate of 40.

FOR FURTHER READING

[Guidelines in blue]

PROCEDURES, LABS, PHYSICAL EXAM

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Table of Contents

Rheumatology

LABS

OVERVIEW

Know everything covered in this topic area about Labs! If this is your first time through the Rheumatology section, go over this topic several times before you continue. What you learn here will enable you to make better sense of lab references later in this section.

Remember: No single blood test makes any rheumatologic diagnosis. For example, ANA can be positive in many non-rheumatologic diseases and in healthy individuals. The key is whether the test results match the clinical picture.

To interpret a test result, it is important to understand the sensitivity and specificity of the test. **Sensitivity** is the proportion of those with a positive test result among patients with disease; tests that are very sensitive are useful for "ruling out" the disease. **Specificity** is the proportion of those with a negative test result among patients without disease; tests that are very specific are useful for "ruling in" the disease.

ANTINUCLEAR ANTIBODIES

ANA

Antinuclear antibodies (ANA) are autoimmune antibodies that attack components of the nucleus. They are found in many autoimmune disorders. The most common ANA tests:

- Indirect immunofluorescence
- Enzyme-linked immunosorbent assay (ELISA)

Indirect immunofluorescence is more sensitive; ELISA is less expensive.

Results are reported as titers (e.g., 1:320), with a particular pattern when positive.

Titers show the dilution at which the antibodies become undetectable. It is shown in doublings: 1:40, 1:80, 1:160, 1:320, 1:640, etc.—so, the higher the titer, the more antibodies in the serum.

Patterns are determined by looking at a specially prepared fluorescent stain slide to ascertain where the antibodies attack the nucleus. There are 6 different patterns: centromere, rim or peripheral, speckled, diffuse, homogenous, and nucleolar. While ANA patterns may provide some information, they do not identify the specific antibody present, nor are they specific for any particular disease. The homogenous and rim patterns can be observed in systemic lupus erythematosus (SLE). Anti-centromere patterns are suggestive of anti-centromere antibodies, which are seen with the limited form of systemic sclerosis (formerly known as **CREST**—**c**alcinosis, **R**aynaud's, **e**sophageal dysmotility, **s**clerodactyly, **t**elangiectasia).

ANA titers are considered positive only if > 1:80. Titers > 1:320 are considered clinically relevant for autoimmune diseases. Some rheumatologic diseases that are ANA+:

- Drug-induced lupus (100%)
- SLE (98–100%): Note that ANA-negative lupus is rare; so ANA is pretty useful for ruling out SLE!
- Mixed connective tissue disease (MCTD; 93–100%)
- Limited systemic sclerosis and diffuse systemic sclerosis (60–90%)
- Sjögren syndrome (48–70%)
- Polymyositis/dermatomyositis (60%)
- Rheumatoid arthritis (RA; 40%)

Example of ruling in vs. ruling out: The ANA is positive in almost all patients with SLE (high sensitivity) but also is positive in many other diseases (low specificity). So, a negative ANA test is helpful for ruling out SLE, but a positive test is poor for ruling it in.

The patterns found with fluorescent staining differ with the various types of ANA patterns. These different ANA attack different points in the nucleus, causing various diseases. We now have tests (below) that identify these antibodies far more precisely than with fluorescent staining.

When the ANA is positive and you suspect a specific rheumatologic disease, order the more specific antibody subtypes (ANA profile). Know which diseases are also associated with specific subtypes (Table 6-1 on page 6-2). Again, the general ANA test is not specific enough to diagnose any disease, only to rule one out.

Specific ANA Tests

Anti-dsDNA (in high titer) and **anti-Smith** (anti-Sm) are very specific for SLE. If one or both of these are strongly positive, the diagnosis of SLE is strongly supported. However, patients with drug-induced lupus can have antibodies to anti-dsDNA (hence, they are ANA positive also).

Anti-U1-RNP is very sensitive for MCTD but not very specific because it can be seen in SLE and other connective tissue diseases. In general, absence of the antibody excludes MCTD. Anti-U1-RNP and anti-dsDNA are often seen together because they bind to related antigens known as epitopes. An epitope, also known as antigenic determinant, is the part of an antigen that is recognized by the immune system. The term epitope is often used interchangeably when describing an antigenic component of a cell.

The clinical significance of **anti-ribosomal P protein** antibodies is their specificity for the diagnosis of SLE. These antibodies have not been found in normal controls and are rare in patients with other autoimmune diseases. There are studies suggesting an association and/or predisposition with CNS and liver disease in

Table 6-1: Antinuclear Antibody Disease Associations

Antibody	Subclass	Associated with:
Specific ANAs	Anti-dsDNA	Specific for SLE; an indicator of disease activity (as are complement levels) and identifies SLE patients with potential for significant renal disease. Absent in classic drug-induced SLE; sometimes develops in patients treated with TNF inhibitors.
	Anti-Sm	Specific for SLE.
	SSA (Ro)	SLE, neonatal SLE, Sjögren's, and sometimes myositis. Usually not found in scleroderma; passively transferred from mother to baby → neonatal heart block. DR3 is associated with SSA.
	SSB (La)	SLE and Sjögren's; sometimes found in patients with +SSA. Also passively transferred from mother to baby → neonatal heart block.
	Anti-U1-RNP	Sensitive for MCTD; also found in SLE—usually in association with anti-Sm or anti-dsDNA.
	Antihistone	Drug-induced lupus and SLE. Mainly used to rule out drug-induced lupus caused by procainamide, hydralazine, chlorpromazine, and quinidine.
	Anti-centromere	Limited scleroderma; identifies increased incidence of pulmonary arterial hypertension and improved survival.
	Anti-Scl-70 (Anti-topoisomerase I)	Progressive systemic sclerosis; identifies increased incidence of interstitial lung disease and reduced survival.
	Antisynthetases	Anti-Jo-1 = type of anti-synthetase antibody; associated with myositis; identifies increased incidence of interstitial lung disease. Anti- SRP (signal recognition protein) is associated with cardiomyopathy and refractory to treatment.

lupus patients. Do not confuse anti-ribosomal with anti-ribonucleoprotein antibodies (not the same)!

Antihistone antibody can be seen both in SLE and drug-induced lupus. The antihistone antibody test is very sensitive (> 95%) for drug-induced lupus (DIL). Drugs commonly associated with DIL include: procainamide, hydralazine, chlorpromazine, isoniazid, sulfasalazine, methyldopa, quinidine, minocycline, and anti-TNF agents. The absence of the antihistone antibody effectively rules out DIL in patients taking any of these agents, with the exception of patients who are on anti-TNF therapy or minocycline. It is rare to see antihistone antibodies in patients on anti-TNF biologics or minocycline, even though they manifest symptoms suggestive of DIL. Further information on DIL can be seen on page 6-17.

Anti-Scl-70 (a.k.a. **anti-topoisomerase I**) is specific for progressive systemic sclerosis, formerly known as diffuse scleroderma; it is present in ~ 75% of cases. Its presence supports a diagnosis of a systemic, diffuse process (not a limited cutaneous one) and is associated with progressive skin involvement, pulmonary fibrosis, and a higher mortality.

Before going further, let's clarify the terms **Ro** and **La**. Anti-Ro (or just "Ro") was the term given for the specific ANA antibody causing the "speckled" ANA pattern found mainly in SLE and Sjögren syndrome. During the same period, a serum antibody was discovered in these patients, which was named anti-SSA (or SSA). These 2 antibodies turned out to be the same antibody. So, these terms can be used interchangeably—you commonly see them together; e.g., Ro/SSA, SSA (Ro). Similarly, SSB is identical to La and commonly seen as La/SSB or SSB (La). The "SS" in SSA and SSB stands for Sjögren syndrome. The most important thing to remember about Ro and La is their association with congenital heart block. Patients with SLE who are pregnant or who plan to become pregnant should be tested for Ro and La antibodies.

ANCA

Anti-neutrophil cytoplasmic antibodies (ANCAs) are, as the term indicates, autoimmune antibodies against antigens in the cytoplasm of neutrophils. ANCAs are markers for vasculitis, including drug-induced vasculitis (Table 6-2).

It is thought that the vasculitis may be caused by the ANCA antibodies, which stimulate the release of lytic enzymes from neutrophils.

QuickQuiz

- What two ANA subtypes are specific for a diagnosis of SLE?
- Anti-U1-RNP is a very sensitive indicator for what rheumatologic disorder?
- Which antibody is associated with drug-induced lupus?
- Which drugs are associated with drug-induced lupus?
- Which rheumatologic disease is associated with a positive c-ANCA and anti-PR3?
- Name 2 diseases that are p-ANCA+ and anti-MPO+.

Two ANCAs are identified by their immunofluorescence (IF) pattern:

1) c-ANCA: Antibodies are diffuse in the cytoplasm.
2) p-ANCA: Antibodies are perinuclear.

These ANCAs can then be subdivided based on the antigen, or epitope, they are directed against: anti-proteinase 3 (anti-PR3; PR3 ANCA) or anti-myeloperoxidase (anti-MPO; MPO ANCA). Laboratories determine these antigens using an enzyme-linked immunosorbent assay (ELISA). This further analysis of the ANCA helps you narrow down a diagnosis.

So again, we have 2 ANCAs (c-ANCA and p-ANCA) that are further categorized, based on ELISA, into whether or not antibodies are directed against the PR3 or MPO antigens. (Proteinase 3 and myeloperoxidase are enzymes located in neutrophil cytoplasmic alpha granules.)

1) c-ANCA—anti-PR3
2) p-ANCA—anti-MPO

c-ANCA and anti-PR3 are strongly related while p-ANCA and anti-MPO are more loosely related. PR3 antigens usually cause the diffuse pattern seen in c-ANCA+ IF tests.

The combination of c-ANCA+ and anti-PR3+ is very specific for granulomatosis with polyangiitis (GPA; previously Wegener granulomatosis).

p-ANCA is less helpful because this IF pattern is nonspecific. Table 6-2 shows you that many diseases are p-ANCA+ (especially in the anti-MPO category). Further test any p-ANCA+ results with ELISA for anti-MPO antibodies.

If a patient is anti-MPO+, think vasculitis: microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), Churg-Strauss, pauci-immune rapidly progressive glomerulonephritis (RPGN), anti-GBM disease, and drug-induced ANCA-associated vasculitis.

The most common causes of anti-MPO+ drug-induced ANCA-associated vasculitis are the anti-thyroid drugs propylthiouracil (PTU) and methimazole. Many other drugs are much less commonly associated.

In summary:

- c-ANCA+ plus anti-PR3+: Think GPA.
- p-ANCA+ plus anti-MPO+: Think MPA, EGPA, Churg-Strauss, pauci-immune RPGN, Anti-GBM, and drug-induced.

The sensitivity and specificity of these antibody tests are, in general, not high enough for them to be used for screening. Pretest probability of the disease in question is important and should be considered before ordering ANCAs.

COMPLEMENT

The complement system is comprised of a variety of small proteins that function to enhance, or complement, the action of antibodies and phagocytic cells. Hypocomplementemia is seen in SLE, vasculitis, rheumatoid arthritis, and infective endocarditis.

There is more on the complement pathway in Allergy & Immunology, Book 4. But note: Complement components can be decreased due to a genetic deficiency, consumption during complement activation, or underproduction—as in eclampsia or **HELLP** syndrome (**h**emolysis, **e**levated **l**iver enzymes, **l**ow **p**latelets).

Table 6-2: ANCAs

IF ANCA	ELISA	Disease
c-ANCA	Anti-PR3+	GPA
p-ANCA	Anti-MPO+	MPA EGPA Churg-Strauss Pauci-immune RPGN Anti-GBM disease Drug-induced; e.g., PTU, methimazole
	Anti-MPO–	Crohn disease Ulcerative colitis Chronic active hepatitis Primary sclerosing cholangitis Primary biliary sclerosis Chronic arthritides

Know:

- **C2** or **C4**—usually a genetic allele deficiency.
- **C3** is consumed with any activation of the complement pathway (classical or alternative).
- **C4** is consumed only with activation of the classical pathway (as with SLE).
- **CH50** assay measures total hemolytic complement of the classical pathway and requires all components (C1–C9) of the classical pathway for a normal result.

The CH50 assay is most useful as a screening tool for disease states resulting in hypocomplementemia. A low CH50 should prompt you to order the individual complements listed above to help you in your diagnosis. For example, patients with recurrent or severe neisserial (meningococcal or gonococcal) infections may have terminal complement deficiency (C5–C9). Patients with SLE may have low C3 and C4; C3 is a more sensitive index of disease activity in SLE. Therefore, normalization of individual complement levels and CH50 can be used to follow disease activity.

RHEUMATOID FACTOR AND ANTI-CCP

Rheumatoid factor (RF) is an auto-antibody that binds to the Fc region of IgG. It is positive in 80–85% of patients with RA, which makes RF a fairly sensitive test for RA, but it is not specific because a positive RF can be seen in other diseases, including: chronic lung disease, chronic infections (e.g., TB, HIV, viral hepatitis), Sjögren's, SLE, infectious endocarditis, and hematologic malignancies.

The anti-citrullinated cyclic peptide (anti-CCP antibody), however, is highly specific for RA (specificity ~ 97%) and tends to portend a poorer prognosis. The presence of both RF and anti-CCP antibodies is associated with more aggressive RA and extra-articular manifestations (e.g., rheumatoid nodule, rheumatoid lung/interstitial lung disease).

Table 6-3: Incidence of HLA-B27

Ankylosing spondylitis	90%
Reactive arthritis; typically secondary to GU/GI infections	60–80%
C. jejuni and *C. trachomatis* arthropathy	50%
Uveitis	50%
Healthy Caucasian population	7–8%
Rheumatoid arthritis, osteoarthritis, rubella arthritis	10%

Although it does not cause reactive arthritis, *Klebsiella pneumoniae* has an enzyme (not encoded) that cross-reacts with the HLA-B27 test.

MAJOR HISTOCOMPATIBILITY COMPLEX: HUMAN LEUKOCYTE ANTIGENS

Overview

There are 2 main classes of major histocompatibility complex (MHC) human leukocyte antigens (HLA) antigens:

- Class I includes the HLA-A, HLA-B, and HLA-C antigens, which interact with CD8 or T suppressor cells.
- Class II includes the HLA-D antigens; e.g., DR2, DR3, and DR4, which interact with CD4 or T helper cells.
- Note: An easy way to remember this relationship between MHC and CD T cells is that both form a product of 8—MHCI x CD8 = 8, while MHCII x CD4 = 8.

HLA-B27

Know when HLA-B27 is found:

- Reactive arthritis: 60–80%, higher when sacroiliitis is present.
- Ankylosing spondylitis (AS): 90%.
- Psoriatic arthritis: up to 60% (particularly with spinal/axial disease).
- Inflammatory bowel disease (IBD) with associated axial joint arthritis: up to 60%. But there is no HLA-B27 association when only appendicular joint disease is present in IBD patients.

Note that if axial disease is present, HLA-B27 is typically positive. Keep in mind that 7–8% of the healthy Caucasian North American population carries this haplotype; therefore, an individual with HLA-B27 has only a 10–20% risk of developing an HLA-B27-related disease. Consequently, this test has limited clinical usefulness if not ordered in the right clinical scenario. A negative HLA-B27 test is useful in ruling out ankylosing spondylitis. See Table 6-3.

HLA-DR2, 3, 4

DR2 and DR3 are associated with SLE. DR3 is occasionally found in Sjögren syndrome and polymyositis. DR4 antigens are associated with severe RA. More in Allergy & Immunology, Book 4.

Other important general HLA associations to know:

1) HLA-B5701 is strongly associated with abacavir hypersensitivity reaction (see Infectious Disease, Book 1).
2) HLA-B51 is associated with Behçet disease.
3) HLA-DQ2/DQ8 is associated with celiac disease (see Gastroenterology, Book 1).

QuickQuiz

- Name 2 diseases that consume complement during a flare.
- Other than rheumatoid arthritis, a positive RF can be seen with what other diseases?
- What antibody test is more specific than RF for rheumatoid arthritis?
- Compare and contrast "normal," "noninflammatory," "inflammatory," and "septic" joint fluid. (See Table 6-4.)
- Describe gout crystals and their birefringence.

ERYTHROCYTE SEDIMENTATION RATE AND C-REACTIVE PROTEIN

The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most common acute phase reactants (APRs; inflammatory markers) used in clinical medicine. They are most helpful in determining disease activity and response to therapy.

Unfortunately, they are of limited diagnostic utility. Although they are sensitive markers of inflammation in general, they are not specific for any particular disease. Diagnostically, they are most helpful in ruling out inflammatory disease, especially when the pretest likelihood is low to moderate. Note that an extreme elevation of the ESR (> 100 mm/hr) is almost always a hallmark of serious underlying disease, most commonly malignancy, infection, or vasculitis.

THE JOINT

SYNOVIAL FLUID AND CRYSTAL ANALYSIS

Synovium and synovial fluid: Type A cells of the synovial membrane are phagocytic, whereas type B cells probably synthesize hyaluronic acid. Chondrocytes make the cartilage. Cartilage is avascular and depends on the synovial fluid for nutrients. The chondrocytes can produce only a limited amount of collagen, so only slight damage is repairable.

Joint fluid is categorized based on the inflammatory response (WBC/mm^3). The WBC count in aspirated joint fluid decreases rapidly, so analyze it immediately. See Table 6-4.

Also, know that frank blood (hemorrhagic joint) can be caused by trauma, bleeding diathesis, tumor, and pigmented villonodular synovitis (PVNS).

Look for crystals in inflammatory fluid using the polarizing microscope. Look for monosodium urate crystals (gout) and calcium pyrophosphate dihydrate (CPPD) crystals (pseudogout). Both types have 2 colors: blue and yellow; hence, they are termed "birefringent." The crystals are identified, however, by the color of the crystals that are parallel to the microscope's color compensator. (Crystals perpendicular to the color compensator are the opposite color.) Be concerned only about the crystal color that is parallel! If the crystals are yellow when parallel to the compensator, they are termed "negatively birefringent," and when they are blue, they are "positively birefringent."

Uric acid (gout) crystals are yellow when parallel to the compensator (negatively birefringent), and they are needle-like. (Helpful hint: The double Ls in "yellow" are parallel to each other.)

Table 6-4: Synovial Fluid Analysis

Joint Fluid	WBC (cells/mm^3)	Other Findings	Disease Associations
Normal	0–200	None RBC	Normal or OA Internal derangement
Noninflammatory	200–2,000	None RBC	OA, trauma, neuropathic joints, hypertrophic arthropathy, TB, PVNS; occasionally SLE, scleroderma, and rheumatic fever.
Inflammatory	2,000–50,000	None Intracellular, strongly negatively birefringent crystals (yellow) Intraceullar, weakly positively birefringent crystals (blue) RBC	RA, gout, pseudogout, SLE, scleroderma, reactive arthritis, ankylosing spondylitis, TB or fungal infection
Septic	50,000–100,000	None Organisms on Gram stain	Septic joint (but gonococcal septic joint can be 10,000 cells/mm^3) RA (very inflammed), gout, pseudogout

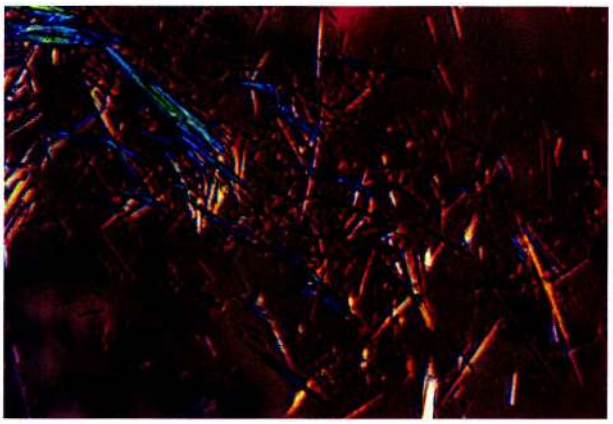

Image 6-1: Birefringent crystals

CPPD (pseudogout) crystals are blue (weakly positive birefringent) when parallel to the compensator; they appear as small, rhomboid structures.

CPPD crystals attract neutrophils and can cause a purulent joint similar to gout with high synovial fluid WBC count. To be very certain that the crystals are actually causing the inflammatory reaction in the joint, you must see intracellular crystals, which are crystals within the neutrophils, as opposed to crystals just floating around freely in the joint space. Important: Crystalline and infectious arthritis can coexist, so it is important to always send studies for both.

Again, you cannot simply look at a photo of a crystal and see whether it is positively or negatively birefringent; you must know the direction of the compensator dial. For instance, in Image 6-1, you see needle-shaped crystals (so probably uric acid), but you won't know they are negatively birefringent unless the compensator is vertical and the vertical crystals are yellow (yellow → parallel = gout).

IMAGING STUDIES

Weight-bearing knee films are the initial diagnostic tests of choice for nontraumatic knee disorders (RA or OA) because weight bearing allows a more realistic evaluation of the joint space. If necessary, MRI can visualize all the components, except for normal synovium (too thin).

GENETIC COLLAGEN DISORDERS

The inherited disorders of collagen encompass several different diseases, many of which cause hypermobility—e.g., Marfan syndrome, Ehlers-Danlos syndrome (EDS), and homocystinuria. Defects in elastic fiber formation (Marfan syndrome) or in type II collagen (Stickler syndrome) are well defined; different proteins are responsible for these syndromes.

The following are the ones to remember.

Marfan syndrome:

- Long limbs (outstretched arm length > height)
- Pectus excavatum (sternum dips inward), or pectus carinatum (sternum protrudes outward)
- Aortic aneurysm/dissection
- Ectopia lentis (lenses displaced upward)
- Heart valve disease

Ehlers-Danlos syndrome: variable skin hyperelasticity and joint hypermobility. Several classifications:

- Classic type (old Types I and II) = includes most severe form (easily scarred skin and hypermobile joints)
- Hypermobility type (old Type III) = manifestations predominantly joint, not skin
- Vascular type (old Type IV) = manifestations predominantly skin, not joint, and predilection for rupture of large vessels
- Several other rarer types

Osteogenesis imperfecta (OI): Defects in procollagen genes cause the variants, but all have:

- Osteopenia
- Multiple bone fractures
- Varying degrees of blue sclera
- Lucent (brittle) teeth
- Hearing loss

There are 7 types of OI; Type I is autosomal dominant and the mildest.

Pseudoxanthoma elasticum: autosomal recessive and involves skin (easy bruising), blood vessels, and eyes. The main problem is recurrent UGI bleeds as they affect the elastic media of blood vessels. Classic findings include a cobblestone appearance of the skin with yellow papules and plaques that resemble "plucked chicken skin" on the neck/axillae and angioid streaks on funduscopic exam. (But this also occurs in Paget disease!)

RHEUMATOID ARTHRITIS

OVERVIEW

The worldwide prevalence of RA is ~ 0.5–1%. Women outnumber men 3:1. The typical age of onset is 40–50 years. Etiology of RA is multifactorial and basically unknown. There is a low concordant incidence of RA in identical twins, but RA does seem to have some genetic basis (~ 10% of patients have a 1st degree relative with RA; higher concordance in identical twins than in fraternal ones).

It is now recognized that RA is a heterogeneous disease with various HLA polymorphisms resulting in anything from mild joint involvement to severely erosive

QuickQuiz

- Describe pseudogout crystals and their birefringence.
- Which factors suggest aggressive RA?
- How long is the typical morning stiffness in RA? In OA?
- What are the essential diagnostic criteria for RA?

joint deformity. These genetic haplotypes have been identified, and tests are commercially available to help predict which patients will develop aggressive disease and benefit from early pharmacotherapy.

As mentioned under Labs, rheumatoid factor (RF) is positive in only 80–85% of patients with RA. It may take up to 2 years for patients with RA to become RF positive.

Know that anti-CCP antibody:

- appears earlier than RF,
- has greater specificity for the diagnosis of RA (97%), and
- is associated with more aggressive disease and extraarticular involvement.

Antibodies play a prominent role in the current 2010 ACR/EULAR diagnostic criteria for RA. A high titer of either RF or anti-CCP contributes 3 of the 6 points required for the diagnosis.

Poor prognostic indicators of RA include:

- presence of HLA-DR4 antigen (HLA-DRB1*0401),
- high-titer RF or anti-CCP antibodies,
- elevated acute phase reactants (ESR and CRP),
- multiple joint involvement (> 6),
- constitutional symptoms,
- radiographic evidence of erosive disease, and
- extraarticular disease (e.g., rheumatoid nodules, vasculitis, lung involvement).

In an affected RA joint, there is inflamed synovium (with increased type A and B synovial cells). In its chronic phase, this inflamed membrane of granulation tissue (pannus) stimulates the release of cytokines, which leads to cartilage destruction, bone erosion, and an inflammatory synovial fluid that has decreased viscosity.

Present in the synovium of the rheumatoid joint are cytokines and chemokines, which are secreted by activated lymphocytes, macrophages, and fibroblasts; these probably account for most of the destructive effects of RA.

They include:

- interleukins (especially IL-1, IL-6, and IL-17interferons),
- B cells forming antibodies (RF and anti-CCP),
- colony-stimulating factors (CSF),
- growth factors, and
- tumor necrosis factor (TNF-α; also important when considering treatment for RA).

SIGNS / SYMPTOMS OF RA

Signs and symptoms of RA include > 1 hour of morning stiffness/pain that improves with activity, fatigue, low-grade fever, anorexia, and weight loss. Remember: Noninflammatory joint diseases, such as OA, cause < 30 minutes of stiffness, and pain is worse with activity.

Buzzwords for both RA and SLE: The arthritis is symmetric and polyarticular. There is specific involvement of the hands—especially the MCP and PIP joints (Image 6-2); the DIP joints are spared! Boutonnière and swan-neck deformities occur in advanced disease, although they are nonspecific for RA.

Symptoms of RA may be intermittent (15–30%) or progressive. Intermittent disease has remissions lasting up to 1 year and is considered a variant of RA known as palindromic rheumatism.

Know the diagnostic criteria for RA, which changed in 2010. A complete list of criteria can be found in the 2010 ACR/EULAR guidelines on the American College of Rheumatology website at www.rheumatology.org.

From this, remember the following essentials—RA can be diagnosed when all of the following are present:

- Inflammatory arthritis (from 1 to 10 joints)
- RF and/or anti-CCP
- Increased ESR or CRP
- Duration > 6 weeks

Other causes must be excluded (especially if symptoms have been present for < 6 weeks), such as SLE, Sjögren's, overlap syndromes, sarcoidosis, and viral reactive arthritis (i.e., hepatitis B and C, parvovirus B19).

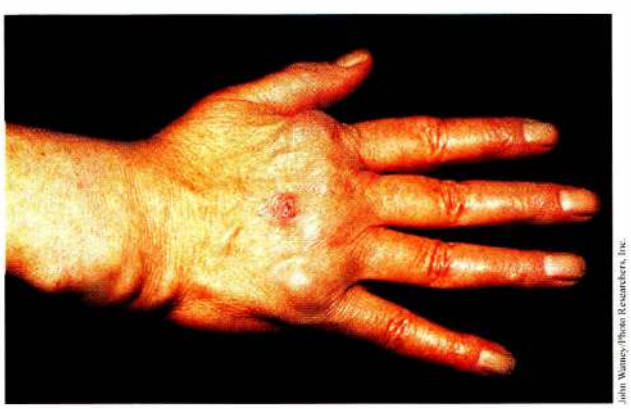

Image 6-2: Rheumatoid arthritis of the metacarpophalangeal joints, with an endarteritis-associated ulcer on dorsum

Seronegative RA is diagnosed when patients meet other criteria but lack both RF and anti-CCP. These patients tend to have less severe disease than what is seen in antibody-positive patients.

Hemochromatosis is another disease that commonly involves the 2nd and 3rd MCP and PIP joints, but the arthropathy of hemochromatosis is distinctly asymmetric. Also, hemochromatosis has hook-like osteophytes on the MCP joints and chondrocalcinosis—neither finding is seen in RA. Patients can easily be screened for hemochromatosis with iron studies. An elevated transferrin saturation (Fe/TIBC of > 45%) or elevated ferritin level suggests the diagnosis. Know these clues for differentiating RA and SLE from hemochromatosis.

Hoarseness, sore throat, and/or neck pain may indicate involvement of the cricoarytenoid joint in the patient with RA. The temporomandibular joints may also be affected.

The knee is the most common single joint initially involved in RA; but, over time, small joints—in a symmetric fashion—are more commonly involved. In fact, the forefoot has proven to be the site of earliest radiographic changes in RA, and the head of the 5th metatarsal bone may be the location of the earliest erosion. Carpal tunnel and tarsal tunnel syndromes can occur in RA. If a patient with inflammatory knee arthritis presents with a swollen calf, suspect a ruptured Baker cyst (popliteal cyst) causing pseudophlebitis. Occasionally, a Baker cyst can cause extrinsic venous compression that can simulate a deep vein thrombosis.

C-spine: Patients with chronic, severe disease may develop cervical instability at the atlanto-axial articulation (C1–C2). The rest of the axial skeleton is spared.

While patients can be asymptomatic, suspect cervical (C1–C2) involvement when a patient with RA complains of:

- recurrent occipital headaches,
- limited neck range of motion, or
- paresthesias of the hands and feet.

If these symptoms are present, order cervical spine x-rays with flexion and extension views. In RA patients scheduled to undergo endotracheal intubation, an evaluation for cervical instability is mandatory. Acute subluxation, which may occur with extension of the neck for intubation, can cause spinal cord compression or vertebral artery compression leading to quadriparesis or sudden death. Remember: All patients with long-standing RA should have flexion and extension neck films before surgery to assess for subluxation.

The thoracic, lumbar, and sacral spine and the SI joints are usually spared in RA (in contrast to ankylosing spondylitis and psoriatic arthritis). Again, RA does not present as lumbar spine pain. If you see a patient with RA and spine pain, think about the myriad other potential causes of spine pain; e.g., compression fractures, infections—not a flare of RA.

EXTRAARTICULAR MANIFESTATIONS

Remember: Extraarticular manifestations of RA are more common in the presence of RF and anti-CCP antibodies (seropositive RA). Know these extraarticular manifestations of RA:

Cardiac:

- Pericarditis (with effusion or thickening) and myocarditis.
- Rheumatoid nodules on the valves.
- Atherosclerosis—3x increased risk of atherosclerotic cardiovascular disease (sudden death and MI). Coronary artery disease is the leading cause of death among patients with RA.

Renal (all very rare):

- Drug-related renal disease
- Amyloid renal disease occurring late in RA

Lungs (males more often):

- Exudative pleural effusion with low glucose (< 30 mg/dL) and pH.
- Diffuse interstitial fibrosis and intrapulmonary rheumatoid nodules; when caused by mine dust, it is called Caplan syndrome (mine dust pneumoconiosis).

Vasculitis:

- May resemble polyarteritis nodosa and cause nailfold infarcts and splinter hemorrhages.
- Necrosis with ulceration may occur, especially over the malleoli.

Nerves:

- Mononeuritis multiplex, which may manifest as foot or wrist drop
- Carpal and tarsal tunnel syndromes
- Cervical myelopathy

Eyes:

- Episcleritis
- Scleritis
- Sicca/secondary Sjögren syndrome

Skin:

- Rheumatoid nodules occur in 25% and indicate potential for more severe disease. These nodules usually appear on extensor surfaces but may also be found in the lungs and on heart valves.

Quick Quiz

- What is the pattern of arthritis in RA?
- Which part of the spine is sometimes involved in RA? Which parts are never involved?
- What is the most common manifestation of RA in the lungs?
- What is Felty syndrome?
- Name some indicators of active RA. If a patient has these indicators, when do you start treatment? With what?

Blood and lymphatics:

- Anemia of chronic disease
- Neutropenia (seen in Felty syndrome and large granular lymphocyte [LGL] syndrome)
- Increased risk of lymphoma (particularly in longstanding, untreated, active disease)

Felty syndrome consists of the classic triad of rheumatoid arthritis, splenomegaly (the spleen can be "felt-y"), and neutropenia. These patients usually have long-standing disease associated with high titers of rheumatoid factor and subcutaneous rheumatoid nodules and suffer increased mortality from infections. Treatment: methotrexate, cyclosporine A, corticosteroids, granulocyte colony-stimulating factor (GCSF), and, if needed, splenectomy. If splenectomy is ineffective, the prognosis is poor. TNF inhibitors are currently being evaluated.

Large granular lymphocyte (LGL) syndrome may be difficult to distinguish from Felty syndrome since it also presents with neutropenia, splenomegaly, and susceptibility to infections. It differs from Felty syndrome in that it is less commonly associated with RA and rarely may progress to LGL leukemia. In contrast to Felty syndrome, these patients do poorly with splenectomy. Definitive diagnosis can be made by detecting clonal T-cell gene rearrangement, which is not present in Felty syndrome.

TREATMENT OF RHEUMATOID ARTHRITIS

Overview

Drugs used to treat RA (see Table 6-5) are categorized as nonsteroidal antiinflammatory drugs (NSAIDs), which help with pain but do not modify the disease course:

- Nonbiologic disease-modifying antirheumatic drugs (DMARDs)
- Immunosuppressants
- Biologics or biologic response modifiers (BRMs)
- Miscellaneous (steroids, minocycline, doxycycline)

Trials have shown that 70% of patients with active, polyarticular, RF-positive disease develop joint damage or erosions within 2 years of onset. Other trials show that early treatment with a DMARD may alter the course of the disease. Trials with combination DMARDs in early disease also show benefit. NSAIDs may help with inflammation and pain, but do not prevent the formation of either erosions or joint deformities. Glucocorticoids, like DMARDs, can alter the course of disease but are associated with significant long-term side effects.

Current treatment paradigms focus on early diagnosis and early aggressive therapy to allow patients a chance at remission. The goal is to try to initiate DMARD therapy within 3 months of symptoms and, if needed, to titrate drugs (add additional DMARDs or biologic agents) to attain low disease activity or remission. Previously, treatment of RA followed a pyramid regimen consisting initially of NSAIDs and glucocorticoids—with DMARDs added only as the disease progressed. Now we know that RA-associated disability can be drastically reduced when treated early and aggressively.

Recognize that glucocorticoid use in RA is controversial—influenced by the efficacy of the biologics and the well-known side effects of systemic glucocorticoids. Generally, as the patient improves on early aggressive therapy, the more toxic drugs, such as steroids, are withdrawn, while DMARDs and/or biologics are used as maintenance therapy.

Now we'll discuss these RA medications in more detail.

Table 6-5: Drugs Used to Treat RA

Nonsteroidal	Nonselective (e.g., ibuprofen, naprosyn, nonacetylated salicylates) and COX-2 inhibitor
Nonbiologic DMARDs	Methotrexate, leflunmide, hydroxychloroquine, sulfasalasine
Immunosuppressants	Azathioprine, chlorambucil, corticosteroids, cyclophosphamide, cyclosporine, mycophenolate mofetil, tacrolimus
Biologics	TNF inhibitors (monoclonal antibodies and soluble receptors), IL-1 and IL-6 antagonists, anti-B cell antibody, T-cell inhibitor
Miscellaneous	Acetaminophen, colchicine, dapsone, IVIG, plasmapheresis/ plasma exchange, thalidomide, intraarticular viscosupplementation

NSAIDs

NSAIDs are part of the initial treatment. NSAIDs decrease inflammation and joint swelling but do not alter the course of the disease. Again, know that DMARDs (next) are now given with onset of RA symptoms. NSAIDs are added to help control pain.

For patients with ASA allergy, use a sodium, magnesium, or choline salicylate. These nonacetylated salicylates do not cause an ASA allergy reaction and also may have less GI toxicity (but may be less effective).

What about the COX-2 inhibitors? Selective COX-2 inhibitors, like other NSAIDs, inhibit cyclooxygenase-2 but, unlike other NSAIDs, do not inhibit cyclooxygenase-1. Currently, the only COX-2 inhibitor available in the U.S. is celecoxib (Celebrex®), which is approved for treatment of RA, OA, ankylosing spondylitis, and acute pain (and adjunctive for familial adenomatous polyposis).

The antiinflammatory effects of COX-2 inhibitors are comparable to other NSAIDs, with possibly reduced GI irritation and ulcer development.

Other benefits of selective COX-2 inhibitors: no effect on platelet function, so bleeding time is unchanged; less risk of bleeding in anticoagulated patients; less likely than other NSAIDs to precipitate bronchoconstriction in patients with aspirin-induced asthma.

The problem with selective COX-2 inhibitors (and NSAIDS in general) is that they increase the risk for adverse cardiac events such as myocardial infarction, stroke, heart failure, and sudden cardiac death in some patient groups. Celecoxib is contraindicated in patients who are in the postoperative recovery phase after artery bypass graft. One trial of 4,000 patients showed celecoxib increased risk of death or recurrent MI (~ 2x) if taken longer than 1 month after an MI. Analysis of 2 recent long-term adenoma prevention trials studying celecoxib concluded there is an increased risk of serious cardiovascular events that may be dose-dependent.

Patients who are allergic to sulfa appear to have a high risk of rash with COX-2 inhibitors.

Know these important drug interactions: NSAIDs and lithium have common excretory pathways, so check lithium levels periodically if a patient is receiving both meds. ASA decreases the breakdown of oral hypoglycemics, so decrease dosage of these when given with ASA. All NSAIDs, selective and nonselective, may precipitate or worsen heart failure and may raise blood pressure.

DMARDs

General Characteristics

Disease-modifying antirheumatic drugs (DMARDs):

- Methotrexate (MTX)
- Leflunomide (LEF)
- Hydroxychloroquine (HCQ)
- Sulfasalazine (SSZ)
- Azathioprine (AZA)
- Cyclosporine A (Cyc A)
- Cyclophosphamide (Cytoxan®)

DMARDs are a major component of RA treatment. They have a slow onset of action (several months), so concurrent NSAIDs or low-dose glucocorticoids are required initially. HCQ and SSZ are sometimes used first in cases of early, mild RA; these drugs are also safe in pregnancy and breastfeeding. DMARDs are started with onset of symptoms. Aggressive treatment with MTX, LEF, SSZ or combination DMARDs is recommended for patients with moderate-to-severe disease. The following DMARDs are recommended by the 2012 American College of Rheumatology updated clinical practice guidelines.

Methotrexate

MTX is an antifolate agent with antiinflammatory properties that is very effective in the treatment of RA. Because it has the most predictable benefit and is usually the best tolerated, the 2012 American College of Rheumatology updated clinical practice guidelines recommend MTX as the initial DMARD for patients with moderate-to-severe RA without poor prognostic features and as the main DMARD when combination therapy is used in those with poor prognostic features. Again, most experts are now starting DMARDs with onset of RA symptoms! Some patients begin to improve within 6 weeks. It is administered orally, subcutaneously, or intramuscularly 1x/week and is often combined with other agents to maximize disease control. Preexisting liver disease (e.g., HBV, HCV, heavy alcohol use), severe renal disease, and pregnancy are contraindications to using this drug.

Common side effects and complications of MTX include:

- Alopecia
- GI distress (nausea, vomiting, diarrhea, mucositis)
- Bone marrow suppression even at low doses (Prescribe folate replacement 1 mg/day for prevention. Coadministration of sulfa drugs or antifolate agents can worsen cytopenias, so follow CBC.)
- Increased liver transaminases (AST/ALT)

QuickQuiz

- Which DMARDs are used to treat mild RA and are relatively safe during pregnancy?
- Which DMARD is recommended by the American College of Rheumatology as 1st line for all moderate-to-severe cases of RA?
- What are methotrexate contraindications?
- Name another DMARD recommended to treat RA in patients who cannot tolerate methotrexate.
- What follow-up is required in patients treated with hydroxychloroquine?

Other serious, but less common, reactions to be aware of include:

- increased susceptibility to opportunistic infections,
- severe hepatotoxicity (follow AST/ALT),
- nephrotoxicity (follow creatinine), and
- pneumonitis/pulmonary fibrosis.

The MTX pneumonitis is idiosyncratic (i.e., non–dose-related). Initial symptom is nonproductive cough. Radiograph is initially normal but shows alveolar infiltrates in later stages.

MTX-related toxicities are not age-related. Monitor CMP and CBC every 4 weeks for the first 3 months of therapy, then every 12 weeks thereafter; labs should be monitored more frequently if clinically indicated. Baseline hepatitis B and C serologies and CXR should be obtained prior to initiating therapy. Order pulmonary function tests in patients with symptoms of dyspnea or a history of COPD (pay attention to the carbon monoxide diffusing capacity [DLCO]). Monitoring renal function is important because most of MTX is excreted unchanged in the urine. Renal failure from any cause leads to accumulation of the drug and increased toxicity.

Leflunomide

LEF (Arava®) is used to treat RA. It is a pyrimidine antagonist and may be used as an initial DMARD in patients unable to take MTX.

Its side effects are very similar to MTX. Minor adverse reactions include diarrhea and respiratory infections. Its major side effect is hepatotoxicity, and it should be avoided in those with preexisting liver disease. Other important side effects include cytopenias, renal dysfunction, interstitial lung disease, peripheral neuropathy, and opportunistic infections.

Screen for latent TB before prescribing this drug. CBC, LFTs, and creatinine need to be monitored frequently, as with MTX. The drug is contraindicated in pregnancy and unsafe for lactation.

Important: Because LEF has an extremely long half-life and is teratogenic, women planning to conceive must discontinue the drug and undergo treatment with cholestyramine to eliminate the drug.

Hydroxychloroquine

The main side effect to know is retinopathy. The usual risk is considered to be 1/5,000 patients after prolonged use. If renal dysfunction occurs, the risk of retinopathy rises greatly. Patients started on HCQ need a baseline ophthalmologic evaluation to serve as a reference point and to rule out existing retinopathy. After 5 years of continuous HCQ, annual exams are recommended in average-risk patients. Routine CBC and CMP should be obtained every 3–6 months. Also, consider monitoring muscle strength periodically because of the risk of myopathy. Know that the use of HCQ in psoriatic patients may exacerbate psoriasis.

Sulfasalazine

Also used for inflammatory bowel disease (IBD). In RA, the sulfapyridine portion of the molecule produces effects; in IBD, the 5-amino salicylic acid (5-ASA) portion is the effective component. The most common side effects are sulfa-allergic reactions, nausea, vomiting, diarrhea, and crampy abdominal pain. It may cause reversible oligospermia (no effect on female reproduction), cytopenias, and an elevation in transaminases (monitor with periodic CBC and LFTs). The 5-ASA component can cause Reye syndrome in patients vaccinated with the varicella vaccine (because it's a live virus vaccine). Check G6PD levels in patients at increased risk for G6PD deficiency (e.g., males of African or Mediterranean descent).

DMARDs in Pregnancy

Essentially any DMARD or antirheumatic drug taken during pregnancy, especially during the 1st trimester where organogenesis is predominant, can pose a risk to the fetus. The general rule is to avoid any and all drugs if at all possible. If a medication is required, the minimal effective dose to maintain the disease under control is recommended.

The following are general recommendations:

- Hydroxychloroquine and sulfasalazine are allowed during pregnancy.
- Azathioprine, IVIG, cyclosporine A, and cyclophosphamide are relatively contraindicated (weigh risks vs. benefit).
- Methotrexate, leflunomide, and mycophenolate mofetil are absolute contraindications.

Biologic Agents

See Table 6-6 for a synopsis of the biologics currently approved for RA. Biologics are made with animal, microbial, or human proteins, in contrast to DMARDs, which are made from chemicals. The biologics have opened a new era in RA treatment in that they are highly selective in their targets, yielding better efficacy with improved safety profiles. They are designed to inhibit specific components of the immune system that regulate inflammation. They can be broken down into those that inhibit tumor necrosis factor (anti-TNFs) or those that inactivate other pivotal sites related to inflammation.

Anti-TNF Biologics (TNF Inhibitors)

Infliximab, adalimumab, certolizumab, and golimumab are monoclonal antibodies that bind and inactivate tumor necrosis factor (TNF), an important mediator of the inflammatory response in RA. Etanercept is a soluble TNF receptor that is linked to IgG1 and also binds and inactivates TNF. It has been suggested that monoclonal anti-TNF agents may cause greater risk for infections (e.g., TB, herpes zoster, nonserious infections [NSIEs]) compared to etanercept. The anti-TNF drugs are approved for a variety of indications, including RA, psoriasis, psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease.

Table 6-6: Biologics

Drug Name	Brand Name	Approved Use	Most Common Side Effects
TNF-α inhibitors			**Boxed warnings: Serious infections and TB**
Infliximab	Remicade®	RA, P, AS, Crohn's, UC	URI, nausea, headache, infusion reactions, DIL with antinuclear and anti-dsDNA ab
Adalimumab	Humira®	RA, P, AS, Crohn's	URI, headache, rash
Certolizumab	Cimzia®	RA, Crohn's	URI, headache, nausea
Golimumab	Simponi™	RA, P, AS	URI
Etanercept	Enbrel®	RA, P, AS	URI, headache, rash, local site reaction, DIL with antinuclear and anti-dsDNA ab
Non-TNF-α inhibitors			
IL-1 antagonist			
Anakinra	Kineret®	Refractory RA	**Boxed warning: Serious infections, do not combine with TNFi** Neutropenia, headache, local site reaction
IL-6 antagonist			
Tocilizumab	Actemra®	Refractory RA	**Boxed warning: Serious infections and TB** URI, increased LFTs, neutropenia, serious GI infections
Anti-CD20			
Rituximab	Rituxan®	RA (with MTX) anti-CD20+ NHL anti-CD20+ CLL GPA MPA	**Boxed warning: Fatal infusion reactions, progressive multifocal leukoencephalopathy, severe mucocutaneous reactions** Fever, nausea/diarrhea, cytopenias, peripheral edema, hypertension or hypotension, rash, headache, neuropathy
T-cell inhibitor			
Abatacept	Orencia®	Refractory RA	**Boxed warning: COPD exacerbation, avoid combining with TNFi** Infections, headache

RA = rheumatoid arthritis; P = psoriasis/psoriatic arthritis; AS = ankylosing spondylitis; UC = ulcerative colitis; NHL = non-Hodgkin lymphoma; CLL = chronic lymphocytic leukemia; MTX = methotrexate; GPA= granulomatosis with polyangiitis; MPA= microscopic polyangiitis

QuickQuiz

- What are the categories of biologics used to treat RA?
- What are representative drugs for each category of biologics?
- Name some serious complications of the various biologics.
- What is the most common side effect of the non-TNF biologics?

[Know:] For RA, these agents are most beneficial when combined with methotrexate and have been shown to halt and possibly heal erosive damage!

These agents have been associated with drug-induced lupus as well as other side effects including: injection site/infusion reactions, infections, increased risk for skin cancer, cytopenias, CNS demyelination, and worsening heart failure. They are not recommended for patients with NYHA class III/IV heart failure and an ejection fraction ≤ 50% because they may worsen CHF symptoms and increase morbidity. Infliximab has been associated with fatal hepatosplenic T-cell lymphoma.

Non-TNF Biologics

Interleukin antagonists (anakinra = IL-1; tocilizumab = IL-6) are used to treat RA refractory to the MTX/TNF inhibitor combination. Anakinra is associated with a high percentage of injection site reactions. Leukopenia, LFT abnormalities, and hyperlipidemia have been associated with tocilizumab.

Rituximab is an anti-CD20 antibody directed against B cells, which are believed to mediate progression of RA. It is used in combination with MTX to treat RA in patients refractory to TNF inhibitors. Stevens-Johnson syndrome, toxic epidermal necrolysis, tumor lysis syndrome, and deadly infusion reactions (e.g., hypotension, bronchospasm, acute respiratory distress syndrome, MI, progressive multifocal leukoencephalopathy [PML]) have been described in patients receiving rituximab. In the last few years, there have been case reports of PML associated with rituximab. If there is a scenario where an RA patient has new onset CNS symptoms after receiving rituximab, PML should be on the differential diagnosis. Abatacept is a selective T-cell costimulation inhibitor used to treat refractory RA. Activated T cells are increased in the synovium of patients with this disease.

Avoid live-virus vaccines in patients prescribed a biologic, and screen all patients for tuberculosis.

These potential complications sound terrible (and they are!), but know that they are not common—the most common side effect is an increase in NSIEs as upper respiratory tract infections and urinary tract infections.

Patients with active infections that have potential to progress to serious infections need to discontinue their biologic or delay treatment until the infection has resolved. Less common but noteworthy complications include worsening psoriasis and reactivation of HBV.

[Know:] Because DMARDs and biologics can suppress the immune system and increase susceptibility to infection, routine vaccinations for influenza and pneumonia are recommended; patients on biologics, prednisone > 20 mg/day, methotrexate > 25 mg/week, and azathioprine > 3 mg/kg/day should avoid live vaccines per ACIP 2012 guidelines. The only live vaccines that are relevant to clinical practice are MMR and shingles vaccines.

Immunosuppressants

Azathioprine

AZA has shown some benefit for RA, but is much more commonly used in SLE. Its main side effects include bone marrow suppression, N/V, diarrhea, and hepatotoxicity.

It is important to understand AZA's metabolism. It is first metabolized to 6-mercaptopurine (6-MP) by the liver. AZA and 6-MP are inactive prodrugs. 6-MP can then be metabolized by 3 different pathways.

Two important things to know:

1) Thiopurine methyltransferase (TPMT) is an enzyme in the main metabolic pathway for 6-MP. Patients with heterozygous or homozygous mutations in this enzyme (10% of population) are prone to severe AZA toxicity. Some experts recommend testing for this mutation because patients with this deficiency should be given lower doses of AZA.
2) Xanthine oxidase (XO) is an enzyme in another important metabolic pathway for 6-MP. This is important because allopurinol, a drug that inhibits XO, can lead to increased levels and toxicity of AZA. The recommendation is to decrease the dose of AZA by at least half in the patient on allopurinol or febuxostat and to monitor CBC and LFTs closely.

Cyclosporine A

In doses of 2.5–4 mg/kg/day, it has been shown to have synergistic effects when added to MTX, but its use has been limited by renal toxicity and hypertension.

Cyclophosphamide

In RA treatment, use is limited to treating RA-associated vasculitis.

Miscellaneous

Minocycline and Doxycycline

These drugs are not FDA-approved for RA. They are occasionally beneficial as mild DMARDs for some RA patients because of their metalloproteinase inhibition, although they may be more effective in patients with spondyloarthropathies.

Glucocorticoids

Low-dose oral prednisone (< 10 mg/d or equivalent) and joint injections of glucocorticoids are very effective for relieving symptoms of RA. Joint injections have dramatic but temporary effects on symptoms but do not slow the systemic disease process. Low-dose oral glucocorticoids may decrease the rate of erosion; however, the side effects of glucocorticoids limit their use—weight gain, infection, osteoporosis, easy bruising, adrenal insufficiency, diabetes mellitus, peripheral edema, hypertension, insomnia. Due to risk for RA flare and also adrenal insufficiency, glucocorticoids should be tapered slowly.

SYSTEMIC LUPUS ERYTHEMATOSUS

MANIFESTATIONS OF SYSTEMIC LUPUS

Overview

Systemic lupus erythematosus (SLE) is the prototypic autoimmune disease. It ranges from mild rash, arthralgias, and fatigue to severe, life-threatening manifestations (renal/CNS). SLE primarily affects women of childbearing age; prognosis is worse in males, African-Americans, and Hispanics. Any organ system can be affected.

SLE: Joints

Lupus arthritis is inflammatory and nonerosive. Involved joints may be symmetrical, asymmetrical, oligoarticular, or polyarticular; the small joints of the hands and wrists and the knees often are affected (Image 6-3). Jaccoud deformities of SLE appear like boutonnière deformities of RA, but with SLE, these deformities are easily reducible (looks like normal hands when you stretch out the joints; RA hands won't yield to pressure). Note that some SLE patients may have concomitant RA (lupus-RA overlap or "rhupus"); in these cases, joints may have erosions.

SLE: Skin and Mucous Membranes

All lupus rashes are photosensitive and can occur even when the weather is cloudy.

Classification of lupus rashes:

- Chronic cutaneous lupus erythematosus (**CCLE**), a.k.a. discoid lupus erythematosus (**DLE**): hyperpigmented edges, which may be raised, frequently cause central scarring/atrophy with destruction of melanocytes and hair follicles. Many patients with SLE also have discoid rashes, but patients with discoid lupus have only a 5% chance of developing SLE (Image 6-4 and Image 6-5) and typically have a milder disease course devoid of significant renal manifestations.
- Acute cutaneous lupus erythematosus (**ACLE**): erythematous, concentrated on sun exposed areas—malar rash ("butterfly" that spares nasolabial fold; Image 6-6), forehead, upper chest, neck, ears, upper extremities, and back that flares with systemic disease.
- Subacute cutaneous lupus erythematosus (**SCLE**): annular rash. This rash can be seen with Sjögren's as well; patients can have negative ANAs with +Ro/La. Certain medications may bring out this rash, including calcium channel blockers.
- "Other": lots of other rashes (e.g., tumid lupus, chilblains lupus, urticaria, vesicles, lichen planus).

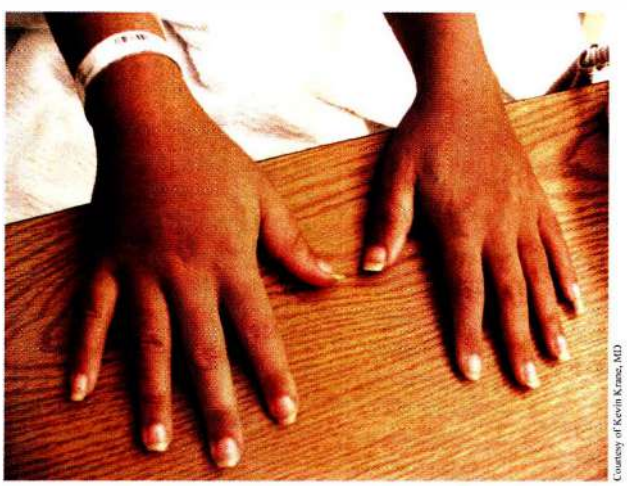

Image 6-3: Symmetric polyarthritis of SLE

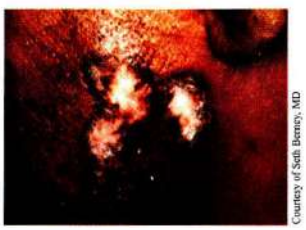

Image 6-4: Discoid lupus

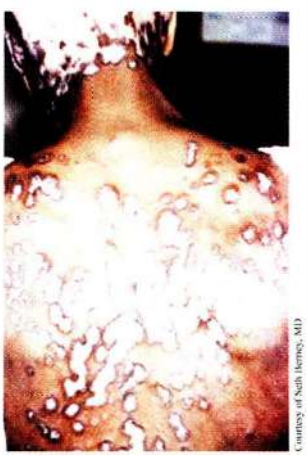

Image 6-5: Discoid lupus

Quick Quiz

- Characterize the pattern of arthritis in SLE.
- What are the patterns of skin rashes in SLE?
- What is the most common cause of death in patients with SLE?
- What is the increase in risk of myocardial infarctions in women with SLE?
- Which autoantibodies are associated with development of lupus nephritis?
- What classifications of SLE kidney disease require treatment with cytotoxics?

Alopecia is common; typically nonscarring.

Aphthous (mucosal) ulcers are usually painless and can occur in the nasal passage as well as the oropharynx.

SLE: Lung

Lung disease in lupus can manifest as pleuritic chest pain +/– effusion (most common), alveolar infiltrates, pneumonitis (with subsequent fibrosis and pulmonary arterial hypertension), and alveolar hemorrhage—a medical emergency that carries a 50% mortality rate!

SLE: Heart

The Framingham Offspring Study revealed that women ages 35-44 with SLE have a 50-fold increase in myocardial infarctions. The early CAD is thought to be due to chronic inflammation and steroid use, both of which accelerate atherosclerosis.

Other cardiac involvement found in SLE patients includes: pericarditis (most common), myocarditis, and Libman-Sacks endocarditis (sterile fibro-fibrinous vegetations that can mimic infectious endocarditis and are commonly associated with antiphospholipid abs). CAD is the most common cause of death in patients with SLE.

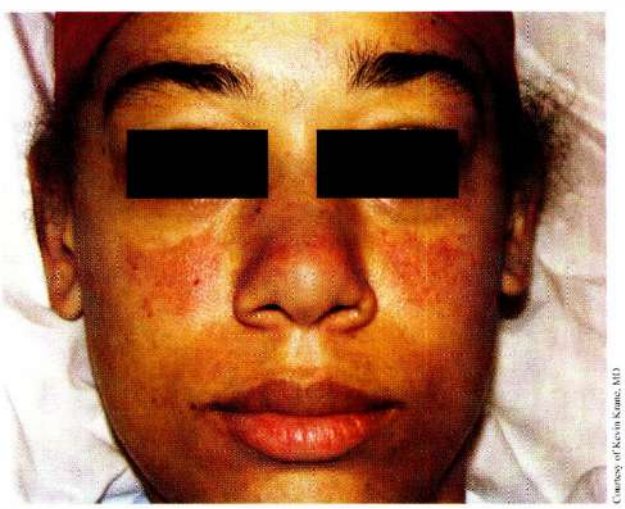

Image 6-6: Malar rash of SLE

SLE: Kidney

Glomerulonephritis is a major cause of morbidity and mortality in SLE patients. The presence of anti-dsDNA is associated with glomerulonephritis and the nephrotic syndrome.

African-American lupus patients are more likely than Caucasians to develop aggressive renal disease. Once lupus nephritis develops, lifetime recurrences are likely.

"Bad" kidney disease (advanced classifications) is associated with an active urine sediment: proteinuria (usually > 500 mg/day or nephrotic > 3.5 g) and microscopic hematuria, as well as a high titer of anti-dsDNA. Always perform a U/A on any patient whom you suspect has SLE.

Kidney disease is staged by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS)—this replaced the WHO classification system. These classifications organize renal disease according to chronicity and activity level. Although the classification system focuses on glomerular disease, know that systemic lupus also can affect the tubules and vasculature.

ISN/RPS classification (treatment) of glomerulonephritis in SLE:

- **Class I**: minimal mesangial (no treatment needed)
- **Class II**: mesangial proliferative (no treatment)
- **Class III**: focal proliferative; ≤ 50% of glomeruli (steroids and cytotoxics)
- **Class IV**: diffuse proliferative (steroids and cytotoxics)
- **Class V**: membranous (steroids, cytotoxics, and ACE inhibitor or ARB to decrease proteinuria)
- **Class VI**: advanced sclerotic; ≥ 90% sclerotic glomeruli (disease irreversible)

Combinations of the above stages may occur. The letters "A" and "C" are also listed as subcategories to reflect whether the changes are "active" or "chronic."

Important: Treat class III and IV disease with cytotoxics and corticosteroids to prevent end-stage kidney disease, which develops within 2 years in untreated patients. Cytotoxics typically used are cyclophosphamide, mycophenolate mofetil, or azathioprine.

Note: Membranous nephropathy is often associated with nephrotic syndrome, and thrombophlebitis is a complication.

SLE: Blood

Immune mediated cytopenias are common and can include: leukopenia (specifically lymphopenia), thrombocytopenia, and hemolytic anemia. Note that headache + thrombocytopenia + microangiopathic

hemolytic anemia + acute renal failure in a SLE patient suggests TTP—mortality is high if unrecognized and untreated! Plasmapheresis is indicated (more in Hematology, Book 4).

SLE: CNS (Neuropsychiatric Lupus)

Cognitive/behavioral changes (most common), headaches, psychosis, mood changes (e.g., depression), aseptic meningitis, organic brain syndrome, seizures, chorea, and strokes occur with SLE. Even severe abnormalities may clear rapidly with regression of disease. Spinal fluid may be normal, even with severe symptoms; but you may find elevated protein or WBCs (mostly lymphocytes), especially in patients with cerebritis. MRI of the brain may show scattered areas of increased intensity, suggesting a vasculopathy.

Evaluate all neuropsychiatric lupus patients for infection, including lumbar puncture, particularly if immunosuppressed. Know that anti-Smith, anti-neuronal, and antiribosomal P protein antibodies are associated with CNS disease.

DIAGNOSIS

The 1997 ACR classification criteria can be useful to establish a diagnosis of SLE. These criteria are designed to enroll a homogenous patient population into clinical trials, but can suggest SLE diagnosis in a patient with several signs/symptoms.

The following are the ACR diagnostic criteria in SLE, presented in the "SOAP BRAIN MD" mnemonic:

- **S**erositis: pleuritis, pericarditis
- **O**ral ulcers: usually painless
- **A**rthritis: nonerosive
- **P**hotosensitivity
- **B**lood disorders: low WBC, lymphs, hemolytic anemia
- **R**enal disease: proteinuria, RBC casts
- **A**ntinuclear antibodies
- **I**mmunologic phenomena (e.g., +anti-dsDNA; anti-Smith [Sm] antibodies, anti-cardiolipin [ACL] abs)
- **N**eurologic disorder: seizure or psychosis
- **M**alar rash
- **D**iscoid rash

The ANA is the most sensitive test for SLE (99% of patients with active disease have a positive test), but it has very poor specificity (can be positive in patients without the disease). Among the subtypes of ANA, anti-dsDNA and anti-Sm in high titers are very specific (usually negative in patients without disease; i.e., rarely false-positive), but they have low sensitivity (sometimes they are negative in patients with true disease). Never check anti–single-stranded DNA. It's a worthless test that is positive in many illnesses.

Know that patients with active SLE usually have low levels of C3 and C4. Current ANA testing uses a human cell line (HEp-2 cells) as the substrate and rarely produces a false-negative test. So, a negative ANA basically excludes SLE.

In summary, in working up a case of possible SLE, first do an ANA. If negative, SLE is excluded. If the ANA is positive, continue on with an ANA profile.

SLE AND PREGNANCY

Patients with SLE have a higher incidence of failed pregnancies. Pregnancy is not advised until disease has been quiescent for 6 months or longer. Risk of pregnancy complications (flares or fetal problems) is much greater if disease is active (especially renal manifestations) or if the mother has anti-dsDNA or antiphospholipid antibodies.

Women with antiphospholipid syndrome (APS) and a history of recurrent miscarriages can be treated with heparins (low-molecular-weight or unfractionated) plus low-dose aspirin to decrease the incidence of miscarriage. Patients with antiphospholipid antibodies are also at increased risk for **HELLP** syndrome (a variant of preeclampsia with **h**emolysis, **e**levated **l**iver enzymes, and **l**ow **p**latelets).

In fetuses/infants of mothers with SLE who have SSA (Ro) and SSB (La) antibodies, heart block can begin as early as the 2nd trimester (Table 6-1 on page 6-2). For these patients, begin serial fetal echocardiograms at about 16–18-weeks gestation. The risk for heart block and neonatal lupus is decreased with hydroxychloroquine.

Favorable pregnancy outcomes are associated with quiescent disease, minimal medical therapy, and medications that can be continued during pregnancy (e.g., prednisone, hydroxychloroquine, and azathioprine).

Measure baseline complement levels, anti-dsDNA, SSA/SSB, and a 24-hour urine protein before or very early in the pregnancy. Manage flares during pregnancy with glucocorticoids. Refer pregnant women with systemic lupus to a high-risk obstetrician (and pediatric cardiologist, if appropriate).

Sometimes distinguishing a lupus flare with renal involvement from preeclampsia is difficult because both may present with increasing proteinuria, hypertension, lower extremity edema, deterioration in renal function, and thrombocytopenia. With lupus flares, SLE disease activity markers may be abnormal (high dsDNA Ab titer, low complements), serum uric acid is normal (< 5.5 mg/dL), and urine sedimentation may be active (white cell casts, high number of red blood cells). These changes are not seen in patients with preeclampsia.

- What hematologic changes in SLE are among the criteria for diagnosis?
- A pregnant woman with SLE has SSA (Ro) and SSB (La) antibodies. What abnormality can occur in her fetus?
- What are potential complications of chronic corticosteroid treatment in patients with SLE?
- Which drugs are associated with drug-induced lupus?
- How does drug-induced lupus differ from SLE?

PROGNOSIS

10-year survival of systemic lupus is ~ 90% if patients receive optimal treatment. Elevated anti-dsDNA and low complement levels indicate worse prognosis, with increased risk for nephritis. Elevated anti-U1-RNP in the setting of a high-titer ANA and negative anti-Smith may indicate a better prognosis, because the disease may actually be mixed connective tissue disease (MCTD) and not SLE. Patients with SLE are also at higher risk for infections (due to immunosuppression), malignancy (especially hematologic ones), osteoporosis (secondary to glucocorticoids), and premature death from CAD (from disease inflammation and glucocorticoids).

TREATMENT OF SLE

Stress exacerbates SLE. Avoid surgery during active disease and encourage sunscreen to protect against the ultraviolet-sensitive rash. Note that sunburn releases self-antigens that are detected by the immune system and trigger a chain reaction to systemic flare! Tell your patients to use sunblock of at least SPF 30 and reapply often. Tobacco cessation should be strongly encouraged—recent studies note that tobacco use can increase lupus disease activity.

Treatment of SLE is focused on the organ that is affected. Start with NSAIDs for joint disease. (Remember, lupus arthritis is nonerosive.) Hydroxychloroquine is effective for treating skin rashes and arthritis, and it can also help prevent disease flares.

Use high-dose glucocorticoids only for patients with severe disease and major organ involvement. Fatigue and alopecia may improve as well. Low-dose maintenance corticosteroids (< 10 mg daily or every other day) are frequently required to control symptoms and prevent flares. Remember: Up to 1/3 of SLE patients on chronic high-dose glucocorticoids develop avascular necrosis of the hip/knee/humerus!

Cytotoxics (azathioprine, mycophenolate mofetil, or cyclophosphamide) are added to corticosteroids for serious flares of SLE, particularly renal and CNS disease. Cyclophosphamide and corticosteroids improve survival in patients with SLE and class III or IV glomerulonephritis.

Anti-B-cell drugs (e.g., rituximab and belimumab) are occasionally used in patients with disease that is refractory to corticosteroids, hydroxychloroquine, and cytotoxics. Rituximab is a monoclonal antibody directed against B-lymphocyte CD20 surface antigens, and belimumab is an antibody directed against the B-lymphocyte stimulator (BLyS) protein. It decreases the amount of abnormal B cells, which are hypothesized to be a mechanism of action in lupus. Specific use of these drugs is reserved for specialists.

DRUG-INDUCED LUPUS

Classic drug-induced lupus (DIL) can be caused by procainamide, hydralazine, chlorpromazine, propylthiouracil, phenytoin, and TNF inhibitors. Think about drug-induced lupus in any patient who develops constitutional symptoms (fever, arthralgias), serositis, and/or rash while taking any of the above drugs. ANA is positive and antihistone antibody is generally positive (remember that SLE patients can have antihistone antibodies, too!). In contrast to non-drug induced SLE, C3 and C4 usually are normal, anti-dsDNA is rarely positive, and there commonly is no kidney or CNS involvement.

DIL can be a tough diagnosis to make. Ideally, you find:

- a positive ANA with antihistone antibodies, and
- a history of exposure to one of the above drugs.

Sometimes you confirm the diagnosis only in retrospect by observing complete resolution of symptoms after discontinuing the drug.

Treatment: Symptoms usually resolve within 4–8 weeks after stopping the offending agent, but the ANA may remain positive for months. NSAIDs and antimalarials may be useful. Corticosteroids work well but are only rarely needed.

SERONEGATIVE SPONDYLOARTHRITIS

"Spondylo-" means spine. Seronegative spondyloarthritides are a group of inflammatory spinal arthritides that are rheumatoid factor- and ANA-negative. These arthritides have been categorized as "axial" or "peripheral," depending on which manifestation is primary in the presentation. These include:

- Ankylosing spondylitis (most common)
- Reactive arthritis
- Psoriatic arthritis
- IBD-associated arthropathy

Seronegative spondyloarthritides share some common features:

- Predilection for the spine, SI joints, and entheses (where the tendons, ligaments, and joint capsules attach)
- Asymmetric, large-joint oligoarthritis, usually of the lower extremities
- Extraarticular manifestations (see below)
- Variable association with HLA-B27

Enthesitis refers to inflammation at the insertion site of a ligament, tendon, or joint capsule. Enthesitis on the finger leads to the appearance of the "sausage digit." Note: The nail bed is also an enthesis; onycholysis (separation of the nail from the nail bed) is a sign of enthesitis in these diseases!

Again, sacroiliitis and thoracolumbar and sacral spine inflammation do not occur in RA! Sausage-shaped digits referred to as dactylitis are common in the spondyloarthropathies but not in RA. When the "sausage digit" buzzword is combined with "pitted nails," the diagnosis is psoriasis!

ANKYLOSING SPONDYLITIS

Overview

Ankylosing means "fusing," while spondylitis means "inflammation of the spine." Ankylosing spondylitis (AS) is a systemic disease marked by ascending axial inflammation, which, if left untreated, leads to eventual spinal and SI joint fusion resulting in a radiographic bamboo spine (Image 6-7). Presentation and upper body involvement increases with age. Patients have significant morning stiffness/pain, which is improved with activity. Most adults with ankylosing spondylitis have symptomatic painful sacroiliitis, although for some patients, mild stiffness is the only complaint.

Usual onset is in young adulthood with a peak age of onset between 20 and 30 years, and it affects men more than women (2–3:1). Teens eventually diagnosed with AS may present with lower extremity large-joint oligoarthritis and have a 90% incidence of HLA-B27–positive antibodies.

There is only a 60% occurrence of ankylosing spondylitis in identical twins, so environmental factors also play a role.

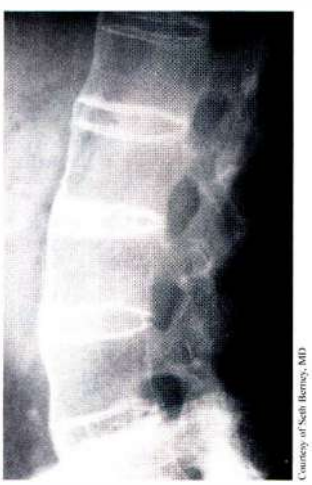

Image 6-7: Bamboo spine; ankylosing spondylitis

Extraarticular manifestations of AS include:

- iritis/uveitis (about 1/3 of patients),
- conjunctivitis,
- ischemic heart disease,
- aortic insufficiency/aortitis,
- apical pulmonary fibrosis, and
- IgA nephropathy.

Iritis or uveitis may precede sacroiliitis and usually presents as unilateral pain, photophobia, and increased lacrimation. The uveitis associated with spondyloarthritis is typically an anterior uveitis where most of the inflammation is localized in the anterior chamber of the eye; this is the opposite of what is seen in sarcoidosis, which features a posterior uveitis. Conjunctivitis may be mild and bilateral; progressive burning and eye irritation are prominent features. Apical pulmonary fibrosis is a late and rare manifestation that can be associated with pulmonary restriction. IgA nephropathy is associated with AS and should be suspected in any patient with AS who develops an active urine sediment. These patients should be sent immediately to a nephrologist for renal biopsy.

Diagnosis

Inflammatory back pain has different characteristics compared to other causes of back pain (e.g., disc disease). First, understand what the "regular" mechanical back pain looks like. Mechanical back pain usually is characterized by the following:

- The patient is often obese, sedentary, and otherwise "out of shape."
- A physical trigger (e.g., "Doc, I was lifting this box, and it felt like I pulled something").
- Pain, often radicular and maximal at onset.
- Red flag and systemic signs are absent—by definition! (See Low Back Pain on page 6-58.)

Classic "inflammatory" back pain is a completely different animal:

- The patient can be young and otherwise in good shape.
- There is no known physical trigger.
- There is no radicular pain.
- The patient complains principally of stiffness, particularly morning stiffness.
- Extraarticular manifestations (see above) are often present (if you take a stellar history!).

A useful bedside tool used in the physical examination of a young adult male with inflammatory signs of low back pain is the Schober test. This test assesses lumbar spinal mobility. Although it is not specific for AS, it is a sensitive measure in detecting limited spinal mobility.

Plain radiographic signs of sacroiliitis (calcification and SI joint fusion resulting in the "bamboo spine"

Quick Quiz

- What are common features of spondyloarthropathies?
- "Bamboo spine" is a buzzword associated with which disease?
- How does a patient with ankylosing spondylitis present?
- Which organisms are associated with reactive arthritis?
- What is the classic triad of findings seen in reactive arthritis?

deformity) may be absent for < 10 years after onset of symptoms. MRI is more sensitive and shows marrow edema in the bones adjacent to the SI joints. Regardless, radiographic changes often are not seen at the time of diagnosis. The clinical and laboratory evaluations are most important in patients with early symptoms.

HLA-B27 test is generally done. Because of the high sensitivity (> 90%), a negative HLA-B27 test is useful in excluding AS in patients. Because of its low specificity, it has little use in supporting the diagnosis of AS.

A condition that can be confused with AS because of its radiographic appearance is diffuse idiopathic skeletal hyperostosis (DISH). Classic x-ray findings in DISH include "flowing" osteophytes anterior to the spinal ligaments predominantly in the thoracic region (unlike the ascending bamboo spine from the lumbar region in AS) that span at least 4 contiguous vertebral bodies. The word "flowing" is used because these calcifications have the appearance of someone pouring candle wax in front of the vertebrae. Patients with DISH are rarely symptomatic, and the diagnosis is typically made as an incidental finding. In those who are symptomatic, "inflammatory back pain" symptoms are not present, and patients can be treated with simple analgesics. Furthermore, DISH primarily occurs in men > 50 years of age, does not affect the SI joint, and is not associated with HLA-B27. Inflammatory markers (ESR/CRP) are typically normal in DISH, but may be elevated in AS. DISH patients have a predisposition to developing diabetes mellitus.

Treatment

As we learn more about AS, treatment goals are changing. Traditionally, spinal and SI joint fusion was non-preventable, so the goal was to help the patients fuse their spines in a functional position. To some degree, this is still the goal, so main forms of treatment include stretching exercises, posture training, and proper pillow positioning during sleep. (Sometimes no pillow is best.)

Treatment remains controversial. Bottom line:

- All patients should be on an exercise program.
- NSAIDs are routinely recommended for analgesia and to reduce stiffness.
- Systemic steroids are not recommended due to lack of efficacy and increased risk of osteoporosis and fracture.
- Patients with primarily peripheral disease should be given a trial of therapy with sulfasalazine.
- Axial disease usually should be treated with a biologic drug, mainly anti-TNF agents. Know that the DMARDs sulfasalazine, methotrexate, HCQ, and leflunomide are not useful for axial disease.

If the diagnosis is made early, the prognosis is generally good, but more than 20% of patients have progressive, disabling disease.

REACTIVE ARTHRITIS

Overview

The most common cause of acute, nontraumatic arthritis in a person under the age of 50 is reactive arthritis, which is an immunologic reaction to an infection elsewhere in the body—typically genitourinary (GU) or gastrointestinal (GI) infections. Common causes of reactive arthritis are a GU infection from *Chlamydia trachomatis* and GI infections due to *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Clostridium difficile*. GI causes of reactive arthritis affect men and women equally, but GU causes predominantly occur in men (9:1, M:F). It is also seen in those with common viral illnesses (e.g., enterovirus) and HIV infection. The arthritis typically develops within 2 months of the infection, but the responsible organism usually is not identified. While reactive arthritis is the most common cause of an acute nontraumatic arthritis, it is a very uncommon cause of a spondyloarthritis—AS is more common.

Reactive arthritis (ReA) most commonly presents as an asymmetric, mono- or oligoarticular arthritis of the lower extremities. Enthesitis is common and characteristic, especially at the insertion points of the Achilles tendon and the plantar fascia. Axial spine pain is not a common feature but occurs in about 20% of patients; thus, the categorization of reactive arthritis as a spondyloarthritis.

Extraarticular manifestations are common and include keratoderma blennorrhagicum, mucocutaneous genital lesions, mouth ulcers, conjunctivitis, and iritis. Keratoderma blennorrhagicum classically presents as papules/pustules with central erosion and characteristic crusting on the palms and soles and can be indistinguishable from pustular psoriasis. Circinate balanitis presents as an erythematous pustular or plaque-like lesion on the glans or shaft of the penis. The classic triad of urethritis, conjunctivitis, and asymmetric oligoarthritis is seen in less than 1/3 of patients.

Diagnosis can be tough because the inciting infection often is resolved when the arthritis presents. This is especially true of the enteric pathogens. DNA amplification for genital *Chlamydia* is recommended in patients who have no obvious cause in their history, because *Chlamydia* infections can be asymptomatic, even in males. If a peripheral joint is swollen, arthrocentesis is recommended to exclude bacterial infection and crystalline arthropathies. HLA-B27 testing is not helpful. Radiographs are helpful if osteoarthritis is a possible alternative diagnosis.

Treatment

NSAIDs are recommended for initial treatment. Systemic steroids are used short-term in patients who have refractory peripheral arthritis. For severe or disabling disease, sulfasalazine or methotrexate is used. TNF inhibitors are used rarely and only in extreme refractory cases (Table 6-6 on page 6-12).

The use of antibiotics to treat ReA has been controversial. Some studies show benefits while others refute this claim. It is generally accepted that antibiotics may be useful in treating the initial acute infection and may help prevent the development of ReA, but once the arthritis has begun, long-term antimicrobial therapy is unlikely to modify the course of the disease.

ReA should be at the top of your list for any patient < 50 years old who develops an acute, asymmetric large-joint arthritis in the setting of a recent gastrointestinal or genitourinary infection. Quiz patients about any recent illnesses, especially diarrhea or urethritis/STD (usually during the prior 2–4 weeks), but also ask about viral infections and conjunctivitis.

IBD-ASSOCIATED ARTHROPATHY

IBD-associated arthropathy occurs in about 20% of patients with IBD and clinically manifests in 2 forms:

1) Asymmetric peripheral oligoarthritis of the lower extremities
2) Symmetric polyarticular arthritis of the hands

Asymmetric peripheral oligoarthritis of the lower extremities occurs with flare-ups of inflammatory bowel disease, followed by complete remission of the peripheral synovitis as the bowel disease improves. The peripheral arthritis involves only a few joints in the lower extremities.

Patients may also present with symmetric polyarticular arthritis of the hands, as seen in RA. However, recall that spondyloarthropathies are seronegative (negative ANA, RF, anti-CCP). Extraarticular manifestations such as erythema nodosum, pyoderma gangrenosum, and uveitis may also parallel the flare-ups of IBD.

Axial skeleton involvement (~ 20%) may be clinically and radiographically indistinguishable from AS and runs a course independent of the bowel disease—symptoms do not worsen or improve in response to IBD flares or improvements.

Therapy for IBD (e.g., sulfasalazine, corticosteroids, azathioprine) may help control the peripheral joint symptoms and extraarticular manifestations. Anti-TNF agents are helpful in treating both peripheral joint and spinal symptoms.

PSORIATIC ARTHRITIS

Arthritis with psoriasis is more often seen in patients who have more than just the rash. 20–30% of patients who have nail pitting, onycholysis (separation of the nail from the nail bed), and "oil spots" (brownish discoloration under the nails) also develop joint disease, whereas only 7% of patients who simply have rash develop arthritis (Image 6-8). The rash is classically described as salmon-colored plaques on the extensor surfaces; however, in clinical practice the rash can be quite subtle.

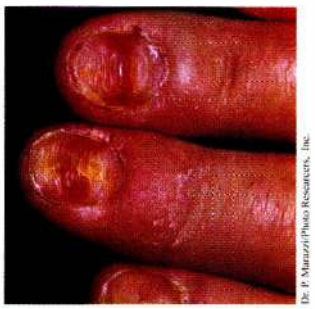

Image 6-8: Dystrophic, pitted nails in a patient with psoriasis

Joint involvement in psoriatic arthritis can have varying presentations:

- **Symmetric polyarthritis**: Looks like RA; can involve the PIPs, MCPs, knees.
- **Asymmetric arthritis** (e.g., oligoarthritis): Usually involves large joints like the knees, ankles, and wrists; typically < 3 joints are affected.
- **Spondylitis**: Presentation is similar to ankylosing spondylitis with inflammatory back pain, but x-rays show an asymmetric sacroiliitis (unlike ankylosing spondylitis and IBD-related spondylitis, where x-rays show a symmetric sacroiliitis).
- **DIP arthritis**: Looks like OA, but there is evidence of nail psoriasis.
- **Arthritis mutilans**: There is severe resorptive destruction of the joint.

Patients can present with more than one pattern of joint involvement. For example, a patient with asymmetric oligoarthritis may also have spondylitis. Imaging is sometimes helpful to distinguish psoriatic arthritis from other forms of arthritis. Hand radiographs may show a classic "pencil in cup" deformity, whereas in inflammatory OA, the classic finding is "gull wings" (see Figure 6-1).

Treatment: NSAIDs are 1st line therapy and are used to control pain and inflammation. In patients with symmetric or asymmetric arthritis, treatment is very similar to RA, with sulfasalazine being the predominant

Quick Quiz

- What are the patterns of arthritis seen with psoriasis? Name some other associated features.
- Which drug, sometimes used in treatment of arthritis, might exacerbate the psoriatic rash?
- "Sausage-shaped digits" are seen in which arthritides?
- What is the pattern of arthritis in osteoarthritis?
- Which joints are typically spared in primary osteoarthritis?
- Which joints of the hand are affected in primary osteoarthritis? What characteristic features are seen in the hands of patients with OA?
- What diagnoses do you consider when you see the pattern of DIP and PIP swelling?

DMARD used in patients with disease refractory to NSAIDs. Anti-TNF agents are reserved for patients with spondylitis and for those with moderate-to-severe arthritis failing to improve with DMARD and NSAID therapy. Paradoxically, there have been increased numbers of reports showing an increase in psoriasis in RA patients who are treated with anti-TNF drugs. The rash resolves with topical steroids or discontinuing anti-TNF therapy. Another drug that is useful for the treatment of psoriatic arthritis is cyclosporine A, which may be used to control both the joint and skin disease (monitor renal function and blood pressure).

Avoid antimalarial drugs (e.g., hydroxychloroquine), lithium, and beta-blockers in psoriatic arthritis because they often exacerbate the skin disease. Systemic corticosteroids should also be avoided because their withdrawal can lead to a severe, life-threatening form of pustular psoriasis. Other conditions that exacerbate psoriasis include skin trauma, sunburn, viral infections, and strep pharyngitis.

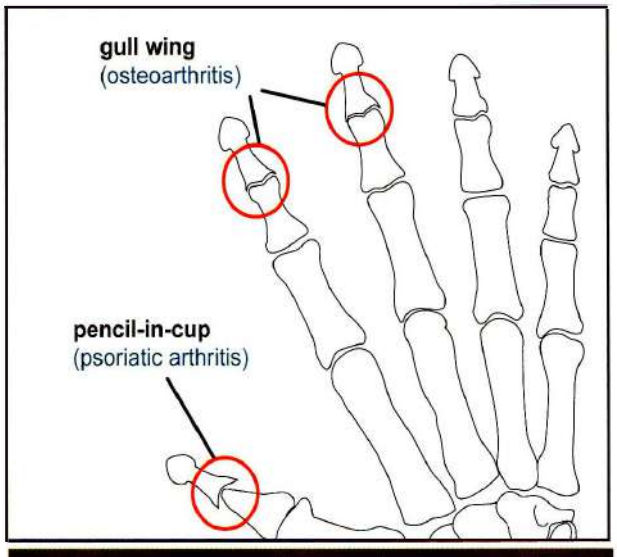

Figure 6-1: Osteoarthritis: gull wing deformity; Psoriatic arthritis: pencil-in-cup deformity

SUMMARY

Sausage-shaped digits are common only in reactive arthritis and psoriatic arthritis. Ice pick–like pitting of the nails is very specific for psoriatic arthritis. Causes of DIP and PIP synovitis are limited (reactive and psoriatic only).

OSTEOARTHRITIS

Osteoarthritis (OA) is, by far, the most common form of arthritis. It can be primary (idiopathic) or secondarily associated with other inflammatory arthritis, such as gout and pseudogout. It's unclear whether the OA or the crystalline arthropathy comes first, although most experts think the latter. OA also can arise after joint damage due to hemochromatosis, trauma, RA, or neuropathic joints related to diabetes. OA pain characteristically worsens with excessive activity and has an insidious progression (contrary to the inflammatory arthritides, such as gout and RA).

The joint damage of OA is classically nonerosive (although there is a rare erosive variant of OA), asymmetric, and without calcium deposition in the cartilage (termed "chondrocalcinosis"). Most commonly affected joints are carpometacarpal (CMC-1) joints of the hands, feet, knees, hips, and the spine. Involvement of the ankle, wrist, and elbow is very rarely due to OA. If a patient's symptoms include swelling of one of these 3 areas, consider pseudogout, gout, RA, or other inflammatory arthritis—not OA!

OA of the hands: Changes most often affect PIPs and DIPs and may be associated with classic enlargements called Bouchard (PIP) and Heberden (DIP) nodes. There is controversy about whether the nodes result from osteophyte formation or development of small cysts around the joints. The enlargement of the hand joints is typically asymmetric, hard, and bony—not soft and spongy, as with inflammatory arthritis. Occasionally, though, these DIP and PIP nodes can become inflamed and very tender, mimicking the inflammatory joint disease of psoriatic arthritis. (Remember, though, that psoriatic arthritis often has nail involvement whereas inflammatory OA does not.) Erosive OA is another term for inflammatory OA; x-rays can reveal evidence of erosions at the DIP joints, where formation of "gull wings" are classic findings. The CMC-1 joints at the base of the thumbs can be involved; "squaring" of the CMC-1 joint is a common physical finding. Note that OA rarely affects MCPs (metacarpophalangeal joints).

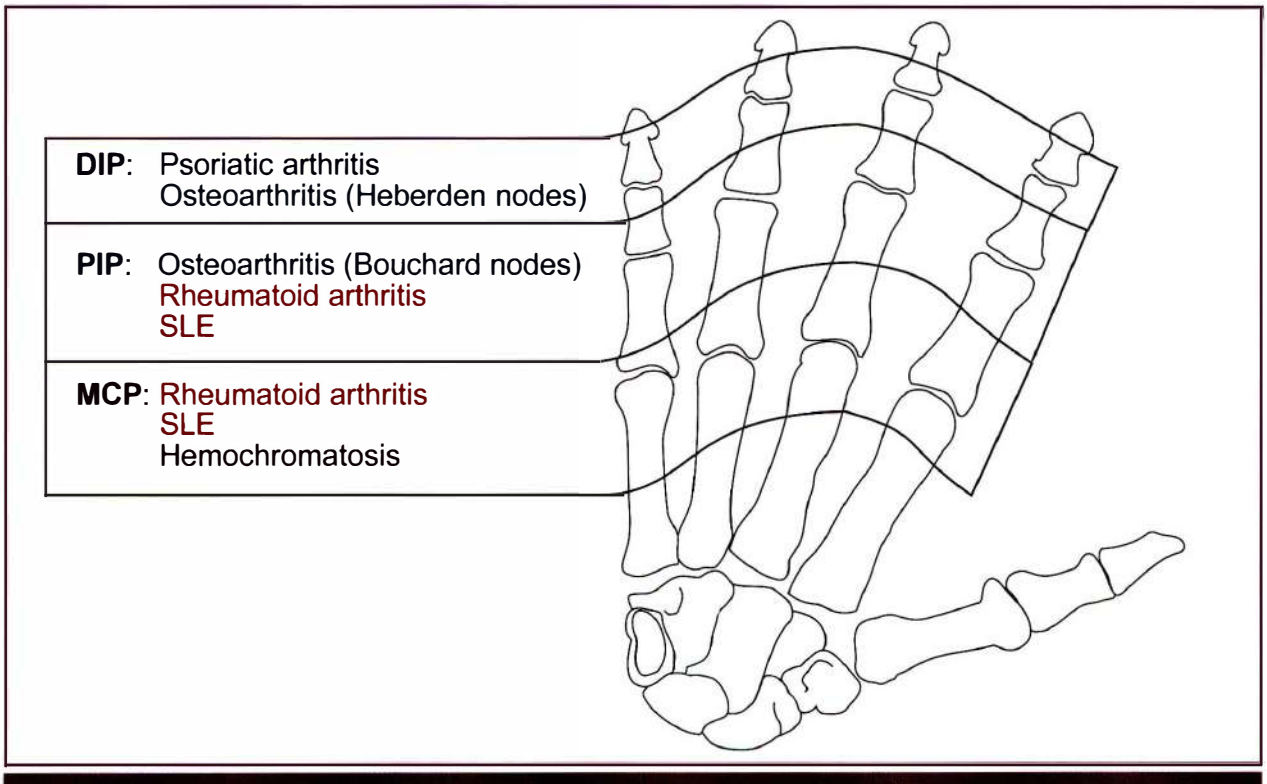

Figure 6-2: Hand Joints Affected by Rheumatologic Diseases

To review: Remember that OA involves the DIPs and PIPs, but not the MCPs, which is seen in RA! (See Figure 6-2.)

Diagnosis of hand OA is supported when there is pain in the hands with 3 of the following clinical criteria (sensitivity 94%; specificity 87%):

1) Bony enlargement of 2 or more: DIPs/PIPs of 2nd and 3rd fingers and 1+ carpometacarpal joints
2) Bony enlargement of > 2 DIPs
3) Fewer than 3 MCP swellings
4) Deformity of 1 of the 10 DIPs/PIPs

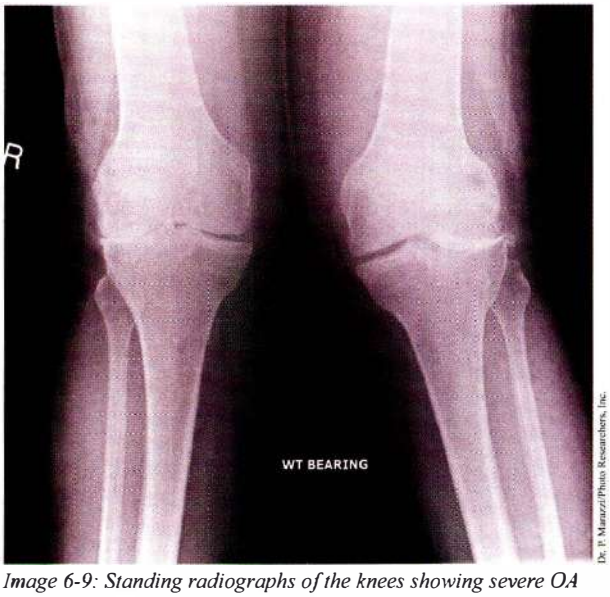

Image 6-9: Standing radiographs of the knees showing severe OA with loss of joint spaces

Hip OA: Pain is usually worse with weight bearing and in the groin area (as opposed to the lateral thigh, which is more often seen with trochanteric bursitis), but it can also be experienced as radiation to the knee.

Diagnosis is supported by hip pain and 2 of the criteria below (and exclusion of other diagnoses):

1) ESR < 20 mm/hr
2) Femoral or acetabular osteophytes on radiograph
3) Joint space narrowing on radiograph (superior migration)

Radiographs and labs do increase diagnostic sensitivity and specificity (89% and 91% respectively, if these criteria are used).

Knee OA: Pain is usually worse with prolonged weight bearing and characterized as a deep ache superior to the patella or deep inside the knee joint. Pain described as medial and inferior to the joint is more likely to be from pes anserine bursitis. And don't forget that pain from hip OA can radiate to the knee. (See Image 6-9.)

Suspect knee OA when the case includes pain and several of the following features:

- Age usually ≥ 50 years
- Obesity
- Morning stiffness < 30 minutes

Quick Quiz

- Characterize the joint synovial fluid in patients with OA.
- At what age does acute gout usually present?

- Bony enlargements (especially if age is < 40 years)
- Knee malalignment: hallux valgus (knock knees) or hallux varus (bow-legged)
- Crepitus
- Noninflammatory synovial fluid (200–2,000 WBCs/mm^3)
- ESR < 20 mm/hr
- Osteophytes on radiograph

The more data you have in combination, the more confident you can be about an OA diagnosis. Clinical criteria alone are about 90% sensitive and specific (higher with labs and radiographs).

Treat knee OA with education (weight loss, exercise, and shoe insoles) and analgesics for pain relief (acetaminophen at maximum dose of 4 g/day and/or NSAIDs). Tramadol alone, or in combination with acetaminophen +/– NSAID or celecoxib, is helpful for refractory pain. Long-term opiates should be minimized, especially in the elderly.

Intraarticular glucocorticoids are useful in patients unable to tolerate NSAIDs, receive inadequate analgesia from acetaminophen, and/or have only 1 or 2 painful joints. Limit intraarticular steroid injections to no more than 3–4 a year.

Viscosupplementation with intraarticular injection of hyaluronic acid may also be effective in reducing pain in some patients, although a recent metaanalysis suggested it had limited efficacy. Some patients who do not respond to intraarticular steroids may respond to hyaluronic acid. Watch out for post-injection flares.

Randomized, placebo-controlled trials and metaanalyses have shown no difference in pain with glucosamine + chondroitin.

If the patient does not respond to the above therapies, knee replacement is indicated.

CRYSTAL DEPOSITION ARTHRITIDES

GOUT

Gout is caused by an excess of uric acid in the serum with deposition of monosodium urate crystals into joints, causing recurrent bouts of acute arthritis and, ultimately, chronic arthropathy. Crystals also can accumulate in tissues, causing tophi and kidney stones.

Acute gout usually presents after 10–30 years of sustained hyperuricemia—in male patients > 40 years of age and after menopause in females (estrogen appears to be a uricosuric agent). Comorbidities and certain drugs can increase the risk for gout.

The following have been linked to gouty arthritis:

- Intake of beer or liquor (not wine)
- High intake of fatty foods, organ meat, red meat, and seafood
- Soft drinks/fructose consumption
- Trauma
- Surgery
- Starvation/Dehydration
- Drugs: thiazide and loop diuretics, nicotinic acid, low-dose aspirin, tacrolimus, cyclosporine, ethambutol

Factors associated with reduced gout flares:

- Caffeine
- Vitamin C (be careful of oxalosis when using vitamin C in patients with chronic kidney disease)
- Dairy intake (at least 2 servings/day)

Excess uric acid (UA) is caused by either decreased renal excretion (underexcretors; 90%), its increased production (overproducers; < 10%), or a combination of the two. Again, most cases (90%) of gout are due to decreased renal excretion. Note that most patients with hyperuricemia never develop gout, tophi, or nephrolithiasis!

Hyperuricemia can be primary, in which case it is usually permanent, or it can be secondary, as a result of comorbid diseases or drugs.

Decreased renal excretion of uric acid can be idiopathic or secondary to:

- chronic renal disease,
- lead nephropathy,
- alcohol,
- drugs, or
- diabetic ketoacidosis.

Increased production of uric acid can be idiopathic, or secondary to:

- leukemia,
- hemolytic anemia,
- tumor lysis syndrome,
- psoriasis,
- exercise,
- fructose ingestion, or
- G6PD deficiency.

To determine whether a patient is an "underexcretor" or an "overproducer," measure the amount of UA in the urine over 24 hours. Underexcretors have low-to-normal 24-hour urine UA levels in the setting of increased

serum levels (or < 600 mg); overproducers often have > 800 mg per 24 hours.

Definitely do these measurements in premenopausal females and in males < 25 years of age who develop acute gout. (Often the hyperuricemia is hereditary, and many get kidney stones.) Also, do these measurements if you intend to prescribe a uricosuric agent, to ensure that the patient's rate of elimination won't result in stone formation if you increase the excretion rate with drug intervention. In most other cases, these measurements usually are not performed because they rarely result in a change in management.

Acute gouty arthritis classically presents as an acutely tender and swollen joint that may occur at night and awakens the patient from sleep. Pain reaches maximum intensity within the first 24 hours and self-resolves within a few days to several weeks. In 50% of patients, the initial attack occurs in the metatarsophalangeal (MTP) joint of the great toe (termed "podagra"). The knee is the next most commonly affected joint. In the early stages of gout, the patient is completely asymptomatic between attacks ("intercritical period")—a useful clue to help distinguish gout from other arthritides if the diagnosis is in question. With chronic tophaceous gout, patients often have symptoms between flares.

Acute polyarticular gout is much less common. It is more often seen in patients with myelo- or lymphoproliferative disorders (e.g., leukemias), post-organ transplant, chronic kidney disease, and longstanding disease.

Diagnose gout by performing an arthrocentesis and looking for intracellular crystals in the joint fluid. Arthrocentesis classically shows inflammatory joint fluid with > 2,000 WBCs/mm^3 and a predominance of neutrophils. Monosodium urate crystals are "needle-shaped" and are strongly negatively birefringent under polarized light. (The crystals that are parallel to the color compensator are yellow.) To be diagnostic, the crystals must be intracellular. See Image 6-10. It is very important that the crystals be seen inside cells before gout is considered as the cause of an acute arthritis. Occasionally, urate crystals are found floating in the joints of patients who do not have gout. So, merely finding a floating uric acid crystal does not make gout the diagnosis.

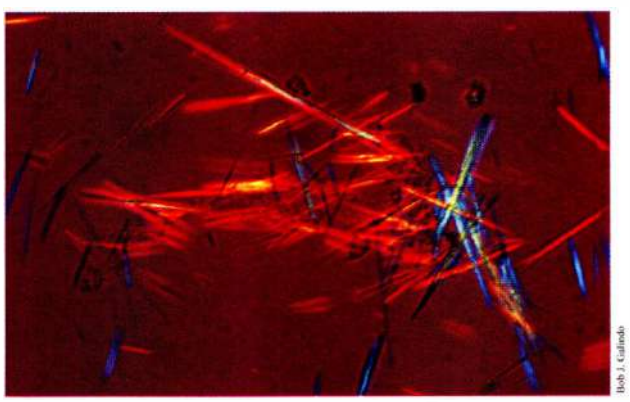

Image 6-10: Uric acid crystals under polarized light

Rarely, monosodium urate crystals are not identifiable in the joint fluid, and the fluid characteristics can make this presentation hard to differentiate from septic arthritis. In that situation, gout is the most likely diagnosis if the patient has evidence of uric acid deposition in the tissues (e.g., linear densities overlying cartilage visible on ultrasound; uric acid deposits visible on CT; and subcortical bone cysts visible on plain radiographs or MRI indicative of bony tophi). Always send the joint fluid for routine Gram stain and culture because gout can coexist with infection.

It is important to know that a rapid decrease or, less commonly, an increase in uric acid level is thought to precipitate gouty attacks. The uric acid level does not correlate with an attack of acute gout—often patients have normal or low levels when the acute arthritis is present. Conversely, an elevated serum uric acid does not confirm the diagnosis of gout, but it does indicate patients who are at risk. As serum UA levels increase > 9–10 mg/dL, incidence of gouty attacks increases to 5% per year.

Quick review: Gout = intracellular monosodium urate crystals, needle-shaped, yellow when parallel, negative birefringence.

Acute Treatment

NSAIDs, corticosteroids, or oral colchicine are all appropriate 1st line agents for acute gout. Know that the earlier any treatment is initiated the better the response.

Treat the acute attack with ice packs and consider intraarticular corticosteroids if only 1 or 2 joints are involved and suspicion for infection is low. Use NSAIDs or colchicine if multiple joints are involved and if there are no contraindications. Traditionally, indomethacin has been the choice NSAID for the treatment of gout, but any NSAID, including a COX-2 inhibitor, will work.

Low-dose oral colchicine (1.2 mg x 1 dose, then 0.6 mg 1 hour later) followed by prophylactic doses if needed can be used in patients instead of NSAIDs. This low-dose regimen has equivalent efficacy and better GI tolerability when compared with the older, higher-dose regimen (e.g., 1.2 mg followed by 0.6 mg every hour for 6 hours). Side effects of colchicine typically are nausea, vomiting, and diarrhea, but myopathy and bone marrow suppression can be seen with long-term use, especially in patients with advanced chronic kidney disease. IV colchicine is no longer available in the U.S. because of its side effect profile.

Corticosteroids are especially useful for patients when NSAIDs or colchicine are contraindicated or ineffective. Either local steroid injections or systemic therapy are effective, but exclude infection first.

Quick Quiz

- How is gout definitively diagnosed?
- Characterize the crystals of gout when observed under a polarizing microscope.
- How could you treat a gout flare in a single joint?
- What drugs used for chronic treatment of gout are contraindicated during an acute gouty attack?
- What is the goal uric acid in a patient who has more than 1 attack of gout a year?
- With which drugs do you have to adjust the dose of allopurinol downward?

Commonly used is prednisone or methylprednisolone as monotherapy or in combination with colchicine. Note that the combination of steroids and NSAIDs increases the risk of gastric toxicity.

Antihyperuricemic drugs that are given for chronic treatment of gout (e.g., allopurinol, febuxostat) should not be started during an acute gout attack, but should be continued if the patient is already taking the drug.

Chronic Treatment

Overview

The goal of therapy should be to reduce uric acid load and to prevent a subsequent attack. Chronic treatment of gout includes:

Dietary/lifestyle modifications. Avoidance of precipitants, including the foods and drugs previously mentioned on page 6-23, may not be practical or may be adhered to poorly. Patients should be counseled on low-purine diets and alcohol avoidance, which can lower the frequency of acute gout attacks, but may not be effective long term in lowering UA levels (e.g., decline ~ 1 mg/dL). In addition, many patients do not adhere to dietary modifications given that these are less palatable than their usual diet. The best diet is simple caloric restriction with an emphasis on complex carbohydrates (in lieu of processed simple sugars)—the goal is to effect weight loss, which does lower the incidence of gout.

Urate lowering therapy (ULT). The goal of ULT is to reduce the serum uric acid (SUA) to < 6.0 mg/dL, which is below the saturation point of monosodium urate. [Know this!] When SUA levels are < 6.0, urate crystals are reabsorbed from the joint and tophi, resulting in reduction in frequency of gout flares. Patients with tophi and more severe disease would benefit from an even lower serum uric acid level (< 5.0 mg/dL). Remember: Start chronic treatment after the acute attack resolves completely and titrate dose to goal uric acid.

Prescribe ULT to patients with the following:

- Tophi
- Uric acid kidney stones or 24-hour urine uric acid level > 1,100 mg/day (but do not use a uricosuric drug)
- Radiographic signs of chronic gouty arthropathy
- Recurrent acute attacks (> 1/year)

Xanthine Oxidase Inhibitors

First-line ULTs are the xanthine oxidase inhibitors (XOIs), which include allopurinol and febuxostat. These agents reduce SUA in both underexcretors and overproducers. Remember that underexcretion of UA is the most common cause of hyperuricemia.

Allopurinol is the most commonly prescribed XOI. It is cheap and effective. Common side effects include nausea, vomiting, and diarrhea. Allergic reactions can occur, ranging from a simple drug rash to rarely fatal hypersensitivity reactions: toxic epidermal necrolysis (TEN)/Stevens-Johnson syndrome (SJS).

TEN/SJS is manifested by fever, acute kidney injury, eosinophilia, liver dysfunction, blistering mucosa, and typical TEN/SJS rash. Patients with impaired renal function are at greater risk for developing hypersensitivity reactions. For this reason, recent guidelines recommend that the starting dose of allopurinol should not exceed 100 mg/day. In those with moderate-to-severe kidney disease, the starting dose should be even lower (e.g., 50 mg/day).

More recently, a strong association has been discovered between HLA-B*5801 and allopurinol-related TEN/SJS. Screening for this gene has been suggested prior to initiation of allopurinol; however, due to cost and availability of the test, testing may not be practical.

Another important item to know about allopurinol is that the dose must be decreased by 66–75% in patients taking azathioprine or mercaptopurine. Because metabolism of these drugs is inhibited by XOIs and can lead to increased drug toxicity such as bone marrow suppression, labs should be monitored closely.

Febuxostat is much more expensive than allopurinol. Side effect profiles are similar to allopurinol; the drug is useful in patients who cannot tolerate allopurinol, including those with drug hypersensitivity to allopurinol. Reduction in uric acid is rapid with febuxostat, and there is no need to adjust dosage for a glomerular filtration rate (GFR) below 30 cc/min. Avoid using febuxostat with azathioprine or mercaptopurine because it is a more potent XOI than allopurinol.

Also note that both allopurinol and febuxostat can reduce the clearance of theophylline, which increases theophylline levels. Monitor theophylline levels in patients who are on concomitant therapies with XOI and theophylline.

Uricase

Uricase is an enzyme that oxidatively degrades uric acid to soluble allantoin that can be readily excreted. Humans and higher primates lost uricase expression during the course of evolution. **Rasburicase** is a uricase approved for tumor lysis syndrome and has been shown to help reduce tophi burden in patients with chronic tophaceous gout; however, the drug is not FDA-approved for gout because it is highly antigenic and has poor tolerability and sustainability.

Pegloticase, a pegylated recombinant mammalian uricase, was approved by the FDA for use in refractory tophaceous gout. The drug has less immunogenicity, but infusion reactions and anaphylaxis are still concerns.

Uricosuric Agents

Uricosuric agents inhibit urate transporter URAT1 to increase uric acid renal clearance; these agents are rarely used due to poor adherence. Probenecid, the only uricosuric approved in the U.S., requires multiple daily doses and ingestion of > 1 gallon of water/day to prevent uric acid renal stones. It is considered a 2nd line agent in underexcretors who are resistant/intolerant to XOIs. Probenecid should be avoided in patients:

- Who are overproducers or underexcretors of uric acid
- With history of renal stones
- With tophi
- With renal insufficiency where GFR ≤ 30 cc/min or Cr > 2.0 mg/dL, because the drug would be ineffective given its mechanism of action

Though its use as a monotherapy drug may be limited, new gout guidelines suggest that adding a low-dose uricosuric agent to an XOI may be a means to reach target uric acid goal.

Use Acute Gout Prophylaxis While Lowering Uric Acid

The risk for an acute gout attack is high when ULT is initiated. Remember, a rapid increase or decrease in uric acid level can precipitate gouty attacks. To lower the rate and severity of flares during ULT, the American College of Rheumatology (ACR) recommends that patients receive pharmacologic antiinfllammatory prophylaxis with low-dose colchicine (0.6 mg qd to bid) or NSAIDs (with a PPI when indicated). If colchicine or NSAIDs are not tolerated, are ineffective, or are contraindicated, then low-dose prednisone (< 10 mg/day) can be considered. Prophylactic therapy should be continued for at least 6 months if tophi are present, 3 months if there are no tophi.

Chronic Treatment Summary

1) Decrease red meat and fish. Increase other proteins. Decrease carbohydrates. Decrease alcoholic drinks.
2) Control HTN.
3) Start treatment with an XOI. Allopurinol is the drug of choice. Give febuxostat if patient is unable to tolerate allopurinol or if allopurinol is not effective.
4) Use pegloticase for symptomatic tophaceous gout not controlled by an XOI.
5) Give low-dose cholchicine until 3–6 months after urate levels return to normal.

Gout Pearls

Know the following!

- Low-dose aspirin (e.g., ≤ 325 mg/day) interferes with urate excretion. High-dose aspirin (e.g., ≥ 1–3 g/day) causes uricosuria. Therefore, at commonly used doses, aspirin interferes with UA excretion.
- Differential Dx for acute monoarticular joint swelling = infection vs. crystalline vs. fracture/trauma.
- Gout can cause fever.
- Premenopausal women rarely get gout. (Estrogen is a uricosuric.)
- Older women may present with polyarticular pseudo-rheumatoid crystalline arthritis (gout or pseudogout that presents similarly to RA). So, think of gout or pseudogout in the older woman who looks like she has suddenly developed RA. Always look for crystals in joint fluid!
- Gouty joint radiographs may have a characteristic erosion with an overhanging edge, termed marginal erosion or "rat-bite" erosion that is caused by a tophus.
- RA and gout rarely coexist.
- Acute gout + joint infection is uncommon, but should never be missed.
- Goal uric acid should be < 6.0 mg/dL; for patients with tophi, the goal uric acid should be < 5.0 mg/dL.
- Give antiinflammatory prophylaxis while lowering uric acid to prevent flares.

CPPD DEPOSITION DISEASE

Calcium pyrophosphate dihydrate (CPPD) crystals cause chondrocalcinosis (calcium in the cartilage) and subsequent damage to joints. Most idiopathic CPPD deposition occurs in patients > 65 years of age and who have underlying joint damage from OA or trauma. However, when you see CPPD deposition in a patient < 50 years of age, consider these predisposing conditions:

- Primary hyperparathyroidism
- Hemochromatosis (see Hemochromatosis Arthritis on page 6-32)

Quick Quiz

- Inflammatory arthritis of certain joints should make you think of CPPD disease. Which joints are they?
- What do CPPD crystals look like under polarized light?
- Which diseases are associated with CPPD?

- Hypothyroidism
- Hypomagnesemia
- Hypophosphatemia

The presentation ranges from asymptomatic deposition of crystals in joint cartilage (visible only on radiographs) to an acute monoarticular arthritis (often referred to as "pseudogout," similar to uric acid gout) to presentations similar to OA and RA.

Chondrocalcinosis is calcification of cartilaginous tissue and is a hint to underlying CPPD, so think of this diagnosis if you're shown obvious calcifications in the cartilage on a radiograph of a small joint. If the presentation is one of an acute arthritis, the arthrocentesis usually reveals an inflammatory joint fluid (WBCs > 2,000 cells/mm^3) with an excess of neutrophils, some of which will contain CPPD crystals.

CPPD arthropathy usually affects the knee. Other common joints affected by CPPD include wrists, 2nd and 3rd MCPs, shoulders, elbows, and ankles. Recall from the OA section, we said that OA rarely involves these joints! If your patient has wrist synovitis in the face of OA, first think CPPD deposition—not OA only! Also, when chondrocalcinosis is visible on radiographs of the wrists or MCPs, think CPPD.

Diagnose CPPD by finding intracellular crystals that are blunted, rhomboid, and are weakly positively birefringent under polarized light. (Crystals are light blue when parallel to the color compensator.) See examples of intracellular and extracellular CPPD crystals in Image 6-11 and Image 6-12. Recall: Uric acid crystals are needle-shaped and are strongly negatively birefringent (bright yellow when parallel to the compensator). Be able to distinguish uric acid and CPPD crystals from photomicrographs (based on color) and from descriptions of the crystals.

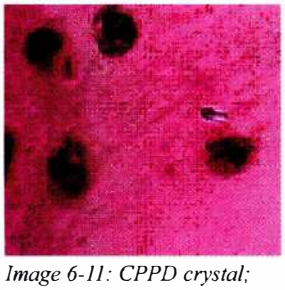

Image 6-11: CPPD crystal; extracellular

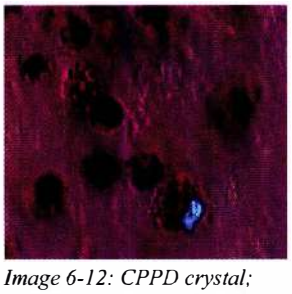

Image 6-12: CPPD crystal; intracellular

CPPD crystals dissolve and change their birefringence when stored > 12–24 hours, so analyze the fluid immediately. Urate crystals are much less likely to dissolve. If your fluid cannot be examined within a few hours, refrigerate it to slow the decomposition of crystals and white cells.

Quick review: CPPD crystals = rhomboid, positive birefringence (light blue when parallel), chondrocalcinosis. Management of acute arthritis is extrapolated from gout data and is essentially identical to the treatment of acute gout. First-line therapy would be joint aspiration and NSAIDs and/or intraarticular glucocorticoid administration. Colchicine can be used but may be less effective. Use oral prednisone if patients have refractory disease or are unable to take NSAIDs/colchicine. Low-dose colchicine also can be used as prophylaxis for acute attacks. There is no equivalent drug to XOI in CPPD disease that can reduce the burden of crystals in the joints. However, in patients with associated metabolic conditions (e.g., hemochromatosis), treatment of the underlying disease may decrease the number of attacks. In hemochromatosis, phlebotomy may not change the joint calcification, but other manifestations of the disease, such as diabetes and liver disease, can improve.

Again, look out for the patient with wrist arthritis who also has Bouchard (PIP) and Heberden (DIP) nodes consistent with OA—think CPPD and screen for hemochromatosis, hyperparathyroidism, and hypothyroidism in patients younger than ~ 50 years of age.

HYDROXYAPATITE ARTHROPATHY

Hydroxyapatite arthropathy (HAA) also is known as basic calcium phosphate arthropathy or calcium apatite deposition disease. Hydroxyapatite is the primary mineral in bone and teeth. Abnormal accumulation may occur idiopathically; in hypercalcemic/hyperparathyroid states; in damaged tissues; and in scleroderma and dermatomyositis. Crystal arthropathy in dialysis patients is sometimes due to HAA, and both CPPD and HAA are associated with OA. The most common joint affected is the shoulder.

Think about HAA in elderly patients (especially women) who have a destructive arthropathy of the shoulders ("Milwaukee shoulder"), hips, knees, and/or hands with noninflammatory synovial fluid (increased mononuclear cells) and no visible crystals. Radiographs show calcification in and around the joints +/– erosions, depending on how bad the disease is.

Confirm diagnosis of HAA arthropathy with identification of the HAA crystals in the joint fluid. Unlike urate and CPPD crystals, these crystals are very small, nonbirefringent, and can be seen only by electron microscopy or light microscopy with special staining (using alizarin red, done by pathologists).

Treatment for acute HAA is the same as for acute CPPD. For dialysis patients, controlling serum phosphorus levels helps prevent flares.

INFECTIOUS ARTHRITIDES

SEPTIC ARTHRITIS

Overview

There are 2 classifications of septic arthritis: nongonococcal (organisms other than *Neisseria gonorrhoeae*) and gonococcal arthritis.

Septic (bacterial) arthritis is inflammatory and usually monoarticular, occurs from seeding during bacteremia, and is associated with fever. In most cases, joint aspirate is inflammatory (average WBCs = 100,000 cells/mm^3) with predominance of neutrophils, and a Gram stain frequently shows the infecting organism, but not always. An indolent history with noninflammatory fluid suggests mycobacteria or fungi as etiologies, or a noninfectious cause of arthritis.

Know these septic joint associations and portals of entry that allow dissemination of the bacteria (Table 6-7):

- *S. aureus* >> *S. viridans* = usual cause (60–70%) of septic native joints in adults, especially in RA patients. Portal of entry: skin, wound infection.
- Adolescents and young adults = *N. gonorrhoeae* (most common cause of infectious arthritis in this age group!) often with concomitant *Chlamydia trachomatis*. Remember that synovial WBC counts may be in only the 10,000 cells/mm^3 range. Portal of entry: oropharynx and genitourinary tract.
- Sickle cell anemia = *Salmonella* and pneumococcus, but staph is still most common. Portal of entry: bloodstream due to asplenia.
- Human bites = anaerobes and *Eikenella*.
- Animal bites = *Pasteurella multocida*.
- Extensive comorbidities = gram negatives, group A streptococci, pneumococcus.
- Indolent, chronic, and with noninflammatory fluid (+/– bloody) = mycobacteria, fungus, or noninfectious.
- Injection drug users = staph, strep, gram negatives (especially *Pseudomonas*); predilection for axial disease (e.g., sternoclavicular and sacroiliac joints).

Table 6-7: Microbial Causes of Septic Arthritis

Host	Bacteria	Port of Entry	Main Trait
Adolescents, adults	*N. gonorrhoeae*	Oropharynx GU tract	WBC in joint usually lower than typical septic joint. Can be 10,000 cells/mm^3. *Chlamydia* can coexist; joint cultures usually negative
Children, adults	*S. aureus*	Skin/wound infection	Accounts for 2/3 of all septic arthritis
Children, adults	Anaerobes *Eikenella* spp.	Human bites	
Children, adults	*Pasteurella* spp.	Animal bites	Cat bite wounds
Sickle cell patients	*S. aureus* *Salmonella* spp. Pneumococcus spp.	Hematogenous	Infection can precipitate a sickle cell crisis
Patients with prosthetic joints	*S. aureus* Coagulase-negative staph	Hematogenous, local wound infection	Loosening of prosthesis concerning for infection
Injection drug users	Staph, strep, gram-negative bacteria	Hematogenous	Predilection for axial joints, sternoclavicular, sacroiliac
Patients with many comorbidities	Gram negatives, staph, group A strep, pneumococcus	Respiratory, hematogenous	Get blood cultures as well
Immunosuppressed patients	Mycobacteria, fungus	Hematogenous, local wound infection, respiratory	Infection is indolent, chronic; synovial fluid may be bloody and noninflammatory
Fisherman, aquarium hobbyist	*Mycobacterium marinum*	Local wound infection	Cultures may be negative from synovial fluid, need culture from mucosal surfaces

- What is the typical cell count in the synovial fluid of a septic joint? Which type of cells are they?
- What are common pathogens associated with septic joints?
- How do you diagnose gonococcal arthritis?
- What is special about the approach to diagnosis of gonococcal arthritis compared to traditional septic joint workup?

- Prosthetic joints = *S. aureus* or coagulase-negative staph; "loosening of the prosthesis" is very concerning for infection.

Gonococcal Arthritis

Pregnancy and menstruation are predisposing factors for disseminated gonorrhea. Patients with deficiency of terminal complement components are also at high risk. Presentation is fever, migratory polyarthritis, tenosynovitis, and dermatitis (red papules that become pustular). Gonococcal joint infection is always from dissemination, but you might have missed the clinical signs/symptoms during dissemination. Remember to consider this diagnosis in the adolescent with knee pain.

In gonococcal arthritis, arthrocentesis often reveals a WBC count > 50,000 cells/mm^3, but it may be as low as 10,000–20,000. Joint cultures are usually sterile and blood cultures are positive in < 50% of cases.

Know that in disseminated gonorrhea, you culture all mucosal surfaces that could be harboring the organism (i.e., cervix, rectum, and oropharynx in women; urethra, rectum, and oropharynx in men), in addition to any skin lesions, joint fluid, and blood. *N. gonorrhoeae* is a relatively fragile organism, susceptible to temperature changes, drying, UV light, and other environmental stresses. Strains of *N. gonorrhoeae* are fastidious and variable in their cultural requirements, so that media containing hemoglobin, NAD, yeast extract and other supplements are needed for isolation and growth of the organism.

Therefore, adequate cultures require direct plating of the specimen on Thayer-Martin ("chocolate") agar at the bedside. So, go to the lab first and get your special media before you do an arthrocentesis. Then, squirt some of the joint fluid directly onto the chocolate agar plates—in addition to sending the fluid for routine Gram stain, culture, and sensitivity. If you have the option of sending joint fluid for gonococcal PCR, do that—the results are highly sensitive. The aggregate yield of detecting the pathogen by culturing all mucosal sites is 70–90%. In contrast, blood, synovial, and skin cultures are typically negative.

Nongonococcal Arthritis

In nongonococcal septic synovitis, the joint is hot and tender, and the patient may be febrile. Try to get blood cultures and aspirate your joint fluid before administering antibiotics. Fluid is inflammatory, and Gram stain of the joint fluid usually shows WBCs and organisms. Fluid cultures grow the organism most of the time, and about half the time, blood cultures are also positive. Direct inoculation of blood culture vials with joint fluid may increase the likelihood of isolating the organism, although studies are divided about whether or not direct inoculation makes a difference.

Treatment for septic arthritis includes systemic antibiotics targeted to the Gram stain result: nafcillin or vancomycin for gram-positive cocci; broader coverage for gram negatives, pneumococcus, and gonococcus if no organisms are seen; and antipseudomonal coverage if injection drug use is suspected. Repeated drainage of the joint may be necessary. Patients who don't improve with antibiotics and repeated aspiration should go for laparoscopic or open lavage. Intraarticular antibiotics are not recommended.

Patients who have prosthetic joints but need to undergo procedures (e.g., dental, urologic) are at risk for developing transient bacteremia and seeding of their joint. However, there is no evidence to recommend routine antibiotic prophylaxis in patients with prosthetic joints undergoing invasive dental, GU, or GI procedures.

Acute Rheumatic Fever

Acute rheumatic fever (ARF) is a rare immunologic complication that typically occurs 1–5 weeks after a previous group A beta-hemolytic strep infection. Polyarthritis is one of the World Health Organization's criteria for diagnosis. Consider ARF in adolescents and young adults (rare after age 30) who fulfill the ARF criteria (below).

The Jones criteria (2 major, or 1 major and 2 minor) should be viewed as a guide to determine who is at high risk but cannot be used to define diagnosis with absolute certainty. An exception includes chorea, which can present as the sole manifestation of ARF, in spite of negative laboratory results.

Jones major criteria—**CCEPS**:

- **C**arditis (e.g., prolonged PR interval)
- **C**horea
- **E**rythema marginatum (pink macules with central clearing, typically on the trunk)
- **P**olyarthritis (typically migratory)
- **S**ubcutaneous nodules (painless)

Jones minor criteria:

- Fever, arthralgias.
- A throat culture positive for *Streptococcus* is found in approximately 25% of patients at the time of presentation.

WHIPPLE DISEASE

Whipple disease is a rare and chronic bacterial infection caused by *Tropheryma whipplei*. It predominantly affects white, middle-aged men (M > F 4:1) and causes recurrent episodes of nondestructive seronegative inflammatory arthritis that predominantly affect large joints (e.g., knee). It is also commonly associated with GI manifestations including diarrhea, malabsorption, and weight loss, fevers, lymphadenopathy, skin hyperpigmentation, and neurologic findings. The main neurologic symptom is memory loss due to a slowly progressive dementia. "Oculomasticatory myorhythmia" (convergent-divergent nystagmus with concomitant masticatory contractions) is pathognomonic for Whipple disease. Importantly, the joint manifestations usually precede other symptoms by 5 years or more, providing a critical window for diagnosis and treatment. That's a lot of systems to remember. Basically, think about Whipple's in white middle-aged men with diarrhea, fat malabsorption/weight loss, CNS symptoms, and recurring episodes of inflammatory arthritis.

The diagnosis is made by finding macrophages containing periodic acid-Schiff (PAS)-positive gram-positive bacilli in tissue biopsies from any system that is involved. PCR can also be used.

Treatment usually requires parenteral antibiotics (e.g., ceftriaxone) initially to ensure CNS penetration, followed by oral therapy, such as double-strength TMP/SMX x1–2 years! Recurrences are common.

TUBERCULOUS ARTHRITIS

Tuberculous arthritis typically presents as an indolent chronic monoarthritis (months to years). Hip and knee joints are most commonly affected. The arthritis is either an expression of primary TB or a site of reactivation, but most patients do not have associated active pulmonary TB. Remember that immunosuppressive agents, particularly anti-TNF inhibitors, are risk factors for reactivation TB.

Joint fluid may show inflammation (average WBCs = 20,000 mononuclear cells/mm^3). Know that acid-fast smears and cultures are useful, but their sensitivities are not great. Synovial cultures are positive in ~ 80% of people with infection.

As with pleural TB, biopsy of the synovium for pathology and culture is most helpful. (Pathology shows granulomas.)

Send the fluid for TB PCR—the test is very sensitive. A positive TB skin test in a patient with a chronic joint effusion should make you think about (and investigate for) TB! As with pulmonary TB, TB skin tests aren't always positive in people with infection, so do not let a negative test dissuade you from the workup if you suspect TB based on the history or other data.

Treatment is the same as for active pulmonary TB: isoniazid, rifampin, pyrazinamide, and ethambutol x 2 months—until you get the organism and its sensitivities. Then, narrow therapy to 2 drugs x 4–7 more months (6–9 months total). Treat longer if the patient is HIV+.

VIRAL ARTHRITIS

Viral diseases can cause a true infection of the joint (aseptic arthritis) or a reactive (immunologic) arthritis (previously discussed on page 6-19).

Patients with aseptic arthritis frequently have a pseudo-RA picture, which resolves with minimal therapy (NSAIDs) and typically does not recur.

Parvovirus B19 is one of the more common causes of aseptic synovitis in adults. Think about parvovirus B19 when you see a young adult female with a history of exposure to school-aged children who presents with symmetric synovitis of the hands (mimicking RA) and macular rash (75%)—the synovitis has been present for weeks, and she may even describe a recent "slapped cheek" rash in the children. Again, the history of exposure to sick children 1–2 weeks prior to the arthritis should alert you to the possibility of parvo as the cause of hand arthritis. The diagnosis can be confirmed by positive IgM against parvovirus B19.

Other causes of aseptic synovitis: rubella, mumps, acute HBV (oligoarthritis/arthralgias associated with maculopapular rash, fever, and urticaria before jaundice), chronic HCV, and enteroviruses.

LYME ARTHRITIS

Remember endemic areas for Lyme disease include: the Northeast and North Central states (Minnesota, Wisconsin), as well as the West Coast, particularly Northern California. Lyme arthritis is a late manifestation of Lyme disease. It occurs a few months, and up to 1–2 years, after the disease-causing tick bite in 50% of untreated patients.

True Lyme arthritis is an intermittent or persistent, asymmetric, monoarticular or oligoarticular arthritis, usually affecting only 1 or a small number of large joints (knee most commonly). Up to 50% of patients never have evidence of early Lyme disease (e.g., erythema migrans, carditis, cranial nerve abnormalities, peripheral neuropathies, mononeuritis multiplex, or meningoencephalitis). A small number of patients actually develop destructive, erosive arthritis. (See Infectious Disease, Book 1.)

Criteria have been established for diagnosis and treatment of Lyme disease by the Infectious Diseases Society of America ([IDSA] initially updated in 2006; reviewed for accuracy in 2011). Diagnose Lyme arthritis using a serum ELISA test for anti-*Borrelia burgdorferi* IgG. The IgM ELISA test is not appropriate because arthritis represents a late manifestation (thus, IgG is

QuickQuiz

- What are presenting features of Whipple disease? The organism involved?
- Describe the presentation of tuberculous arthritis.
- How do you diagnose Lyme arthritis?
- What are the features of adult-onset Still's disease?

more appropriate), and these IgM tests are often falsely positive. Do not do any further testing if the IgG ELISA test is negative; a negative test excludes Lyme as the cause of arthritis.

False-positive Lyme ELISA serology can be caused by many diseases, including SLE, RA, Rocky Mountain spotted fever, and other spirochetal diseases (syphilis and leptospirosis), and is seen at a high rate in healthy controls. So, order a Western blot as a confirmation test in patients with a +IgG ELISA.

Although the test is not readily available commercially, DNA amplification is useful on joint fluid. The rate of false positives is high, so do not order this test unless the patient has a positive IgG ELISA and Western blot. The DNA can persist in the joint long after adequate treatment; hence, a positive PCR test does not identify whether disease is active or treated. Antibody tests on the joint fluid are not helpful.

Lyme arthritis without neurologic involvement should be treated with a course of oral doxycycline or amoxicillin for 21 days; then reassess.

Persistent synovitis after oral antibiotics can be treated with NSAIDs and observation, as occasionally the inflammation of Lyme takes weeks to improve. If the patient still has synovitis after oral antibiotics and a period of observation and NSAIDs, retreatment with another 21 days of oral doxycycline or amoxicillin is appropriate. Ceftriaxone can be used for 14--21 days in patients who do not improve at all after the initial oral regimen.

Once Lyme arthritis has been treated with ceftriaxone x 21 days, or 2 regimens of oral antibiotics, the patient has been definitively treated, and any further symptoms/inflammation should be treated conservatively by a rheumatologist. Options include NSAIDs, hydroxychloroquine, and intraarticular steroids.

Know that any patient with Lyme arthritis who has neurologic involvement (except for isolated Bell's palsy) should undergo a lumbar puncture and be considered for treatment with intravenous ceftriaxone, instead of oral antibiotics.

Some patients with persistent symptoms that are indistinguishable from chronic fatigue syndrome or fibromyalgia receive the diagnosis of "chronic Lyme disease," but know that definitive data do not exist to support this claim. Thus, some prefer the term post-Lyme syndrome. As such, it is inappropriate to treat any form of Lyme disease with prolonged oral or intravenous antibiotics. In very rare circumstances, a patient with late neurologic involvement may require an additional 1 month of parenteral ceftriaxone after the 1st month of treatment, but no patient should receive more than two 28-day parenteral regimens. Multiple months of oral or parenteral antibiotics, and antibiotics that are ineffective against the organism (e.g., azithromycin, tetracycline, tinidazole, rifampin, atovaquone/proguanil Hcl, artemisia), are not considered standard of care by the IDSA.

LESS COMMON ARTHROPATHIES

This section contains joint diseases that are associated with systemic illness; although they are less commonly seen in clinical practice, they seem to show up on Board exams!

Adult-Onset Still's Disease

Adult-onset Still's disease (AOSD) is an uncommon illness that occurs primarily in adults in their 20s to 30s; onset after age 60 is unusual. A similar disorder, called systemic-onset juvenile arthritis, is more commonly seen in children younger than 16 years. AOSD presents with a distinctive "evanescent" (means "vanishing" or "disappearing"), macular, salmon-pink rash that coincides with a daily ("quotidian") high, spiking fever and significant leukocytosis (Yamaguchi criteria). The coincidence of a rash that appears with the fever and disappears at defervescence is a big clue to the diagnosis in practice. Include AOSD in the differential diagnosis of fever of unknown origin (FUO).

Mild oligoarthritis usually develops in most patients. Joint fluid is inflammatory (average WBCs = 13,000 cells/mm^3). Other signs/symptoms include sore throat, lymphadenopathy, splenomegaly, myalgias, arthralgias, and serositis. Some patients may progress to a destructive polyarthritis, and their joints can actually fuse (especially the wrists), but this is not common.

Associated lab abnormalities include:

- anemia of chronic inflammation (or anemia of chronic disease),
- reactive thrombocytosis,
- increased ESR or CRP,
- liver transaminase elevations, and
- very high serum ferritin levels.

Besides the rash, a high serum ferritin level (> 10x normal) is strongly associated with this disease and correlates with more severe disease activity.

Initial treatment for mild disease includes NSAIDs, but most patients ultimately require systemic steroids. Methotrexate is the most common DMARD used for

those with severe disease and as a steroid sparing agent. Biologics with IL-1 inhibitors have been shown to be effective, though some patients may respond to anti-TNF therapy.

Hemochromatosis Arthritis

About 20-40% of patients with hemochromatosis develop arthritis; in many, the arthritis is the presenting symptom. Usually, this happens in patients > 50 years of age.

Monthly menstrual cycle acts as a form of phlebotomy, so women with hemochromatosis may not have a manifestation of CPPD until after menopause. Therefore, still consider this diagnosis in postmenopausal women.

The arthritis affects small joints first. Think of hemochromatosis when you see synovitis of the 2nd and 3rd MCPs. Larger joints (e.g., knees, ankles, shoulders) are affected later. The joint fluid is noninflammatory (a big clue to help you distinguish this arthritis from the inflammatory ones that also affect the MCPs, such as RA). The morning stiffness of this arthritis is also usually < 30 minutes; x-rays show narrowed joint spaces.

Remember that CPPD deposition occurs in association with hemochromatosis—in ~ 50% of patients with the arthritis. So, you also may see chondrocalcinosis on radiographs and/or weakly positive birefringent crystals in the joint fluid.

Treating hemochromatosis with phlebotomy may help other manifestations of disease but not the arthropathy. Treat chronic joint disease with acetaminophen and NSAIDs. Intraarticular steroids and NSAIDs can be used for acute CPPD arthritis flares (see CPPD deposition disease, above). Hemochromatosis can easily be screened for with iron studies. An elevated iron saturation level (iron/TIBC of > 45%) or elevated ferritin level (> 200) suggests the diagnosis.

Neuropathic Arthropathy (Neuropathic Joints)

We used to call these Charcot joints—joints that are destroyed via 2 proposed mechanisms:

1) Repeated trauma secondary to loss of pain sensation and/or proprioception
2) Autonomic dysfunction that leads to regional hyperemia, osteoclastic stimulation, and active bone resorption

Diabetes mellitus is the most common cause.

Joint findings are similar to severe OA, with osteophytes, except that erosions also can occur. The metatarsophalangeal, tarsal, and talar joints are most commonly involved and radiographs confirm the diagnosis. Bony fragments, reminiscent of the trauma, are often seen floating in the joints on radiographs. To try to repair the damage, bone becomes overgrown, known as periostitis, and noninflammatory joint effusions develop. Eventually, the joints become unstable and lax. Think about this diagnosis in a diabetic patient with a horrific-looking joint (especially the foot) and minimal associated pain. Treat joints with stabilization and focus on the underlying disease.

Hypertrophic Pulmonary Osteoarthropathy

Think about hypertrophic pulmonary osteoarthropathy (HPOA) when you see polyarthritis/joint effusion in a smoker who also has clubbing of the fingers. HPOA can be primary or familial, but it is most often associated with lung malignancies (termed "secondary HPOA"). We don't know the mechanism for this condition, but it is associated with periosteal bone formation, joint effusions (due to synovial proliferation and inflammation), and clubbing (due to effects on connective tissue).

The bone changes can be associated with dull, aching pain that is intense when you apply pressure to the arms and legs. The arthropathy is usually slight and appears noninflammatory (effusion WBCs < 500 cells/mm^3). Hands are generally not part of this presentation, other than clubbing!

In early stages, radiographs show periosteal bone growth adjacent to radiolucencies, especially in the diaphysis. Later, irregular cortical thickening appears, mostly over metaphyses. Use imaging to look for an intrathoracic malignancy, especially lung cancer. Infectious etiologies are also seen in this syndrome, including bronchiectasis, lung abscess, and TB. If the cause is a lung infection, the arthropathy and clubbing usually disappear after antibiotics.

Remember: Think HPOA in the patient with polyarthritis (similar to RA), clubbing of the fingers and toes, and periostitis of the long bones. When you see this triad, evaluate the patient for lung cancer.

Post-Streptococcal Reactive Arthritis

Post-streptococcal reactive arthritis (PSRA) is considered a separate entity from acute rheumatic fever (ARF) and from typical HLA-B27–associated reactive arthritis. Onset of PSRA is within 10 days of group A streptococcal infection; patients may present with prolonged or recurrent arthritis that is additive (rather than migratory). There is a bimodal distribution: childhood and middle age; incidence of developing carditis is low. There is little consensus on treatment, but aspirin, NSAIDs, and steroids have been used. The role of antibiotics is controversial.

Quick Quiz

- Does hemochromatosis initially affect large or small joints?
- Characterize the typical patient who develops primary Raynaud's.
- Mixed connective tissue disease has features of which diseases?

OTHER CONNECTIVE TISSUE DISEASES

RAYNAUD PHENOMENON

Primary Raynaud phenomenon (idiopathic; called Raynaud disease) usually begins in young women within a few years following menarche and is not associated with any rheumatologic disease. In ~ 90% of young women with Raynaud phenomenon, the condition is primary (i.e., the disease) and without any significant sequelae. Raynaud disease can cause livedo reticularis.

Secondary Raynaud phenomenon is typically more severe and occurs in association with connective tissue diseases and with certain prescription and illegal drugs. It is present in most scleroderma patients, but also is seen frequently in RA, SLE, Sjögren's, mixed connective tissue disease (MCTD), primary biliary cirrhosis (PBC), and dermatomyositis. Common drugs that may exacerbate Raynaud's include:

- Serotonin agonists (e.g., triptans, beta-blockers, ergots)
- Chemotherapeutic agents (e.g., bleomycin, vinblastine, cisplatin)
- Sympathomimetics (e.g., decongestants, clonidine, cocaine, and methamphetamines)

Smoking decreases digital blood flow and must be avoided.

Raynaud phenomenon is defined and manifested as a sequential, tricolor change of the fingers and/or toes that occurs as a result of vasoconstriction with exposure to cold or emotional stress—even the stress of going to the doctor can elicit the response in some patients (Image 6-13). Fingers and/or toes blanch or turn white (as a result of vasoconstriction); when cyanosis due to decreased oxygenation occurs, the digits turn blue; finally, with vasodilation upon rewarming, the digits flush red (white → blue → red). A patient may still have Raynaud's even though they do not have the classic triphasic color changes; digits may turn white, then flush red without becoming blue. If rewarming and vasodilation do not occur, the digits can become necrotic. Paresthesias, pain, and clumsiness may be associated with the vasospastic episode. Fingertip ulcerations are an indicator of associated rheumatologic disease, because ulcerations rarely occur in primary Raynaud phenomenon.

Image 6-13: Raynaud syndrome

The following suggest secondary Raynaud phenomenon: male, age > 30, asymmetry of findings, fingertip ulcerations, and coexistent vascular or autoimmune disease.

An easy test to distinguish primary from secondary Raynaud's is nailfold capillaroscopy. Apply clear water-based lubricant over the nail beds and examine them with an ophthalmoscope. Abnormal, dilated, and tortuous capillaries at the nail bed are highly indicative of a microvascular abnormality seen in rheumatic diseases. Nailfold capillaroscopy is the diagnostic test of choice to confirm suspicion of secondary Raynaud phenomenon in an autoimmune disease! Treatment includes avoiding the cold and drugs that cause vasoconstriction. Smoking/tobacco use is contraindicated. Treatment includes: calcium channel blockers, alpha-blockers, sildenafil, and nitroglycerin transdermal. Localized digital sympathectomy should be limited to patients who have failed medical treatment and who continue to experience ischemia or are at risk of losing a digit. When stress triggers Raynaud's, relaxation techniques may be helpful.

Acrocyanosis may be confused with Raynaud's. It is distinguished by persistent blue/cyanotic fingertips/toes and the absence of pain. Thromboangiitis obliterans (TAO, a.k.a. Buerger disease) may also resemble Raynaud's. TAO is a vasculitis characterized by recurring progressive inflammation and thrombosis of small and medium arteries and veins of the hands and feet in association with tobacco use. Claudication and ischemia with digital necrosis are common. Smoking cessation is the mainstay of treatment.

MIXED CONNECTIVE TISSUE DISEASE

These patients have signs of several diseases, including SLE, polymyositis, and systemic sclerosis—but mixed together. Mixed connective tissue disease (MCTD) typically presents with arthritis/arthralgias and Raynaud phenomenon. The patient may present with a mild myositis and/or serositis, as well as "swollen hands." Interstitial lung disease may be the most severe complication. This disorder predominantly affects women (9:1).

Anti-U1-RNP is the autoantibody to remember: High titers are associated with MCTD, and it has a sensitivity approaching 100%, so a negative result essentially rules out MCTD. Although SLE may also have anti-U1-RNP, MCTD usually does not have antibodies against dsDNA, Smith, SSA (Ro), or SSB (La) and renal involvement is uncommon.

Only rarely do these patients get heart failure from myocarditis or severe pulmonary hypertension.

IgG4 RELATED DISEASES

These are typically seen in middle aged and older males. They are caused by infiltrative disease of IgG4-positive plasma cells with fibrosis. Presentation may include a localized mass, retroperitoneal fibrosis, autoimmune pancreatitis, sclerosing sialadenitis, and aortitis. Symptoms can mimic malignancies, infections, and autoimmune diseases.

Diagnose with elevated serum IgG4 level and biopsy of affected organs. Treat with prednisone and DMARDs (rituximab). There may be a risk for malignancy in these patients.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) can be primary and idiopathic, or it can be secondary and associated with another disease (usually SLE), drugs, or an infection. APS is characterized by the presence of 1 or more antiphospholipid antibodies along with the following findings of either vascular thrombosis or pregnancy morbidity:

- One or more of the antiphospholipid (AP) antibodies:
  - Lupus anticoagulant (LAC)
  - Anticardiolipin antibodies (IgG or IgM in medium/high titer)
  - Anti-$ß_2$-glycoprotein 1 antibodies (IgG or IgM at any titer)

Plus either of the following:

- Vascular thrombosis: venous (e.g., deep venous thrombosis and/or pulmonary embolism) and/or arterial clots (e.g., stroke, myocardial infarction)
- Pregnancy morbidity presenting as:
  - Miscarriage of a normal fetus at ≥ 10-weeks gestation
  - Birth of 1 or more premature babies at < 34-weeks gestation because of eclampsia/preeclampsia/placental insufficiency
  - Multiple miscarriages (≥ 3) at < 10-weeks gestation

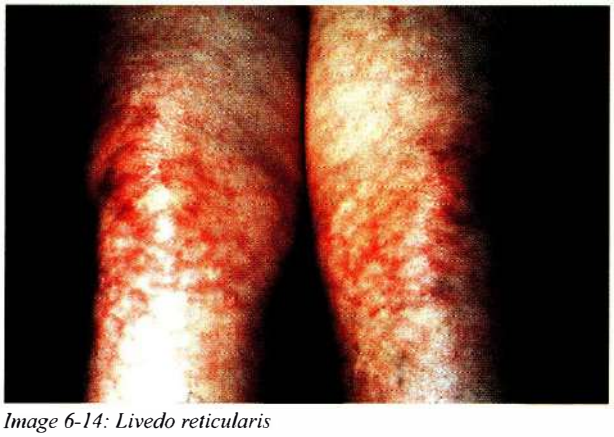

Image 6-14: Livedo reticularis

Because other conditions can be transiently associated with AP antibodies, but not the syndrome, the antibodies must be present on 2 separate occasions at least 12 weeks apart for diagnosis of APS.

While not included as criteria for diagnosis, other findings seen with APS include:

- Livedo reticularis (Image 6-14)
- Sterile cardiac vegetations (Libman-Sacks endocarditis)
- Thrombocytopenia
- Prolongation of the partial thromboplastin time (PTT) caused by LAC. (Mixing studies are done on plasma to differentiate factor deficiency from factor inhibitor. In a mixing study, the patient's plasma is mixed 50:50 with normal plasma. If the patient's prolonged PTT is due to factor deficiency, the mixing with normal plasma will provide the missing factor and correct the problem. If the PTT initially corrects and then again prolongs after the mixing study, then the coagulopathy is most likely secondary to a clotting factor inhibitor.)

Patients with APS are physiologically hypercoagulable, despite appearing to be "anticoagulated" (elevated PTT) from a laboratory standpoint!

LAC and anticardiolipin IgG antibodies tend to be the most pathogenic. Patients with elevated levels of these APL antibodies, but without clots and/or fetal wastage syndrome, are treated prophylactically with ASA 81 mg daily.

Catastrophic APS is a rare variant that carries a 50% mortality and manifests as multiorgan dysfunction secondary to numerous thromboses. Treatment includes anticoagulation, glucocorticoids, and plasma exchange.

Acute treatment of APS: Acute clots are treated with anticoagulation, usually low-molecular-weight heparin (LMWH).

Chronic treatment of APS: Treat the underlying disease if APS is secondary. Anticoagulation is usually given. Lifelong anticoagulation is used to treat primary disease. Warfarin is given to maintain the INR 2.0–3.0. The addition of hydroxychloroquine has been shown to be beneficial as well; the drug has antithrombotic effects.

Patients with a history of pregnancy-related morbidity should receive prophylaxis for subsequent pregnancies with LMWH and ASA 81 mg. Warfarin should not be given because it is teratogenic.

SJÖGREN SYNDROME

Sjögren syndrome is caused by a CD4+ T-cell lymphocytic infiltrate that destroys the exocrine glands (lacrimal and salivary glands), resulting in decreased secretions from these glands.

QuickQuiz

- What are the features of antiphospholipid syndrome?
- Sjögren patients are at increased risk for developing what other disease?
- Which autoantibodies are associated with diffuse SSc? What complication are the antibodies associated with?
- What are the key features of limited SSc?

Primary Sjögren disease (not associated with a concurrent rheumatologic disease) occurs commonly in middle-aged women (F:M, 9:1) who present with sicca complex (dry eyes and dry mouth) along with parotitis and adenopathy. Some patients have subacute cutaneous lupus erythematosus ([SCLE]; see SLE: Skin and Mucous Membranes on page 6-14), purpura, and interstitial nephritis (with Type 1 [distal] RTA). These patient findings resemble SLE clinically, but not serologically. 70% are RF+, and 20% are ANA–. 65% are SSA (Ro)+, and 50% are SSB (La)+. Note: SSA antigen may be present without SSB; however, it is rare to find SSB antigen alone without also having SSA.

Secondary Sjögren syndrome can occur with any of the connective tissue diseases (RA, SLE, polymyositis, and systemic sclerosis) and can be associated with the same autoantibodies. There is an association with DR3 (as seen in SLE and occasionally in polymyositis).

There is up to a > 40-fold increased risk of B-cell lymphoma with Sjögren syndrome! Follow patients for persistent lymphadenopathy. Close attention to dental care is paramount because these patients are at high risk for dental caries and extractions due to the sicca symptoms: xerostomia (dry mouth), xerophthalmia (dry eyes). Also, remember that children born to mothers with anti-Ro and anti-La antibodies (especially anti-Ro) are at risk for congenital heart block and neonatal lupus (can present as a SCLE rash in a newborn).

To diagnose Sjögren's: Assess history for xerostomia and xerophthalmia; check for autoantibodies; and perform a biopsy of minor salivary glands to confirm the diagnosis. Xerophthalmia is diagnosed with a positive Schirmer test: < 5 mm of wetting in 5 minutes (normal result is ~ 15 mm).

Treatment of Sjögren syndrome is symptomatic: wetting agents, pilocarpine tablets, and punctal plugs for the eyes. Corticosteroids and other immunosuppressants do not improve the sicca symptoms in patients with Sjögren's, so use is reserved for patients who have extraglandular disease; e.g., peripheral neuropathy or lupus-like features. Antimalarial agents can help with arthralgias, fatigue, and rashes. Parasympathomimetic and muscarinic agonists (pilocarpine and cevimeline) may be helpful for xerostomia symptoms, but have limited efficacy for xerophthalmia.

SYSTEMIC SCLEROSIS / SCLERODERMA

OVERVIEW

Systemic sclerosis was formerly known as scleroderma. Scleroderma is the term used to describe shiny, hard, thickened skin. Morphea is when sclerosis is isolated or localized to a small cutaneous area, but when the sclerosis is widespread with the potential for involving internal organs, it is called "systemic sclerosis" (SSc). We will focus on SSc.

SSc can be diffuse or limited in its expression depending on the extent of skin involvement. The general rule of thumb: If skin is involved above the elbow and the knee (approaching or involving the torso), diffuse SSc is present; if skin involvement starts at the fingertips and extends up to the elbow or from the toes to the knee), then limited SSc is present. The face can be involved in both diffuse and limited SSc.

ANA is positive in ≥ 95% of those with SSc.

TYPES OF SYSTEMIC SCLEROSIS

Diffuse SSc (~ 20%)

Diffuse SSc (dcSSc) causes diffuse skin thickening and is more likely than limited SSc to have multiorgan involvement. 30% of patients with dcSSc have anti-Scl-70 (antitopoisomerase I) antibody-positive. The antibody is associated with development of interstitial lung disease and reduced survival. The other antibody associated with dcSSc is anti-RNA polymerase III. It is associated with a much higher risk of scleroderma renal crisis, but a lower risk of interstitial lung disease when compared to those with anti-Scl-70 antibodies. Diffuse SSc has a wide range of presentations based on what organs are affected. Scleroderma renal crisis (SRC) is a medical emergency and almost exclusively occurs in dcSSc.

Limited SSc (~ 80%)

Limited SSc (lcSSc) causes skin thickening distal to the elbows and knees and can affect the face and neck. It affects the internal organs to varying degrees. Limited SSc may also be referred to as CREST syndrome. Its key features are well described by the acronym **CREST** so you can still use it as a mnemonic:

- **C**alcinosis (Image 6-15)
- **R**aynaud phenomenon (secondary; see page 6-33)
- **E**sophageal dysmotility
- **S**clerodactyly
- **T**elangiectasias (mucosal; Image 6-16)

Not all features of CREST need to be present. Anti-centromere antibody (ACA) is specific for lcSSc and is seen in about 50% of patients. Pulmonary hypertension can occur in limited scleroderma (10%), while interstitial lung disease usually does not (good candidate for an exam question). Patients who are ACA+ tend to develop more severe digital ischemia and pulmonary hypertension.

Systemic Sclerosis Sine Scleroderma

This form of systemic sclerosis affects about 1% of patients. It is characterized by visceral disease without skin involvement.

MANIFESTATIONS OF SSc

SSc: Skin

Skin changes follow a progression of mucinous edema, then induration, and finally fibrosis and atrophy.

Limited SSc typically involves the distal extremities and face.

Raynaud's eventually occurs in almost all patients with both limited and diffuse types of SSc, and severe vasoconstriction can be associated with digital tip ulcerations, osteomyelitis, and black fingertips. Acroosteolysis subsequently develops. In lcSSc, Raynaud's usually occurs first—several years before other manifestations, but in dcSSc, Raynaud's commonly occurs at the time of other manifestations. See page 6-33 for a more extensive discussion on Raynaud's.

Telangiectasias (the T in CREST) occur in dcSSc but are much more likely in lcSSc (Image 6-16).

Diffuse SSc skin changes characteristically involve entire extremities, chest, abdomen, and face.

Sclerodactyly is the term used to describe localized scleroderma of the fingers or toes (either type).

Abnormal nailfold capillaries may occur in either type of SSc. These capillaries are reduced in number, while the remaining enlarged capillaries form visible giant loops. These are important because there is a direct correlation between degree of abnormality of the nailfold capillaries and severity of the SSc. Remember, the nailfold capillaroscopy can be used in this setting to detect abnormal microvasculature in these patients.

SSc: Joints

Patients with SSc can have a mild, symmetric (like RA and SLE) hand stiffness +/– synovitis, but it rarely involves the hand joints (unlike RA and SLE). Patients with dcSSc can have a tendon friction rub, such as at the elbow, which is considered pathognomonic for SSc.

SSc: Muscles

Patients have mild muscle pain and weakness along with mild CPK elevations. Occasionally, there are features similar to polymyositis ("overlap syndrome")—or, the mild CPK elevation may be due to muscle atrophy from disuse, secondary to skin tightness.

SSc: Lungs

Lung disease is the main cause of morbidity and mortality in SSc. Cause of lung death in SSc is often pulmonary hypertension from 1 of 2 causes:

1) Pulmonary arterial hypertension: intimal proliferation without interstitial or alveolar inflammation (especially in anti-centromere+, lcSSc)
2) Interstitial fibrosis secondary to alveolitis and pulmonary fibrosis

Order pulmonary function tests (PFTs) with spirometry regularly (every 6–12 months) to monitor for pulmonary involvement. A decreased DLCO may be the 1st sign of pulmonary hypertension.

Cyclophosphamide may be used for interstitial lung disease with active alveolitis. Pulmonary hypertension is often treated with drugs that cause vasodilation of the pulmonary vasculature such as prostaglandins, bosentan, sildenafil, and/or inhaled iloprost.

Lung transplant is occasionally a viable option for scleroderma patients with lung disease.

Patients are at increased risk for lung cancers, especially if they smoke.

Image 6-15: Calcinosis of the fingertips

Image 6-16: Telangiectasia

Quick Quiz

- Abnormal nailfold capillaries are more commonly seen in which autoimmune disease?
- What lung manifestation is often the cause of death in patients with diffuse SSc? With limited SSc?

SSc: Kidney

Diffuse SSc only: Before ACE inhibitors, scleroderma renal crisis was the major cause of morbidity and mortality. Renal crisis presents within the first 5 years of diffuse disease and is associated with prior or current glucocorticoid use and anti-RNA polymerase III antibodies. Patients develop acute malignant hypertension and renal failure with an active urine sediment. Always consider the diagnosis of dcSSc in a young female who presents with acute malignant hypertension and renal failure. Patients may even present with thrombocytopenia and microangiopathic hemolytic anemia (MAHA), which mimics thrombotic thrombocytopenic purpura (TTP).

ACE inhibitors are started early and are useful even if overt renal failure develops—because renal failure may be reversed with their use.

SSc: GI

Diffuse SSc only: Wide-mouthed diverticula are pathognomonic of dcSSc, but not lcSSc.

Limited SSc only: associated with primary biliary cirrhosis (PBC) and positive anti-mitochondrial antibody.

Both dcSSc and lcSSc: Dysmotility throughout the GI tract, but especially the esophagus (the E in CREST) and the stomach (gastroparesis) are problematic for patients with lcSSc or dcSSc. Also, as the disease progresses, the lower esophageal sphincter relaxes, so patients develop severe GERD with a propensity for chronic esophagitis, strictures, and Barrett disease. Proton pump inhibitors are used in symptomatic patients. Prokinetic agents, like erythromycin, may also be helpful.

Mucosal telangiectasias may be present throughout the GI tract. Telangiectasias in the stomach can lead to bleeding and iron-deficiency anemia. This syndrome is called gastric antral vascular ectasia (GAVE) or "watermelon stomach" because of its endoscopic appearance.

Dysphagia, constipation, intestinal pseudoobstruction, and malabsorption are also seen in both dcSSc and lcSSc.

SSc: Heart

Cardiac involvement is common in SSc, and symptomatic disease portends a poor prognosis. Heart findings include cor pulmonale, restrictive pericardial disease, and conduction defects/arrhythmias. The majority of patients have reperfusion defects on thallium stress tests, but true coronary artery disease is frequently absent. The abnormal stress result is presumed to be due to episodic vasospasm. Diastolic dysfunction is common.

TREATMENT

Treatment is generally symptomatic and organ-specific, as reviewed above. No medicines change the course of scleroderma.

Localized skin disease can be treated with ultraviolet light therapy.

For patients with systemic sclerosis, cyclophosphamide is now being used in patients with diffuse disease and early pulmonary involvement.

Patients suspected of pulmonary hypertension should be evaluated with an echocardiogram. Have a low threshold to evaluate the patient for ILD with a high resolution CT scan and/or PFTs, especially in those with antitopoisomerase I (anti-Scl-70) antibody positivity. Steroids and an immunosuppressant usually are given to treat alveolitis. Bosentan, sildenafil, or the prostacyclin analogs (e.g., epoprostenol) are options for pulmonary hypertension. Some patients require a lung transplantation.

Patients with diffuse disease should monitor their blood pressure monthly. Every 3 months, check the urine protein:creatinine ratio and estimate the glomerular filtration rate (GFR). Proteinuria and a > 20% reduction in GFR predicts renal crisis. Prescription for an ACEI or ARB should be given as soon as the blood pressure changes so as to prevent renal crisis. Also, remember that corticosteroids have little to no efficacy in SSc and are associated with the development of renal crisis, so they should be avoided in most circumstances (except alveolitis).

Limited SSc has a better prognosis than diffuse. But remember that these patients can get pulmonary hypertension (especially those anti-centromere Ab+), and severely elevated pulmonary arterial pressures are associated with increased mortality.

Diffuse SSc usually progresses within the first 5 years, after which no new organ systems are affected (although the organ systems that were initially affected continue to deteriorate). After this first explosion of disease, the skin usually begins to atrophy and loosen up, except for the hands. Know that the extent of skin disease in dcSSc is a marker for the severity of visceral disease. If renal crisis is going to happen, it typically occurs within the first 5 years of disease. Blood pressure elevations signal impeding renal disease and eventual renal crisis if not controlled.

EOSINOPHILIC FASCIITIS

Eosinophilic fasciitis (EF) causes both scleroderma-like and nonscleroderma-like skin changes in the extremities—often sparing the hands (typically without Raynaud's, and without SSc-associated antibodies, including ANA). EF can follow unaccustomed rigorous exercise or be paraneoplastic (e.g., lymphoma, myeloma).

Tender, migrating edema of the extremities or a polyarthritis of the hands may be present in some patients.

So, 3 useful clues to help you distinguish this SSc mimic from SSc are:

1) Negative ANA
2) Absence of Raynaud phenomenon
3) Symptoms with preceding vigorous exercise

Nailfold capillaries are normal, and systemic symptoms are unusual. The nonscleroderma-like skin changes include peau d'orange-type induration (a late feature due to thickening and tethering of the fascial layers), which often occurs on the proximal forearms and upper legs but not the distal extremities. The affected areas have a characteristic "woody" consistency on palpation.

Also unlike SSc, most patients have a peripheral eosinophilia, which appears early in the disease course, and an increased sedimentation rate. A full-thickness excisional skin biopsy shows an eosinophilic infiltrate and fibrosis of the subcutaneous fascia.

Eosinophilic fasciitis is occasionally self-limited, but most patients require moderate-dose corticosteroids (40 mg/day) or steroid-sparing agents (MTX).

INFLAMMATORY MYOPATHIES

POLYMYOSITIS AND DERMATOMYOSITIS

Overview

Inflammatory diseases of skeletal muscle include dermatomyositis and polymyositis (about equal occurrence), as well as some less-common disorders, such as inclusion body myositis. In 1975, Bohan and Peter divided myositis into the following classification, which is commonly used today:

1) Polymyositis ([PM]; adult)
2) Dermatomyositis ([DM]; adult)
3) Myositis associated with malignancy
4) Childhood polymyositis or dermatomyositis
5) Myositis associated with connective tissue disease (SLE, SSc, MCTD)

Polymyositis

Features of polymyositis (PM) may be found in patients with other autoimmune disorders, such as SLE and MCTD. It is occasionally associated with the MHC Class II HLA antigen DR3.

PM manifests as symmetric proximal muscle weakness and, in some patients, mild myalgias. PM (and dermatomyositis) typically does not cause neuropathy, only myopathy. Weakness usually occurs first in the proximal muscles (hips and thighs > shoulders and arms) and mimics muscular dystrophy. These patients may present with difficulty rising from a squatting or kneeling position. Remember: Myositis generally presents with weakness, not pain! This is an important feature in distinguishing myositis from polymyalgia rheumatica, which presents primarily as muscle pain and not a myopathy. Further, CK is high in myositis, while in PMR the ESR and CRP is high but CK is normal. Know how to distinguish between these two entities! Also know how to distinguish both of these diseases from fibromyalgia.

As PM progresses, dysphagia (from tongue, pharynx, and upper esophageal dysfunction), dysphonia, dyspnea (from diaphragm weakness), and cardiac/ECG changes (from myocarditis or CAD) can occur, which may require hospitalization and aggressive immunosuppressive therapy.

Dermatomyositis

Dermatomyositis (DM) is similar to PM in terms of weakness, but skin involvement also occurs. In some patients, the skin manifestations may be quite severe—or even the sole area of involvement (amyopathic dermatomyositis).

Skin changes in DM: consist of a moderate-to-deep, purple-red, papular, sometimes scaly, photosensitive rash that occurs on the face, neck ("V sign" or "shawl sign"), and extensor surfaces of the joints. There is an associated periorbital edema with a heliotrope rash (Image 6-17). This rash is violaceous and classically appears on the upper eyelids, but it also may appear on the cheeks and forehead. (SLE's butterfly rash does not involve the eyelids.) Gottron papules are flat-surfaced, reddish-to-violet, scaling papules on the knuckles (these actually look more like "cigarette-paper" crinkling of the skin over the MCPs), and these are the most specific indication of DM (Image 6-18). Vasculitic lesions can also develop, more commonly on the extremities. A psoriatic-like rash can appear on the scalp. The scalp

Image 6-17: Heliotrope rash

Quick Quiz

- Compare and contrast polymyositis and dermatomyositis.
- Which autoantibodies are associated with poly- and dermatomyositis?

will be very itchy—this is one of the main complaints of patients! Changes in nail bed capillaries, as discussed under Raynaud's, can be seen in DM (also seen with scleroderma and SLE).

Antisynthetase Syndrome

Antisynthetase syndrome is a specific presentation of PM or DM that is characterized by very acute onset of disease, fevers, and weight loss, Raynaud phenomenon, cracking and discoloration of the hands (termed "mechanic's hands"), polyarticular and nonerosive arthritis, and a predilection for interstitial lung disease. Anti-Jo-1 antibodies (a type of antisynthetase antibody) are often found with this presentation. Interstitial lung disease often is more significant than the myositis. The disease is typically refractory to treatment.

Another myositis specific autoantibody is the anti-SRP (signal recognition particle) antibody. These patients have PM and often develop cardiomyopathy. Prognosis is poor.

Diagnosis of PM and DM

PM and DM peak between 30 and 50 years of age. The following findings help establish the diagnosis of PM and DM:

- In 95% of patients, increased CPK with numbers in the thousands (not hundreds); you also may see an increase in other muscle enzymes, such as aldolase, LDH, AST, and ALT.
- Abnormal, myopathic electromyogram (EMG) (increased fibrillations, decreased amplitude, and spontaneous repetitive activity) with early recruitment.
- Abnormal muscle biopsy (gold standard); increase the yield on biopsy by targeting an involved muscle, or by using MRI to select an optimal site. Avoid biopsy of sites recently studied by EMG; instead use the contralateral side.
- Skin biopsy in DM: Biopsy of the Gottron papules or erythroderma associated with the shawl sign; may make diagnosis and avoid need for muscle biopsy. Light microscopy and immunofluorescence show abnormalities at dermal-epidermal junction.
- ANA are present in about 60% of patients. The presence of other autoantibodies (anti-Ro, -La, -Sm, -RNP) suggest that the diagnosis is not PM or DM, but another connective tissue disorder (e.g., SSc, SLE, MCTD, or overlap syndrome). Know other myositis specific antibodies because they are associated with characteristic phenotypes.
- Anti-Jo-1: strongly associated with ILD and the "antisynthetase" syndrome described above.
- Anti-Mi-2: classic DM with V sign and shawl sign. Mild weakness and very good response to therapy.
- Anti-SRP (signal recognition protein): very acute severe PM and cardiac involvement; poor response to immunosuppression.
- Anti-p155/p140: strongly associated with cancer-associated DM.

Cancer in PM and DM

Cancer is present in adults in 7–10% of PM and 15–20% of DM patients at the time of, or soon after, diagnosis of the muscle disease. There is no increased cancer risk in juvenile dermatomyositis. The risk increases with age, up to ~ 30–40% in patients > 65 years of age. The patient with cancer is usually older than 50 years and has dermatomyositis more often than polymyositis. Remember that cancer is most strongly associated with DM, especially in those who are positive for anti-p155/p140, where the risk of cancer approaches 70%. Every patient who is newly diagnosed with either PM or DM must be evaluated for underlying malignancy with age-appropriate cancer screening, unless something in the H&P suggests a specific cancer or a location to image. Risk for cancer is highest within the first 5 years of diagnosis. Current data do not support routine total body PET/CT as a screen for cancer in newly diagnosed PM/DM. The most common associated malignancies are ovarian, lung, pancreatic, colon, and lymphoma.

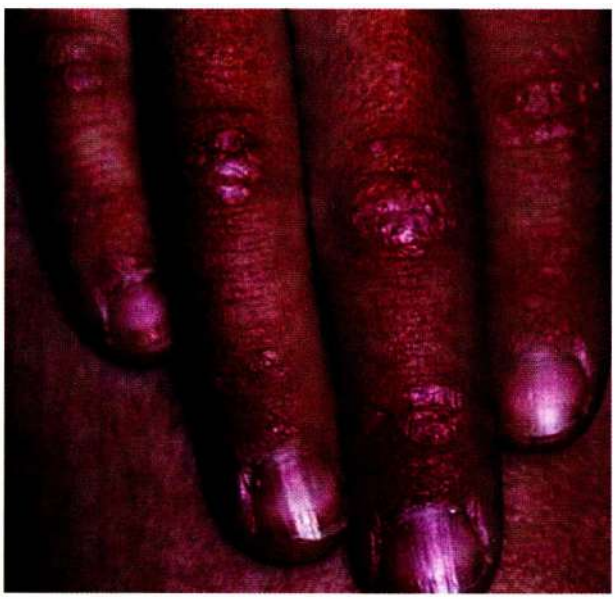

Image 6-18: Gottron papules

Treatment of PM and DM

Polymyositis and dermatomyositis are typically treated with a high-dose prednisone that is slowly tapered while a steroid sparing agent is added (e.g., azathioprine or methotrexate). 80% begin to respond to the steroid within a few days to 6 weeks.

Patients with life-threatening manifestations usually receive intravenous pulse glucocorticoids.

Antimalarials, such as hydroxychloroquine, are helpful for the rash in dermatomyositis. IV immunoglobulin (IVIG) may be effective in patients who do not respond to the other medications. Recent trials with rituximab for the treatment of myositis have been disappointing.

Every adult patient should have cancer screening performed; if there is a poor response to treatment, reassess for cancer!

Important points on steroid use:

- Remember to prescribe vitamin D, calcium, and bisphosphonate therapy for those on chronic glucocorticoids (all patients, not just those with PM/DM).
- Think about superimposed steroid myopathy in a patient with PM/DM who initially improves with glucocorticoids but then develops progressive weakness despite improvement in CPK levels. Treatment is to taper glucocorticoids gradually to avoid a flare in the disease.

INCLUSION BODY MYOSITIS

Inclusion body myositis (IBM) is the most common inflammatory myopathy in persons > 50 years of age, and it occurs more commonly in Caucasian men.

IBM is a more indolent disorder characterized by prominent asymmetric distal weakness (buzz words = weak handshake), although proximal weakness is common, especially affecting the quadriceps. Dysphagia is often a prominent symptom and can lead to aspiration pneumonia.

History should focus on possible drug exposures (e.g., antimalarials, glucocorticoids, colchicine, statins, cocaine) and alcohol use.

No lab studies are helpful except for muscle biopsy! CPK may be only mildly elevated. Markers of inflammation are absent, and no autoantibodies are developed.

Diagnosis is made by a suggestive history in combination with a muscle biopsy showing vacuoles and filamentous inclusions.

Take patients off the precipitating drugs and give a trial of steroids. Unlike PM/DM, inclusion body myositis is only minimally responsive to treatment.

COLCHICINE MYOPATHY / NEUROPATHY

Colchicine myopathy/neuropathy mimics polymyositis with proximal muscle weakness, paraesthesias, and elevated CPK. Suspect this in the gout patient with renal insufficiency who is taking long-term colchicine. But remember, PM and DM cause myopathy, not neuropathy.

DRUG-INDUCED MYOPATHY

Lipid-lowering drugs and chronic corticosteroids are the most common drugs that cause myopathy. Illicit drugs such as ethanol, cocaine, and heroin are also causes.

Statins, especially when combined with gemfibrozil, a fibrate, are a known cause of drug-induced myopathy. Patients may present with myalgias and normal CPK levels; severe muscle pain and rhabdomyolysis also can occur. Depending on severity, patients may have weakness of the proximal muscles as well. If the myopathy is severe (weakness, CPK elevations > 3x normal, or myoglobinuria), stop the drugs. Usually, the patients improve when the drug is stopped.

Glucocorticoid myopathy typically presents in one of two ways:

1) Chronic myopathy:
   - Chronic use of prednisone ≥ 30 mg/day
   - Proximal muscle weakness
   - Normal CPK and EMG
2) Acute quadriplegic myopathy:
   - High-dose IV steroids
   - Severe generalized weakness
   - Elevated CPK +/– myoglobinuria; abnormal EMG
   - Most commonly associated with concurrent use of neuromuscular blocking agents in critically ill patients

Consider the acute form as a possible cause of diaphragm weakness in patients who are difficult to wean from the ventilator. Glucocorticoid myopathy is an exclusionary diagnosis; patients improve when you stop the drugs and start physical rehab.

NONARTICULAR RHEUMATISM

FIBROMYALGIA

Fibromyalgia (FM) is a hypersensitivity syndrome characterized by hyperalgesia. This noninflammatory disorder has been associated with neurochemical imbalances that result in increased sensitivity and heightened response to painful stimuli. More women are affected than men, estimated female:male ratio is 10:1. Patients often complain of diffuse myalgias, all-day stiffness, excessive fatigue, and nonrestorative sleep.

The previous American College of Rheumatology (ACR) criteria relied heavily on finding "tender points"

QuickQuiz

- Which drugs cause myopathy?
- Which drugs are used to treat fibromyalgia?

on exam. In 2010, the ACR released new criteria for fibromyalgia based on a quantitative measure of widespread pain (in lieu of a tender point exam) using:

1) the widespread pain index (WPI: 0–19), and
2) the symptom severity (SS) scale (0–12), which is composed of 4 variables: degree of fatigue, waking unrefreshed, cognitive impairment, and general somatic symptoms.

Significant impairment, consistent with a diagnosis of FM, is defined as:

- WPI > 7 and SS > 5, or
- WPI 3–6 and SS > 9.

Symptoms must be present at a similar level for ≥ 3 months, with pain above and below the waist; all other causes of similar symptoms must be excluded first. Understand that other entities (e.g., obstructive sleep apnea, hypothyroidism) can cause symptomatology similar to fibromyalgia and that fibromyalgia can coexist with other diseases.

Consider the following labs to evaluate for other disorders: ESR, TSH, CPK, CBC, and liver transaminases. A sleep study may be needed to reveal sleep apnea or another cause of excessive daytime somnolence.

Patients with fibromyalgia often have associated disorders including: depression/anxiety, stress, history of emotional and/or physical trauma (e.g., sexual abuse), migraines, unexplained paresthesias (unsupported by EMG), and self-reported yet undetectable Raynaud phenomenon. "Symptomatic" mitral valve prolapse, irritable bowel syndrome, interstitial cystitis, and "chronic fatigue syndrome" diagnoses tend to be comorbid conditions. Remember, fibromyalgia can coexist with autoimmune disorders such as SLE and RA. So, if an RA patient is not getting better despite aggressive immunosuppression and without clinical evidence for inflammation on exam or labs, consider fibromyalgia as the cause of their pain.

Nonpharmacologic therapy is the foundation of FM treatment. Physicians need to set realistic expectations with patients and reassure them that this is not a dangerous condition, while at the same time acknowledging that their pain/symptoms are real. Stress reduction, cognitive behavioral therapy, and behavioral feedback have been shown to help reduce symptoms. Regular exercise and sleep restoration are essential components of treatment.

Pharmacologic interventions include: antidepressants or combination of antidepressants (low-dose tricyclics +/– SSRIs or reuptake inhibitors), antiepileptics, and/or nonnarcotic analgesics). Steroids and NSAIDs are useful only for coexisting inflammatory conditions. Opioids should be avoided because they have limited efficacy and significant risks.

Tramadol has been shown to be effective, possibly because the drug has an SSRI-like effect. In general, do not prescribe narcotics for FM patients.

Tricyclic antidepressants (TCAs) increase the duration of stage 4 sleep, which has been found to be decreased in these patients. Cyclobenzaprine has a chemical structure similar to TCAs and is also commonly used. In studies, deprivation of stage 4 sleep causes many otherwise healthy people to get the symptoms of fibromyalgia! Whether there is a causal connection is uncertain. **Duloxetine** and **milnacipran** are FDA-approved "dual reuptake inhibitors" that block reuptake of both serotonin and norepinephrine. Adding an SSRI or a reuptake inhibitor to a tricyclic is sometimes used in patients who complain of fatigue or exhaustion coupled with mood disturbances. Be aware that this combination increases the risk of serotonin syndrome. Note that combining tramadol with an SSRI increases the risk for serotonin syndrome.

Pregabalin (antiepileptic) is the 1st medication FDA-approved specifically for fibromyalgia, but gabapentin, which is less expensive, is a frequently used and effective off-label treatment. Both alleviate the pain.

There may be an increased incidence of suicidal thoughts in patients taking pregabalin, duloxetine, or milnacipran.

MYOFASCIAL PAIN SYNDROME

Myofascial pain syndrome, also known as "regional fibromyalgia," can manifest as localized myalgias or muscle spasms; patients can have localized tender points in the muscles. The condition is considered different from fibromyalgia in that myofascial pain syndrome is thought to originate from the injured muscle, whereas comparable fibromyalgia pain is thought to originate from an aberration in the CNS processing of pain. Whiplash and repetitive microtrauma have been associated with myofascial pain syndrome.

Massage, physical therapy, muscle relaxants, NSAIDs, and local injection of anesthetic into the tender points may be helpful.

COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS), previously known as reflex sympathetic dystrophy (RSD), is a form of chronic pain that usually affects a distal extremity (upper > lower).

CRPS is divided into 2 types, both with similar signs and symptoms:

- **CRPS 1**: Previously called reflex sympathetic dystrophy; this type accounts for 90% of the cases and occurs after an illness or trauma in which the nerves in the affected extremity were not directly damaged. Fracture is the most common trigger in type 1.
- **CRPS 2**: Ensues after a direct injury to the nerve.

In addition to pain, patients typically have sensory, motor, or autonomic dysfunction manifested by pain, hyperalgesia, edema, temperature asymmetry, muscle atrophy, decreased ROM, or weakness. The dysfunction often appears to be disproportionate to the inciting event. In severe cases, flexion contractures may develop. Profound osteopenia may be seen on x-ray imaging. The diagnosis is clinical, but 3-phase bone scans may be helpful in diagnosing CRPS (sensitivity is 40–60%). The most specific findings on bone scan include diffuse increased activity with juxtaarticular uptake on the delayed (phase 3) images. Although there have been limited studies evaluating the role of MRI in diagnosing CRPS, MRI is often used to exclude other etiologies of localized pain. MRI has less sensitivity compared to triphasic bone scans.

Treatment of CRPS consists of NSAIDs; pain modifiers, such as tricyclic antidepressants or gabapentin; physical therapy; short course of glucocorticoids; and sympathetic nerve block as needed. Early, aggressive therapy can prevent the chronic changes described above.

OTHER CAUSES OF NONARTICULAR RHEUMATISM

Other causes of myalgia: Alcohol is the most common myotoxin and can cause acute rhabdomyolysis with very elevated CPK-MM. Hypothyroidism frequently presents with myalgias and stiffness and commonly has an elevated CPK-MM. Statins are also a relatively common cause of muscle pain.

VASCULITIS

OVERVIEW

Vasculitis is the inflammation of blood vessel walls that can lead to narrowing, obstruction, ischemia, or aneurysm formation. The clinical presentation is protean and varies according to the histologic type of inflammation, the size of the blood vessels involved, and the organs affected. Vasculitis is typically classified by the size of blood vessel affected and the presence (or absence) of antineutrophil cytoplasmic antibodies (ANCAs). The most common ANCA-associated vasculitides (AAV) are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (a.k.a. eosinophilic granulomatosis with polyangiitis [EGPA] or allergic granulomatosis).

Vasculitis is most often the result of an immune reaction caused by either immune complex deposition or complement activation. It can affect small, medium, or large vessels. Often, vasculitis is hard to diagnose because symptoms may be systemic and nonspecific.

Frequently, presenting signs/symptoms include myalgias/arthralgias, neuropathy, fever, malaise, and weight loss. Consider vasculitis in a patient with palpable purpura or mononeuritis multiplex!

Because of the wide spectrum of symptoms, suspect vasculitis in patients with fever of unknown origin (FUO), especially in those with constitutional symptoms such as weight loss and fatigue. Also consider vasculitis in the differential diagnosis when there is no satisfactory explanation for the following conditions: myositis, arthritis, palpable purpura (e.g., rash that does not blanch), mononeuritis multiplex manifested as foot drop, multisystem disease, glomerulonephritis, GI, cardiac, or CNS disease.

Again, constitutional symptoms are big in vasculitis. (Rheumatoid arthritis eats at the joints and nips at the body; vasculitis nips at the joints and eats at the body.)

Typical lab findings include an increased ESR/CRP, thrombocytosis (the platelet count is a "poor man's sedimentation rate"), anemia of chronic disease, and hypoalbuminemia. Not all vasculitides present with elevated ESR or CRP; e.g., primary CNS angiitis may have normal ESR and CRP!

Diagnosis of vasculitis is confirmed with biopsies or angiograms. Skin biopsies may not be specific enough, although polyarteritis nodosa can be diagnosed by skin biopsy in some cases. Muscle and nerve biopsies are very specific, but not very sensitive—although sensitivity increases with an increase in symptoms and with electromyogram (EMG) findings. Do a testicular biopsy if the patient has testicular pain and/or swelling—sensitivity and specificity are good. Kidney biopsies (in a patient with systemic vasculitis symptoms) showing a necrotizing glomerulonephritis with crescent formation is virtually diagnostic for vasculitis (but may be seen in several different vasculitic syndromes). Remember: Biopsy the most involved tissue whenever possible.

LARGE VESSEL VASCULITIS

Overview

Large vessel vasculitis includes:

1) Giant cell arteritis (remember, polymyalgia rheumatica may coexist)
2) Takayasu arteritis
3) Aortitis

Quick Quiz

- What are the typical lab findings in a patient with vasculitis?
- What is a typical presentation of GCA? What are the atypical presentations?
- How do you diagnose GCA? What is a serious complication of GCA within the first 5 years of diagnosis?

Giant Cell (Temporal) Arteritis

Giant cell arteritis (GCA), also called temporal arteritis, is part of a spectrum of systemic inflammatory diseases associated with polymyalgia rheumatica (PMR).

GCA primarily affects the carotid arteries and their branches (ophthalmic and temporal) in patients > 50 years of age (average age = 70 years). Female: male ratio is 3:1. The disease is most commonly seen in Caucasian Northern Europeans and is rare in African-Americans.

Multinucleated giant cells infiltrate blood vessels arising from the aortic arch in a patchy or segmental fashion. Symptoms include temporal headache, diplopia, amaurosis fugax, scalp tenderness, and jaw claudication. Jaw claudication is a very specific symptom! Untreated, 40–50% get ischemic optic neuropathy with unilateral irreversible blindness (increased risk in the setting of thrombocytosis; the risk may decrease by adding ASA).

GCA occasionally has a masked presentation; consider it in workups for FUO, failure to thrive, and/or anemia of chronic disease.

It also can present similarly to Takayasu's, with symptoms of large-vessel vasculitis and peripheral claudication. Extracranial involvement in patients with GCA increases the risk of thoracic aortitis.

Erythrocyte sedimentation rate (ESR) is virtually always > 60 mm/hr in GCA; and in patients whose ESR is not elevated, C-reactive protein (CRP) may be elevated. While extremely rare, GCA can occur even in the setting of a normal ESR and CRP.

Confirm diagnosis by a temporal artery biopsy (Image 6-19). Ultrasonography of the temporal arteries has been studied as a means of diagnosing GCA. However, the accuracy of the test is dependent on the skills of the technician and the interpreter. Glucocorticoid therapy is started as soon as the diagnosis is suspected.

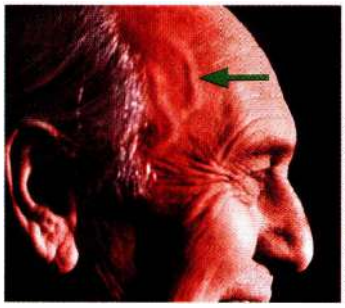

Image 6-19: Inflamed temporal artery

Don't wait for the biopsy! If you suspect GCA, treat right away to decrease the risk of vision loss. While the biopsy should be performed as early as possible, studies show that even a delay of 1–2 weeks doesn't significantly impact biopsy results. Biopsy a large piece of artery (3–5 cm) and do multiple cross-sectional cuts. Even so, because of the patchy involvement, a negative biopsy does not exclude GCA. Bilateral temporal artery biopsies may improve sensitivity by about 5% compared to a unilateral biopsy, but they are somewhat controversial.

If a patient with suspected GCA develops vision loss—a medical emergency—treat the patient with high-dose IV methylprednisolone 1,000 mg/day for 3–5 days before switching to oral glucocorticoids. Otherwise, initial treatment for GCA is prednisone at ~ 60 mg/day. Once symptoms resolve, slowly taper to 20 mg/day over 1 month, then more slowly over the next 9–12 months. Most patients require prednisone for ≥ 2 years, and relapses are especially common during the first year.

Follow the sedimentation rate because it frequently correlates with disease activity. Low-dose aspirin decreases the risk of stroke in these patients, so this is started along with the steroids. Steroid-sparing agents may be used (especially in patients with diabetes or who are intolerant of steroids). Their efficacy, however, is controversial at this time.

The risk for aortic aneurysms is increased in patients with GCA; risk is highest within the first 5 years of diagnosis. Screening for aneurysms should be considered, particularly if they have additional risk factors (e.g., tobacco use, hypertension, diabetes).

GCA is a common exam topic. You may be given a case of an elderly Caucasian patient with shoulder aches, headache, and vision complaints. You must determine whether the patient has polymyalgia rheumatica (PMR) with GCA, retinal artery occlusion, carotid artery disease, or some ophthalmic disorder. Body pain + vision complaints in the elderly + high sed rate = PMR with GCA! Also know that GCA can present as a FUO or weight loss in the elderly.

Polymyalgia Rheumatica

Polymyalgia rheumatica (PMR) is a clinical syndrome that is classically associated with giant cell arteritis and may be a milder manifestation of the same disease. 20% of PMR patients develop GCA. Conversely, in those with GCA, 50% also have symptoms of PMR or have already been diagnosed with PMR.

A PMR-like illness can be present in other conditions. Elderly-onset RA can present as a syndrome indistinguishable from PMR initially, although a significant inflammatory polyarthritis eventually develops. (RF is often negative.) Presence of an otherwise unexplained fever in a patient with PMR may indicate the development of GCA.

Think of PMR in the older patient with a history of profound morning stiffness, bilateral shoulder girdle and hip aching, and hand swelling (mimicking RA).

Remember: PMR pain is out of proportion to exam findings. PMR presents with aching and stiffness, not weakness—in contrast to myositis, which generally presents with weakness, not pain! In addition, PMR is distinguished from polymyositis by the absence of both objective weakness and elevated muscle enzymes. CK is normal in PMR even though the muscle aches and the patient feels stiff.

Sedimentation rate is typically elevated (> 50 mm/hr) but may be normal in ~ 5%.

Treatment: PMR responds dramatically to low-dose prednisone (about 10–20 mg/day), although it must be slowly tapered, usually over 2–3 years for cure. If the exam gives you an older patient with shoulder pain who improves dramatically overnight after 1–2 doses of prednisone, the diagnosis is PMR. PMR may occasionally respond to NSAIDs, but risk for PMR turning into GCA is increased if inflammation is not controlled.

In atypical cases of PMR, especially those individuals who do not respond to low-dose glucocorticoids (10–20 mg/day with dramatic response expected within 1–3 days), think GCA or an alternative diagnosis, such as cancer.

As with GCA, the ESR correlates with disease activity; so, follow it during treatment. If there are any signs of GCA (e.g., visual changes, headache), you must do a complete reevaluation immediately, including temporal artery biopsy and an increase in the prednisone dose.

Takayasu Arteritis

Takayasu arteritis ("pulseless disease") commonly involves the aorta and its proximal branches. It primarily affects young women (< 40), particularly of Asian descent. This may present initially with nonspecific inflammatory features such as a FUO (inflammatory phase); then, months to years later, with claudication of the upper extremities, strokes, TIAs, or renovascular hypertension with bruits ("pulseless phase"). Patients also may have Raynaud's, erythema nodosum, and aortic regurgitation from dilatation of the ascending aorta.

Diagnose using conventional angiogram or MR angiogram (MRA) demonstrating large artery narrowing, referred to as "beading" or "string of pearls," and/or characteristic aneurysms. Exacerbations or recurrences of inflammation are indicated by an increase in the ESR/CRP, anemia, and artery wall inflammation visible on MRA. Unlike GCA and many of the other vasculitides, tissue biopsy has little role in the diagnosis of this disorder. (Trying to nick the aorta for a tissue sample = really bad idea!)

Treat with glucocorticoids (main) or DMARDs. Biologics have been used to treat the acute inflammatory stage. Revascularization with angioplasty, stenting, or bypass surgery may be needed for severely stenotic arteries. Ideally, these procedures should be performed when the acute inflammatory phase is controlled. Patients may require antiplatelet or anticoagulation for very stenotic vessels. Takayasu arteritis tends to recur and has a guarded prognosis.

Cardiovascular disease is the major cause of death in Takayasu arteritis. Strict management of traditional cardiovascular risk factors is mandatory. Remember: A patient with history of Takayasu may present with low BP in one arm, but don't forget to check the BP in the other arm and both legs. Hypertension may be undetected and not appropriately treated in these patients!

Aortitis

Aortitis is associated with several systemic inflammatory diseases. Exam questions typically ask about the most common associations: syphilis, endocarditis with mycotic aneurysm, GCA/Takayasu, and spondyloarthropathies. IgG4-related disease is a relatively new disorder known to cause aortitis. Know that syphilitic aortitis is a tertiary manifestation associated with aneurysm formation and valve regurgitation, but aortic dissection and rupture are extremely rare!

MEDIUM / SMALL ARTERY VASCULITIS

Overview

Most common and frequently tested medium/small artery vasculitides:

1) Polyarteritis nodosa (PAN)
2) Churg-Strauss (allergic eosinophilic granulomatosis with polyangiitis [EGPA])
3) Granulomatosis with polyangiitis (GPA, previously "Wegener granulomatosis")
4) Microscopic polyangiitis (MPA)

Of these four, know that PAN is the only one not associated with ANCA autoantibodies.

Review the material on ANCAs on page 6-2.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) affects medium-sized arteries and is strongly associated with hepatitis B. The vasculitis results in inflammation in the walls of arteries (but not capillaries or veins) with subsequent formation of aneurysms. Unlike many of the other vasculitides, the inflammation in PAN is not granulomatous; instead, it is marked by the accumulation of neutrophils and mononuclear cells with fibrinoid necrosis.

Classic PAN commonly affects the arteries that supply the skin, peripheral nerves, GI tract, and kidney, but spares the lungs. Symptoms of PAN include anorexia

Quick Quiz

- What are differences in the clinical presentations of myositis and PMR?
- How does the treatment of PMR differ from the treatment of GCA?
- With which virus is PAN associated?
- How do you diagnose PAN?
- Which organs/tissues are commonly involved in GPA?

with weight loss, fevers, malaise, arthralgias, mononeuritis multiplex, CNS symptoms, abdominal symptoms, and lower extremity rashes (palpable purpura, livedo reticularis, nodules, and bullae/vesicles). The abdominal symptoms are related to mesenteric arteritis, causing infarct or perforation. Renal involvement usually presents as hypertension, mild proteinuria, and hematuria without red cell casts. Note: PAN does not cause glomerulonephritis; thus, the absence of RBC casts. Instead, disease affects the walls of the arteries that supply blood to the nephron. Essentially, renal ischemia is the primary pathology, with activation of the renin-angiotensin-aldosterone system and development of hypertension.

PAN can affect virtually all organ systems, including the coronaries. But PAN does not classically cause disease of the pulmonary arteries nor does it cause glomerulonephritis! Patients may present with pulmonary edema as a consequence of left heart failure, but PAN does not cause pulmonary hemorrhage or infarction. These tidbits help you exclude PAN as a cause of a pulmonary-renal vasculitis. If you see a patient with a pulmonary-renal vasculitic syndrome, you should think GPA, MPA, or EGPA—not PAN!

Suspect a diagnosis of PAN in a patient with multiple diverse symptoms; e.g., chest pain (pericarditis), abdominal pain (mesenteric arteritis), foot drop (mononeuritis multiplex), and testicular pain.

Diagnosis of PAN: If there is no obvious peripheral involvement (e.g., nerve, muscle, testicle), do an angiogram. An angiogram of the mesenteric or renal medium-sized arteries can show diffuse, small, saccular aneurysms or stenoses that are diagnostic. If there is peripheral involvement, biopsy the affected site. Again, biopsy the testicle(s) if pain is present. If there is mononeuritis multiplex, biopsy the sural nerve. If the kidney is affected in PAN, the involvement is in the artery, and biopsy is frequently diagnostic. (Remember: This is not glomerulonephritis.) Important to note: ANCA tests are usually negative. Test for hepatitis B infection whenever PAN is suspected.

These symptoms and a positive ANCA, especially with a positive anti-PR3, are more consistent with a diagnosis of granulomatosis with polyangiitis (GPA)—definitely not PAN.

Treatment of PAN includes treating chronic HBV, if present, and giving prednisone +/– cyclophosphamide, depending on severity at presentation. IV cyclophosphamide-pulse therapy may be less effective at inducing a sustained remission, but it is tried because toxicity is less. PAN is a severe disease, and patients die if not treated (10–20% survive 5 years). Sometimes, treatment only slows the progression of the disease.

There is a skin variant termed "cutaneous PAN" that has skin lesions and neuropathy as clinical features. The skin lesions can be severe and ulcerative, so immunosuppression may still be required.

Eosinophilic Granulomatosis with Polyangiitis (a.k.a. Churg-Strauss Vasculitis)

Eosinophilic granulomatosis with polyangiitis (EGPA) is a necrotizing, pulmonary-renal vasculitis marked by eosinophilic granulomas. Patients typically have a history of severe asthma +/– sinus disease or allergies (including allergic rhinitis and nasal polyps). Mononeuritis multiplex is particularly common. Glomerulonephritis is less common compared to GPA or MPA.

Lab: peripheral eosinophilia > 10%, p-ANCA+, anti-MPO+.

Treatment is the same as for PAN, although many patients respond well to glucocorticoids alone.

Granulomatosis with Polyangiitis

The hallmark of granulomatosis with polyangiitis (GPA) is necrotizing granulomas; this is a small vessel vasculitis that commonly involves the sinuses causing a "saddle nose deformity," lungs with cavitary nodules, and kidneys (a classic pulmonary-renal syndrome). Patients occasionally develop skin rashes and/or ulcerations and may have migratory large joint arthritis (Image 6-20). Recurrent sinusitis and other upper respiratory issues are extremely common.

Sinus tissue biopsy in GPA can show any of these following 3 findings:

1) Small vessel vasculitis
2) Necrosis
3) Granulomatous inflammation

The biopsy yield is low because only 30–40% of patients have any 1 of these findings and only 15% have all 3. Even so, the site of any oral, nasal, or sinus abnormality is the preferred 1st biopsy site because it's the least invasive. Among the organs commonly involved in GPA, lung biopsy followed by kidney biopsy has the highest diagnostic yield.

Remember the antibody tests, page 6-1: Patients with GPA are often c-ANCA+ and anti-PR3+. This helps exclude Goodpasture syndrome, which is caused by anti-glomerular basement membrane (GBM) antibodies. Of interest, patients who are anti-GBM+ and c-ANCA+ have a better prognosis than those who are only anti-GBM+.

c-ANCA+ is seen in > 90% of patients with diffuse GPA, but in only ~ 50% with limited GPA. (Limited typically = no renal involvement.) ANCAs occasionally appear in rapidly progressive glomerulonephritis (which can be considered renal involvement of the vasculitis) and in microscopic polyangiitis ([MPA] discussed next), but these vasculitides are usually p-ANCA+ and MPO+.

The diagnosis of GPA is made with biopsy. If the patient has no upper respiratory abnormalities appropriate for biopsy, then biopsy either the kidney or the lung, depending on which is most affected and which biopsy the patient can best tolerate. Renal biopsies are not specific enough to allow differentiation between GPA and microscopic polyangiitis, but the differentiation is not important because the treatment is identical. The point is to get tissue that has an artery in it for diagnosis of vasculitis.

GPA, like PAN, rapidly progresses to death without treatment. Therapy consists of high-dose steroids and cyclophosphamide or rituximab, with the latter being approved by the FDA in 2011. In clinical trials, rituximab demonstrates efficacy for GPA even in severe cases that are refractory to cyclophosphamide; toxicity of the drug is less than that of cyclophosphamide. In patients with mild pulmonary and renal involvement (defined as normal oxygenation and < 50% increase in creatinine), methotrexate, azathioprine, and leflunomide have been used.

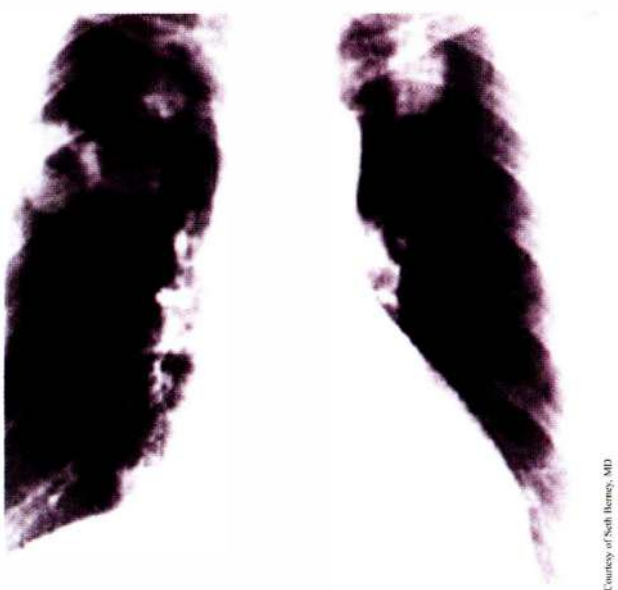

Image 6-20: Nodules in granulomatosis with polyangiitis (GPA)

Prescribe trimethoprim/sulfamethoxazole because of increased risk for *Pneumocystis jiroveci* pneumonia ([PJP] formerly known as PCP). It is unknown whether it is the illness itself or the cyclophosphamide treatment that predisposes these patients to PJP, but preventing this lung infection may help prevent GPA-associated lung exacerbations.

Remember: Side effects of cyclophosphamide include short-term problems, such as bone marrow suppression and infection, and longer-term problems, such as sterility, amenorrhea (higher risk > age 35), bladder effects (hemorrhagic cystitis and cancer), and leukemia/lymphoma.

Microscopic Polyangiitis

Microscopic polyangiitis (MPA) is also a pulmonary-renal syndrome with glomerulonephritis being much more common than pulmonary capillaritis. MPA causes a necrotizing, crescentic glomerulonephritis and may present as a FUO. In contrast to GPA and EGPA, granulomatous inflammation is absent. GPA and MPA are referred to as "pauci-immune" vasculitides since immune complex deposition is not detected to any significant degree, unlike in SLE. MPA never has angiographic changes since it involves small vessels. Upper airway and pulmonary nodules are not typical of MPA and when present suggest GPA. Diagnosis is based on biopsy of affected tissue. MPA is often p-ANCA+ and MPO+.

Treatment is essentially identical to GPA. Rituximab is also approved for the treatment of MPA.

OTHER SMALL-VESSEL VASCULITIDES

Overview

Other important small vessel vasculitides to remember include:

- Hypersensitivity vasculitis (leukocytoclastic vasculitis)
- Henoch-Schönlein purpura (IgA vasculitis)
- Cryoglobulinemia
- Anti-glomerular basement membrane disease

Hypersensitivity Vasculitis

Hypersensitivity vasculitis is a confusing term. It is appropriately used to define a small vessel vasculitis of the skin with minimal or no involvement of other organs. On biopsy, these skin lesions typically display "leukocytoclastic vasculitis," which is the histopathological correlate for hypersensitivity vasculitis. Leukocytoclastic vasculitis refers to PMNs permeating through vessel walls with concomitant cellular death and debris. Although the lesions may not always be palpable, the classic skin manifestation is "palpable purpura"

QuickQuiz

- Which antibodies are specific for GPA?
- Why is trimethoprim/sulfamethoxazole given to patients with GPA?
- Leukocytoclastic vasculitis is associated with which diseases?
- Mixed cryoglobulinemia is associated with which hepatitis virus?

("crops" of purple papules or large petechiae), most often seen on the lower extremities.

About 40–50% of hypersensitivity vasculitis is idiopathic, but the most common identifiable causes include:

- Drug reactions (especially beta-lactams, sulfonamides, NSAIDs, diuretics, phenytoin, and allopurinol)
- Infections (e.g., viral hepatitis, beta-hemolytic strep, HIV, endocarditis)

Other causes of small-vessel vasculitis, discussed below, must be excluded.

Hypersensitivity vasculitis due to a drug reaction can occur 1–10 days after drugs are started. Keep in mind the rash may occur after the drug has already been discontinued (as in antibiotics). Treatment of hypersensitivity vasculitis involves treating the underlying condition, or when known, discontinuing the causative medication. In idiopathic cases, hydroxychloroquine, dapsone, or colchicine can be tried. Glucocorticoids can be used for more resistant disease.

The histopathological finding of "leukocytoclastic vasculitis" can also be found on skin biopsy with vasculitides that affect other organs in addition to the skin, such as IgA vasculitis or cryoglobulinemia.

Henoch-Schönlein Purpura (IgA Vasculitis)

Henoch-Schönlein purpura (HSP) is an IgA-mediated, small-vessel vasculitis that can affect arterioles, capillaries, and venules. Organs affected often include: the skin from the waist down (crops of papules, "palpable purpura"), kidneys (biopsy findings identical to IgA nephropathy), GI tract (abdominal pain and bleeding, intussusception), and joints (typically the knees and ankles). Most cases are self-limited; about 20% have a repeat attack, and 5% develop chronic HSP. About 75% of cases are in children, predominantly those 2–11 years old; 25% in adults. Upper respiratory and streptococcal infections often precede HSP (hence a peak in incidence during autumn and winter months), but foods, medications, and insect bites have been linked to this vasculitis. IgA levels may be elevated.

Diagnosis can be confirmed by identifying the presence of IgA deposits in the vessel wall on skin biopsy. It is usually benign and resolves spontaneously but occasionally causes renal failure (up to 10% of adults and < 5% of children). Treatment is often supportive. Glucocorticoids may improve joint and GI symptoms, but there is no compelling evidence that they help kidney disease. Give corticosteroids or cytotoxic agents only for life-threatening symptoms.

Cryoglobulinemia

Cryoglobulins are immunoglobulins that precipitate in a serum specimen when chilled < 98.6° F and redissolve when warmed. Cryoglobulins are normally cleared by the liver. Buildup occurs with overproduction or decreased elimination from chronic liver disease.

There are 3 types of cryoglobulinemia:

Type I is least common (10–15%). It is due to a single monoclonal antibody (IgM, IgG, or IgA) and is usually found in patients with multiple myeloma or Waldenström macroglobulinemia.

Type I does not have rheumatoid factor activity like Types II and III; hence, complement is not activated. Therefore, patients are typically asymptomatic until the cryoglobulin level rises high enough to cause symptoms of hyperviscosity such as neurologic symptoms (headache, blurred vision, vertigo, deafness, nystagmus), livedo reticularis, purpura, and Raynaud phenomenon.

Type II is most common (50–60%). It is considered a mixed cryoglobulin where the immune complex consists of monoclonal IgM rheumatoid factor attached to polyclonal IgG. Most patients have an associated hepatitis C (HCV) infection. Patients who do not have HCV but have these cryoglobulins are considered to have "essential" mixed cryoglobulinemia.

Type III (25–30%) is similar to Type II in that it is also a mixed cryoglobulin, but has immune complexes typically composed of polyclonal IgM rheumatoid factor and polyclonal IgG. 1/2 of patients have HCV infection, and the others usually have a chronic autoimmune disorder (e.g., SLE) or a lymphoproliferative malignancy.

A low C4 out of proportion to C3 is a clue to the presence of cryoglobulins.

Types II and III cryoglobulinemia produce similar symptoms. They both activate complement and frequently present with a small vessel vasculitis, most commonly with lower extremity purpura, glomerulonephritis, peripheral neuropathy, and hypocomplementemia. Patients may eventually get hyperviscosity symptoms discussed in Type I.

Patients with HCV and mixed cryoglobulinemia (Types II and III) can get membranoproliferative glomerulonephritis (MPGN). These patients have low C3, C4, and CH50 (classical complement activation), and their

rheumatoid factor (RF) is very high (because Types II and III are RFs). MPGN frequently causes renal failure. When the patient gets renal disease, prognosis is poor. Cryoglobulin assays are difficult to perform, and false-negative rates are high. When possible, do a skin biopsy and send for histology and direct immunofluorescence (DIF), which can reveal the type of immunoglobulin and complement deposition.

Treatment with pegylated interferon alfa and ribavirin (+/– new protease inhibitors) is often effective for the vasculitis caused by HCV. In patients with more severe disease (visceral or renal), glucocorticoids or more potent agents may be required. Rituximab has been used off-label effectively.

DDx: Do blood cultures to exclude endocarditis. Other diseases that mimic this form of vasculitis include cardiac atrial myxoma emboli and cholesterol atheroembolism. Obtain an echocardiogram when emboli are suspected. Especially consider cholesterol atheroembolism in a patient with severe atherosclerosis who has just had an arteriogram. This is important if the patient has hypereosinophilia (90% of patients) and/or hypocomplementemia (50% of patients). Skin biopsy of punctate lesions can confirm the diagnosis of cholesterol atheroembolism.

ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE / GOODPASTURE SYNDROME

Anti-glomerular basement membrane (GBM) disease results from anti-GBM antibodies that deposit in the pulmonary and/or glomerular capillaries. The clinical presentations include a rapidly progressive glomerulonephritis without lung involvement (termed "anti-GBM disease") or a rapidly progressive glomerulonephritis with pulmonary hemorrhage (Goodpasture syndrome). Goodpasture's has a bimodal age distribution: 20–30 years (M > F) and 60–70 years (F > M). Smoking has a strong correlation with alveolar hemorrhage, especially in young males.

Diagnose anti-GBM disease by measuring anti-GBM antibodies in the serum and with renal and/or lung biopsy, which will demonstrate evidence of the anti-GBM antibodies on immunofluorescence.

~ 15% of patients who are anti-GBM+ also are ANCA+ and can have symptoms of systemic vasculitis. These patients with double antibodies are treated the same as patients with anti-GBM only and tend to have a better prognosis.

Remember that patients with pulmonary hemorrhage may have an increased DLCO.

Treatment involves plasmapheresis to remove circulating anti-GBM antibodies and immunosuppression with glucocorticoids and cyclophosphamide to inhibit further autoantibody formation.

Remember the pulmonary-renal syndromes (rheumatic diseases that can cause alveolar hemorrhage and glomerulonephritis):

- Goodpasture syndrome
- CTD: SLE, RA, PM or DM, PSS
- Systemic vasculitis: GPA, MPA, EGPA, HSP, Churg-Strauss
- Drug-induced: propylthiouracil (PTU)
- Behçet disease
- Cryoglobulinemia

BEHÇET DISEASE

Behçet disease is a unique vasculitic syndrome that can affect any organ and vessels of any size, although it has a predilection for veins. It primarily affects young adults in their 20s to 30s who live in the Middle East or Asia, and is rare in North America. The diagnosis is made clinically because there is no pathognomonic laboratory test, though HLA-B51 and HLA-B5 have been associated with this disease. Ulcers are very painful (whereas in SLE, ulcers are typically painless). Current international criteria for the diagnosis of Behçet's include:

Recurrent oral ulceration plus 2 of the following:

1) Recurrent genital ulceration
2) Ocular lesions (uveitis, retinal vasculitis)
3) Skin lesions (erythema nodosum, acneiform nodules)
4) Positive pathergy test ("skin prick test")

The pathergy test is fairly specific for Behçet's but not very sensitive: The patient develops a sterile papule or ulcer 1–2 days after minor trauma, such as a needle stick. A positive pathergy test also can occur in pyoderma gangrenosum.

Peripheral arthritis is common and patients can develop a gastrointestinal disorder that mimics Crohn disease (due to intestinal ulcerations or mesenteric vasculitis). The most serious complications include blindness, CNS disease (meningoencephalitis, cranial nerve palsies, seizures), and thrombosis or rupture of large aneurysmal vessels.

First-line therapy for oral and genital ulcers includes topical/oral glucocorticoids. Sucralfate suspension can also be used. First-line oral therapy should be colchicine with thalidomide, which is reserved for more serious mucous membrane involvement given its significant side effect profile. Treat more severe disease (vascular or neurologic) with systemic corticosteroids, azathioprine, cyclophosphamide, and anti-TNF biologic agents. Relapse is common.

Quick Quiz

- What are the clinical features of Behçet's?
- What complications can be seen with Behçet's?

RELAPSING POLYCHONDRITIS

Relapsing polychondritis (RP) is an inflammatory disorder of cartilage (ear, nose, larynx, and trachea) and tissues rich in proteoglycans (eyes and heart valves). While RP is most often a primary disorder, it is frequently associated with other diseases, most commonly some form of systemic vasculitis, connective tissue disease, or myelodysplastic syndrome.

Patients present with unilateral or bilateral ear inflammation which can mimic cellulitis, except that the ear lobe is spared (no cartilage). It also can cause arthritis, ocular disease (scleritis, iritis), hearing loss/vertigo, and vasculitis (10–20%). RP can cause aortic dilatation and a valvulitis leading to aortic and/or mitral regurgitation. Skin findings are frequent and can mimic those found in Behçet's.

MAGIC syndrome is an overlap disorder (Behçet's and relapsing polychondritis) characterized by **m**outh **a**nd **g**enital ulcers with **i**nflamed **c**artilage. Suspect in a patient presenting with hoarseness, saddle-shaped deformity of the nose, and swelling of the ear's cartilage with sparing of the ear lobe.

Glucocorticoids are the cornerstone of treatment. Occasionally, steroid-sparing agents are required.

RHEUMATOLOGIC ISSUES ASSOCIATED WITH MALIGNANCY AND DIABETES MELLITUS

Malignancy (also see Oncology, Book 4) is associated with:

- Hypertrophic pulmonary osteoarthropathy (HPOA) (page 6-32)
- Amyloidosis (check with rectal biopsy or an abdominal fat pad biopsy)
- Secondary gout
- Carcinomatous polyarthritis (resembles RA; especially consider with breast cancer or leukemia)

Diabetes mellitus (see more in Endocrinology, Book 4) is associated with:

- Dupuytren/flexion contractures: occur in poorly controlled longstanding diabetes mellitus. This and the preceding limited joint mobility are known as cheiroarthropathy. This may also present with thickening of the skin of the fingers. (Remember that systemic sclerosis causes thickening of skin proximal to the metacarpals in addition to the fingers.) On physical exam, the "prayer sign" may be seen. This is the inability to press the palms together completely without a gap remaining between opposed palms and fingers.
- Carpal tunnel syndrome
- Frozen shoulder
- Foot disorders that include neuropathic arthropathy (page 6-32)
- Osteomyelitis

PAGET DISEASE

Paget disease of the bone (see Geriatrics in General Internal Medicine, Book 5) is associated with:

- Osteoarthritis.
- Fractures, including stress fractures.
- Serum alkaline phosphatase and urinary hydroxyproline are elevated because both of these are indications of increased bone turnover.
- Osteosarcoma occurs in about 1%!

First-line treatment for Paget disease is bisphosphonates. Teriparatide should not be prescribed for these patients because it is associated with osteosarcoma, and patients with Paget's are already at increased risk for this condition.

AMYLOIDOSIS

Amyloidosis results from abnormal deposition of autologous extracellular proteins into organs and tissues, causing a disruption of function. Symptoms can include joint pain, macroglossia with dysphagia, polyneuropathy, congestive heart failure, and renal and liver dysfunction. Different types of amyloidosis have been described based on site and pathology of the lesions.

Reactive systemic AA amyloidosis (secondary amyloidosis; fibrils composed of serum amyloid **A** [SA**A**] proteins). This can be a long-term consequence of chronic inflammatory diseases like RA, Crohn's, juvenile idiopathic arthritis, autoinflammatory syndromes, malignancies, and infections. The kidneys are most commonly involved, followed by the liver and spleen. Very rarely are the heart and nervous system affected.

AL (primary) amyloidosis results from monoclonal immunoglobulin light-chain (**L** for **L**ight) deposition (typically, lambda light chains). This type of amyloidosis is commonly seen in patients with smoldering myeloma (e.g., MGUS). Any organ except the CNS can be involved. At time of diagnosis, the kidney (66%) and heart (50%) are commonly affected.

Dialysis associated ($A\beta_2M$) amyloidosis is a complication from long-term hemodialysis where

$ß_2$ microglobulin is not cleared by dialysis. After about 5–7 years of dialysis, patients develop symptomatic lesions, often involving bones/joints; visceral and vascular deposits also can occur.

Senile systemic amyloidosis (ATTR amyloid). Fibrils are composed of transthyretin (**t**rans**t**hyretin-**r**elated **a**myloidosis; hence ATTR); deposition occurs in those > 70 years of age and is universal in those > 90. Typically, deposits are microvascular, but when the heart is involved, congestive heart failure can occur.

Biopsy of affected tissue is the gold standard to confirming the presence of amyloid. The pathognomonic finding is "apple green-red birefringence" when stained with Congo red dye and viewed under polarized light. Abdominal fat pad aspiration has been studied as a tool to detect senile systemic amyloidosis. It has a sensitivity of 80–90%, and a specificity of 100%. Serum amyloid P (SAP)-labeled scintigraphy is useful to evaluate the whole body burden and distribution of amyloid.

Therapy is 2-fold:

1) Maintenance of organ function or replacement of organ
2) Reduction/elimination of fibril precursor protein (e.g., control the underlying inflammatory process—treat the RA, malignancy, etc.)

OFFICE ORTHOPEDICS

OVERVIEW

Know this section very well. The common aspects of office orthopedics and rheumatology will very likely be on the exam.

OSTEOPOROSIS

Osteoporosis is covered in General Internal Medicine, Book 5, under Geriatrics.

BURSITIS

Bursae are small fluid-filled sacs that provide a gliding surface to reduce friction when muscles and tendons slide across bone. Healthy bursae are necessary for a smooth, frictionless surface making normal movement painless. Bursitis is the inflammation of a bursa secondary to mechanical irritation, bacterial infection, RA, gout, or pseudogout. Bursitis or tendonitis usually causes severe pain with any active movement of the joint—especially against resistance. Passive range of motion is much less painful, or even painless.

Prepatellar bursitis (housemaid's knee or clergyman's knee), olecranon bursitis (student's elbow), trochanteric bursitis, subacromial bursitis, and pes anserine bursitis are the most frequently tested—probably because they are the most common. Know that the knee has several bursae (suprapatellar, infrapatellar, prepatellar, and pes anserine), and that the pes anserine bursa is located on the medial aspect, just inferior to the knee. Pes anserine bursitis is described as pain +/– swelling ~ 2 cm inferior and medial to the patella. In all locations, there is frequently a serosanguineous effusion within the bursal sac. More information on these bursitis presentations is included later in this section.

Diagnosis is usually clinical but requires exclusion of infectious bursitis if the area is inflamed and/or the patient is systemically ill, especially in patients on immunosuppressants; e.g., patients with RA on chronic corticosteroids. Aspiration of the bursa with fluid studies, including Gram stain and culture, helps you determine whether infection is present. If no sample is obtained for microbiology, empirical treatment with an antistaphylococcal drug may be necessary.

Treatment consists of rest of the affected area. Glucocorticoids can be injected, provided that the bursa is not infected. Mild infection in immunocompetent patients can often be treated with oral antibiotics, but serious infections in immunocompromised patients should be treated parenterally. Resistant, chronic cases sometimes require surgical excision of the bursa.

JOINT PAIN

Overview

Joint pain can be caused by a problem within the joint, a problem with associated ligaments or tendons, or inflammation of a bursa (just discussed).

When an extremity joint is acutely swollen without a history of trauma, it should be tapped and analyzed for crystals, cell count with differential, and Gram stain with culture.

Remember the mnemonic for the **3 Cs**: **c**ell count, **c**rystals, and **c**ulture.

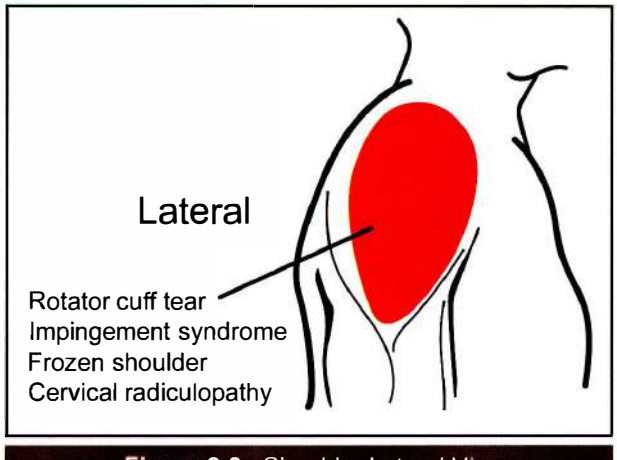

Figure 6-3: Shoulder Lateral View

Quick Quiz

- Name some bursae that commonly become inflamed.
- What is the workup for nontraumatic arthritis?

A word about terminology:

- Abduction = away from the midline.
- Adduction = toward the midline.
- Dorsiflexion = pulling the foot upwards, as in taking the foot off the gas pedal.
- Plantarflexion = pressing the foot down, as in pressing on the gas pedal.

Shoulder

True shoulder pain usually extends from the acromion to the insertion of the deltoid. Refer to Figure 6-3 through Figure 6-5 as you read this topic.

Many of the shoulder syndromes affect the glenohumeral joint and limit range of motion due to pain. This is demonstrated by the "painful arc" test. In this test, the patient actively raises the arm laterally from the side to an overhead position. Pain-induced limitation of motion in the middle of the arc indicates a positive test.

Thoracic Outlet Syndrome

Thoracic outlet syndrome (TOS) results from compression of the neurovascular structures supplying the upper extremity. Problems in the neck/shoulder can cause irritation of the brachial plexus as it moves from the neck and chest cavity into the arm. Impingement of the nerves causes shoulder pain that may be localized or extend from the base of the neck, over the top of the shoulder, and down the arm. This pain may extend into the hand and is often accompanied by paresthesias and weakness. If the vascular supply (subclavian/axillary vessels) is also affected, patients will have hand claudication +/– Raynaud's and ulcers in severe cases.

TOS has been classified into 3 categories based on etiology, symptoms, clinical presentation, or anatomy:

1) Arterial TOS (1%; digital ischemia, claudication, typically related to a cervical rib)
2) Venous TOS (2–3%; due to subclavian vein obstruction from thrombosis/scarring, upper limb swelling is common)
3) Neurogenic TOS (95%; brachial plexus is compressed; paresthesia and pain in the neck, shoulder, and arm are common; symptoms are worse with overhead motion)

Diagnosis is difficult because PE is usually normal unless provoked by certain maneuvers. The elevated arm stress test (Roos test) is a good test to detect neurogenic TOS: Patients abduct their arms to 90 degrees while elbows are flexed at 90 degrees; then they open and close their hands for 3 minutes. If they cannot maintain this position due to symptoms, the test is positive.

The Adson test is another common maneuver used to evaluate for vascular TOS. Locate the patient's radial pulse while the patient turns their head toward the tested shoulder. The patient then extends their neck while the examiner laterally rotates and extends the patient's shoulder with the arm straight. The patient then takes in a deep breath and holds it. The test is considered positive if there is loss of the radial pulse and reproduction of TOS symptoms. If you suspect the syndrome, do a chest radiograph (looking for cervical ribs that sometimes are a cause) and/or EMGs with nerve conduction studies to see if the brachial plexus is affected.

Treat with shoulder exercises and education about avoiding the postures that elicit symptoms. Cervical ribs can be surgically removed if they are the cause.

Shoulder OA

Primary OA in the shoulder is rare unless repetitive use of the joint and trauma is the contributing factor, which is much more common in the acromioclavicular (AC) joint than in the glenohumeral joint. Pain in AC joint arthritis is usually localized over the AC joint, while the pain in glenohumeral arthritis can be anterior in the shoulder or nebulous and ill-defined. Although x-ray films can appear normal early on, they may show joint-space narrowing and osteophytes over time. Treat as you would all cases of OA with education and nonnarcotic analgesics. Surgery is used only in very refractory cases.

Amyloidosis

Long-term dialysis patients are likely to get amyloid deposition (beta-2 microglobulin) in the joints. This causes painful joints and tends to affect the shoulder and wrist, causing carpal tunnel syndrome.

Adhesive Capsulitis or "Frozen Shoulder"

This condition is most commonly seen in patients who are 40–60 years of age and who typically have an underlying predisposition; e.g., chronic bursitis/tendonitis, fracture, or rotator cuff injury. Diabetes and thyroid disease are also risk factors. However, adhesive capsulitis can occur in the absence of any apparent cause.

Diagnosis is suggested by shoulder pain, stiffness, and decreased range of glenohumeral motion in all directions. PE shows significantly reduced range of motion (< 50% of normal), both actively and passively, in all directions. Radiographs are often normal.

Symptoms usually resolve in 1–2 years. Physical therapy and range of motion exercises are important to help

patients regain their function. Intraarticular corticosteroids are occasionally used. Refractory cases may require surgery (< 10% of cases).

Impingement Syndrome

This syndrome refers to compression of the subacromial bursa or regional tendons in the space between the acromion and the humeral head. The biceps tendon and all of the rotator cuff tendons go through this area. For this reason, bicipital tendonitis and some rotator cuff injuries are often considered impingement syndromes.

Impingement typically causes pain when the patient reaches overhead or sleeps on the affected shoulder. Except in longstanding cases, strength in the shoulder is normal.

As with several other shoulder syndromes, these patients have a positive painful arc test. For diagnosis of impingement syndrome, use the following provocative maneuvers that are more specific. If any of the following tests elicit pain, the patient likely has an impingement syndrome:

- **Neer** test: Stabilize the scapula while passively lifting the arm in forward elevation toward the ear (forward flexion of glenohumeral joint).
- **Hawkins** test: With the patient's arm 90 degrees forward and the elbow in flexion, internally rotate the shoulder.
- **Yocum** test: While the patient touches the uninvolved shoulder, lift up on the flexed elbow.

Diagnosis of impingement is clinical; imaging is usually performed only when patients are refractory to therapy and require orthopedic referral.

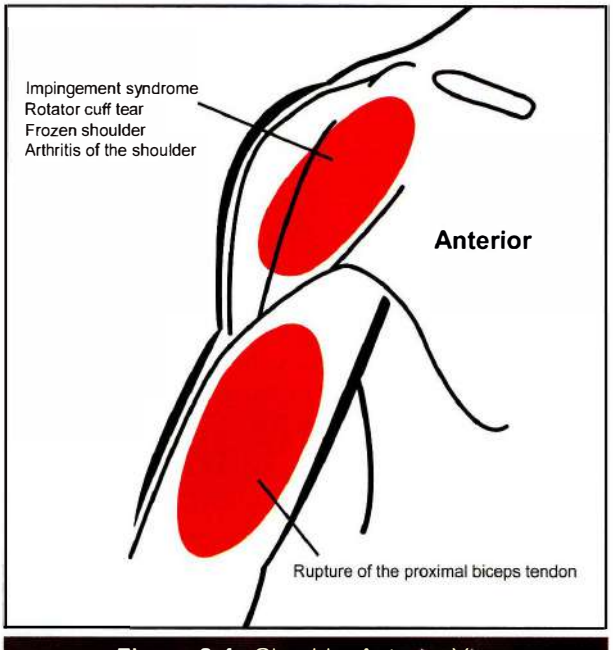

Figure 6-4: Shoulder Anterior View

If strength is normal, conservative management is best initially: rest from aggravating activities, ice, and physical therapy for 3 months. Treat the pain with a short course of NSAIDs. Intraarticular glucocorticoid injections sometimes are used if the patient doesn't get better quickly.

Refer for orthopedic evaluation if the patient still has pain after 3 months of therapy or if weakness/muscle atrophy is present at initial evaluation, which might suggest a rotator cuff tear.

Subacromial Bursitis

This is also called deltoid bursitis. Patients present with pain both at rest and with movement. The pain with this bursitis is referred to the lateral aspect of the arm. Consider this diagnosis when the patient reports waking from sleep with pain in the shoulder and arm. It can be associated with a rotator cuff tear (definitely consider this if weakness is present) and impingement.

On exam, the middle arc of the active abduction is painful, while the extremes are painless. Several other problems can cause this painful middle arc; e.g., calcification/tear/tendonitis of the supraspinatus tendon or a fracture in the humeral tuberosity, where the supraspinatus tendon attaches. Occasionally, pain is so severe that the patient cannot accomplish any active movement, especially abduction. Passive range of motion shows pain with abduction only.

Treat with range of motion exercises, NSAIDs, and ice. Consider intrabursal glucocorticoid injections if infection has been ruled out and the patient does not respond to more conservative measures.

Rotator Cuff Abnormalities

The rotator cuff is comprised of 4 muscles (teres minor, infraspinatus, supraspinatus, and subscapularis) that stabilize the shoulder and allow the arm to elevate and rotate. Injuries or degeneration of the rotator cuff are the

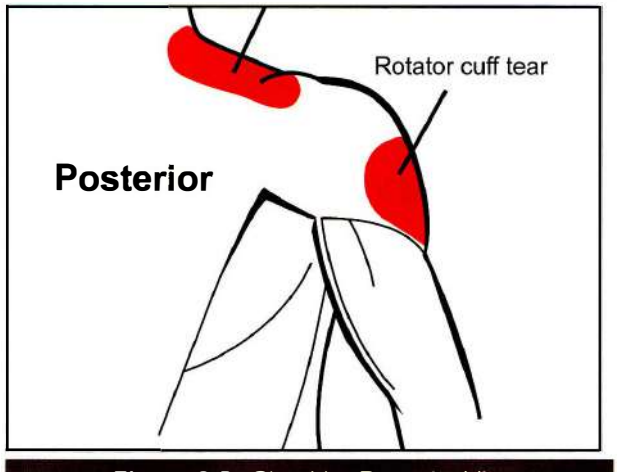

Figure 6-5: Shoulder Posterior View

Quick Quiz

- Name and describe 3 tests to assess shoulder impingement.
- Compare and contrast the presentation of shoulder OA, impingement syndrome, subacromial bursitis, and rotator cuff injuries.
- Olecranon bursitis is associated with which systemic diseases?
- How is lateral epicondylitis treated?

most common causes of shoulder pain. Some tears, even severe ones, can sometimes occur without pain—and manifest only as weakness! Consider a tear in patients who play overhead sports (e.g., baseball), have had shoulder trauma, are > 50 years of age, or have RA.

Pain with overhead reaches and night pain are classic features. The injury also can cause a subacromial bursitis, so always suspect a tear when patients present with bursitis features.

Exam of partial tears demonstrates a positive painful arc test +/– weakness. The trick here is to determine whether apparent weakness is due to pain or a true muscle tear, because patients with pain guard their shoulder. (Lidocaine injections help diagnostically in this situation.) Another exam maneuver is to observe active adduction: Patients who cannot adduct smoothly (called the "drop-arm sign") may have a tear. The Neer and Hawkins tests help differentiate this from impingement syndrome.

Complete rotator cuff tear is very debilitating. It generally involves separation of the supraspinatus tendon, but it may involve the adjacent subscapularis or infraspinatus tendons. These tendons blend with the shoulder joint capsule, and a separation of the tendons generally involves the joint capsule. This allows "communication" between the shoulder joint and the subacromial bursa. Complete tears due to chronic repetitive injury usually occur in patients > 60 years of age. Patients are unable to abduct the arm due to weakness +/– pain, except by rotation of the scapula (shrugging the shoulder). Complete tears can also be caused by acute injuries from falls on an outstretched arm.

If you suspect a tear, start with plain radiographs because they can sometimes show you abnormalities in the positioning of the humeral head, acromion, and glenoid. MRI also can make the diagnosis, but abnormalities have to be clinically correlated because lots of asymptomatic people have tears visible on MRI.

Treatment of most tears is conservative: rest, nonnarcotic analgesics, and physical therapy. Full-thickness tears in a healthy person are treated with surgery. Surgery is also considered when conservative treatment fails.

Elbow

Olecranon Bursitis

This type of bursitis can be traumatic, septic, gouty, or secondary to RA. Traumatic bursitis ("student's elbow") is caused by chronic pressure. The bursa should be aspirated if there is any question about possible infection.

Treat uninfected bursitis with aspiration and NSAIDs or glucocorticoid injection. Treat septic bursitis with incision, drainage, and antibiotics. Oral antibiotics can be used for mild infections—IV is needed in severe inflammation. (See Figure 6-6.)

Lateral Epicondylitis

"Tennis elbow" presents with tenderness and pain well localized to the front of the lateral epicondyle of the elbow, where the extensor tendons of the forearm insert. Symptoms usually resolve spontaneously with decreased use of the elbow, although it may take 2 or more years.

Treatment: NSAIDs and splinting to reduce supination/pronation motion. A glucocorticoid injection may provide short-term benefit, but physical therapy, rehabilitation exercises, and activity modification are the mainstays of therapy.

Medial Epicondylitis

"Golfer's elbow" is similar to tennis elbow, but involves the "medial" epicondyle of the elbow. Treatment is the same.

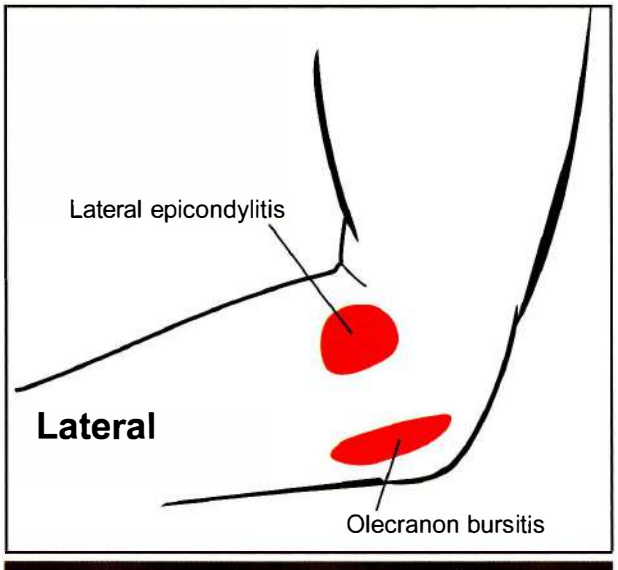

Figure 6-6: Elbow Lateral View

Wrist

Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) presents as paresthesias and dysesthesias in the median nerve distribution (thumb through middle of 4th finger) that are usually most bothersome during sleep. The symptoms can be reproduced by tapping on the volar aspect of the median nerve (Tinel sign) and/or forced flexion of the wrists for 30–60 seconds (Phalen test). Patients often describe tingling/numbness in the middle of the night where they would have to flick or shake out the hand.

Certain groups of patients are more susceptible; e.g., pregnant women or those on oral contraceptives; dialysis patients; and those with arthropathy associated with wrist synovitis (e.g., RA). Hypothyroidism, diabetes, acromegaly, and amyloidosis are also associated with CTS.

Pain only in the shoulder or elbow is an atypical presentation. Nerve conduction studies aid in the diagnosis.

Initial treatment consists of NSAIDs and a wrist splint worn day and night for 3–4 weeks. Conduct carpal tunnel release in patients with axonal (motor) loss, weakness/atrophy of thenar eminence, or in cases refractory to conservative treatments, such as splinting or steroid injections.

Remember: CTS causes numbness in the thumb and 2nd, 3rd, and 1/2 of the 4th fingers, whereas cubital tunnel syndrome (entrapment of the ulnar nerve) causes numbness in the 4th and 5th fingers.

Ganglion Cyst

Ganglion cysts can occur at any joint or tendon sheath, but they are most commonly found on the dorsum of the wrist at the scapholunate joint. The cyst is attached to a tendon sheath or the joint capsule. There is no communication between the inside of the joint capsule and the interior of the ganglion. They are usually asymptomatic but may cause pain due to compression of a nerve or joint space. Ganglions generally are not treated, but temporary resolution may be provided by firm pressure or aspiration. The old remedy was slamming the ganglion with the family Bible! But this should be avoided because it may cause an inflammatory response and recur. Definitive treatment is surgical.

De Quervain Tenosynovitis

This is a chronic or subacute inflammation of the flexor tendons or the abductor pollicis longus tendon of the thumb. It is characterized by pain and well-localized tenderness over the styloid process of the distal radius. It is often caused by repetitive twisting of the wrist with certain motions, like wringing clothes. The Finkelstein test (forced ulnar motion of the wrist with the thumb adducted and clasped by the other fingers) reproduces the pain. Natural healing is very slow. Splinting, steroid injections, and NSAIDs can be beneficial for milder cases. Surgery, which is curative, should be reserved for patients with severe disability.

Hand

Dupuytren Contracture (Palmar Fibromatosis)

This flexion contracture of the fingers is caused by thickening and contraction of the palmar fascia. The palmar fascia extends from the termination of the palmaris longus tendon on the wrist to the proximal and middle phalanges of the fingers. The ring and 5th fingers are the most frequently affected. As the contraction progresses, you can see cord-like bands on the surface of the palm.

The cause is unknown, but these contractures are associated with a positive family history, epilepsy, diabetes, alcoholism, malignancies, and recurrent occupational vibratory stimuli. Dupuytren contractures are primarily seen in Caucasians, usually men.

Until recently, the cornerstone of treatment has been surgical, but contractures tend to recur in the young. In 2010, the FDA approved injectable collagenase clostridium histolyticum for the treatment of Dupuytren contracture with a positive cord. This medication, which contains 2 collagenases, is injected into the "cord" and provides hydrolyzing activity on the collagen, which helps reduce the degree of contraction and improve range of motion.

Trigger Finger

When a finger gets "stuck" in flexion at the PIP joint, we call it "trigger finger" or digital tenosynovitis stenosans. It is "unstuck" only with strong effort or with passive movement using the other hand—which causes significant pain. There is tenderness at the base of the finger (palmar aspect); often a tendon nodule can be felt. The cause is swelling of the flexor tendon and the opening of the flexor tendon sheath at the base of the finger. The middle or ring finger is most commonly affected. Chronic tenosynovitis can progress to Dupuytren contractures.

Splinting and local steroid injections can help, but a simple surgery is required to cure the condition. It consists of incising the mouth of the fibrous flexor sheath longitudinally.

Hip

Trochanteric Bursitis

This bursitis is the most common cause of lateral thigh discomfort. Patients report "hip" pain when lying on the involved side, draping the involved leg over the non-involved limb, or bearing weight on the affected

Quick Quiz

- Carpal tunnel syndrome affects which fingers? What about ulnar entrapment neuropathy?
- Which patients are at risk for AVN (osteonecrosis) of the hip?
- Should MRI evaluation of AVN include one or both hips? Why?
- How does pain from hip OA differ from pain from trochanteric bursitis?

side. When asked specifically to point to the area of most intense pain, patients with bursitis will point to the lateral aspect of the thigh over the greater trochanter (Figure 6-7 and Figure 6-8). This helps distinguish bursa pain from true hip joint pain, which causes a point of maximum intensity in the groin (may radiate to the buttock).

NSAIDs, local heat, PT, and/or glucocorticoid injections are very helpful.

Avascular Necrosis

Avascular necrosis (AVN), also called osteonecrosis, is a poorly understood condition resulting from an impaired blood supply to the bone. The compromised blood supply can be due to trauma, certain medical conditions, medications/drugs, or idiopathic disease. It most commonly affects the epiphysis (ends) of the femur (affecting the hip > knee joints), followed by the humerus. Patients on chronic glucocorticoids or who abuse alcohol have a significant risk of AVN. Medical conditions associated with AVN include sickle cell disease, pregnancy, HIV/AIDS, Gaucher disease, hypercoagulable states, pancreatitis, IBD, and SLE. Patients with femoral neck fractures or traumatic hip dislocations are especially susceptible because the blood supply to the femoral head is disrupted.

AVN is best diagnosed early with an MRI showing the classic "crescent sign" signifying subchondral collapse (when plain radiographs may still be normal). Be certain to image both hips with plain radiographs and/or MRI because the risk of bilateral AVN is high, even if the patient is not symptomatic in the alternate hip (called "Stage 0"). Most patients with AVN eventually need surgery. Early-stage disease can be treated with a revascularization procedure (core decompression +/– bone graft), which may eliminate the need for hip replacement. Total joint replacement is the treatment of choice for late-stage disease.

Hip OA

Hip osteoarthritis presents as increased pain with use that is relieved with rest; the maximum point of pain intensity is localized to the groin (Figure 6-7 and Figure 6-8), a feature that distinguishes hip joint pain from trochanteric bursitis. The pain also may refer to the knee. Patients may complain of morning stiffness (< 30 minutes) and "gel phenomenon" (stiffness that occurs after inactivity and resolves with use).

Exam usually does not reveal any inflammation, but decreased range of motion and crepitus might be obvious. Standing or "weight-bearing" radiographs show joint-space narrowing +/– subchondral sclerosis and/or osteophytes. In patients with typical pain and abnormal radiographs, no further imaging is necessary.

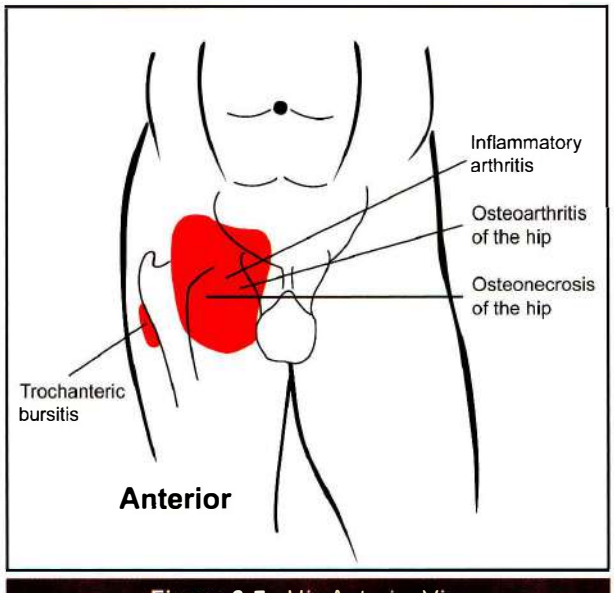

Figure 6-7: Hip Anterior View

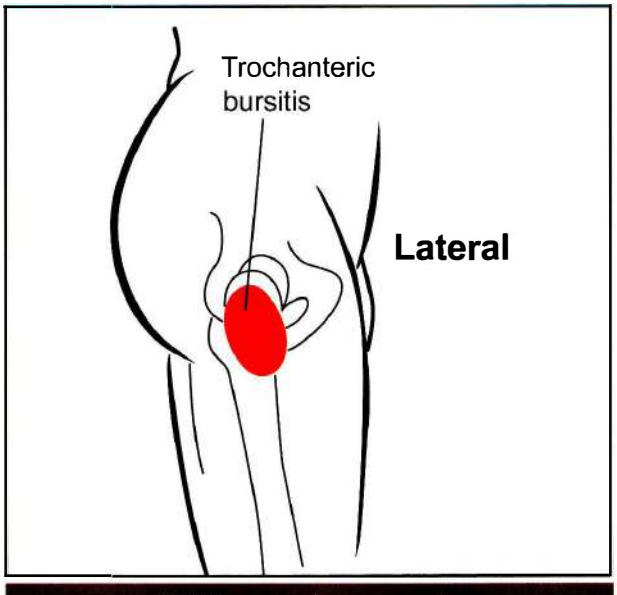

Figure 6-8: Hip Lateral View

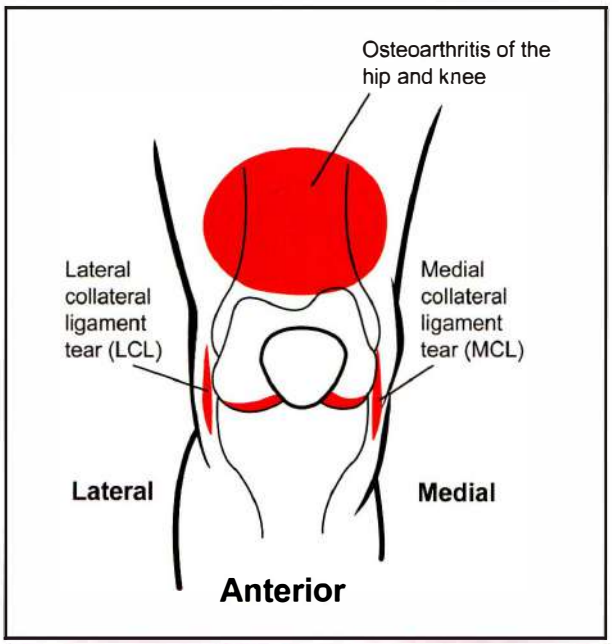

Figure 6-9: Knee Anterior View

Treat patients with education on weight loss and nonnarcotic analgesics. Conservative measures should be exhausted (especially weight loss, physical therapy, and use of assist devices, such as canes) before referral for total hip arthroplasty.

Knee

Knee OA is discussed on page 6-22. (See Figure 6-9.)

Baker Cyst (Popliteal Cyst)

This is simply a posterior herniation of the synovial cavity of the knee caused by a tense knee effusion (Figure 6-10). This forms a synovial, fluid-filled sac in the midline behind the knee or in the upper calf. A Baker cyst usually occurs as a result of chronic arthritic conditions in which there is persistent synovial effusion (e.g., rheumatoid arthritis) or meniscal tears. If an arthritic patient with knee involvement presents with a painful swollen calf, suspect a ruptured Baker cyst causing pseudo-phlebitis. Phlebitis and deep venous thrombosis (DVT) also should be considered.

Prognosis is usually good.

On exam, the cyst can be palpated in the posterior knee when the knee is partially flexed. Or, have the patient stand while you look at the posterior knee for swelling. Occasionally, a Baker cyst can cause extrinsic venous compression that also can simulate phlebitis. The diagnostic test of choice is an ultrasound or LE Doppler, which can rule out DVT and visualize the cyst. Further imaging with MRI adds no useful information.

Treatment is rest, NSAIDs, and treatment of the underlying cause. If the cyst is very large or causes significant pain, you can aspirate the knee (not the back of the knee!) and inject glucocorticoids. Refractory effusions may require surgical excision.

Prepatellar Bursitis ("Housemaid's Knee" or "Clergyman's Knee")

This bursitis localizes pain over the patellar bursa and is caused by kneeling on hard surfaces (Figure 6-11). If the symptoms worsen despite treatment with rest,

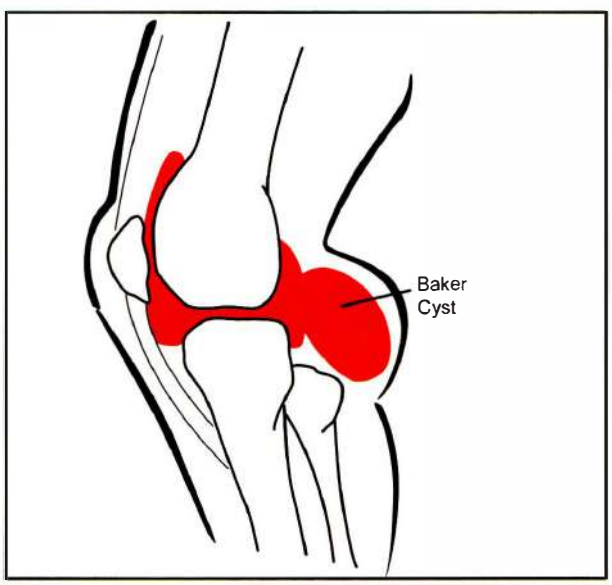

Figure 6-10: Lateral View of Baker Cyst

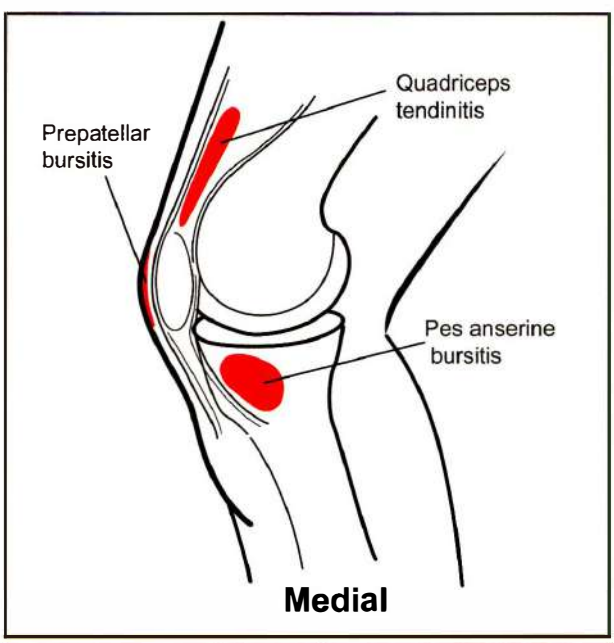

Figure 6-11: Knee Medial View

QuickQuiz

- What intervention can be used to treat a Baker cyst?
- What is the specific presentation of pes anserine bursitis?

ice, NSAIDs, +/– steroid injection, consider a bacterial infection of the bursa, which may occur without an obvious source. If in doubt, aspirate the bursa and send for Gram stain and cultures.

Pes Anserine Bursitis

This bursitis is caused by inflammation of the pes anserine bursa, located over the medial aspect of the proximal tibia 2 inches below the knee joint line (Figure 6-11). This is just proximal to the area where the 3 tendinous extensions of the gracilis, sartorius, and semi-tendinous muscles insert into the medial aspect of the tibial tuberosity. The symptom is pain in this area—especially when climbing stairs.

Pes anserine bursitis is associated with knee OA and obesity. Diabetes may be a predisposing factor.

Remember to aspirate and exclude infection as a cause if there's any question about the source.

Treatment is rest and analgesics, +/– steroid injection.

Pigmented Villonodular Synovitis

Pigmented villonodular synovitis (PVNS) is an idiopathic, monoarticular, benign synovial tumor that causes recurrent hemarthrosis, usually of the knee in young adults. Patients have recurrent bleeding into the knee, resulting in a darkly pigmented joint aspirate.

MRI is diagnostic with nodular intraarticular masses that demonstrate low signal intensity.

PVNS responds to synovectomy or radiation for recurrent cases.

Spontaneous Osteonecrosis of the Knee

Spontaneous osteonecrosis of the knee (SONK) most commonly affects the medial femoral condyle and may be the result of chronic mechanical stress or mild trauma in the elderly (60–70-year-olds), especially women. Unlike secondary AVN (osteonecrosis) of the knee, SONK is typically unilateral. There is no known etiology, although it seems to be associated with osteopenia and osteoarthritis. Weight-bearing pain is present initially on the medial aspect of the knee, and symptoms often resolve with conservative management, including protected weight bearing and analgesics.

Do an MRI to exclude a tear in a meniscus.

In contrast to secondary osteonecrosis, which usually requires surgical management (i.e., arthroplasty), SONK with small to mid-sized lesions has been shown to be responsive to nonoperative treatment. However, large lesions may still require unicompartmental or total knee arthroplasty.

Foot

Morton (Plantar) Neuroma

This benign neuroma causes painful, burning paresthesias and tenderness in the interdigital webbing due to repeated nerve trauma. It is usually unilateral and most often appears between the 3rd and 4th toes. It is much more common in women and thought to be related to high heels and tight fitting shoes. Palpation of the involved interspace produces sharp pain that often radiates into the toes, and squeezing the forefoot often reproduces the patient's symptoms. Patients may feel like they are standing on a pebble in their shoe. Treatment includes lowering the heel and wearing wider, soft-soled shoes with metatarsal arch support. Glucocorticoid injections may be helpful, and severe cases may require surgical excision of the nerve.

Plantar Fasciitis

This foot pain occurs most commonly in patients 40–60 years old, with increased incidence in runners and ballet/aerobic dancers (Figure 6-12). It is generally idiopathic, benign, and self-limiting. The hallmark of plantar fasciitis is a history of severe heel pain with the first few steps in the morning or after other long periods without weight bearing.

Radiographs are usually not necessary, but can assist in excluding diseases that present similarly, such as

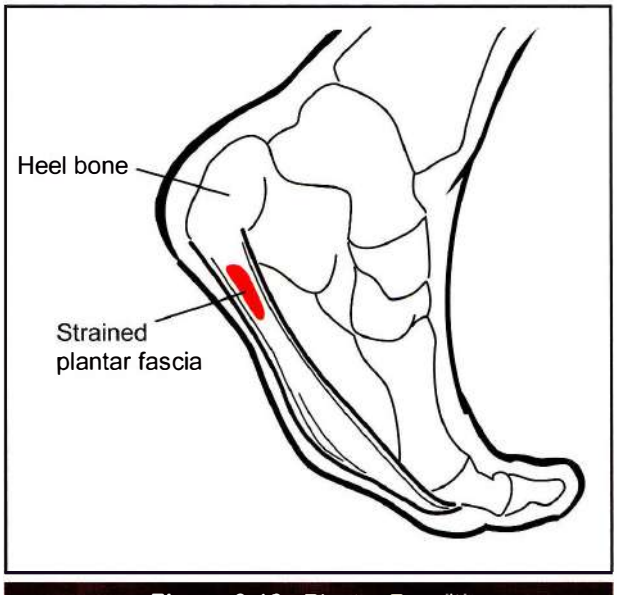

Figure 6-12: Plantar Fasciitis

calcaneal stress fractures and Paget disease. Look for evidence of a spondyloarthropathy in any patient who presents with plantar fasciitis.

Treatment is conservative: rest, NSAIDs, avoidance of high heels, calf stretches, shoes with arch support, and heel inserts. Injection of mixed steroid/anesthetic can be done in refractory cases. Recurrent steroid injections should be avoided because they cause fat pad atrophy.

LOW BACK PAIN

Overview

Acute lower back pain is one of the most common reasons why patients visit their primary care doctor. There are several causes of nonspecific, acute back pain. These include a moderately prolapsed disk, catching of the synovial membrane in a facet joint, transient subluxation with ligament strain, and basic muscle strain. Certainly worse diagnoses can cause lower back pain (e.g., spinal stenosis, infection, or metastatic cancer), so your task is to differentiate the simple causes from ones that require imaging and/or aggressive treatment.

General Approach to Lower Back Pain

Evidence-based practice guidelines issued by the American College of Physicians in 2007, and updated in 2011, focus on stratifying patients with back pain, based on an initial assessment of historical risk factors for cancer/systemic disease ("red flags") and exam evidence of neurologic deficits.

Nonspecific lower back pain, sometimes called lumbago, is diagnosed when the patient gives the classic history and has no red flags to suggest a more serious etiology. Treat with education (e.g., early mobility and heat application) and analgesics of "proven benefit" = acetaminophen +/– NSAIDs.

Only patients who have neurologic deficits, a "serious" underlying condition (e.g., cancer), or other "red flags" should receive urgent imaging. The main things you need to worry about when it comes to back pain red flags are infections (discitis, osteomyelitis, paraspinal abscesses) and cancer (principally, prostate cancer and multiple myeloma).

Treat others conservatively for 1 month and then reassess with imaging reserved for refractory pain.

Underlying conditions that indicate a need for urgent imaging:

- Known cancer diagnosis
- Multiple risk factors for cancer
- Risks for osteomyelitis: Injection drug users, +TB screening test, recent TB exposure
- Urinary retention
- Fecal incontinence
- Progressive motor weakness

By imaging, you are ruling out:

- Disk herniation
- Spinal stenosis
- Compression fracture
- Malignancy
- Infection

Muscle Strain

More than 50% of adults experience at least 1 episode of back strain at some time. Classic presentation is agonizing, lower back pain with a history of lifting a heavy object or making a sudden movement. Pain is increased when bending, lifting, turning, or coughing. Sometimes initial pain is so severe that any movement of the torso is difficult.

Physical exam typically reveals guarding of movement due to pain and no true muscle weakness or neurologic deficit. Straight leg raises do not cause pain. This is a clinical diagnosis. Know that imaging does not assist in diagnosis of or treatment for muscle strain.

Most get better quickly: 40% in 1 week, 90% in 2 months. With acute back strain, continuing ordinary activities as tolerated leads to a more rapid recovery than bed rest. Surgery is usually not required; studies show that in non-emergent patients initially considered surgical candidates, conservative treatment is just as effective as surgery in the long term.

Disk Herniation

Herniation presents with local or radicular pain—and with weakness, if severe. Herniated disks are most common at L5/S1 because of progressive thinning of the posterior longitudinal ligament. Central disk herniation can cause saddle pain, anesthesia, and/or incontinence. Classic disk pain is worse when sitting or bending and better when standing or lying.

On exam, patients have pain when performing the straight leg raise. MRI without contrast is the test of choice for diagnosing a symptomatic herniated disk.

Long-term outcomes comparing surgery and conservative management are equivalent. Neurologic deficits or intractable pain are indications for surgery (i.e., microdiscectomy). See Neurology, Book 5, for more discussion of disk disease.

Spondylolysis and Spondylolisthesis

Spondylolysis is a defect in the isthmus of the neural arch (pars interarticularis) of the 5th (rarely the 4th) lumbar vertebra. This loss of bony continuity is visible, especially on the oblique view of a lumbar x-ray film.

Although it was formerly thought to be congenital, spondylolysis is now thought to be more likely secondary to a stress fracture during childhood.

Quick Quiz

- Name another disease that must be considered in a patient with plantar fasciitis.
- Which patients should get urgent imaging of the spine if they present with lower back pain?
- What diagnosis should you consider in injection drug users who present with pain in their buttocks?

These patients are more susceptible to spondylolisthesis—a spontaneous subluxation (usually forward) of one lumbar vertebra over another (usually anterior subluxation of L4 over L5). Occasionally, spondylolisthesis results in sciatica, but generally it does not affect the nerves of the cauda equina. Don't confuse these terms with spondylosis, which refers to osteoarthritis of the spine.

Spinal Stenosis

Spinal stenosis (a.k.a. neurogenic claudication) is discussed in Neurology, Book 5. The stenosis of the spinal canal in the lumbar region may cause a crimping or claudication-like symptom due to nerve compression of the cauda equina. Symptoms typically consist of a progressively severe, heavy, aching sensation in the lower extremities after walking or standing several minutes. Symptoms of spinal stenosis worsen with back extension (descending stairs) and improve with back flexion (ascending stairs, leaning forward on a grocery cart). Disc herniation is the opposite. This entity must be distinguished from ischemic claudication, which presents as pain with ambulation classically relieved with rest and associated with obvious vascular disease on examination (e.g., bruits, lower extremity hair loss, poorly palpable pulses).

Pain in the SI joint area is not common and, when present, may be due to a spondyloarthropathy (page 6-58). Much less commonly, OA can cause pain in the SI area due to lumbar facet joint arthritis, and TB is also a cause (especially in developing countries). Think about infectious sacroiliitis in an injection drug user who presents with buttock-area pain.

Spinal stenosis is usually treated conservatively (i.e., analgesics, physical therapy). Surgery is recommended (most commonly a decompression laminectomy) if symptoms are severe or haven't responded to more conservative measures.

FOR FURTHER READING

[Guidelines in blue]

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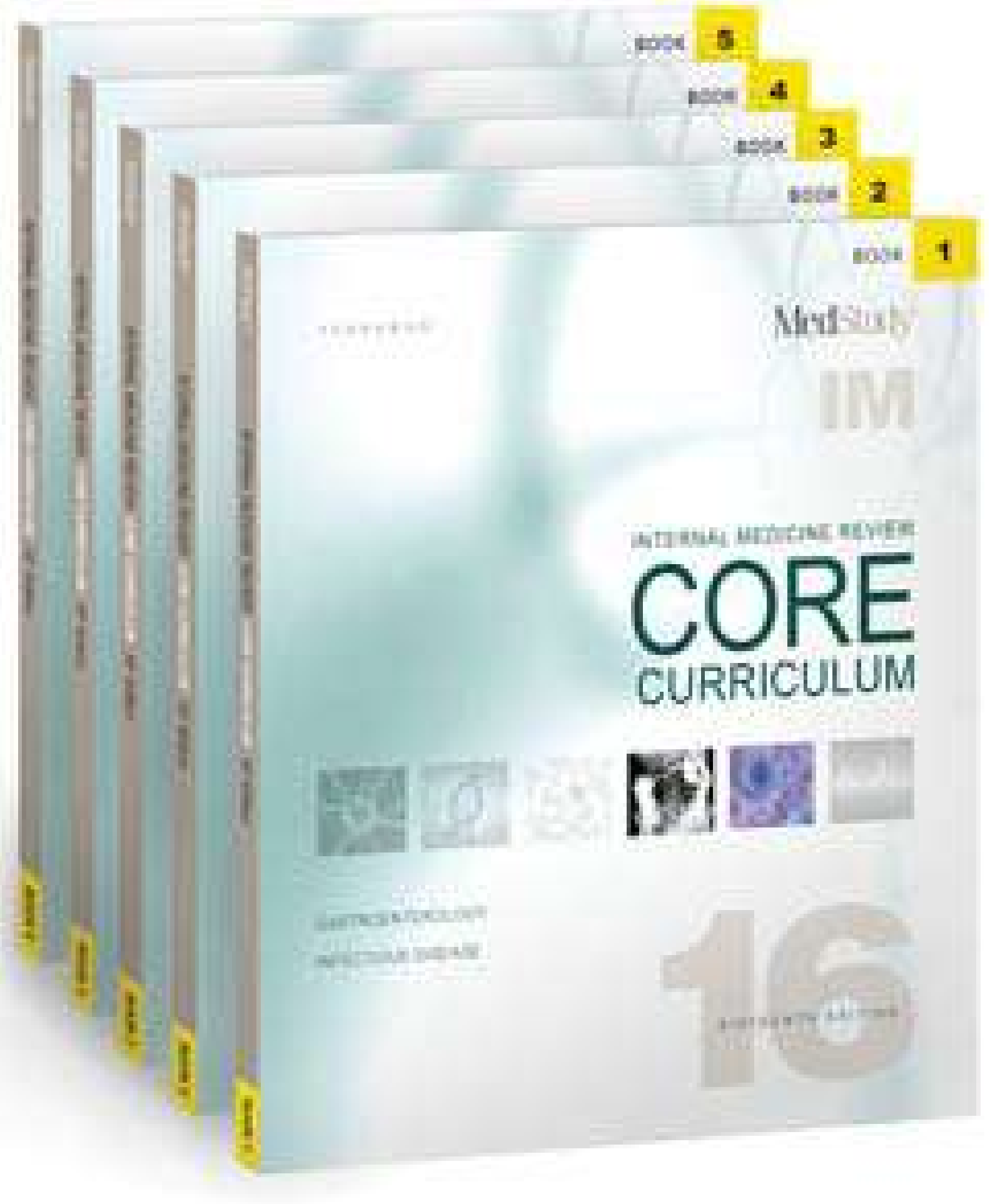
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Endocrinology

HELPFUL GENERALITIES

If you want to test for hyposecretion of a hormone, try to stimulate it. Example: In cases of suspected adrenal insufficiency, the ACTH stimulation test is performed to stimulate cortisol production.

If you want to test for hypersecretion of a hormone, try to suppress it. Example: In cases of suspected Cushing syndrome, the dexamethasone suppression test is performed to suppress production of cortisol.

Important characteristics to know about a hormone:

- What is its function?
- Where is it produced and secreted?
- What stimulates and inhibits its release?
- Where are these controls?
- How is it secreted? Is it diurnal or tonic?

Note: Many endocrine glands are responsive to regulatory feedback mechanisms, which determine the extent of hormone secretion by either negative feedback or positive feedback. Negative feedback decreases the deviation from an ideal normal value and is important in maintaining homeostasis. Most endocrine glands are under the control of negative feedback mechanisms.

PRIMARY vs. SECONDARY vs. TERTIARY

With regard to glandular abnormalities:

Primary refers to disease in the gland that secretes the hormone. Example: Primary hypothyroidism means the thyroid gland is diseased and not producing thyroxine.

Secondary refers to disease of the gland that controls the primary gland. Example: Secondary hypothyroidism means the pituitary is diseased and not producing TSH to stimulate the thyroid to make thyroxine.

Tertiary refers to disease of the gland that controls the gland that controls the primary gland. Example: Tertiary hypothyroidism means the hypothalamus is diseased and not producing TRH to stimulate the pituitary to release TSH to stimulate the thyroid to make thyroxine.

Let's do one more example:

Primary hyperaldosteronism means that the disease is in the gland that makes aldosterone, which is the adrenal. This would be an aldosterone-secreting tumor.

Secondary hyperaldosteronism means that the disease is in the gland that controls aldosterone release. The kidney releases renin, which stimulates the adrenal to produce aldosterone. So, in secondary hyperaldosteronism, disease is at the level of the kidney. This would be renovascular disease or a renin-secreting tumor.

POSTERIOR PITUITARY

The pituitary gland is considered the master gland. Functionally, it is comprised of the anterior pituitary and the posterior pituitary, each of which participates in different hormonal axes. Each axis has a different set of hormonal output and controls.

The hypothalamus controls output of the anterior pituitary by means of hormones. It controls the output of the posterior pituitary (neurohypophysis) by direct nerve stimulation. The posterior pituitary stores and releases oxytocin and antidiuretic hormone ([ADH]; also called vasopressin). The anterior pituitary contains osmoreceptors, which control ADH release and are responsible for the sensation of thirst.

Above a certain threshold of serum osmolality (relatively less water than solute), the kidneys have a compensatory and proportionate response of concentrating the urine in response to the secretion of ADH. The threshold set point is decreased (ADH is released at a lower osmolality) by pregnancy and pre-menses; the set point is increased by chronic hypervolemia, acute hypertension, and corticosteroids. Volume contraction both increases the amount of ADH released and decreases the threshold set point.

Serum osmolality can be estimated. Remember the formula: Osmolality = 2[Na+] + (Glucose/18) + (BUN/2.8).

ADH also is released in response to non-osmotic factors; the most potent of these is nausea, which increases ADH levels to several hundred times normal. Thirst begins when serum osmolality exceeds 295 mOsm/L and becomes more intense as serum osmolality increases. Dehydration and hypovolemia also increase thirst and thereby increase the secretion of ADH, but only in extreme circumstances such as shock.

ANTERIOR PITUITARY GLAND

OVERVIEW

The anterior pituitary contains 6 hormones:

1) Adrenocorticotropic hormone (ACTH)
2) Growth hormone (GH)
3) Luteinizing hormone (LH)
4) Follicle-stimulating hormone (FSH)
5) Prolactin (PRL)
6) Thyroid-stimulating hormone (TSH)

The hypothalamus-pituitary-target organ loops stimulate hormone production when serum levels are low and inhibit hormone secretion when serum hormone levels are high. The hypothalamus stimulates pituitary hormone secretion, which then stimulates target organ hormone production. Target organ hormones negatively feed back to both the pituitary and the hypothalamus.

There are 2 types of signals that control the release of anterior pituitary hormones:

1) The stimulatory hormones produced by the hypothalamus (e.g., thyrotropin-releasing hormone)
2) Target organ hormone feedback (e.g., thyroxine, cortisol)

ACTH has a diurnal variation with a peak at 3–4 a.m. and a nadir at 10–11 p.m. ACTH stimulates the adrenal gland to produce corticosteroids and androgens, and it has a regulatory effect on production of mineralocorticoids. ACTH increases in response to corticotropin-releasing hormone (CRH) and physical or psychological stresses.

GH is secreted in a pulsatile fashion and is regulated by 2 hypothalamic-releasing hormones—growth hormone-releasing hormone (**GHRH**) and somatostatin (also known as growth hormone-inhibiting hormone or **GHIH**). GHRH causes release of GH from the pituitary, and somatostatin/GHIH inhibits release of GH from the pituitary. Somatostatin/GHIH also has the capability to inhibit the release of TSH from the pituitary.

LH and **FSH** are produced by gonadotrophs, and production is regulated by pulsatile secretion of gonadotropin-releasing hormone (**GnRH**) from the hypothalamus. **Inhibin** (produced in the ovary and testis) inhibits only FSH secretion.

PRL is different from the other hormones because it is under tonic inhibition by hypothalamic dopamine sent down the pituitary stalk.

TSH secretion is stimulated by hypothalamic thyrotropin-releasing hormone (**TRH**) and inhibited by T_4, T_3, and somatostatin/GHIH.

PITUITARY TUMORS

Overview

Pituitary tumors are most often found incidentally or following imaging of the brain secondary to a patient's symptomatic complaints. Pituitary tumors are due to the abnormal proliferation of cells of the anterior pituitary. The first step in evaluating a pituitary tumor is to determine whether it is functionally abnormal and whether it is secreting an abnormal amount of any of the various hormones.

If functionally abnormal, any of the following cell types can be responsible for the tumor growth and may have any of the following effects:

- **Lactotrophs** (prolactinomas) --› hyperprolactinemia; tied with gonadotrophs as the most common type of macroadenomas
- **Gonadotrophs** → variable presentation:
  - Mass effect + clinically silent
  - Mass effect +/– gonadotropin deficiency/ partial panhypopituitarism
  - Mass effect +/– gonadotropin hypersecretion; tied with lactotrophs for most common type of macroadenomas
- **Somatotrophs** → hypersecretion of GH resulting in acromegaly
- **Corticotrophs** --› hypersecretion of ACTH resulting in Cushing disease
- **Thyrotrophs** → hyperthyroidism = least common
- **Mixed cell type** (somatotrophs + lactotrophs) → features of both acromegaly and hyperprolactinemia

It is important to check prolactin in somatotroph tumors and IGF-1 in lactotroph tumors.

Common mass effect symptoms include headaches, diplopia or visual field defects (bitemporal hemianopsia, most commonly), and seizures. Less commonly, adenomas can extend and cause CSF rhinorrhea. Acute hemorrhage into an adenoma causes apoplexy.

Especially suspect a pituitary adenoma when a patient presents with multiple hormone abnormalities, such as a mixture of hypothyroid and adrenal insufficient symptoms (i.e., reflexes with delayed returns, confusion, alopecia, constipation, menorrhagia or amenorrhea plus hyponatremia, nausea/vomiting, low-grade fever, and postural hypotension).

When given FSH and LH levels, always determine whether the levels are appropriate for the reproductive stage of the female (pre- vs. postmenopausal). For example: If a postmenopausal female patient has inappropriately low or normal FSH and LH levels (should have an elevated FSH level), there is a disruption in production of gonadotropins.

Diagnosis: If a patient's history/PE suggests a pituitary tumor (or if an imaging study done for other reasons shows an incidental pituitary mass), the initial goal is to determine which cell type has expanded into a mass. Start by imaging the tumor with an MRI (if not already done), and assessing the following hormones for excesses or deficiencies:

- Prolactin
- IGF-1 to screen for acromegaly
- 24-hour urine free cortisol concentration or 1 mg overnight dexamethasone suppression test (if suspect cortisol excess) or ACTH stimulation (if suspect cortisol deficiency)
- TSH and free thyroxine (FT_4)
- α subunit, FSH, and LH

α subunits are inactive pieces of glycoprotein and, when found in increased amounts, they support a diagnosis of gonadotroph adenoma. Finding these subunits indicates that a pituitary mass is definitely pituitary in origin (vs. non-pituitary, such as craniopharyngioma). On MRI, craniopharyngiomas present as calcified cystic suprasellar lesions and are considered to be benign. However, they may cause symptoms secondary to mass effect and impingement on the optic nerve.

When and how to properly order these hormone tests is discussed in their representative sections that follow.

QuickQuiz

- What is meant by positive and negative feedback regulation in endocrine diseases? Which is most common: positive or negative feedback?
- What are the definitions of primary, secondary, and tertiary hormone diseases?
- What are the hormones of the posterior pituitary?
- What is the formula to estimate serum osmolality?
- What are the hormones of the anterior pituitary?
- What are typical signs and symptoms of a pituitary tumor?
- Aside from a prolactinoma, what are the other causes of hyperprolactinemia?

Radiologists may occasionally report an "empty sella." An apparent empty sella may be caused by loss of the pituitary, but it may also be normal. 90% of the patients with empty sella syndrome are multiparous women whose pituitary has been displaced and compressed by CSF but functions normally. No treatment is needed for empty sella syndrome if no hormone deficiencies are associated. Of course, the sella may actually be "empty," and the patient may have hypopituitarism.

Hyperprolactinemia and Prolactinomas

A serum prolactin concentration that is repeatedly >20 ng/mL is elevated and is termed "hyperprolactinemia."

A level of 21–40 ng/mL is considered a slight elevation and can be caused by many factors:

- Drugs that are dopamine antagonists; i.e., metoclopramide, verapamil, and certain antipsychotics (phenothiazines, haloperidol, risperidone)
- Diseases of the hypothalamus and/or pituitary stalk that interfere with production or transport of dopamine; e.g., sarcoidosis and trauma
- Pregnancy or estrogen use (Estrogen inhibits dopamine outflow.)
- Nipple stimulation in lactating women
- Chest wall injuries
- Hypothyroidism
- Chronic kidney disease
- Prolactinomas
- Food intake (So prolactin should be checked fasting.)

A serum prolactin concentration > 200 ng/mL almost always is caused by a prolactinoma.

Prolactinomas are the most common functional pituitary tumor. They are usually microadenomas (< 1 cm in diameter), but they can also be space-occupying macroadenomas (≥ 1 cm in diameter) associated with visual field defects. The elevated PRL level decreases the release of GnRH, thereby causing a decrease in LH and FSH. A decreased LH and FSH may result in erectile dysfunction in men and amenorrhea and hirsutism in women. PRL levels generally correlate with tumor size (> 100 μg/L for macroadenomas); if the tumor is ≥ 1 cm, and the PRL level is < 100 μg/L, then the tumor is not a prolactinoma.

Due to amenorrhea, prolactinomas are found earlier in women than in men. Decreased libido is the earliest symptom of a prolactinoma in males and is often ignored; so men tend to present later with visual field defects. By the time most men seek care, the tumor has grown considerably. Galactorrhea occurs in most women with prolactinomas but rarely in men. Long-standing, unrecognized disease is associated with decreased skeletal bone mineralization in both men and women.

Treatment for these tumors is started when the size of the tumor causes neurologic symptoms (headaches, visual field disturbances) or when hypogonadism exists.

Microadenomas usually do not increase to > 1 cm, so observation may be an appropriate option for these patients; however, serial MRIs should be done to assess any change in size. For patients who do require an intervention, therapeutic options include medical and surgical treatment.

For most patients, medical therapy with dopamine agonists such as cabergoline and bromocriptine is the best initial option. Dopamine agonists reduce both the PRL level and tumor size. Cabergoline is better tolerated (twice-weekly dosing and less nausea) and is now available as a generic formulation. Cabergoline is associated with increased cardiac valvulopathy when administered at very high dosages as in the treatment of Parkinson's. Cabergoline is contraindicated in patients with known lung, heart valve, and retroperitoneal fibrotic disease.

Transsphenoidal surgery is used when the patient cannot tolerate drug therapy, or when it is ineffective. Postoperatively, an elevated PRL level is indicative of a recurrence, particularly in the case of macroadenomas. Radiation is usually reserved for postsurgical cases to eradicate any remaining tumor.

When a patient on drug therapy for a prolactinoma becomes pregnant, the drug is stopped, and the patient is observed using a good review of systems, physical exam, and visual fields testing. About 1/3 of macroadenomas enlarge during pregnancy. If the tumor enlarges enough to cause symptoms, bromocriptine can be restarted. If vision is threatened, surgery is a therapeutic option. Both bromocriptine and cabergoline are FDA pregnancy category B drugs.

Acromegaly

Growth hormone (GH) is required for normal growth. GH is suppressed by hyperglycemia, somatostatin, and chronic corticosteroid use and stimulated by hypoglycemia and estrogens.

A single value of GH is not useful in diagnosing acromegaly because its secretion is pulsatile and levels in the blood can vary greatly in a healthy individual. Insulin-like growth factor-1 (IGF-1) is produced by the liver and mediates the growth-promoting effect of GH. Unlike GH, IGF-1 levels are stable throughout the day. IGF-1 is the 1st test done in the workup of acromegaly. Normal levels almost always exclude the diagnosis. If the IGF-1 levels are elevated, perform a GH suppression test (following an oral glucose load). Inadequate suppression confirms the diagnosis of acromegaly.

Gigantism is due to GH excess in childhood, which results in abnormally high linear growth while the epiphyseal growth plates of the long bones are open. Acromegaly is the same disorder of GH excess; however, it occurs during adulthood after the growth plate cartilage fuses. Excessive soft tissue growth is characteristic of acromegaly and may recede following treatment. Long bones changes, however, do not recede following treatment.

Greater than 99% of acromegaly cases are due to a benign, well-defined adenoma that is easily recognized on CT or MRI.

Acromegaly has an insidious onset associated with an increased mortality when untreated and is usually diagnosed late in the course of disease. Affected patients typically are symptomatic in their late 30s to mid 40s.

Signs and symptoms of acromegaly include:

- Enlarging hands and feet
- Coarsening of the facial features
- Deepening of the voice
- Carpal tunnel syndrome
- Acanthosis nigricans
- Skin tags
- Pronounced jaw growth (which leads to multiple dental problems)
- Excessive sweating, body odor
- Sleep apnea

The most important long-term problem associated with acromegaly is cardiovascular disease, including:

- Ischemic heart disease
- Cardiomyopathy
- Diastolic dysfunction
- Hypertension
- Left ventricular hypertrophy
- Increased strokes

Associated diseases include obstructive sleep apnea, insulin resistance and diabetes, and colon polyps that have an increased risk of malignancy.

Screen by checking for a high age-adjusted IGF-1 level. Confirm the diagnosis by demonstrating a failure of GH to suppress after a 75-gm oral glucose load (OGTT). A post-OGTT GH level > 1 ng/mL is diagnostic of acromegaly. Do not order a random GH level. Also check prolactin (elevated due to co-secretion in 25% of GH tumors). Large tumors disrupt thyroid and gonadotropin release, so these levels may also need to be assessed.

Treat all patients with transsphenoidal surgery, even if they are asymptomatic. Give somatostatin analogs (octreotide), +/– dopa agonists (bromocriptine or cabergoline), or GH receptor antagonists (pegvisomant) as adjuvant treatment to patients with residual tumor or to those who are poor surgical candidates. Some experts recommend medical therapy with somatostatin analogs as initial therapy. Radiation is used only as adjuvant treatment. All patients with a diagnosis of acromegaly should have a screening colonoscopy and echocardiogram regardless of age.

Other Pituitary Tumors

We discussed gonadotroph tumors in the Overview. Recall they are tied with prolactinomas for being the most common type of macroadenomas. Gonadotroph tumors can present variably as:

- mass effect and hormonally silent, or
- mass effect with symptoms of hypogonadism/partial panhypopituitarism, or
- mass effect with symptoms of gonadotropin excess (rare).

A diagnosis of gonadotroph adenoma is supported by finding an increase in free α subunits or high levels of FSH and/or LH.

Transsphenoidal surgery is indicated for symptomatic nonfunctioning or gonadotroph tumors.

For asymptomatic patients with preserved endocrine function and no mass encroachment on vital structures, observation with serial imaging studies may be appropriate.

Radiation is an option for certain types of tumors but primarily is used postsurgically to contain residual tumor mass. Patients who have had pituitary radiation need their anterior pituitary function monitored indefinitely.

With severe primary hypothyroidism (disease of the thyroid gland), the pituitary thyrotrophs become hyperplastic and may simulate a tumor—imaging shows a pituitary mass. Free T_4 is low, TRH and TSH levels increase, and the elevated TRH suppresses dopamine, which increases PRL; thus, the patient may be mistakenly diagnosed with a prolactinoma. Treatment with thyroxine replacement causes the thyrotrophs to shrink, and PRL levels to normalize.

Metastatic cancer can be seen in the pituitary—the posterior part of the gland is most often involved. Posterior pituitary mets present as diabetes

QuickQuiz

- How do you test for acromegaly?
- Which cancers metastasize to the pituitary?
- What is the workup for a pituitary incidentaloma?
- What is the clinical presentation of pituitary apoplexy? The treatment?

insipidus. Breast and lung cancer mets are most common. Lymphoma and leukemia can present as primary cancer of the pituitary.

PITUITARY INCIDENTALOMA

Some pituitary tumors are incidentally found when brain imaging is performed for other reasons (termed an "incidentaloma").

Formally test visual fields of patients who have tumors that impinge on the optic nerve or abut the chiasm. Work up the patient for hyper- and hypo-secretion of hormones:

- Measure PRL because prolactinomas are common.
- Check IGF-1 to screen for acromegaly.
- Order either a 24-hour urine free cortisol or a low-dose overnight dexamethasone suppression test if you suspect cortisol excess (e.g., HTN, hyperglycemia, associated physical characteristics). A random ACTH level is not recommended at time of initial screening.
- Check TSH and FT_4.
- Check a morning cortisol to assess hyposecretion.
- Check LH, FSH and testosterone.
- Gonadal function in premenopausal women can be assessed by history and physical exam alone.

If the tumor is nonfunctional, does not impinge on the optic chiasm, and there is no hyposecretion of hormones, then the tumor can be reimaged in about 6 months and again in 1 year to assess growth.

Indications for surgical removal include visual field or other ophthalmologic defects, a lesion in or abutting the optic chiasm or compressing the optic nerve, apoplexy, or discovery of acromegaly or Cushing disease.

Additionally, recognize that the tumor could also be a metastatic focus—lung and breast are most common.

Apoplexy and Sheehan Syndrome

Pituitary apoplexy is a neurosurgical emergency caused by hemorrhage into a pituitary mass. Suspect apoplexy in the patient who presents with a variable onset of severe headache, N/V, meningismus, vertigo, visual defects, and fluctuating consciousness. These symptoms may be superimposed on chronic symptoms of hormone excess or deficiency if there is an underlying adenoma. Laboratory values should show decreased ACTH and cortisol levels. On stimulation with cosyntropin, the cortisol level increases since the adrenals remain intact. The most dangerous situation is an acute, life-threatening hypotension from central or secondary adrenal insufficiency.

The symptoms may occur immediately ("mule kick in the head") or may develop over 1–2 days. Diabetes with microvasculature changes, radiotherapy, and concurrent warfarin use are risk factors. Patients may present with an acute onset and complaints of "the worst headache of my life." Apoplexy and Sheehan syndrome may be difficult to distinguish from subarachnoid hemorrhage. Pituitary hormones are abnormal in apoplexy and Sheehan syndrome.

Diagnose with CT/MRI ("high-density mass in the sella") and differentiate from a leaking aneurysm.

Treatment: If the symptoms are mild, only corticosteroids are necessary. Edema may cause a mass effect and require emergent decompression. Consult a neurosurgeon to make the call on whether to use corticosteroids or take the patient to surgery.

Sheehan syndrome (1/10,000 deliveries) is postpartum hypopituitarism caused by ischemic necrosis due to blood loss and hypovolemic shock during and after childbirth. It always involves the anterior pituitary and sometimes also affects the posterior pituitary, but rarely causes central diabetes insipidus.

In mild cases, the syndrome presents with postpartum amenorrhea and failure to lactate. Severe cases present with symptoms of adrenal insufficiency (weakness, lethargy, anorexia) and failure to lactate.

Other causes of hypopituitarism include pituitary and parasellar tumors, radiation, infections, inflammation, and infiltrative processes, such as sarcoidosis or histiocytosis X.

DIABETES INSIPIDUS

Diabetes insipidus (DI) can be neurogenic (decreased ADH production) or nephrogenic (decreased ADH effect on the kidneys). Neurogenic DI is either genetic (50%) or acquired. The acquired neurogenic form is caused by CNS injury, infiltrative diseases (e.g., eosinophilic granuloma, sarcoidosis, granulomatosis with polyangiitis), or cancer; however, occasionally, it is idiopathic or vascular (e.g., Sheehan syndrome). Nephrogenic DI is also either genetic (due to gene mutations in the ADH receptor or in an aquaporin [aquaporins are discussed in Nephrology, Book 2]) or acquired. Drugs are an important cause of DI, especially lithium. Any cause of hypercalcemia > 11 mg/dL for an extended period also can cause acquired DI. Also know that Sjögren's and sickle cell disease can cause DI.

Understand that expression of DI, whether central (neurogenic) or nephrogenic, is variable with subsets of disease being named "partial central" and "partial nephrogenic" DI. Know how to distinguish central from

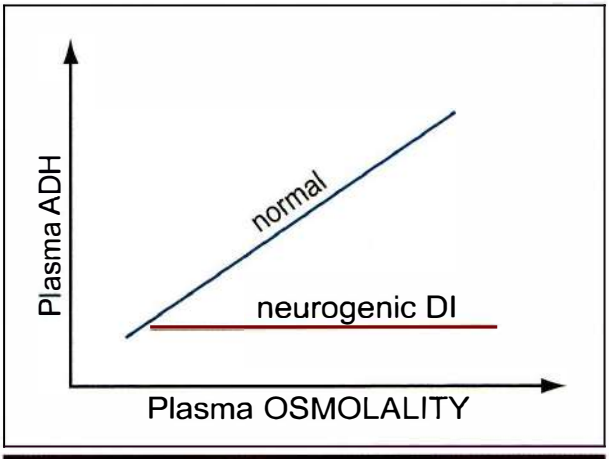

Figure 7-1: Neurogenic DI

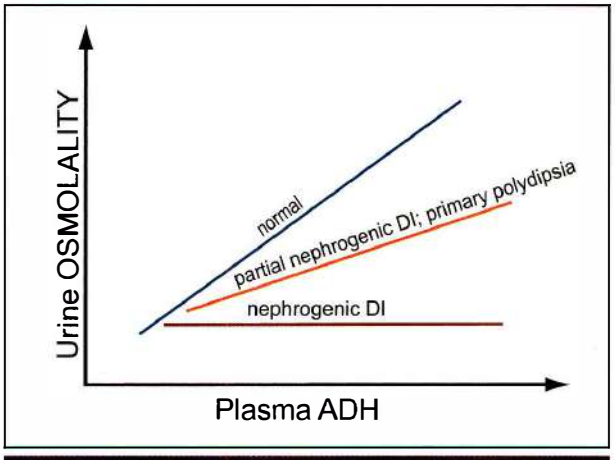

Figure 7-2: Nephrogenic DI

nephrogenic disease. And know that primary polydipsia mimics DI, which should be considered in patients with polydipsia and polyuria. The water deprivation test helps to differentiate between DI and psychogenic polydipsia.

Nocturia usually is the 1st symptom of DI. Volume depletion rarely occurs, except in patients with impaired thirst or decreased access to water; e.g., infants, nursing home patients. With water restriction, DI causes very dilute polyuria (> 3L/day) and hypernatremia.

Diagnose the cause of DI with the water-deprivation test, in which you measure hourly ADH and plasma + urine osmolality. The 2 mechanisms for proper diagnosis can be shown with 2 simple graphs, which are important to know.

The first graph, Figure 7-1, has ADH as a function of plasma osmolality. If ADH does not increase with increasing plasma osmolality, the cause of the DI is central (neurogenic). If only numbers are given (instead of a graph), diagnose central DI when the urine fails to concentrate with water deprivation, but does concentrate after desmopressin administration.

The second graph, Figure 7-2, has urine osmolality as a function of plasma ADH. If there is increasing ADH with no associated increase in urine osmolality, the diagnosis is nephrogenic DI. If only numbers are given, diagnose nephrogenic DI if the urine fails to concentrate with water restriction and desmopressin administration.

Treat neurogenic DI with desmopressin (DDAVP®, Stimate●), either subQ or intranasally. Occasionally, desmopressin may be administered orally to patients with mild neurogenic DI. Nephrogenic DI is treated with a low-sodium diet and thiazide diuretics +/– amiloride.

If the thirst and ADH osmoreceptors are damaged, a patient has recurrent hypernatremic dehydration without thirst (adipsic hypernatremia). ADH does not increase with increasing osmolality but does respond to all the other stimulants mentioned above. To exclude, observe whether the patient develops thirst as serum osmolality increases.

SIADH

Aside from being idiopathic, the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has many causes, including CNS trauma or infection, pulmonary disease, drugs, and ectopic hormone production---especially with small cell lung cancer.

Generally, the patient has normal volume status but inappropriate urinary concentration for the hyponatremic, hyposmolar state. Serum osmolality is low, and urine osmolality is inappropriately high (the patient should be excreting water, not absorbing more). See Nephrology, Book 2, for more discussion of SIADH.

THYROID GLAND

NORMAL PHYSIOLOGY

TRH in the hypothalamus stimulates the pituitary to secrete TSH, which then stimulates secretion of thyroxine (T_4) by the thyroid. Triiodothyronine (T_3) is the active hormone, and some is secreted by the thyroid, but 80% is produced by deiodination of T_4 in the peripheral tissues. T_4 binds very tightly to TBG (thyroxine-binding globulin) and weakly to albumin. T_3 also binds to these proteins, but not as strongly. Only a very small fraction of the total T_4 and total T_3 is unbound—and, therefore, free and active. The free component is generally the fraction that you want to measure when testing for thyroid disorders.

THYROID FUNCTION TESTS

"Thyroid function tests" (TFTs) include TSH, FT_4, and sometimes FT_3. The T_3 resin uptake test has been replaced by the FT_4 assay.

When screening for primary thyroid disease, start with a TSH to detect abnormalities of thyroid function—both hyper- and hypothyroidism. If the TSH is high, then order a FT_4 to assess for hypothyroidism. If the TSH is low, then order a FT_3 + FT_4 to assess for hyperthyroidism (Table 7-1).

QuickQuiz

- What happens to the urine specific gravity and serum sodium in a patient with diabetes insipidus who is on water restriction?
- What are the urine specific gravity, serum sodium, and serum osmolality in a patient with SIADH?
- What is the first screening test of choice for hypo- and hyperthyroidism?
- What is the difference between the thyroid uptake and the thyroid scan? What do the different tests tell you?

OTHER THYROID TESTS

Uptake and Scan

If hyperthyroidism is established (with a low TSH and high FT_4), then the next step in the workup is to determine the cause of thyroid dysfunction. Two tests, the radioactive iodine uptake (RAIU) and thyroid scan (also called "scintigraphy"), help to establish a diagnosis by measuring the degree and pattern of iodine uptake by the thyroid. In clinical practice, these tests are often referred to as "the uptake scan," but recognize these are 2 different tests (the uptake and scan). The RAIU uptake measures the degree of iodine uptake (given as a percent uptake) by the thyroid. The scintigraphy scan assesses the pattern of iodine uptake (takes a "picture"). With thyroid scintigraphy, a diffuse, focal, or multifocal pattern is noted and helps to make a specific diagnosis.

RAIU: The patient is given a small dose of radioactive iodine; and then later, a radiation detector over the thyroid determines the percentage of the dose that was taken up by the gland. Know the uptake results (high, low, or normal) for various causes of thyroid disease.

RAIU is increased in:
- Graves disease
- TSH-secreting pituitary tumor
- Hot nodules (solitary or toxic multinodular goiter [MNG]), if hot enough
- hCG secreting tumor
- Iodine deficiency

RAIU is decreased in:
- Thyroiditis
- Excess exogenous T_4 or T_3
- Iodine excess (contrast dye, diet, amiodarone)
- Factitious hyperthyroidism

Thyroid scan (scintigraphy): The patient is given a dose of ^{99m}Tc or radioiodine (^{123}I) and a scintillation scanner produces a rough picture indicating how these isotopes localize in the thyroid. So the scan gives information on the size, shape, and overall activity of the gland. It also shows hot (hyperfunctioning) and cold (underfunctioning) spots. The scan is typically used for assessing goiters and nodular disease. It tells you whether a nodule is hot or cold and single or multiple.

The thyroid RAIU and scintigraphy scan are essential in determining the cause of hyperthyroidism and are never used in the workup of a hypothyroid patient.

Again: RAIU produces a number; the scan produces a picture.

Table 7-1: Overview of Thyroid Function Tests

TSH	FT_4	Clinical Status
High	Low	Primary hypothyroidism, chronic lymphocytic thyroiditis (Hashimoto's)
	Normal	Incipient/subclinical hypothyroidism
	High	Pituitary (secondary; TSH-induced) hyperthyroidism, thyroid hormone resistance syndromes
Low	High	Thyrotoxicosis (primary hyperthyroidism), subacute or silent thyroiditis
	Normal	Euthyroid sick syndrome, incipient/subclinical hyperthyroidism, multinodular goiter with autonomous production
	Low	Pituitary hypothyroidism

Ultrasound

Ultrasound (U/S) is used to determine the size and number of nodules, to determine whether a nodule is cystic or solid, to stratify a nodule's malignancy risk (low, medium, or high), to localize a nodule for fine needle aspiration, to follow up a nodule's size over time when malignancy is suspected, and to follow up a patient after thyroid cancer resection. U/S is discussed further in the section on the workup of thyroid nodules.

When a patient presents with a palpable nodule and is hyperthyroid, a RAIU and scintigraphy should always precede a thyroid ultrasound (U/S). When a patient presents with a palpable nodule and is hypothyroid or euthyroid, the next step in the workup is to go directly to U/S. This is discussed further under Nodule Workup (see page 7-13).

Biopsy

Fine needle aspiration (FNA) is a biopsy method used to evaluate a thyroid nodule (discussed on page 7-13).

HYPOTHYROIDISM

Findings

Chronic autoimmune thyroiditis (previously Hashimoto disease) is the most common cause of hypothyroidism.

It normally presents as gradual hypothyroidism, but it can present with a hyperthyroid phase, so-called "Hashitoxicosis." Other causes of thyroiditis also can be associated with a transient, self-resolving state of hypothyroidism.

Symptoms of hypothyroidism, regardless of cause, include:

- Cold intolerance
- Weight gain
- Fatigue
- Menstrual irregularities
- Mental slowness
- Constipation
- Puffiness in the face
- Extremity swelling
- Hoarseness
- Coarse hair/alopecia
- Brittle nails
- Dyspnea with exercise
- Carpal tunnel syndrome

Signs on physical exam include:

- Cool/Pale skin
- Coarse hair
- Periorbital and non-pitting edema
- Tongue enlargement (severe cases)
- Bradycardia
- Delayed reflexes

Abnormal labs/studies include:

- Hyponatremia
- Normochromic/normocytic anemia (pernicious anemia in 10% of cases)
- Hyperlipidemia (increased total cholesterol and LDL)
- Rare pericardial effusions on echocardiograms and possibly an increased PRL level (although usually < 100)

If a woman has an elevated PRL and amenorrhea, check thyroid function first. The elevated PRL and amenorrhea resolves with thyroxine treatment if they are due to hypothyroidism. If the patient is not hypothyroid, evaluate for a prolactinoma. And if the PRL level is > 200, the woman almost assuredly has a prolactinoma, even if she is also hypothyroid.

Diagnosis of Hypothyroidism

Check the TSH and the FT_4. Values are used together to determine whether the patient is hypothyroid and whether disease is most likely primary (in the thyroid), secondary (in the pituitary), or tertiary (in the hypothalamus):

- High TSH (> 10 mU/L) and low FT_4 = overt primary hypothyroidism.
- High TSH (5–10 mU/L) and normal FT_4 = "subclinical" or incipient primary hypothyroidism. Adrenal insufficiency can also slightly increase the TSH.

Subclinical hypothyroidism is an area of evolving understanding. We know TSH drifts up as we age and possibly as we gain weight. Studies indicate that patients with TSH 5–10 mU/L develop overt hypothyroidism at a rate of about 4% per year. The incidence of overt disease is proportional to the degree of TSH elevation (TSH > 6 mU/L indicates the most risk). A family history of autoimmune thyroid disease and evidence of associated anti-thyroid peroxidase (anti-TPO) are risk factors.

Treating subclinical hypothyroidism to reduce rates of hyperlipidemia and ischemic heart disease is too controversial for testing on Board exams; and in clinical practice, the decision to treat is very individualized. The guidelines at this time generally recommend no treatment for patients whose TSH is < 10 mU/L.

Low or inappropriately normal TSH with a low FT_4 = secondary or tertiary hypothyroidism except in hospitalized, sick patients who may have euthyroid sick syndrome (see page 7-12). Suspect secondary/tertiary disease when you see a deficiency of multiple hormones. (Isolated hypothyroidism due to pituitary or hypothalamic dysfunction almost never occurs.)

Secondary and tertiary diseases are differentiated by imaging the sella; no routine stimulation test is available. TRH is never given to stimulate TSH in order to distinguish secondary from tertiary disease because results are not reliable.

Treatment of Hypothyroidism

Treatment for overt hypothyroidism is levothyroxine (T_4) alone. Adding T_3 might help with some neuropsychological symptoms, but randomized controlled trials show that T_3 does not confer any benefit beyond that achieved with T_4 monotherapy. In addition, T_3 therapy is harder to regulate and may cause hyperthyroid effects, such as atrial fibrillation. T_3 has a short half-life—so short that wild swings in blood levels are noted when T_3 is used therapeutically; therefore, it is not recommended in the treatment of hypothyroidism.

T_4 has a long half-life and takes weeks to equilibrate, so in most cases, you can start patients on 50–100 μg/day.

You need to allow enough time for the blood level to come to a steady state, so don't check the TSH again until a full 6–8 weeks after a dose adjustment. For patients with the potential for coronary artery disease, especially the elderly, start low and slowly titrate up.

QuickQuiz

- What are common signs and symptoms of hypothyroidism? Lab tests?
- How do you make a diagnosis of secondary or tertiary hypothyroidism?
- What are the risks of overtreating hypothyroidism?
- What are signs and symptoms of myxedema coma?
- What is the treatment for myxedema coma?

Follow the TSH to evaluate treatment, and keep the level within the lower half of the normal reference range for your laboratory. Adjust the dose of levothyroxine upward in increments of 12.5–25 μg. Don't overtreat, because you risk inciting complications of hyperthyroidism, such as atrial fibrillation and osteoporosis.

Know that a TSH elevation > 10 mU/L in a patient prescribed > 200 μg/day of T_4 is most commonly due to nonadherence.

Watch out for other conditions and drugs that interfere with absorption of thyroxine, raise TBG levels, or increase the metabolism of T_4 (and that could be a cause of persistently elevated TSH despite usual dosages of T_4): malabsorption syndromes, estrogens, cholestyramine, iron/calcium/aluminum supplements, and resin binders.

If a patient is hypothyroid and needs emergent surgery for another reason, do it! Otherwise, try to restore euthyroidism before surgery.

Always treat pregnant hypothyroid patients and follow their TSH levels during pregnancy because their requirements increase (dose needs to be adjusted upwards 50% or more over the pre-pregnancy dose). Failure to treat maternal hypothyroidism during pregnancy can adversely affect the baby.

Myxedema Coma

Myxedema coma is one of 2 thyroid emergencies (the other being thyroid storm). Mortality is 30–40% and is higher in the elderly and in those with heart disease. The diagnosis depends on recognition of classic signs and symptoms. Management includes providing supportive care and instituting empiric treatment for hypothyroidism, possible adrenal insufficiency, and possible infection until the case is completely investigated.

Any cause of hypothyroidism can lead to myxedema coma. Patients usually present with a history of progressive hypothyroid symptoms. If not diagnosed, long-standing hypothyroidism can develop into myxedema coma; or, patients with known but inadequately treated hypothyroidism can develop coma precipitated by infections, exacerbations of heart disease, opiates, or cold temperatures. For the patient who presents to the emergency department obtunded with multi-system failure, quiz relatives for possible antecedent signs and symptoms of thyroid dysfunction.

Decreased mentation and hypothermia (even body temps down to 74° F!) are the classic findings. Other signs indicate a generalized slowing of systemic processes: hypoventilation, hypoglycemia, hypotension, and bradycardia.

Other symptoms depend on why the patient has thyroid disease:

- If the disease is primary, there may be no other symptoms; but, be aware that, rarely, primary autoimmune processes can affect both the thyroid and the adrenal.
- If the disease is secondary, the patient may have symptoms of other hormone deficiencies—again, adrenal insufficiency is especially important.
- Rarely, a patient can present psychotic ("myxedema madness") instead of obtunded.
- Patients may have a pericardial effusion.
- Up to 25% of patients have seizures.

Other lab abnormalities: hyponatremia, hypoglycemia, anemia, and hyperlipidemia.

Diagnose myxedema coma by history and PE.

Treatment of myxedema coma: Before initiating treatment, draw a serum TSH and FT_4, baseline cortisol, and ACTH to rule out coincident adrenal insufficiency; then give a dose of cosyntropin. Follow up cortisol measurements at 30 and 60 minutes to assess whether the patient has an appropriate rise in response to the ACTH stimulation (see Adrenal Gland on page 7-15).

Treat with either T_3 (preference of some experts because of rapid onset and decreased conversion of T_4 to T_3 during acute illness) or intravenous T_4 (due to reduced absorption with oral) or both T_3 and T_4 (preferred by most experts) using a loading dose and a smaller daily dose thereafter.

Give empiric glucocorticoids until the results of stimulation testing are available to determine whether to continue the steroids long-term. Once adrenal insufficiency has been eliminated, the steroids can be discontinued.

Give empiric broad-spectrum antibiotics until infection is excluded. Pay particular attention to gradually warming the body temperature, maintaining adequate blood pressure with IVF, and normalizing the serum sodium.

Know that the mortality of myxedema coma is directly related to the degree of hypothermia, and that passive rewarming is one of the most important elements of supportive care.

HYPERTHYROIDISM

Findings

The most common cause of hyperthyroidism is autoimmune Graves disease. Other common causes include toxic multinodular goiter (MNG), toxic adenomas, and thyrotoxicosis due to chronic autoimmune thyroiditis (hashitoxicosis). Subacute and postpartum thyroiditis also can cause thyrotoxicosis, but these are typically transient illnesses not associated with long-term primary hyperthyroid disease.

Symptoms of hyperthyroidism, regardless of cause, include:

- Anxiety and restlessness
- Irritability
- Insomnia
- Impaired concentration (even confusion or psychosis)
- Weight loss
- Diarrhea
- Heat intolerance
- Alopecia
- Onycholysis
- Dyspnea
- Menstrual irregularities (oligo- or amenorrhea, impaired fertility)
- In males: gynecomastia, decreased libido, impaired spermatogenesis, and/or erectile dysfunction

Exam may reveal:

- Warm skin
- The "hyperthyroid stare"(exophthalmos)
- Lid-lag
- Hypertension
- Increased heart rate
- Atrial fibrillation or ectopy in up to 20% of patients (more common in elderly)

Abnormal general labs/studies:

- Low total cholesterol and LDL
- Normochromic/normocytic anemia
- Hypercalcemia with increased bone alkaline phosphatase
- Osteopenia/osteoporosis
- Increased cardiac output, dilated cardiomyopathy, and any tachyarrhythmia

Be especially alert to diagnose hyperthyroidism in the elderly patient who may have new-onset atrial fibrillation or depression (termed "apathetic hyperthyroidism"). Hyperthyroidism in the elderly can cause a "failure-to-thrive" picture with apathy, anorexia, and weight loss. In practice and on exams, you may need to distinguish thyroid disease from polymyalgia rheumatica and clinical depression or adjustment disorder.

Graves Disease

Overview

Graves disease is the most common cause of thyrotoxicosis. It is caused by thyroid-stimulating immunoglobulins, IgG antibodies that bind to and stimulate the TSH receptors in the thyroid gland.

Specific Graves disease physical findings (in addition to those listed above; also see Image 7-1):

- A diffuse, soft, symmetric goiter (but not always).
- Ophthalmopathy: Exophthalmos and periorbital edema with impaired extraocular movements → diplopia, corneal ulcerations, visual impairment. Know that the risk of Graves ophthalmopathy (GO) is increased in both active and passive smokers. Smoking is also associated with progression of GO after RAI therapy and adversely affects the course of GO during treatment with steroids and orbital radiotherapy. Know that 90% of Graves patients have ocular involvement on MRI or CT. Clinically apparent GO requires formal eye testing and imaging to determine the degree of eye inflammation. If a patient with mild-to-moderate GO decides on RAI treatment, pretreatment with steroids is warranted in order to prevent the progressions of GO. RAI is not indicated for patients with severe eye inflammation.
- Dermopathy: Pretibial myxedema is a thickening and redness of the dermis due to a lymphocytic infiltrate that gives it a peau d'orange appearance (looks different from the myxedema seen in hypothyroid patients).
- Immune-mediated hematologic abnormalities, such as pernicious anemia and idiopathic thrombotic purpura.

To diagnose Graves', use a good clinical exam + TFTs + thyroid uptake scan (TUS). TSH is low (usually < 0.01 mU/L), FT_3 and FT_4 are elevated (rarely, only FT_3 is increased with normal FT_4), and the TUS shows increased diffuse uptake. Other common lab abnormalities: elevated alkaline phosphatase, hypercalcemia, anemia, and thrombocytopenia. Autoantibodies are generally not measured, but TSI (thyroid-stimulating immunoglobulins) are positive in > 90% of cases of Graves disease.

Image 7-1: Proptosis & lid retraction

Quick Quiz

- What is apathetic hyperthyroidism?
- What specific physical findings confirm the diagnosis of Graves disease?
- What is the result of the thyroid uptake scan in a patient with Graves'?
- What are side effects of medications used to treat Graves'?
- What are the precipitating events leading to thyroid storm?
- In addition to PTU or MMI, beta-blockers, and iodine, what other drug is given to patients to treat thyroid storm?
- What causes subacute thyroiditis?

Treatment of Graves Disease

Treat with antithyroid drugs (methimazole [**MMI**] or propylthiouracil [**PTU**]) and/or thyroid **ablation** with ^{131}I or surgery.

MMI is now the preferred drug in non-pregnant patients because of lower toxicity than PTU. PTU received a FDA boxed warning for increased risk of death due to acute liver failure or severe liver injury, so PTU is no longer 1st line therapy in non-pregnant patients and children. PTU is still 1st line treatment for Graves disease in pregnant patients in the 1st trimester and is still used for thyroid storm.

The most serious side effects of PTU and MMI are hepatic toxicity and agranulocytosis, which are rare and unpredictable. LFTs and CBCs do not require monitoring. Check only if the patient becomes symptomatic (jaundice, dark urine, prolonged fever/sore throat). Side effects almost always disappear when the drug is promptly discontinued.

Beta-blockers help patients with adrenergic symptoms while waiting on the effects of PTU or MMI.

Relapse is much less likely when stimulatory immunoglobulins disappear with treatment, but this happens in a small minority of cases.

In the United States, most patients with Graves disease are treated with thyroid ablation using ^{131}I. Virtually all patients are pretreated with beta-blockers, and many patients are treated with MMI (or PTU) prior to radioiodine ablation. Most patients become hypothyroid months to years after ^{131}I therapy.

Surgery may be indicated in pregnancy, in patients with an associated cold nodule or relapse after radiation, and in some young patients with a large goiter. Worrisome complications of surgery are loss of all parathyroids and damage to recurrent laryngeal nerves.

Thyroid Storm

Storm is the 2nd thyroid emergency that is associated with a high mortality rate (the other is myxedema coma). Storm is most often a precipitated event in patients known or suspected to have undiagnosed or inadequately treated hyperthyroidism. Precipitating events include surgery, infections, or an iodine load, such as amiodarone or contrast dye.

Symptoms of storm are identical to symptoms of hyperthyroidism, only more exaggerated: hypertension, tachycardia, congestive heart failure, fever, psychosis, or delirium. Some patients have constitutional symptoms of nausea, vomiting, and diarrhea. Oddly, some patients develop jaundice. Diagnose the condition with measurement of TSH and FT_4. In virtually all cases, TSH is immeasurable and FT_4 markedly increased.

Storm is characterized by a severe level of metabolic stress that the patient can no longer tolerate. This severe stress results in a relative adrenal insufficiency, even though the adrenal glands may be functioning perfectly and secreting a large amount of cortisol. Patients in storm die from cardiovascular collapse. The most important aspect of treatment is large amounts of glucocorticoids.

Other aspects of treatment include the following:

- Interrupt the physiologic response to excess thyroid hormone: IV propranolol or esmolol.
- Block new hormone synthesis: high-dose thionamide (PTU or MMI).
- Block release of preformed hormone from the gland: stable iodide.
- Block peripheral conversion of T_4 to T_3: iodinated contrast agent, propranolol, and corticosteroids. PTU also does this (but not MMI).
- Give empiric broad-spectrum antimicrobial coverage until infection is excluded.
- Provide supportive care in the ICU with diligent attention to volume status, temperature, and heart rate.

THYROIDITIS

Thyroiditis is divided into the following categories:

- Acute: caused by bacterial infection of the gland (rare).
- Subacute: caused by viruses (also called "granulomatous").
- Chronic: Autoimmune-mediated disease is the most common cause (Hashimoto's). Painless and postpartum thyroiditis are considered variants of "chronic."

Subacute thyroiditis is a common problem in 30–50-year-olds, females > males. It is caused by a viral infection that results in granulomas in the thyroid gland, which becomes fibrotic but returns to normal months later. Patients complain of a very tender neck with pain that may radiate to the ear +/– fever, and are fussy about having their neck examined. As in other causes of thyroiditis, patients may be hypothyroid, hyperthyroid, or euthyroid.

Labs/studies: Initially, T_3 and T_4 are increased, TSH is suppressed, and RAIU is initially decreased. ESR is increased but is too nonspecific to use in diagnosis. Over time, temporary overt hypothyroidism develops in some with low T_4 and increased TSH. RAIU returns to normal. Eventually, T_4 and TSH normalize.

The disorder is self-limited and usually does not require treatment. For severe cases, treat inflammation as needed with ASA or NSAIDs. Glucocorticoids are given as an 8-week taper in refractory/systemic cases. Occasionally, a patient may need beta-blockers to ameliorate the thyrotoxicosis symptoms or levothyroxine for overt hypothyroidism. Reevaluate periodically until the patient's thyroid function normalizes.

Chronic autoimmune thyroiditis (e.g., Hashimoto's) is the most common thyroid problem (4% of the population, affecting women > men) and the most common cause of hypothyroidism. Both genetic and environmental factors are important (however not yet well defined). Cases are clustered in families, and the hypothyroidism is sometimes associated with other autoimmune diseases, such as Type 1 diabetes, primary adrenal insufficiency, pernicious anemia, and vitiligo.

Usually, patients become slowly hypothyroid as the gland is gradually destroyed by autoimmunity, but some patients may present with thyrotoxicosis before disease evolves into overt hypothyroidism. Presenting symptoms, therefore, are variable and depend on whether the disease is causing hypo- or hyperthyroidism. Chronic autoimmune hypothyroidism is characterized by a painless, chronic, lymphocytic infiltration of the gland causing a firm and often irregular goiter which sometimes is confused for multiple nodules (ultrasound helps distinguish). Up to 95% of patients have measurable anti-TPO antibodies. Immune-mediated thyroid cell apoptosis is the ultimate cause of hypothyroidism, but how these antibodies specifically cause cell death is unclear.

Presenting FT_4/FT_3 and TSH may vary on disease presentation:

- Incipient hypothyroidism = normal FT_4, rising TSH (2–10 mU/L)
- Overt hypothyroidism = low FT_4, high TSH (> 10 mU/L)
- Hyperthyroidism = high FT_4/FT_3, low TSH

In an exam situation, most patients with chronic autoimmune hypothyroidism present with hypothyroidism, which does not resolve and must be treated with levothyroxine.

Painless thyroiditis and postpartum thyroiditis are considered variants of chronic thyroiditis because, even though these conditions usually are transient and self-resolve, many patients become hypothyroid with evidence of autoimmunity in the future, especially painless thyroiditis cases.

Patients with **painless thyroiditis** have complaints of either hyper- or hypothyroidism, and some are actually asymptomatic. The disease process generally starts with a hyperthyroid stage (2–4 weeks), which progresses to a hypothyroid stage (4–12 weeks). Most patients recover. The gland shows diffuse, painless enlargement in contrast with subacute thyroiditis. 50% of these patients later develop chronic autoimmune hypothyroidism associated with anti-TPO antibodies.

Postpartum thyroiditis is fairly common, affecting up to 10–15% of postpartum women. Patients present with hyper- or hypothyroid symptoms and a painless goiter. ESR is normal, but many patients do have anti-TPO antibodies. RAIU is decreased. Don't hesitate to treat the hypothyroidism—or to give beta-blockers as needed for thyrotoxicosis. Patients universally recover but need annual follow-up because of the risk of overt hypothyroidism later.

Radiation thyroiditis may develop shortly (7–10 days) after exposure to radiation, which may be in the form of radioactive iodine treatment, radiotherapy of head and neck cancer, or accidental exposure (e.g., nuclear accident).

Remember: RAIU helps distinguish Graves' from thyroiditis as a cause for hyperthyroidism. RAIU is high in Graves and low in patients who are hyperthyroid due to thyroiditis, iodine excess, exogenous T_4 or T_3 ingestion, and struma ovarii (thyroid tissue in an ovarian teratoma). Thyroid scintigraphy scans are diffusely high for both Graves disease and hyperthyroidism caused by thyroiditis, but these are not typically done for non-nodular hyperthyroidism workup.

EUTHYROID SICK SYNDROME

Euthyroid sick syndrome (ESS) is seen in critically ill patients. In states of significant illness, the body does not need much T_3 (the active hormone). Instead, the body converts T_4 to reverse T_3 (rT_3), an inactive compound. The FT_3 is very low while both the FT_4 and TSH are low or low-normal.

In an exam question, the FT_3 usually is not included in the labs. Look for a sick hospitalized patient with a mildly decreased FT_4 and TSH near the lower limit of normal. Your first thought should not be pituitary insufficiency or an exotic hypothalamic disorder. If the patient is very ill, it is more likely non-thyroidal illness. The answer is to remeasure the TSH and FT_4 after the illness is improved. If the exam question insists that you prove your diagnosis, order an rT_3.

Remember 2 things:

1) Do not check TFTs in sick patients unless their acute illness is possibly due to a thyroid emergency (storm or myxedema coma).
2) In ESS, most of the T_3 is in the form of rT_3—rT_3 is high, FT_3 is low, and FT_4/TSH are variable. In central hypothyroidism, the rT_3 is low.

Quick Quiz

- What are the results of the thyroid uptake in patients with thyroiditis (all causes)?
- In what situations is it appropriate to check a sick patient's thyroid function?
- Workup of which nodule can cease after the uptake and scan test—a hot or cold one?
- List some characteristics associated with malignant nodules.
- If the TSH is high and an U/S of a solitary nodule is not concerning for malignancy, what is the most likely diagnosis?

Generally, the diagnosis of ESS is presumptive because central hypothyroidism is a very rare entity. An rT_3 level might be useful if you suspect multiple hormone deficiencies (thus, central disease). In this situation, the sella should be imaged too.

NODULES AND GOITERS

Overview

Nodules can be multiple or single, hot or cold. Most solitary nodules are cold, and most of those are benign. Virtually all hot or purely cystic nodules are benign.

A malignant nodule may be primary thyroid carcinoma or a metastasis. 5% of patients who had neck radiation as a child (especially with > 100 rads) get malignant nodules (mostly papillary carcinoma), and even more get nonmalignant ones (colloid adenoma).

Thyroid nodules are common. Now that ultrasound, CT, and MRI usually are employed to evaluate anterior carotid disease, nodules have been found incidentally but in abundance (up to 76% of the population)! Only about 5% of these nodules are malignant, however.

So the task for the internist is to determine which nodules are malignant and which ones aren't—keeping in mind that most nodules are not malignant. Any topic that requires judicious use of resources is important and likely to be emphasized on exams.

Here are some helpful generalities:

- Autonomously functioning nodules ("hot" nodules) are never malignant. So, a single hot nodule is not evaluated further. Histology from a hot thyroid nodule may be indistinguishable from a follicular thyroid malignancy, which could lead to high false positive rates and possibly unnecessary treatment with surgery or RAI. So, do not ever recommend biopsy for a hot nodule! Never, ever!
- The majority of nodules are cold, and the majority of these are benign, but thyroid malignancies also present as cold nodules.
- Cold nodules in a patient with Graves' still are evaluated because they may be malignant.
- **Multinodular goiters** (MNG) can have both hot and cold nodules. (If a hot nodule is hot enough, it becomes a toxic MNG.) Evaluate the cold nodules because cold nodules in MNG and solitary cold nodules have the same overall malignant risk.
- Do not routinely screen for thyroid nodules with U/S unless the patient has risk factors for malignancy; however, all palpable nodules (including MNGs) should be viewed with U/S as a general rule.

Risk Factors for Thyroid Nodules

Palpable nodules should be considered in terms of risks for malignancy. The following are risk factors that increase the possibility that a nodule is malignant:

- Hx head/neck irradiation
- Family Hx of thyroid cancer
- Age < 20 or > 70 years
- Male
- Growing nodule (if the rate of growth is rapid, you must rule out a thyroid lymphoma)
- Firm or hard consistency
- Lymphadenopathy
- Fixed
- Symptoms of compression in a patient without comorbid goiter: dysphonia, dysphagia, and cough
- U/S features: microcalcifications, marked hypoechogenicity, irregular margins, absence of hypoechoic halo around the nodule, lymphadenopathy, local invasion into adjacent structures

General rule: If a thyroid nodule (single, multiple, or within MNG) has any suspicious characteristics by Hx or U/S, refer for fine needle aspiration (FNA).

Again, do not biopsy hot nodules.

Nodule Workup

2010 American Association of Clinical Endocrinologists (AACE) practice guidelines suggest 2 algorithms—one for the palpable nodule and one for the incidentaloma (nodules found by coincidental imaging). The revised 2010 ATA thyroid nodule guidelines determine FNA based on risk factors, U/S features, and threshold size.

Palpable Nodules

Workup of solitary nodules:

Start with a good Hx and PE with focus on risk factors for malignancy. Then, do a thyroid U/S (even if the nodule was found on CT or MRI) and a TSH.

- Suspicious U/S: Do an FNA. Period. Do an FNA no matter the size or type of nodule or the level of TSH.
- Non-suspicious U/S. Consider the TSH:
  - **High**: Note that high levels of TSH correlate with increased likelihood that a nodule is malignant;

any irregular U/S features are important and should prompt biopsy. Large nodules (> 1 cm) usually are biopsied based on size alone (unless the nodule is "hot"). Evaluate for hypothyroidism by measuring free T_4 and anti-TPO antibodies. Treat hypothyroidism with thyroxine.

- **Low**: Do a scintigraphy scan. If nodule is single and hot, stop! You're done! Remember, do not ever biopsy hot nodules! Histologically, hot nodules can look very similar to cancer and biopsying them often can lead to many false positive readings. Treat hyperthyroidism with radioactive iodine or resection. Multiple nodules and cold nodules are discussed next.
- **Normal**: Most experts FNA this nodule if > 1 cm.

Workup of multinodular goiter (MNG):

In patients with a low or low-normal TSH and a MNG, a scintigraphy scan is done to determine which nodules are hot or cold. Do FNA on all cold nodules and any suspicious nodule seen on U/S. If U/S is not concerning, treat hyperthyroidism with ^{131}I or resection. Long-term treatment with anti-thyroid drugs (e.g., methimazole) may be considered in patients who refuse ^{131}I therapy and are not surgical candidates.

If the TSH is normal and the U/S shows no areas of malignant concern, stop! You're done. Very large nodules (> 1 cm) are often biopsied, though, based on size alone.

Further workup of all nodules: What you do after FNA of these nodules depends on what the pathology shows. Know that any "definitely malignant" or suspicious pathology goes to surgery, and nondiagnostic pathology (up to 20% of FNAs) goes for repeat FNA. More on MNGs on next page.

Incidentalomas

Thyroid nodules accidentally found during imaging for other reasons are referred to as thyroid incidentalomas. By definition, they are not palpable. They are worked up the same as other nodules with initial U/S (if not already done) and TSH. Biopsy any nodule with suspicious U/S characteristics, but when to biopsy based on size alone is more controversial than with a palpable nodule. Most experts definitely biopsy if the nodule is > 2 cm, but how to handle the 1–2-cm incidental nodule with a normal-appearing U/S is debatable. 2010 ATA guidelines determine FNA on U/S appearance (e.g., solid, cystic, mixed) and corresponding size thresholds. Do not biopsy cystic-appearing nodules.

Benign Nodular Disease

For nodules and/or MNG established as benign, treat when symptoms develop, such as compression of the trachea or discomfort in the neck. Recurrence of a cystic nodule after aspiration is considered to be an indication for surgical excision, as is persistent patient anxiety and concern about cosmetic appearance.

Toxic Adenoma

A toxic thyroid adenoma is a benign area of autonomous hyperfunctioning thyroid tissue. Most occur as a single nodule of hyperfunctioning tissue within normal tissue that grows slowly, eventually becoming large enough to suppress TSH production. The end result is an autonomous, hyperfunctioning nodule in the midst of "turned-off" thyroid tissue (a "hot" nodule). These are usually diagnosed by TFTs, which demonstrate overproduction of FT_3/FT_4 and suppression of TSH, and thyroid scan (focal uptake in "hot" nodule).

Treatment of thyroid adenomas: If the patient is hyperthyroid, use ablative treatment or perform surgery. Antithyroid drugs do not work long term. For the euthyroid patient with a thyroid adenoma, do not use suppressive therapy with thyroxine because it does not shrink the size of the adenoma, and you risk inducing hyperthyroidism. If the thyroid adenoma is compressing underlying structures or is cosmetically problematic, surgery is the best treatment. Percutaneous ethanol injection of autonomous functioning thyroid nodules is an alternative to surgery and RAI, with restoration of normal thyroid function in the majority of cases.

Review again: Graves disease has an increased RAIU, while hyperthyroidism caused by thyroiditis has decreased RAIU. Other causes of hyperthyroidism with a low RAIU are over-medication with thyroxine supplements and excess iodine; e.g., amiodarone. Besides Graves disease, other causes of high RAIU thyrotoxicosis are toxic MNG and (occasionally) toxic adenoma.

Thyroid Carcinoma

Thyroid cancer has 4 histologic types:

1) **Papillary** carcinoma: most common, usually indolent, spreads via lymphatics to bone/lungs.
2) **Follicular** carcinoma: less common, mimics normal thyroid tissue with early hematogenous spread to bone/lungs/CNS. Capsular invasion is an important part of staging for follicular thyroid cancer and a total thyroidectomy is needed for adequate staging.
3) **Anaplastic** carcinoma: rare, undifferentiated, and highly malignant; death within 6 months of diagnosis; no good treatment available.
4) **Medullary** (MTC): associated with hyperplasia of parafollicular C cells and elevated serum calcitonin; sporadic or inherited with ~ 15% occurring as component of multiple endocrine neoplasia MEN2A and MEN2B syndromes. MEN cases are associated with point mutations in the *RET* proto-oncogene → constitutive production of kinase that phosphorylates tyrosine residues and transduces signals for uncontrolled cell growth.

Treatment of thyroid cancer begins with a thyroid lobectomy (if papillary cancer is limited to one lobe) or a near-total thyroidectomy (for bilateral papillary thyroid cancer or for any follicular thyroid cancer). A near-total thyroidectomy always leaves part of the posterior

QuickQuiz

- What are the 4 histologic types of thyroid cancer? Which is the most aggressive?
- What is the hormone released by medullary thyroid cancer?
- MEN2A and MEN2B are associated with what histologic type of thyroid cancer?
- What is the gene associated with medullary thyroid cancer?
- Thyroid lymphoma is associated with what autoimmune disease?
- Name 3 different hormones that are produced in the adrenal cortex. (Also see Figure 7-3 on page 7-16.)

capsule around the recurrent laryngeal nerve intact. Frequently, a small amount of residual thyroid tissue also remains, and therefore most thyroid cancer patients need postoperative RAI. Additionally, those patients with risk factors for recurrence such as higher staging or larger adenoma size are also candidates for RAI. (You do not need to know the specific staging systems of the various thyroid cancers.) Following surgery, suppressive thyroxine therapy is necessary but is not started immediately after thyroidectomy. Instead, the TSH is allowed to rise on its own over several weeks, or alternatively, thyrogen is used to increase the TSH. When the TSH is > 30, a thyroglobulin level is measured and the patient is given a high dose of radioactive iodine in an attempt to kill any remaining cancer cells.

Several days after ablation, suppressive doses of thyroxine are started. Most differentiated thyroid cancers (follicular type) remain responsive to TSH, so keeping the TSH suppressed below the lower limit of normal helps prevent recurrence. Oversuppression of TSH may increase the risk of developing complications associated with hyperthyroidism; e.g., tachyarrhythmias, dilated cardiomyopathy, osteoporosis.

Long-term follow-up usually involves one or more of the following: neck ultrasound, total body scans, and/or thyroglobulin levels (as long as the patient doesn't have antithyroglobulin antibodies to interfere with the assay). Thyroglobulin levels following surgery and RAI should be 0, so any rise in thyroglobulin levels suggests recurrent disease (thyroglobulin is expressed only by thyroid tissue).

Thyroid lymphoma is associated with chronic autoimmune thyroiditis. Think about this in a patient with chronic autoimmune thyroiditis who develops a fast-growing thyroid mass. The most common tumor type is a diffuse large B-cell lymphoma, and these are treated with chemotherapy and external beam radiation. Surgery is used only for biopsy and diagnosis.

Goiter

Simple, nontoxic goiter is a diffuse enlargement of the thyroid gland with no metabolic symptoms other than enlargement. It may be caused by a lack of iodine or ingestion of a goitrogen; e.g., cassava root, Brussels sprouts, cauliflower, cabbage; but many cases are idiopathic. Diagnose nontoxic goiter with thyroid function tests: FT_4 and TSH are normal.

Treatment: Remove any goitrogens from the diet. If the cause is low iodine, iodine supplements help.

Multinodular Goiter: Nontoxic and Toxic

Nontoxic MNG is fairly common and occurs more often in women. Cause is multifactorial. Nodules of varying sizes are distributed throughout the gland, but patients are generally asymptomatic and euthyroid with a normal TSH. They come to attention because of the size of their gland or because (rarely) the gland gets large enough to compress surrounding structures.

Diagnosis is suspected when various-sized nodules are palpated in a goiter. Perform U/S to look for dominant nodules and features suspicious for malignancy. Nontoxic MNG has 2 main indications for treatment; otherwise, it is managed conservatively:

1) Symptomatic compression of key structures; e.g., trachea or esophagus
2) Cosmesis: surgical correction of a disfiguration

Standard treatment of nontoxic MNG, if indicated, is ablation with ^{131}I or bilateral subtotal thyroidectomy (if signs/symptoms of compression). Most benign nodules do not change size and remain benign. Thyroxine suppressive therapy typically is not used because it does not shrink most nodules, and long-term therapy risks the development of osteoporosis and atrial fibrillation.

Toxic MNG refers to a MNG with thyrotoxicosis. TSH is suppressed, and FT_3 and FT_4 are often increased. The thyroid scan usually shows 1 or more hot nodules.

Toxic MNG may temporarily be treated with antithyroid medications. Normal treatment is ablative therapy with radioactive iodine. This does not destroy all the nodules, but it does destroy those that are hyperfunctioning. Surgery is used in cases that are refractory, or in symptomatic cases, especially if a large goiter is compressing surrounding structures.

ADRENAL GLAND

OVERVIEW

Cortisol, adrenal androgens, and aldosterone are made in the cortex of the adrenal gland.

The adrenal cortex has 3 zones (remember "GFR"):

1) The outer zona glomerulosa (aldosterone = "salt")
2) The middle zona fasciculata (cortisol = "sugar")
3) The inner zona reticularis (androgens = "sex")

The chromaffin cells in the adrenal medulla mainly manufacture epinephrine.

Hypothalamic corticotropin-releasing hormone (CRH) is secreted in response to a low serum cortisol, stress, and circadian rhythm. CRH causes the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which stimulates the adrenal gland to release mineralocorticoids (aldosterone and precursors), glucocorticoids (cortisol and precursors), and androgens (mainly dehydroepiandrosterone [DHEA] and testosterone). ACTH has no effect on epinephrine production from the adrenal medulla.

STEROID SYNTHESIS

Refer to the steroid synthesis diagram (Figure 7-3). This diagram gives you all you need to know for those mind-boggling steroid deficiency questions.

Remember: In response to ACTH, the adrenal gland takes cholesterol and forms 3 products—mineralocorticoids, cortisol, and androgens—through a series of enzyme actions. It makes each of these products in 1 of the 3 layers of the adrenal cortex; hence, these chemicals are often called "adrenocorticoids."

In this diagram [Know it!], the green line represents normal pathways of steroid synthesis. The circles are the genes that code for important enzymes:

- *CYP21A2* = 21-hydroxylase
- *CYP17* = 17α-hydroxylase
- *CYP11B1* = 11β-hydroxylase

An "x" over the circle represents a defect in the gene with subsequent impairment of the enzyme for that step of synthesis. Recognize that whenever a pathway is blocked, precursors build up and push the reactions into the alternate pathways. If you know the effects of the final product of each pathway, then you can easily guess the clinical presentation of excesses that arise when any pathway is blocked and rerouted into other pathways.

Note that the color of the "x" shows what pathway increases if that enzyme is blocked. For example, a defect in either *CYP11B1* or *CYP21A2* results in increased DHEA and decreased aldosterone and cortisol. Not only that, but it causes a buildup in the chemical right before it. For example, a defect in *CYP11B1* causes a buildup of 11-deoxycortisol.

Now, let's go over the actions of the 3 ultimate products:

1) **Mineralocorticoids** (e.g., aldosterone) normally increase Na absorption and K^+/H^+ excretion, so high levels cause hypertension, hypokalemia, and alkalosis.
2) **Glucocorticoids** (e.g., cortisol) stimulate lipolysis, the release of amino acids from the muscles, and gluconeogenesis by the liver. Cortisol inhibits all stages of the inflammatory process and also affects the bones by decreasing the protein matrix. Its immunosuppressive effect is on T cells and their associated cell-mediated immunity and delayed hypersensitivity. Excess cortisol can additionally stimulate mineralocorticoid and androgen receptors with the clinical appearance of aldosterone excess (hypertension, hypokalemia, and alkalosis). Cortisol does not bind androgen receptors.

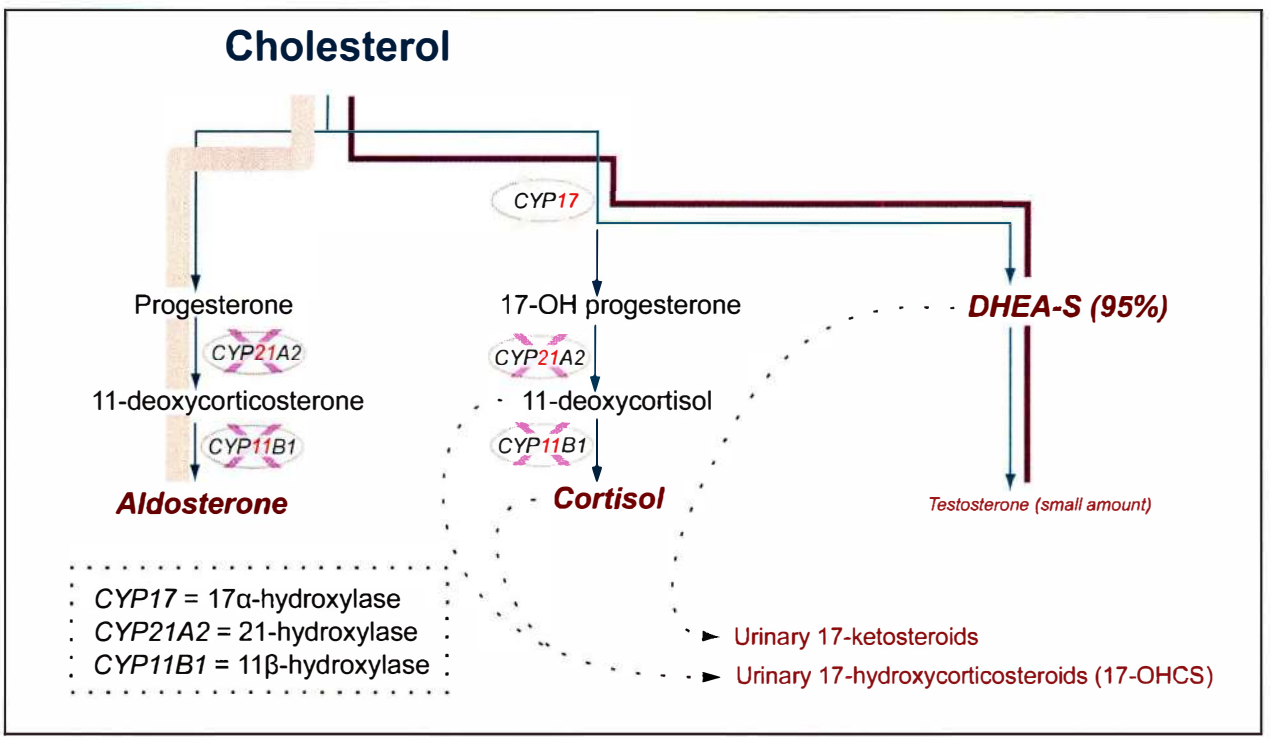

Figure 7-3: Adrenal Steroid Synthesis Pathways

Quick Quiz

- What is produced in the adrenal medulla?
- What genes control steroid synthesis in the adrenal cortex? What cortical hormones are increased and decreased when there is a defect in 21-hydroxylase? 17 α-hydroxylase? 11β-hydroxylase?
- What do mineralocorticoid hormones do?
- What are the effects of excess cortisol?
- What happens to a woman who overproduces adrenal androgens because of a disease process? How does she present?
- Which gene defect is most commonly associated with congenital adrenal hyperplasia?

3) Main androgens produced by the adrenals are **DHEA** and small amounts of **testosterone**.
   - In normal males, adrenal androgens are overshadowed by the effects of testicular androgens.
   - In normal females, the adrenals contribute half of the circulating testosterone. (Ovaries contribute the other 50%.) Together with adrenal DHEA, these androgens slightly virilize the female (small amounts of pubic and axillary hair). In excess, the clinical effects depend on whether disease occurs during gestation (causing ambiguous genitalia in females) or postnatally (causing a lot more hair and abnormal menses). Bottom line: Any time excess hair growth is noted in a female, think about overproduction of androgens by the adrenals or ovaries.

Refer again to the synthesis diagram:
- With defective *CYP21A2* and *CYP11B1*, the increased precursors force the reactions along the purple line with enhanced production of adrenal androgens.
- If *CYP17* is defective, the reaction is forced along the pink line, and more mineralocorticoids are produced.

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia (CAH) is a congenital, autosomal recessive decrease in the production of cortisol. It is caused by defects in the proper expression of any 1 of the 3 genes previously mentioned:
1) *CYP21A2* (95%; enzyme = 21-hydroxylase),
2) *CYP17* (enzyme = 17α-hydroxylase), or
3) *CYP11B1* (enzyme = 11β-hydroxylase).

95% of cases are due to mutations in *CYP21A2*, where 17-hydroxyprogesterone is not converted (and thus accumulates) and cortisol decreases. Complete impairment of *CYP21A2* during gestation forces an increase in DHEA and testosterone (purple line on diagram), which causes ambiguous genitalia in newborn girls.

Postnatal complete *CYP21A2* impairment results in a low cortisol level and an elevated ACTH, which causes hypertrophy of the adrenal gland and:
- increased androgen production (purple line on diagram), with
- subsequent virilization of females, or
- precocious puberty in males.

Late-onset (nonclassical) **CAH** occurs in postpubertal patients and is usually due to partial *CYP21A2* impairment. Genitalia are normal at birth, and the patient presents with signs of androgen excess (acne, hirsutism, accelerated bone age, and irregular menses in females). Labs show an early morning elevation of blood 17-hydroxyprogesterone and increased urinary 17-ketosteroids and blood DHEA. Confirm by observing elevated cortisol precursors (e.g., 17-hydroxyprogesterone) after ACTH stimulation. The most important test to remember for nonclassical CAH due to partial *CYP21A2* impairment is an elevated unstimulated or ACTH-stimulated serum 17-hydroxyprogesterone level.

Less commonly, late-onset CAH is due to impairment of *CYP11B1* with elevated 11-deoxycortisol and 11-deoxycorticosterone (potent mineralocorticoid precursors). Cholesterol is also shunted along the purple line into producing excess DHEA and testosterone. Thus, the clinical presentation is a hypertensive, hypokalemic, metabolic alkalosis with associated hirsutism and menstrual irregularities.

Quick review:

CYP21A2 = 21-hydroxylase deficiency; 95%; pushes pathway into formation of androgens only, with clinical presentation of virilized females (ambiguous genitalia if prenatal; hirsutism and menstrual irregularities if post-natal) and precocious puberty in males.

CYP11B1 = 11β-hydroxylase deficiency; ~ 4%; pushes pathway into formation of androgens and allows for buildup of aldosterone precursors, with clinical presentation of hypertension, hypokalemia, alkalosis + virilization of females or precocious puberty in males.

CYP17 = 17α-hydroxylase deficiency; < 1% [rare!]; pushes pathway into formation of only mineralocorticoids, with hypertension, hypokalemia, alkalosis, and hypogonadism (due to androgen deficiency). (These patients are also deficient of cortisol, but they are generally asymptomatic.) *CYP17* mutations are rare.

CUSHING SYNDROME

Overview

Cushing syndrome occurs when there is excessive adrenal glucocorticoid production causing complaints of proximal muscle weakness and easy fatigability; amenorrhea, hirsutism, and acne in females; easy bruising; and emotional lability (sometimes frank psychosis). Exam reveals facial plethora, thin skin with prominent bright pink-to-purple striae, cervicodorsal fat

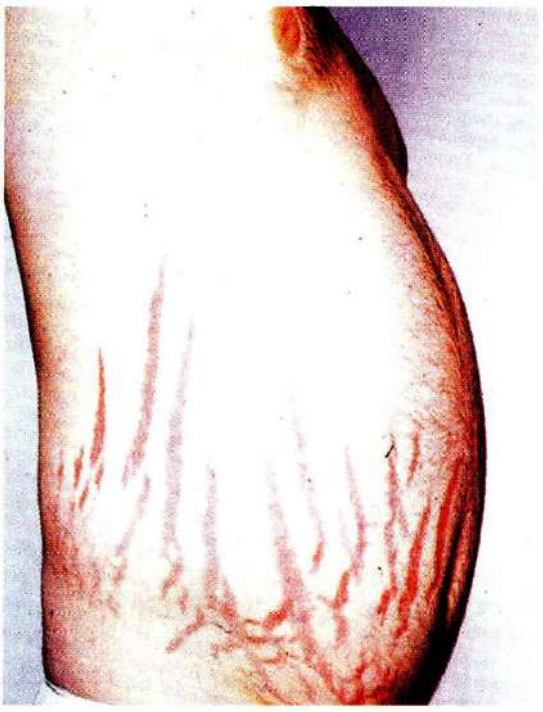

Image 7-2: Abdominal striae in Cushing syndrome.

pad ("buffalo hump"), truncal obesity, and moon facies (Image 7-2). Because cortisol also can stimulate mineralocorticoid receptors, the patient may have edema and hypertension. Comorbid diagnoses include insulin resistance (with Type 2 diabetes in 20%) and osteoporosis.

Labs may show hypokalemia and/or metabolic alkalosis.

Causes of Cushing syndrome in order of most-to-least frequent:

- Iatrogenic cortisol administration
- ACTH-secreting pituitary adenoma (Cushing disease)
- Ectopic ACTH-secreting tumor: bronchogenic, pancreatic, or thymic carcinoma (if age > 60 years, then small cell lung cancer is the most common cause of Cushing's!)
- Non-pituitary–associated, bilateral adrenal hyperplasia
- Adrenal tumors

Obesity, alcoholism, and depression mimic some of the phenotypic features of Cushing's and slightly increase the 24-hour urine cortisol—and/or result in an abnormal low-dose suppression test. These cases are referred to as "**pseudo-Cushing's**"; refer to an endocrinologist.

Cushing syndrome caused by a pituitary microadenoma (disease in the head) is termed Cushing "disease." Next to exogenous steroids, Cushing disease is the most common cause of Cushing syndrome.

Know the following:

- In true **Cushing syndrome**, expect urinary free cortisol to be significantly elevated.
- Recall that ACTH increases the synthesis of not only cortisol but also mineralocorticoids (slightly) and androgens (remember Figure 7-3?). So in **Cushing disease** (disease in the head = pituitary), elevated ACTH stimulates production of adrenal DHEA, and females can present with virilization (hirsutism and acne).
- If an adrenal adenoma is producing the cortisol, ACTH and DHEA are both low.

In clinical practice, Cushing's can be complicated with subtle nuances; so, thankfully, there are endocrinologists who can interpret multiple tests to make a diagnosis. Typical exam question scenarios are straightforward, though, and you can get the right diagnosis using the following strategy.

Cushing Syndrome Workup

1) Initial tests are to establish the presence of cortisol excess.

The suspicion of excess cortisol comes from recognizing the typical clinical presentation. Initial testing uses:

- a 24-hour urine free cortisol (UFC),
- late-night salivary cortisol, and/or
- low-dose dexamethasone suppression test to confirm excess cortisol.

An abnormal test should be confirmed at least once. In the plasma, < 5% of cortisol is free and physiologically active. Only the free cortisol is filtered by the glomerulus, so urinary cortisol is always "free" cortisol and reflects plasma free cortisol levels.

Do not measure plasma total cortisol in a woman on estrogen because estrogen raises sex hormone binding globulin (SHBG), which falsely raises total cortisol.

If your patient is depressed, obese, alcoholic, or sick, check for pseudo-Cushing's before attributing an increased urine cortisol to true Cushing syndrome. Identify pseudo-Cushing's by attempting to suppress cortisol production with low-dose dexamethasone (a synthetic glucocorticoid). Patients with pseudo-Cushing's usually suppress cortisol production with this very small amount of glucocorticoid. True Cushing syndrome does not suppress. If the patient does not suppress cortisol production with the low-dose dexamethasone test and has a high-normal or high UFC, make an endocrine referral.

Remember: Cushing syndrome is the general description for any state of excess cortisol and includes the specific diagnosis of Cushing disease, which refers to an ACTH-secreting pituitary tumor.

2) Is the Cushing syndrome ACTH-dependent or ACTH-independent?

Once you have identified a patient with true Cushing syndrome, check the ACTH level. Normally, a high cortisol completely suppresses ACTH production.

Quick Quiz

- What is pseudo-Cushing's? In what situations does it occur?
- What is the difference between Cushing syndrome and Cushing disease?
- What is the ACTH level in Cushing disease?
- What are your choices for initial tests to evaluate a patient who may have Cushing syndrome?
- Explain what tests are done to differentiate ACTH-dependent Cushing syndrome vs. ACTH-independent Cushing syndrome.
- How does adrenal insufficiency (both primary and secondary) present?

Thus, any measurable ACTH indicates ACTH-dependent Cushing syndrome—either Cushing disease or ectopic ACTH production.

An ACTH too low to be measured indicates ACTH-independent Cushing syndrome—non-pituitary adrenal hyperplasia or adrenal mass.

3) a. If ACTH-dependent Cushing syndrome:

ACTH-dependent Cushing syndrome means the cause is either a pituitary tumor (Cushing disease) or an ectopic, ACTH-secreting tumor. Again ACTH level is elevated.

Image the pituitary with a gadolinium-contrasted MRI and refer the patient to a neurosurgeon if a pituitary tumor is seen.

Some ACTH-producing microadenomas are not visible on MRI. If no pituitary tumor is visible, the patient may have a very small microadenoma, which can sometimes be identified by petrosal sinus venous sampling (detects local production of ACTH). Alternatively, the patient may have an ectopic ACTH-producing tumor, such as primary lung or carcinoid tumors.

To look for these, image the chest and abdomen with high-resolution CT.

You may be asking, "What happened to the high-dose dexamethasone test?" Historically, patients with definite Cushing syndrome were given a high-dose dex suppression test to determine if the source was a pituitary microadenoma (which suppresses with high-dose dex) or an ectopic ACTH-producing tumor or adrenal mass (neither of which suppresses with high-dose dex). Then targeted imaging was performed based on the result.

Measuring ACTH levels is now the best initial test for determining causes of Cushing syndrome—making the high-dose dexamethazone test obsolete. Today, we stratify patients for imaging based on the ACTH result.

We include this topic, however, because general textbooks of medicine are still discussing use of the high-dose dex suppression test to exclude a pituitary microadenoma. In the unlikely event that the high-dose test should show up on exam questions, know:

- Cushing **d**isease, in the head, suppresses with high-**d**ose **d**ex.
- If the patient fails to suppress with high-dose dex, think about ectopic ACTH-producing tumors and adrenal tumors as a cause of Cushing's.

3) b. If ACTH-independent Cushing syndrome:

This patient has high cortisol and low ACTH—most likely an adrenal tumor (adenoma or carcinoma) that is secreting cortisol. Image the adrenals with a contrasted CT and refer to a surgeon for options if a mass is found.

Consider ordering DHEA and testosterone concentrations. Adrenal adenomas have low ACTH and modest DHEA levels, while carcinomas have low ACTH and high DHEA + urine 17-ketosteroids. Again, recall that adrenal tumors do not usually suppress cortisol production in response to high-dose dexamethasone.

ADRENAL INSUFFICIENCY

Adrenal insufficiency (AI) can be primary (Addison disease) or secondary (low ACTH production by the pituitary or withdrawal of glucocorticoids). When AI presents acutely, it is an endocrine emergency.

In industrialized countries, **primary AI** is most often the result of autoimmune adrenalitis (Addison disease, which is sometimes seen in polyglandular autoimmune syndromes I and II); but it can also be caused by granulomatous infections and infiltrative diseases, e.g., HIV/AIDS, CMV, TB, amyloidosis, and sarcoidosis.

Polyglandular autoimmune syndrome I includes chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal/pituitary insufficiencies +/– pernicious anemia, hepatitis, alopecia, chronic autoimmune thyroiditis, and premature gonadal failure.

Polyglandular autoimmune syndrome II includes ≥ 2 of the following: Addison disease, chronic autoimmune thyroiditis, premature ovarian failure, and Type 1 diabetes +/– pernicious anemia, vitiligo, alopecia, sprue, and myasthenia. Watch out for primary AI in patients with AIDS.

The most common cause of **secondary AI** is rapid withdrawal of chronic exogenous glucocorticoids.

Signs and symptoms of AI: The preeminent symptom of adrenal insufficiency is weakness and, as the disease worsens, patients may become bed-bound. Other symptoms include weight loss, N/V, vague abdominal pain, hypoglycemia, and moodiness. Hypercalcemia occurs in 20% of patients due to unknown reasons. Eosinophilia is unusual but is also a clue.

In patients with primary AI (where ACTH is increased), hypotension and hyperpigmentation may be obvious on physical exam. Labs may reveal hyponatremia and

hyperkalemia due to hyperreninemic hypoaldosteronism—since most etiologies of primary AI affect both the zona glomerulosa and zona fasciculata.

Secondary adrenal insufficiency (disease in the pituitary, so ACTH is decreased) is not associated with hyperkalemia because the zona glomerulosa is not diseased and responds normally to angiotensin II.

Diagnosis and treatment of AI: If your patient has acute adrenal insufficiency, it does not matter where the disease is located. It needs to be diagnosed and treated immediately. So your 1st task is simply to determine whether AI exists. You can sort out the level of disease later.

If the patient is in shock and you suspect AI, give fluids and dexamethasone, and perform your stimulation test after the patient stabilizes. Dexamethasone is potent and does not interfere with the cortisol assay, so the post-stimulation cortisol results are reliable. Dexamethasone affects the ACTH level; so if you have time, draw a serum ACTH prior to instituting treatment. Remember that in primary AI, there is usually an associated mineralocorticoid deficiency, so you probably need to also replace mineralocorticoids with fludrocortisone.

In patients who can tolerate an immediate stimulation test: Draw a baseline cortisol level. Then give cosyntropin 0.25 mg IM/IV and recheck cortisol at 30 and 60 minutes. If the stimulated cortisol is not > 18–20 µg/dL, your patient has AI; but you need the ACTH level to determine whether the disease is in the adrenals or the head. The ACTH measurement is a reference test, so it takes days to return. But you're going to give corticosteroids anyway, regardless of level of disease.

Once you know the cosyntropin test is abnormal, check serum aldosterone also. (Often, this can be added to the initial blood sample with the pending ACTH result.)

When your labs return, interpret this way:

Primary AI = abnormal cosyntropin stimulation + high ACTH level and low aldosterone because multiple layers of adrenal are affected by disease process.

Secondary/Tertiary AI = abnormal cosyntropin stimulation + low or low-normal ACTH level and normal aldosterone. Image the sella with MRI.

Clarification: In all causes of AI—primary, secondary, and tertiary—the patients do not respond to ACTH stimulation. This is weird, right? Since secondary and tertiary causes result in a lack of ACTH, shouldn't the adrenals respond if ACTH is supplied? Theoretically, they should—but they don't. Adrenal glands atrophy when they are not stimulated regularly by ACTH. If the gland is not diseased, reinstating ACTH stimulation eventually restores adrenal function, but it takes several days.

In secondary/tertiary AI (disease in pituitary or hypothalamus), the glands do not respond to ACTH stimulation—because they are atrophied. But, they can respond with enough exogenous ACTH over time. In secondary/tertiary AI, serum ACTH is decreased or low-normal. In primary AI (disease in the adrenal cortex), the glands do not respond to ACTH—because they are sick. Serum ACTH is elevated. The point is that even central diseases that result in a failure to produce ACTH result in an abnormal stimulation test.

Schmidt syndrome is the combination of primary adrenal insufficiency and hypothyroidism (and often Type 1 diabetes). Know that you must replace cortisol first because giving thyroid replacement prior to glucocorticoid replacement can increase metabolic demand and cause or worsen shock, leading to death.

MINERALOCORTICOIDS

Overview

Aldosterone is discussed extensively in Nephrology, Book 2. It increases Na^+ resorption and, hence, K^+ and H^+ excretion in the distal tubules. Increased Na^+ resorption means increased water retention and the tendency for hypertension. The release of aldosterone is controlled by both the renin-angiotensin system and the K^+ level.

Review: Renin is released by the healthy kidney from the juxtaglomerular apparatus in response to at least 3 independent factors:

1) Perceived volume depletion, as measured by the juxtaglomerular cells. These are specialized myoepithelial cells cuffing the afferent arteriole.
2) Elevated levels of filtered sodium, as measured by the efferent macula densa cells.
3) Sympathetic nervous system stimulation, which stimulates release of renin in response to assuming the upright posture.

Renin converts angiotensinogen to angiotensin I, which is then converted to angiotensin II by ACE—mainly in the lungs. Angiotensin II has pressor effects and stimulates aldosterone release from the zona glomerulosa in the adrenal glands.

Aldosteronism

Primary aldosteronism (disease in the adrenal) is associated with hyporeninemia, hypertension, and hypokalemia—as are other disease states where mineralocorticoid-type activity is in excess, such as Cushing syndrome and licorice ingestion.

Secondary aldosteronism (disease is in the kidney), a hyperreninemic state. Decreased renal blood flow from either renal artery stenosis or fibromuscular dysplasia → increased renin → increased angiotensin II → increased aldosterone.

Note that primary and secondary aldosteronism, licorice ingestion, and Cushing syndrome can all present with hypertension and hypokalemia.

See Nephrology, Book 2, for more on when and whom to screen.

Quick Quiz

- What electrolyte abnormalities are associated with primary adrenal insufficiency? With secondary?
- How do aldosterone levels affect serum Na^+ and K^+?
- What endocrinopathies should you be concerned about in a patient with untreated hypertension and a $K^+ < 2.8$?
- What are the screening tests to differentiate primary and secondary aldosteronism? How do you interpret them?
- Hypoaldosteronism is usually due to what acquired problem?

Test for primary and secondary aldosteronism with paired plasma aldosterone concentration (PAC) and plasma renin activity (PRA). This also can be presented as PAC:PRA ratio. Know that ACEIs/ARBs and aldosterone blockers such as spironolactone or eplerenone interfere with these screening tests. These agents should be stopped prior to performing screening tests. All other antihypertensive medications can be continued. Interpret the results this way:

- Primary aldosteronism: PAC elevated, PRA suppressed → elevated ratio. Think adrenal disease (tumor or hyperplasia).
- Secondary aldosteronism: PAC and PRA both increased with PAC:PRA usually < 10. Think kidney disease (renovascular or renal tumor).
- Cushing's and excessive consumption of black, natural licorice: PAC and PRA both decreased, with PAC:PRA either normal or elevated.

If the PAC, PRA, and PAC:PRA support primary aldosteronism (PAC high; PRA low; PAC:PRA high), confirm the diagnosis of disease in the adrenal by trying to suppress the excess aldosterone. Give 2 liters of normal saline IV over 3–4 hours to the recumbent patient—nonsuppression of PAC indicates primary aldosteronism. An easier method is to give an oral sodium load for 3 days, then measure the PAC. (Again, nonsuppression suggests adrenal disease.)

Once aldo excess is confirmed, image the adrenals with either high-resolution CT or MRI to determine whether the cause is adrenal hyperplasia or tumor (Conn syndrome). Check with your radiologist so the appropriate testing can be done.

If the PAC, PRA, and PAC:PRA suggest renovascular disease (PAC high; PRA high; PAC:PRA < 10), go straight to renal angiography.

These tests are not as easy as they seem. The patients have hypertension, which is often marked. Giving saline runs the risk of significantly increasing blood pressure.

In many centers, arterial duplex, CT angio, and MRA are very sensitive for diagnosing renal artery stenosis. Depending on cost and sensitivity, arterial duplex, CT angio, and MRA may be preferred over the PAC:PRA as the initial test for renovascular disease.

Hypoaldosteronism

The most common cause of hypoaldosteronism is decreased production of renin in diabetic patients with mild renal failure ("hyporeninemic hypoaldosteronism"). It is also seen in patients with chronic interstitial nephritis, chronic NSAID use, and heparin therapy.

Pick up this diagnosis by observing hyperkalemia and normal anion gap metabolic acidosis out of proportion to the renal disease (no aldosterone leads to failure to excrete H^+/K^+ in the distal tubule). Patients are unable to retain sodium in states of volume contraction, and they develop postural hypotension.

Start the workup by excluding AI as a cause of the hyperkalemia: Perform ACTH stimulation test. Next, measure renin and aldosterone levels during upright posturing and salt restriction (they are low in this diagnosis). Treat with a mineralocorticoid (fludrocortisone) and/or furosemide.

PHEOCHROMOCYTOMA

Because these tumors are rare, a group of international pheochromocytoma specialists have formed a collaborative organization called PRESSOR (Pheochromocytoma & Paraganglioma Research Support Organization). In 2005, PRESSOR issued clinical practice guidelines for diagnosis and management based on the current standard of care. Our discussion is based on the 2005 guidelines (find them here: www.pressor.org), on the 2004 WHO classification of neuroendocrine tumors, and the 2010 North American Neuroendocrine Tumor Society guidelines.

Pheochromocytomas are rare tumors that arise from chromaffin tissue, with symptoms due to secretion of catecholamines: epinephrine, norepinephrine, and dopamine. 10% of pheos are extraadrenal tumors that are called extraadrenal paragangliomas. The distinction is important because the risk of malignancy is higher in the extraadrenal masses. 15% of the time, the pheo tumors are multiple. 10–36% are malignant. Germline mutations are found in up to 30%. 5–15% of patients with these tumors do not have hypertension, and many have sustained, not paroxysmal hypertension. Some even have normal blood pressure.

The differential diagnosis includes labile essential hypertension, anxiety, hyperthyroidism, hypoglycemia, and menopausal flushing—most of which are more common than pheo. Carcinoid can mimic pheo but also is quite rare.

Suspect a catecholamine-secreting tumor in patients who have spells of headaches, sweating, and chest palpitations.

The following risk factors increase the likelihood that a patient may have a pheo:

- Combined HTN + DM
- Refractory HTN
- HTN in young person without a family Hx
- Adrenal incidentaloma
- Dilated cardiomyopathy of unknown cause
- Hx HTN during procedures, with ingestion of tyramine-containing foods, or use of MAO inhibitors
- Family Hx of pheochromocytoma (particularly high risk)
- Family Hx of MEN2, neurofibromatosis, or von Hippel-Lindau disease (particularly high risk)

Diagnosis: Controversy still exists, even amongst experts, as to what the best method is for screening. The most sensitive biochemical screening tests for pheochromocytoma are the following:

- Fractionated metanephrines and catecholamines on 24-hour urine (preferred for screening of low-risk individuals). Patients should be weaned off of tricyclic antidepressants and cyclobenzaprine 2 weeks before testing because these meds interfere with the results. (SSRIs are okay.)
- Plasma fractionated metanephrines; sensitivity is high, so a negative test excludes disease. However, specificity is somewhat low and leads to false-positive results, so measure these only in patients who carry a high pretest probability of disease; i.e., MEN2/NF/VHL, incidentaloma with characteristics of pheo, or family Hx of pheo. The test is not recommended for initial screening of a low-risk population.

For the patient with a possible false-positive result and an increase in plasma fractionated metanephrines, a clonidine suppression test can be performed. The plasma level of fractionated metanephrines is measured before and after the patient receives a dose of clonidine. Plasma metanephrines fall if elevated levels are due to essential hypertension but stay increased if they are due to a pheo.

If the biochemical tests suggest a pheo, perform CT or MRI of the abdomen and pelvis to find the tumor.

If imaging does not show a tumor and you still suspect one given the screening tests and history, look for the tumor using a radioactive tracer (^{123}I, metaiodobenzylguanidine [MIBG] scintigraphy, a norepinephrine analog that concentrates in adrenals and pheos), PET scan, or total body MRI.

Genetic screening is available for the following patient groups:

- Pheo associated syndromes such as MEN2, VHL, neurofibromatosis
- Familial paragangliomas and pheos due to germ-line mutations of genes encoding succinate dehydrogenase subunits B, C, and D (SDHB, SDHC, SDHD), which increase malignancy risk
- Those with a family Hx of pheos or paragangliomas

Treat both pheos and paragangliomas with laparoscopic surgery. Because of the high incidence of bilateral adrenal disease in those with hereditary pheo, partial adrenalectomies are advocated in these patients, thereby decreasing the morbidity associated with medical adrenal hormonal therapy. Metastatic foci or locally invasive disease often require open surgical resection for cure.

Preoperatively, treat with combined alpha and beta blockade. Phenoxybenzamine is preferred for 2 weeks prior to surgery; and ~ 3 days before surgery, add a beta-blocker. Remember never to use the beta-blocker first, because it leads to unopposed alpha stimulation and potential for hypertensive crisis. For those with advanced disease and positive [^{123}I]-MIBG scintigraphy, [^{131}I]-MIBG can be used. For rapidly expanding lesions or those with a negative [^{123}I]-MIBG, a chemotherapy regimen of cyclophosphamide, vincristine, and dacarbazine can provide up to 50% tumor regression. Outcomes are poor in patients with an undiagnosed pheo who go to surgery for an unrelated condition because of hypertensive sequelae.

OTHER ADRENAL MASSES

Many adrenal masses are incidentalomas—a mass, larger than 1 cm, discovered by accident on an imaging study. Up to 15% of patients with an incidentaloma have bilateral masses.

Most incidentalomas are nonfunctioning adenomas. If the patient has a history of malignancy, however, then the mass has a 50% chance of being a metastasis.

Without a history of malignancy, the initial 2 steps are to:

1) Exclude a functioning tumor or adrenal hypofunction.
2) Determine whether the mass is a primary malignancy or a metastasis from an unknown primary. The radiographic characteristics (CT, MRI, or PET) can help to distinguish malignant from benign lesions. Metastases tend to be larger, bilateral, irregular, and inhomogeneous.

All patients with adrenal incidentaloma should have the following tests:

- Blood pressure and serum K^+; add PAC:PRA if hypertension or hypokalemia is present. These tests evaluate the zona glomerulosa for hyperaldosteronism.
- 24-hour urine free cortisol or low-dose overnight dex suppression test; these tests evaluate the zona fasciculata for Cushing syndrome.
- Plasma fractionated metanephrines; this test evaluates the adrenal medulla for pheochromocytoma.
- Females with virilization or males with feminization should have estrogens and androgens measured.

If the results of these tests are normal and the mass is < 4 cm, observation is appropriate with repeat imaging in 3–6 months. Know that FNA is not used to determine whether an adrenal mass is an adenoma or a carcinoma

QuickQuiz

- What screenings are employed to test for pheochromocytoma?
- What are the first steps in working up adrenal incidentalomas?
- What is the definition of primary amenorrhea, and what are the common causes? A female patient with short stature, primary amenorrhea, and little or no breast development probably has what genetic defect?
- What is the definition of secondary amenorrhea, and what are the common causes?

because of the concern of seeding malignant cells during the FNA. An FNA, however, is helpful to determine if a mass is a metastasis.

There are 3 indications for adrenalectomy of an incidentaloma:

1) Tests indicate a functioning tumor
2) Mass is > 4–6 cm
3) Imaging characteristics are suspicious for malignancy

HORMONES OF REPRODUCTION

NORMAL PHYSIOLOGY

Follow along in Figure 7-4.

The hypothalamus secretes GnRH in a pulsatile fashion (60–90-minute cycle), which stimulates the anterior pituitary to then pulse out gonadotropins, LH and FSH.

FSH causes the new ovarian follicle to produce 2 hormones: estrogen (builds up the lining of the uterus) and inhibin (suppresses secretion of FSH). Estrogen normally inhibits FSH and LH production. However at mid-cycle, estrogen has a positive feedback effect causing a surge in the LH and FSH, which then stimulates ovulation.

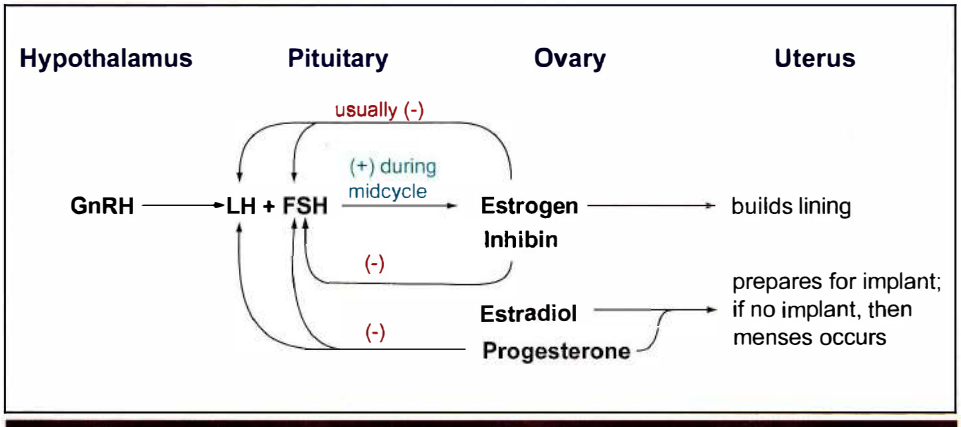

Figure 7-4: Female Hormones of Reproduction

After ovulation, the follicle becomes a corpus luteum that secretes estradiol (main estrogen) and progesterone. Progesterone, in turn, prepares the lining of the uterus for possible implantation and suppresses gonadotropin release.

The theca cells of the ovaries convert circulating androgen precursors (produced by the adrenal gland) into estrogen and a small amount of testosterone. In females, the ovaries and adrenals share the function of producing testosterone––each producing 50%. The major effect of testosterone in females is slight virilization with normal hair development in the pubic and axillary regions.

Amenorrhea

Primary Amenorrhea

Primary amenorrhea in females is diagnosed as a lack of menstruation by age 16 or the lack of development of secondary sex characteristics by age 14. Primary amenorrhea is caused by either a uterine outflow tract abnormality (or absence) or an ovulatory abnormality. Primary amenorrhea is rare, and evaluation is often undertaken by pediatricians; however, you should know a couple of important diagnoses:

- If a patient with primary amenorrhea has short stature, widely spaced nipples, no breast development, webbed neck, and decreased pubic and axillary hair, think of Turner syndrome (karyotype 45,XO).
- If there is no palpable cervix and no uterus, the cause is either a genetic absence of a uterus, in which case she has normal secondary sex characteristics, or androgen insensitivity syndrome (an insensitivity to androgens in a karyotypic female), in which case there is absence of pubic and axillary hair and normal breast development. These patients have an elevated serum testosterone level (within normal range for men).

Secondary Amenorrhea

Secondary amenorrhea is defined as absence of menses for 3–6 months. Know that erratic menstrual cycles are common in the first 1–2 years after menarche and in the 1–2 years prior to menopause.

It is most often caused by pregnancy––once excluded, think about problems with ovulation. Start with a good H&P, looking for signs/symptoms of pituitary disease, systemic disease, and androgen excess, plus a battery of lab tests.

Androgen excess is discussed under Adrenal Gland—Overview and Steroid Synthesis. You might want to go back and review quickly (page 7-15).

Initial labs should include: a pregnancy test and FSH + LH. If the woman is hirsute, and particularly if she is virilized (deepening voice, balding), measure serum total testosterone and DHEA, too. What happens next depends on your test results. The easiest lab to interpret as a cause of amenorrhea is the positive pregnancy test. Next easiest are abnormal gonadotropins (FSH and LH).

Increased FSH and LH levels in the amenorrheic woman tells you that the pituitary has lost negative feedback from the ovaries. The only condition that causes this is ovarian failure. If the woman is < 40 years old, this is called "premature ovarian failure" (POF) and, if the woman is older, "menopausal ovarian failure." (Average age of menopause = 52 years.) In POF cases, consider associated Turner syndrome, galactosemia, or autoimmune polyglandular syndrome, although POF does occur idiopathically in many women.

Decreased FSH and LH levels in the amenorrheic woman tells you that the pituitary is not making the hormones, either because it is diseased or because the hypothalamus is not sending out gonadotropin-releasing hormone (GnRH). This latter state is called "hypogonadotropic hypogonadism," and it has several causes. "Disease" of the pituitary does not always mean disease of gonadotrophs. Recall from the discussion on pituitary adenomas (page 7-2) that prolactinomas and primary hypothyroidism can affect gonadotrophs and levels of FSH + LH as well.

So, check on the following for the amenorrheic woman with low FSH and LH:

- Review of systems and drug use: antiepileptic drugs or psychotropic meds. Is this functional hypothalamic amenorrhea (see below)?
- Prolactin level.
- TSH.
- MRI, if above does not give diagnosis.

Functional hypothalamic amenorrhea (FHA) is caused by stress from an eating disorder and/or prolonged, intense exercise; e.g., long-distance running (but not swimming!). FSH/LH and estrogen are decreased. Measure PRL and TSH to exclude hyperprolactinemia and hypothyroidism before making this diagnosis.

Amenorrhea with Hirsutism

Overview

The amenorrheic woman with virilizing signs needs a good physical exam (evaluate for adnexal masses) and follow-up of blood DHEA and testosterone levels.

The major diagnoses that cause amenorrhea and virilization are polycystic ovarian syndrome (PCOS) and tumors of the adrenal or ovary. Recall from the Steroid Synthesis discussion (page 7-16) that, in the female, both the ovaries and the adrenals contribute to androgen production, almost equally. Usually, normal androgen production causes only growth of pubic and axillary hair. Excess growth of hair in these areas and/or other "masculinizing" signs should prompt concern about either PCOS or adrenal/ovarian tumors.

Polycystic Ovarian Syndrome (PCOS)

PCOS consists of amenorrhea or oligomenorrhea with signs or biochemical evidence of androgen excess (hirsutism, acne, male-pattern balding, or mild increases in DHEA and/or testosterone). It is associated with obesity, insulin resistance, frank diabetes, hyperlipidemia, and obstructive sleep apnea.

In PCOS, the ovaries and adrenals produce excess androgens and estrogens (a result of peripheral aromatization of the androgens) for unclear reasons. The continuous secretion of estrogen decreases FSH secretion but enhances LH secretion such that the LH:FSH ratio often is > 2 (probably > 3 on a Board exam).

The increased LH causes ovarian stromal hyperplasia (more theca cells!) and more production of androgens. It's a chronic cycle! The presence of ovarian cysts as a criterion for PCOS is debatable, as many patients have normal ovaries without any cysts.

While PCOS is associated with small increases in androgens, know that serious increases in these androgens (2–4x upper limit of normal) obligate you to look at the ovaries or adrenals for tumors.

Treatment of PCOS first includes education about weight loss (which treats most) and then is dependent on the degree of hyperandrogenism and whether pregnancy is desired:

- No hirsutism and no desire for pregnancy: Prescribe oral contraceptives or medroxyprogesterone every 1–3 months to induce withdrawal bleeding and to protect the endometrium from hyperplasia.
- Hirsute and no desire for pregnancy: Prescribe combined estrogen-progesterone oral contraceptives. Hirsute symptoms can also be ameliorated with depilatories/shaving. An insulin sensitizer, such as metformin or a thiazolidinedione, may also confer a very modest additional benefit on hirsutism.
- Hirsute and desires pregnancy: Induce ovulation with clomiphene with or without metformin.

Also screen for insulin resistance (oral glucose tolerance test is suggested) in both obese and lean women with PCOS.

Hirsutism

This section is simply a more targeted discussion of hirsutism—a specific virilizing sign (Table 7-2). The history and physical exam are keys in evaluating a hirsute woman. An objective assessment of hair growth and distribution should be made during the

QuickQuiz

- What are the initial labs for the workup of secondary amenorrhea, once pregnancy is excluded?
- What do elevated FSH and LH levels in an amenorrheic woman tell you?
- What testing is done for a woman with secondary amenorrhea who has low FSH and LH levels?
- How does a woman with PCOS present?
- Patients with PCOS should be evaluated for what additional diagnosis?
- What is the most common cause of primary hypogonadism in males?

physical. A scoring system (Ferriman-Gallwey) may be useful to determine whether a patient truly has worrisome features.

The scale shows photos of hair growth in parts of the body subject to androgens: upper lip, chin, chest, abdomen, pelvis, upper arms, thighs, upper back, and lower back. For each location, the amount of hair is assessed and graded on a scale of 0 to 4. This scale is widely available on the Internet under the search terms "Ferriman-Gallwey score." A score > 8 merits further evaluation, especially when the hirsutism is associated with other virilizing signs/symptoms.

In truth, the objective scoring system is not used much in practice. The presence of virilization (clitoromegaly, deepening of the voice, male-pattern balding) and de-feminization (breast atrophy) is more clinically useful.

Recall that the workup for the virilized female includes evaluation of ovarian and adrenal androgens: DHEA and testosterone.

Lab results for these tests in the virilized woman with:

- Mild elevations of DHEA and testosterone are consistent with PCOS.
- Elevated testosterone and very high DHEA are consistent with an adrenal carcinoma.
- Very high testosterone with normal DHEA is consistent with an ovarian stromal tumor; e.g., arrhenoblastoma = Sertoli-Leydig cancer = < 10% of ovarian cancers.

Remember that hirsutism may also be due to late-onset, partial congenital adrenal hyperplasia, which is usually caused by a *CYP21A2* gene defect (→ 21-hydroxylase deficiency). Labs show elevated blood 17-hydroxyprogesterone and increased urinary 17-ketosteroids and blood DHEA (Figure 7-3 on page 7-16).

Cushing disease (in the pituitary) and prolactinoma are uncommon causes of hirsutism. Drugs associated with hirsutism include minoxidil, cyclosporine, and phenytoin.

MEN

In men, luteinizing hormone (LH) stimulates Leydig cells (L stimulates L) to produce testosterone, which in turn inhibits FSH and LH secretion. FSH stimulates the Sertoli cells to secrete inhibin B and androgen-binding globulin, which in turn bind the testosterone, keeping high intratubular levels (allowing maturation of the spermatozoa). Hence, both FSH and LH are required for spermatogenesis.

Primary hypogonadism is usually due to Klinefelter syndrome (47,XXY or mosaic 46,XY/47,XXY). The genetic abnormality results in defective testosterone synthesis by the Leydig cells. Therefore, the testes do not grow properly, and they fail to adequately produce androgens for the life of the male. Clinical presentation is small testes, long arms and legs, fertility problems, lack of virilization (sparse hair growth and muscle mass), and gynecomastia. Some patients have learning disabilities. The expression of this genetic abnormality is somewhat variable, although not fully understood. Occasionally, mosaic individuals are fertile. Testosterone is decreased, and serum LH and FSH are elevated. Diagnose with a karyotype. Treat Klinefelter syndrome with testosterone. Fertility can happen with *in vitro* techniques harvesting spermatozoa from the testes of Klinefelter patients.

Table 7-2: Hirsutism Workup: Lab Results vs. Disease Entities

Serum Hormone Levels	Cushing Disease (central)	Adrenal Cancer	Ovarian Cancer (stromal)	CAH	PCOS
Testosterone level	N, +	N, +	+++	N, +	N, +
DHEA level or urinary 17-ketosteroids	N, +	+++	N, +	N, +	N, +
LH/FSH	N	N	N	N	> 2

N = Normal, + = increased. Notes: 1) DHEA is a precursor to 17-ketosteroids. 2) PCOS is polycystic ovarian syndrome. CAH is congenital adrenal hyperplasia. Results in PCOS, idiopathic, and CAH are similar except for the LH/FSH level. 3) See text to further define CAH. 4) Ovarian cancer has a high testosterone level, whereas adrenal cancer has a high DHEA level. 5) Only "central" Cushing "disease" causes hirsutism; elevations in only cortisol occur in adrenal adenomas (low DHEA and ACTH levels).

Secondary hypogonadism is due to an abnormal hypothalamic-pituitary axis, so testosterone level is low and FSH and LH are low or inappropriately normal. Causes of secondary hypogonadism are either acquired or congenital:

- Hyperprolactinemia.
- Long-standing abuse of exogenous testosterone (anabolic steroids).
- Cushing syndrome (excessive glucocorticoids from any source).
- Congenital gonadotropin deficiency. If some male relatives of the patient have similar hypogonadism, the patient probably has Kallmann syndrome (= GnRH deficiency + anosmia [inability to smell]). Kallmann's is often associated with midline defects such as cleft palate and horseshoe kidney (Figure 7-5).

Erectile dysfunction is discussed in General Internal Medicine, Book 5.

Gynecomastia in men results from an altered estrogen to androgen ratio. Unilateral or bilateral gynecomastia is normal at male puberty. Males who have increased aromatization of circulating androgens into estrogen have this. Also, conditions that produce excess testosterone can result in excess estradiol because of the aromatization. Gynecomastia is seen in advanced age, obesity, cirrhosis, hyperthyroidism, Klinefelter's, germ cell tumors, and certain drugs. In males with gynecomastia and a testicular mass, an elevated hCG and low LH (due to high estradiol levels) suggest germ cell cancer. This is discussed further in Oncology, Book 4.

LIPOPROTEINS

REVIEW

Chylomicrons

Lipoprotein review: Follow along in Figure 7-6.

All **lipoproteins** are particles with a hydrophobic core (triglycerides and/or cholesterol), surrounded by a hydrophilic phospholipid outer layer that facilitates transport through the serum. Apolipoproteins are embedded and bind enzymes or receptors. **Chylomicrons** (with apo B48, CII, and E) are large globules that consist of mostly triglycerides but some cholesterol, and are formed in the intestinal epithelium from dietary fats. The apo B48 on their surface is unique to chylomicrons. Chylomicrons enter the circulation by way of the intestinal lymph ducts. In the circulation, chylomicrons attach to peripheral binding sites in muscles and fat, where the CII apolipoproteins on the surface of the chylomicrons activate lipoprotein lipase (LPL).

The activated LPL removes the triglycerides from the inside of the chylomicrons by breaking down the triglycerides into free fatty acids (FFA), which are either utilized or stored. The shrunken remnant, now high in cholesterol (relative to triglycerides), is called (appropriately enough) a chylomicron remnant. It is taken up by the liver via the liver receptors specific for apolipoprotein E. The liver degrades the remnants, and the cholesterol goes either into bile or on to further synthesis reactions.

To review: The apo B48 is a chylomicron marker; apo CII activates the LPL to suck out the triglycerides; and the apo E is a marker recognized by the liver. If there is a deficiency of either apo CII or LPL, the patient has hyperchylomicronemia, which may cause acute pancreatitis and eruptive xanthomas.

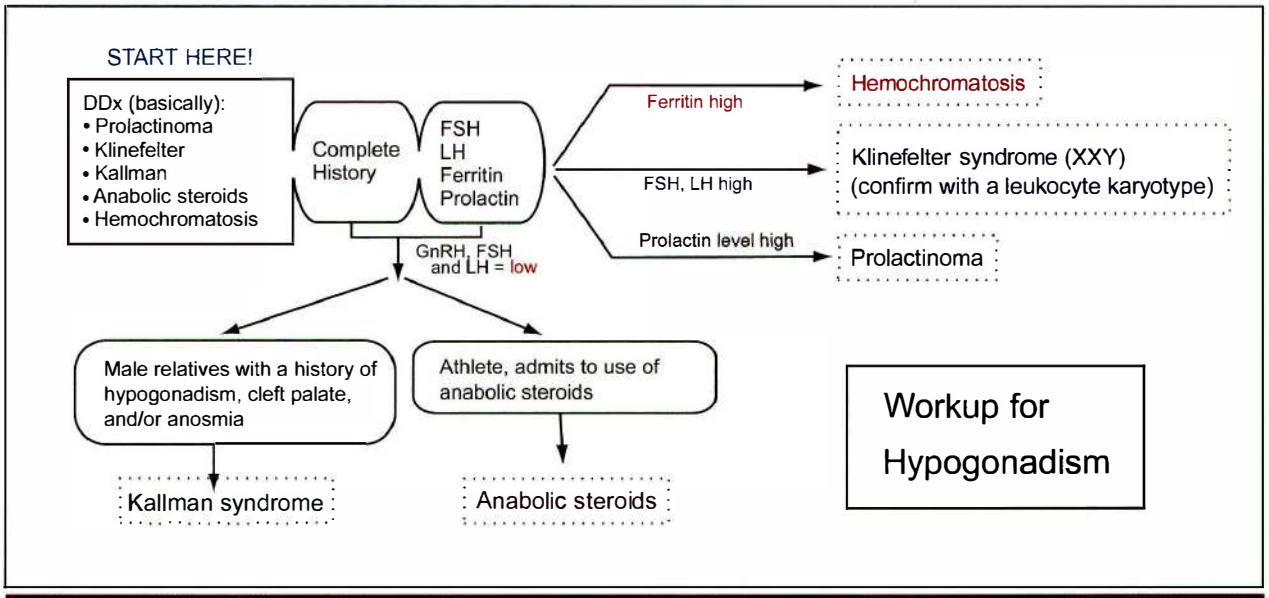

Figure 7-5: Hypogonadism Workup for Males

QuickQuiz

- Differentiate Kallmann syndrome from Klinefelter's.
- In what medical situations do you see gynecomastia, normally and in disease states?
- In what situations are LDL receptors down-regulated? Up-regulated?

VLDL

Very low-density lipoprotein ([**VLDL**]; with apo B100, CII, and E) is synthesized by the liver to supply energy to the body. All subsequent lipoproteins except HDL have apo B100. VLDL is similar to chylomicrons, except that it is smaller and contains less triglyceride and more cholesterol. VLDL function is analogous to chylomicrons in that VLDL transports triglycerides to the capillaries of the muscle and fat and is metabolized by the peripheral LPL (activated by CII).

IDL

Following its excretion from the liver and catalyzation by LPL, VLDL forms a remnant called **intermediate-density lipoproteins** (**IDL**). These still have the triglycerides and some cholesterol. 1/2 of IDL are identified and consumed by the liver via the LDL receptor, which recognizes apo E and apo B100. The other 1/2 remain in the plasma, where they lose the rest of the triglycerides and all of the apolipoproteins, except B100, and thereby are converted to **low-density lipoprotein** (**LDL**). If there is a deficiency of apo E, patients have a high IDL.

LDL

LDL is formed from IDL. LDL (cholesterol only; apo B100 only!) provides cholesterol for the synthesis of hormones, cell membranes, and bile acids. The only apolipoprotein on LDL you need to remember is apo B100 (whew)!

LDL is either taken up by a specific LDL receptor (2/3) or scavenged (1/3)—usually by monocytes or smooth muscle cells. The LDL receptor is present on all cells, but it is much denser in the liver (80%). This receptor binds lipoproteins with apolipoproteins E and B100. Affinity is greater for those with both apo E and apo B100, which is why there is no accumulation of IDL in a healthy person.

LDL receptors are down-regulated or decreased:

- When dietary cholesterol or saturated fats are high
- With age (increasing cholesterol with age)
- In patients with familial hypercholesterolemia, hetero = 50%, homozygotes = 0

LDL receptors are up-regulated or increased:

- When dietary cholesterol or saturated fats are low
- By estrogen
- By thyroxine
- By the "statins" (HMG-CoA reductase inhibitors)
- By a decrease in bile acid uptake from the intestines (as with bile acid resins)

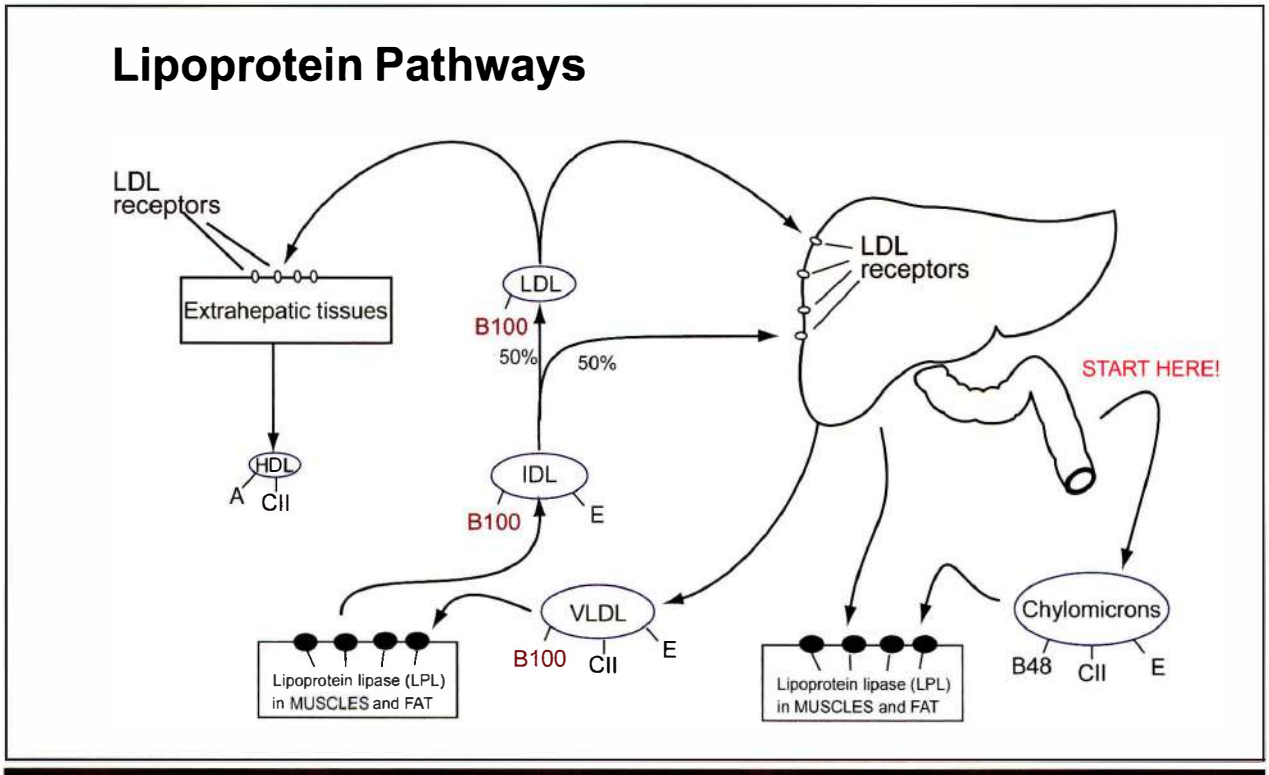

Figure 7-6: Lipoprotein Pathways

Lipoprotein a (Lp(a)) is covalently bound by a disulfide bond to the Apo B100 of LDL. Genetic and epidemiologic studies have identified Lp(a) as an independent risk factor for coronary heart disease and stroke. Its exact mechanism is still unknown; however, because of the high homology of apolipoprotein(a) and plasminogen, it has been hypothesized that Lp(a) is pro-thrombotic. Lp(a) levels are genetically inherited and are twice as high in African-Americans as in Caucasians. Nicotinic acid and mipomersen, an antisense oligonucleotide to apo B100, are the only known drugs that decrease Lp(a). Nicotinic acid decreases Lp(a) only in those patients with concomitant hypertriglyceridemia. Mipomersen, however, decreases Lp(a) levels by 21–27% in patients with familial hypercholesterolemia and severe hypercholesterolemia.

Small LDL particle size is also associated with an increased risk of CHD and endothelial dysfunction. The smaller particles are more easily oxidized, bind arterial wall proteoglycans with more affinity, and bind the LDL receptor with less affinity, thereby reducing their clearance from the blood stream. These mechanisms contribute to their pro-atherogenic nature. Also, the presence of small, dense LDL particles seems to parallel a state of decreased **high-density lipoprotein (HDL)**.

HDL

HDL is mainly composed of protein and phospholipids with very little cholesterol or triglycerides. It scavenges the unesterified cholesterol from cell breakdown. HDL contains mainly apo AI and AII but also apo C.

Apo AI helps esterify the scavenged cholesterol. Then, it is transferred to IDL or LDL and removed via the liver. In this way, the HDL is a sort of reverse transport system.

ABCA1 is a transmembrane protein that helps to move cholesterol from inside the cell to the cell membrane. ABCA1 is expressed when cholesterol loads onto the cell surface and is removed when the apolipoproteins pick up the cholesterol.

Problems arise in HDL levels when something goes wrong with apo AI or ABCA1 (gene or protein). Low HDL is common in cases of premature CHD and is usually either isolated or occurs in combination with elevated triglycerides (TG). Low HDL occurs because of low levels of apo AI (termed hypoalphalipoproteinemia) and happens because the synthesis of apo A is reduced or its breakdown is increased. (There are diseases associated with these, but you don't need to know them in-depth [well, for now anyway!].)

When the HDL level is low, the apo CII level lowers because HDL also acts as a reservoir for apo CII. Because CII activates LPL, there is decreased processing of VLDL and chylomicrons by LPL in the muscle and fat. The end result can be hypertriglyceridemia—as in familial hypertriglyceridemia.

HEREDITARY DYSLIPIDEMIAS

Overview

Dyslipidemias can be classified as familial/primary or acquired/secondary (due to DM2, hypothyroidism, nephrotic syndrome). Of the familial dyslipidemias, known monogenic causes include mutations in the LDL receptor, the PCSK9 enzyme, and the microsomal triglyceride transfer protein (MTTP). It is important to know that the majority of cases of dyslipidemia seen in an internist's clinic are polygenic in origin, which may contribute to the variable response rates to different lipid-lowering therapies. However, regardless of the genetic etiology of a particular dyslipidemia, clinical management is primarily determined based on clinical history, family history, CV risk assessment, and, most importantly, serum LDL-C.

Many cases of premature CHD are related to a familial dyslipidemia. Start screening for lipid disorders at age 20 using the basic fasting lipid panel (FLP). Some experts are looking for the less common familial dyslipidemias by measuring apo B100, apo AI, and Lp(a) when they observe CHD in a patient with a normal lipid profile or if there is a strong family history of CHD and/or ischemic events.

LDL-Associated Dyslipidemias

The familial dyslipidemias below with the "*" are the conditions most likely to be tested on exams.

Familial combined hyperlipidemia* (FCHL) is the most common dyslipidemia and very common in the general population. 1% of the population is autosomal dominant for FCHL, and up to 10% of those with premature CHD have it. It is the most common cause of lactescent plasma. FCHL has an extremely variable presentation with varying elevations of LDL and VLDL. In FCHL, there is increased production of both apo B100 and VLDL, and the increased VLDL stresses the pathways toward increased LDL production. The LDL levels in FCHL are usually less than those in FH (< 230; see next).

Familial hypercholesterolemia* (FH) presents as premature atherosclerosis and tendon xanthomas on physical exam. Homozygous FH (1:1,000,000 incidence) is uncommon, and patients present with an extremely high LDL (usually > 400 mg/dL). Homozygous FH patients have no functional LDL receptors, so they are typically unresponsive to statins. Heterozygous FH is more common with an incidence of 1:500. Heterozygous FH patients have baseline LDL-C levels > 200 mg/dL and have variable response to statins.

Diagnosis is suggested by family history of premature CHD, tendon xanthomas, elevated LDL levels, and an LDL:apo B ratio < 1.2 (vs. > 1.4 in normals).

Familial defective apolipoprotein B100 is an autosomal dominant genetic disorder that causes a problem on the LDL particle at the apo B100 ligand. Like heterozygous FH, LDL levels are 2–2.5x higher than

Quick Quiz

- Which familial dyslipidemia is the most common? What lipoproteins are elevated?
- What lipid test result suggests the need to work up familial hypoalphalipoproteinemia?
- What lab tests should be included in general lipid screening?
- What is the primary endpoint of lipid screening done for primary prevention of CHD?

normal. These 2 disorders have to be distinguished using genetic techniques.

Hyperapobetalipoproteinemia is also caused by excess production of apo B, but LDL levels are normal. Suspect this in patients with premature CHD, especially if they have prominent xanthelasma. Labs show a normal LDL but increased apo B with LDL:apo B < 1.2.

Polygenic hypercholesterolemia is another cause of premature CHD that clusters in families. LDL is increased, but the genetic specifics are unclear.

Other Dyslipidemias

Familial hypertriglyceridemia* contrasts with FCHL in that the apo B and VLDL numbers are normal, but VLDL size is larger and less dense. Like FCHL, it is an autosomal dominant inheritance!

Dysbetalipoproteinemia is autosomal recessive and presents with a high IDL, meaning elevated triglycerides and cholesterol. The IDL has an abnormal apo E, which interferes with the attachment of IDL on the LDL receptor in the liver. The patient must be homozygous (E2/E2) for the defect—plus have DM, be obese, or have an alcohol problem to have significantly elevated IDL levels.

HDL-Associated Dyslipidemias

Familial hypoalphalipoproteinemia is autosomal dominant and results from a mutation in the gene for apo AI (*APOA1*), or for the genes *ABCA1,* or *LCAT*. It results in an isolated low HDL. Current data say the condition is seen in 6% of Japanese patients who have low HDL.

Familial HDL deficiency is also autosomal dominant and is caused by mutations in the gene encoding *ABCA1*. Theoretically, the altered intracellular transport of cholesterol that occurs with an *ABCA1* mutation is associated with increased catabolism of apo AI. It results in an isolated low HDL with premature CHD.

Tangier disease is also due to an *ABCA1* mutation leading to increased catabolism of apo AI. Patients heterozygous for the mutation have low HDL (50% of normal), and homozygous patients have no HDL. This leads to very defective cholesterol handling and diffuse deposition of foam cells causing hepatosplenomegaly, neuropathy, and premature CHD.

EVALUATION OF HYPERLIPIDEMIA

"High cholesterol" means elevated LDL. "High triglycerides" means elevated chylomicrons, elevated VLDL, elevated IDL, or all. Low HDL is a predictor of CHD. Therefore, general cholesterol screening uses the FLP that includes total cholesterol, LDL, HDL, and triglycerides. LDL is calculated and is the value you care about most (discussed next).

TREATMENT OF HYPERLIPIDEMIA

Overview

Treatment exists as:

- **Primary** prevention (in patients without known CHD)
- **Secondary** prevention (in patients with known CHD or with diseases that carry the same risk as CHD, termed "CHD equivalents")

Six large trials have established that primary prevention for dyslipidemia reduces CHD. The most influential U.S. practice guidelines come from the NIH-sponsored National Cholesterol Education Program (NCEP) and were titled, "Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2004 Adult Treatment Panel III)." New ACC/AHA (with the NHLBI) guidelines on atherosclerotic cardiovascular disease (ASCVD) prevention were published in late 2013. These guidelines have not been endorsed by the National Lipid Association (NLA).

Our discussion of lipids is based on 2004 NCEP ATP III, 2013 ACC/AHA guidelines, 2013 NLA response statement, and on the current body of literature. Both traditional and new management guidelines are listed here because there may be a delay in updating this information to the Boards and because some of the recommendations in the new guidelines are controversial (see page 7-31).

General Concepts of Primary Prevention

Start screening using the fasting lipid panel (FLP) at age 20, with follow-up in 5 years if normal or yearly if borderline and < 2 CHD risk factors. If abnormal, start your treatment and follow up in 4–6 weeks.

The primary screening endpoint is LDL. LDL is usually a derived value:

$$\text{LDL} = \text{Total cholesterol} - \text{HDL} - \text{VLDL}$$

$$= \text{Total cholesterol} - \text{HDL} - \text{triglycerides}/5$$

(valid only if triglycerides < 400 mg/dL)

Following achievement of LDL targets, non-HDL cholesterol is a secondary target in patients with hypertriglyceridemia > 200:

$$\text{Non-HDL} = \text{Total cholesterol} - \text{HDL}$$

The non-HDL result is theoretically equivalent to the sum of the remaining atherogenic lipoproteins: LDL + Lp(a) + IDL + VLDL, and may do a better job of predicting plaque formation than just measurement of LDL in those patients with elevated LDL and triglycerides. Watch how this shakes out in the highly anticipated ATP IV updates.

ATP III recommends a priority level of treatment:

- Elevated LDL, then
- Elevated non-HDL, then
- Low HDL

This stratification of priority tells you to correct an elevated LDL first. Do not get distracted by a low HDL or high TG, and prescribe drugs for these until you've addressed the LDL.

After obtaining the FLP, identify whether the patient has any CHD/CHD equivalents—if these are present, treat for "secondary prevention"—and other risk factors for CAD. From this information, determine a patient's risk category and establish the goal LDL.

NCEP ATP III Guidelines

Overview

Again: LDL level is the main lab test used for determining treatment thresholds and goals. [Know all this perfectly!] It is summarized in Table 7-3. When using the table, remember that "CHD equivalents" are considered the same as having CHD. Again, these are considered superceded by some experts by the 2013 ACC/AHA guidelines (page 7-31).

CHD: Risk Factors and CHD Equivalents

1) High LDL is a major risk factor for CHD; high HDL is good and a negative risk factor:

LDL cholesterol:

- Very high: ≥ 190
- High: ≥ 160
- Borderline high: 130–159
- Near optimal: 100–129
- Optimal: < 100

Total cholesterol levels are a bit simpler and used as a reference, but they are not used as treatment goals:

- High: ≥ 240
- Borderline high: 200–239
- Desirable: < 200

HDL limits are:

- < 40 = low
- ≥ 60 = high (which is good and allows you to subtract 1 risk factor!)

2) [Know.] The CHD-equivalent diseases are:

- Diabetes
- Other clinical forms of atherosclerotic disease, such as peripheral arterial disease, abdominal aortic aneurysm, transient ischemic attack, or stroke
- A 10-year risk of CHD of > 20% (using Framingham risk calculators)
- Chronic kidney disease (added by the National Kidney Foundation)

For the target LDL, CHD equivalents are treated the same as having known CHD.

3) The major non-LDL risk factors for CHD are:

- Age: men ≥ 45 years old; women ≥ 55 years old
- Family history of premature CHD (< 55 years old in male, 1st degree relatives; < 65 years old in female, 1st degree relatives)
- Current cigarette smoking
- Hypertension (> 140/90 or on medication)
- HDL cholesterol < 40

0–1 risk factor correlates with a ≤ 10% 10-year risk for CHD; 2+ risk factors correlate with a 10–20% risk for CHD.

HDL cholesterol > 60 mg/dL is a negative risk factor, and you can use it as a "–1" when adding up risk factors.

The goal of treatment is to reduce LDL according to the risk factors. The secondary target is to address metabolic risk, which consists of addressing factors such as: abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance, and prothrombotic and proinflammatory conditions.

Table 7-3: NCEP ATP III Primary Prevention Initiation and Goals Based on LDL Cholesterol

I. Initiation of Therapeutic Lifestyle Changes (TLC)

	Initiation Level ≥:	LDL Goal (mg/dL) <:
No CHD, 0–1 risk factors	160	160
No CHD, ≥ 2 risk factors	130	130
With CHD/CHD equivalents	100	100 < 70 optional

II. Addition of Drug Therapy

	Consideration Level ≥:	LDL Goal (mg/dL) Less than:
No CHD, 0–1 risk factors	190	160
No CHD, ≥ 2 risk factors	160	130
With CHD/CHD equivalents	130	100 < 70 optional

Hint: Just remember > 160/130/100 as the initiation of TLC and 160/130/100 is the goal for both therapies. Add 30 to each initiation level number to determine the point at which you consider adding drug therapy to TLC.
Know that, contrary to this table, statins have now been shown to be beneficial for all patients with CHD/CHD equivalents with or without hyperlipidemia!

Quick Quiz

- Explain the ATP III treatment priority for lipid abnormalities.
- List the CHD-equivalent diseases.
- Per ATP III, what are the non-LDL risk factors for CHD that are considered when you stratify patients for primary prevention of CHD?
- Per ATP III, at what LDL level is TLC started on a 38-year-old man with diabetes? At what level would you start drug therapy?
- Per ACC/AHA ASCVD guidelines, name the 4 statin benefit groups.
- How is a "high intensity" statin defined? A "moderate intensity" statin?

ATP III: Treating for Primary Prevention

Start with **Therapeutic Lifestyle Changes** (**TLC**), which consist of dietary therapy, exercise, and weight loss (Table 7-3).

With 0–1 risk factor: Start TLC when LDL ≥ 160 (goal of therapy is LDL < 160); start drugs at ≥ 190.

With ≥ 2 risk factors: Start TLC when LDL ≥ 130 (goal of therapy is LDL < 130); start drugs at ≥ 160, except in the patient who has a 10-year CHD risk of > 10%. Start that patient on drugs when the LDL is ≥ 130.

ATP III: Treating for Secondary Prevention

Treat those with CHD/CHD equivalents more aggressively than those with 2 risk factors (in primary prevention, above):

- If LDL > 100, start TLC.
- If LDL > 130, start TLC + drug therapy.

In a patient with CHD/CHD equivalents, the goal is to get LDL to < 100. The 2004 ATP III update allows for optional reduction of LDL to < 70 in CHD/CHD equivalents. In 2007, several diabetes and cardiology practice guidelines began to recommend a target LDL of < 70 in patients with CHD, and this has become the national standard.

Statins are 1st line drugs because they improve mortality.

On an exam question, if you are presented with a patient who has limited resources but needs treatment for secondary prevention of CHD, always give this patient a statin. The statins have the highest mortality benefit. Niacin would seem to be a good choice because it is less expensive, but the mortality benefit of niacin is less than statins (and there are many inexpensive generic statins available now in the U.S.).

Follow-up

The maximum effect occurs 4–6 weeks after starting treatment, so wait 6–8 weeks before changing therapy. When LDL < 100 mg/dL, recheck every 2–3 months for the 1st year, then 2x/yr.

2013 ACC / AHA Clinical Practice Guideline on Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease (ASCVD) Risk in Adults

Recommended changes in management:

- Identifies 4 "statin benefit" patient groups in which to focus efforts to reduce ASCVD events in primary and secondary prevention; this is a departure from "treat-to-target" approach for LDL and non-HDL goals.
- These 4 "statin benefit" patient groups are those with:
  1) clinical atherosclerotic cardiovascular disease,
  2) familial hypercholesterolemia,
  3) diabetics 40–75 years of age with LDL-cholesterol levels between 70 and 189 mg/dL and no evidence of atherosclerotic cardiovascular disease, and
  4) diabetics with low lipid levels but a 10-year risk of atherosclerotic cardiovascular disease > 7.5%.
- Identifies which high-intensity statin therapy (resulting in > 50% reduction of LDL) and moderate-intensity statin therapy (30 to < 50% reduction of LDL) should be used in those most likely to benefit.
- TLC should serve as the backbone to any ASCVD prevention clinical management plan.
- Advocates the use of new pooled cohort equations that estimate 10-year risk in both Caucasian and African-American men and women for primary prevention.
- Identifies high-risk groups that may not benefit from primary prevention.
- Advocates consideration of the net benefit of statin therapy; identifies important safety considerations and potential adverse effects.
- Offers guidance on management of statin-associated adverse effects such as muscle symptoms.
- Other factors such as inflammatory biomarkers and noninvasive tests may inform treatment of individuals not in the 4 statin benefit patient groups.
- Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared to their adverse effects in prevention of ASCVD.
- For questions regarding complex lipid disorders for which little or no randomized controlled trial data are available, the guidelines recommend referral to clinicians with lipid expertise for further management.

Note: These guidelines are still considered controversial in that some experts believe that the guidelines-based risk calculator published on the ACC website overstates CV risks by 75–150%, thereby increasing statin recommendations. Additionally, the National Lipid Association

(NLA) has decided to not endorse these guidelines for reasons listed below.

NLA Response Statement on 2013 ACC / AHA Clinical Practice Guidelines

ACC/AHA guideline recommendations limited their review to only high quality RCTs, but NLA believes that other important types of clinical evidence should have been included in order to further address gaps in clinical care.

NLA questions the need to remove LDL and non-HDL treatment targets that have been so widely endorsed and recognized by the clinical community.

NLA finds an absence of discussion regarding other therapeutic options for patients on high-dose statins who still exhibit high residual risk and/or significantly elevated LDL-C levels.

NLA finds a need for more discussion on managing special populations such as older patients (> 75 years of age), those with familial hypertriglyceridemia (FH), those who are statin-intolerant, and younger high-risk patients (< 40 years of age).

Dietary Therapy

Diet is always the 1st line of treatment for the hyperlipidemias. Total fat consumption should be < 30% of daily calories. More specifically, saturated fat should be < 7% of daily calories, and cholesterol should be < 200 mg/d.

Regarding types of fats:

- Hydrogenated ("trans fats") vegetable oils (margarines) not only raise LDL but also lower HDL—doubly bad!
- Decreasing dietary saturated fats increases LDL receptors and so decreases LDL, but HDL also decreases!
- Similarly, changing to a diet high in polyunsaturated fats decreases LDL and VLDL, as well as HDL. In all of these cases, the LDL/HDL ratio is the same or increased—not good!
- On the other hand, monounsaturated fats (olive/peanut/canola oils) decrease LDL, but not HDL—good!
- Omega-3 fatty acids decrease only VLDL (triglycerides).

Table 7-4 summarizes this information.

Drugs for Dyslipidemias

Of the following drugs, statins decrease cardiac events and cardiac mortality by about 25% and overall mortality by 15%. Niacin decreases cardiac events and has inconsistent effects on mortality. Gemfibrozil and cholestyramine show a decrease in cardiac endpoints but no decrease in overall mortality. See Figure 7-7 and Table 7-5 on page 7-34.

HMG CoA reductase inhibitors are the **statins**: lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, and rosuvastatin. These are the primary cholesterol-lowering drugs. HMG CoA reductase is the enzyme in the rate-limiting step of lipid metabolism. Statins inhibit this enzyme and, thereby, up-regulate the LDL receptors—as do the bile acids.

Statins cause a decrease in LDL and may decrease VLDL. There are only modest gains in HDL with statins. As mentioned, all persons with CHD should be on a statin long-term, if they can tolerate it.

Statins may cause myalgias, an elevated CPK, and, rarely, rhabdomyolysis. Check liver transaminases if the patient develops nausea, abdominal pain, or other signs/symptoms of hepatotoxicity.

The risk of myopathy with statins increases significantly when used in combination with cyclosporine, gemfibrozil (but not as much with fenofibrate!), erythromycin, and ketoconazole.

Statins can cause mild elevations in blood sugar level. Statins may cause memory loss and confusion in some people. The FDA added blood sugar and cognitive changes to the warnings in 2012. Both are generally reversible with stopping the drug.

Inhibitor of intestinal cholesterol absorption (ezetimibe): 2nd line LDL-lowering drug (after statins). It is approved for use alone or in combination with a statin or fenofibrate to reduce LDL and apo B in patients with primary or mixed hyperlipidemias. It is also approved for use with atorvastatin or simvastatin to reduce LDL in patients with familial homozygous hypercholesterolemia. Alone, ezetimibe can reduce LDL by up to 17%; in combination with a statin, it provides a further 14% reduction in LDL over the effect of the statin. Ezetimibe can cause myopathy and increases the risk of statin-induced myopathy during combination therapy. Avoid using ezetimibe with gemfibrozil. Moderate or severe hepatic impairment is a contraindication.

Table 7-4: Dietary Therapy and Cholesterol

Diet Modification	LDL	HDL	LDL/HDL	Comments
Change to hydrogenated vegetable oils (trans)	Increase	Decrease	Increase	Doubly bad!
Decrease saturated fats	Decrease	Decrease	Same or increase	Neutral to bad
Change to polyunsaturated fats	Decrease	Decrease	Same or increase	Bad
Change to monounsaturated fats	Decrease	May increase	Decrease	Good!

Quick Quiz

- Which fats are the "good" fats? The "bad" fats?
- What class of drugs is recommended 1st line to reduce LDL?
- What are the major side effects of statins?
- What are side effects of colesevelam?
- What is the main action of the fibrate drugs?

The most interesting news about ezetimibe comes from the clinical trial, ENHANCE (efficacy of simvastatin 80 mg alone or in combination with ezetimibe, using the well-established carotid intima-media thickness [IMT] as a surrogate endpoint in patients with heterozygous familial hypercholesterolemia [FH]). This 2-drug combination lowered LDL and raised HDL significantly better than simvastatin alone, but the IMT was no different between the groups.

The significance of ENHANCE is that it raised more questions than it answered about LDL reduction. Was IMT the best endpoint to use for these FH patients? Is there a threshold below which further reduction of LDL does not provide clinical benefit? Ongoing trials are addressing these issues.

Bile acid resins (cholestyramine, colestipol, and colesevelam) are also 2nd line LDL-lowering drugs. Similar to ezetimibe, bile acid resins are used primarily as adjuvant therapy in combination with statins or monotherapy in patients who cannot take statins. Resins decrease LDL, slightly increase HDL, and may increase triglycerides. By absorbing bile acids in the intestine, and thereby preventing their re-uptake, they cause up-regulation of the LDL receptors in the liver, which increases the processing of serum LDL needed to synthesize replacement bile acids. Although the HDL level remains the same, the LDL/HDL ratio decreases.

Bile acid resins may also cause an increase in the synthesis of VLDL, so the patient may get an increase of triglycerides. Side effects of these resins are nausea, vomiting, constipation, and bloating. The resins can absorb other oral drugs, so give any other medicines 1 hour before or 4 hours after the resins.

Fibric acid derivatives (mainly gemfibrozil and fenofibrate) are used primarily to treat hypertriglyceridemia. These drugs decrease VLDL and raise HDL. Their main mechanism of action is increasing the activity of LPL on VLDL—thus increasing its rate of conversion to IDL. Some of this IDL is then converted to LDL, occasionally causing an increase in LDL. Other actions are increased production of apo AI and AII, which increases HDL and increases excretion of cholesterol into the bile.

Fenofibrate is the latest fibric acid derivative; it appears to have more efficacy than gemfibrozil in lowering LDL, and it does not inhibit statin breakdown (thus contributing to statin myopathy). Fenofibrate is the drug of choice when combining a fibrate with a statin.

The recent ACCORD trial included diabetic patients who were treated with a statin vs. statin plus fibrate to determine if the addition of the fibric acid derivative reduced rates of non-fatal MI, stroke, or cardiovascular death. The end result: The addition did not change these endpoints. So, the current standard is to reduce LDL to < 70 in high-risk patients using drugs that specifically target LDL, e.g., statins.

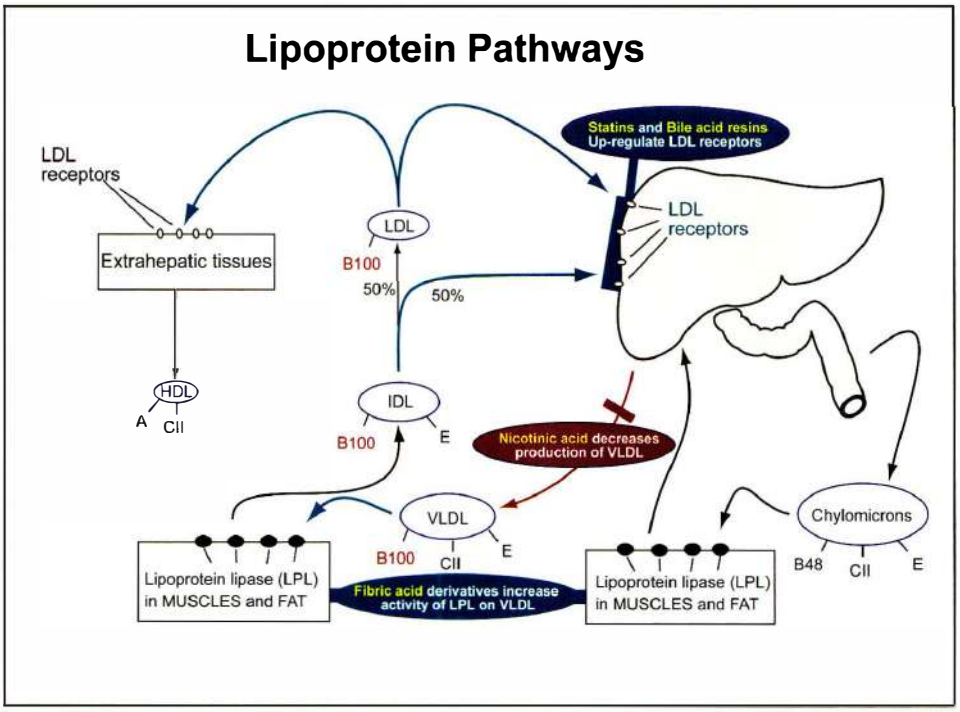

Figure 7-7: Effect of Drugs on the Lipoprotein Pathways

Clofibrate is another fibrate that is available but should not be used because of its association with GI cancers.

Nicotinic acid (= niacin) is great if the patient can tolerate it. It is by far the least expensive agent of those listed. It lowers triglycerides and cholesterol (LDL) and increases HDL. It is the most effective drug available for raising HDL (up to 30%). It lowers triglycerides by blocking the production of VLDL (and therefore LDL). Initially,

Table 7-5: Uses of Currently Available Lipid Drugs

Drug	Use	Side Effects
Statins	Drug of choice for LDL reduction	Myalgias, myositis, elevated transaminases
Ezetimibe	Alternative drug for LDL reduction	Myopathy, elevated transaminases
Bile resins	Alternative drug for LDL reduction	N/V, constipation, bloating
Fibric acid derivatives	Drug of choice for TG reduction	Possible: abdominal pain, GB disease, malignancy
Nicotinic acid	Alternative drug for LDL and TG reduction	Flushing, dry skin, N/V/abdominal pain

give nicotinic acid 100 mg tid, then raise it 100 mg tid each week to the full dose of 1–2 gm tid. Important metabolic side effects include hyperuricemia and insulin resistance; gout and diabetes mellitus are relative contraindications. Annoying side effects include flushing (especially), dry skin, and nausea/abdominal pain. ASA 325 mg given 30 minutes before the dose blocks the flushing reaction. This reaction usually disappears after a week or two. Niacin has been shown to reduce cardiovascular events, but the data are not as strong as the data for statins. The recent AIM-HIGH trial fails to show a clinical benefit of adding niacin to statin therapy even though lipid levels improved.

Omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, in moderate doses, appear to decrease mortality and sudden cardiac death in patients with known CHD. High doses cause a decrease in platelet and neutrophil aggregation, decreased BP, and decreased triglycerides (VLDL) but with an increased LDL. Very high doses may decrease angioplasty restenosis rate. Generally, if a patient has CHD, adding fatty fish (salmon, mackerel, herring, sardines, albacore tuna) to their diet twice a week or a daily fish supplement is recommended.

Summary (see Table 7-5):

- Statins block HMG CoA reductase. Ezetimibe inhibits intestinal cholesterol absorption. Nicotinic acid decreases triglycerides by blocking synthesis of VLDL.
- Statins and nicotinic acid are the only drugs that both decrease LDL and increase HDL.
- Ezetimibe is used in conjunction with either a statin or fenofibrate to reduce LDL and/or non-HDL.
- Both fibric acid derivatives (gemfibrozil, fenofibrate) and nicotinic acid decrease triglycerides; but, whereas nicotinic acid also decreases LDL (good), gemfibrozil may increase the levels of LDL (bad). Fenofibrate increases LDL less than gemfibrozil.
- Combining gemfibrozil with statins significantly increases the risk of myositis. Use fenofibrate if you need to combine with a statin.
- What increases HDL? Nicotinic acid, fibrates, statins, omega-3 fish oils, moderate alcohol intake, exercise, stopping smoking, losing weight if obese, and reducing intake of trans fats.
- What lowers HDL? Beta-blockers (except labetalol), smoking, getting fat, and eating a diet high in hydrogenated (trans) fats or polyunsaturated fats.
- What has no effect on HDL? Bile resins. Monounsaturated fats (peanut, olive, and canola oils) have no effect or may raise HDL only slightly.

Treatment Scenarios

What drugs are indicated for the following if the TLC is insufficient?

Remember: Priority of treatment is LDL first, then non-HDL, then HDL. For secondary treatment goals, many experts recommend focusing on lowering all non-HDL cholesterol first and then raising HDL. All patients with CHD/CHD equivalents should receive statin therapy regardless of lipid levels.

Treatment scenarios:

- Increased LDL, normal TG, normal HDL: statin.
- Increased LDL, normal TG, decreased HDL: statin first. Based on NCEP guidelines, consider adding GI-active drug (ezetimibe or resin) or niacin to achieve further reduction in LDL and raise HDL. Based on 2013 ACC/AHA guidelines, do not add any additional non-statin therapies.
- Increased LDL, increased TG, normal HDL: statin first. Based on NCEP guidelines, consider adding fibrate or niacin to achieve further reduction in LDL/TG. Based on 2013 ACC/AHA guidelines, do not add any additional nonstatin therapies.
- Increased LDL, increased TG, low HDL: statin first. Based on NCEP guidelines, consider adding niacin, ezetimibe, and/or fibrate to achieve further reduction in LDL/TG and raise HDL. HDL is the last abnormality you treat. Based on 2013 ACC/AHA guidelines, do not add any additional nonstatin therapies.
- Normal LDL, increased TG, normal HDL: Isolated high triglycerides are not as associated with CHD. TG > 1,000–2,000 increases risk for pancreatitis; treat with niacin or fibrate or fish oil. Use statin plus niacin or fibrate or fish oil if the patient has CHD. Consider statin, niacin, fibrate, or fish oil if patient has a family history of early CHD or many risk factors.
- Normal LDL, increased TG, low HDL: fibrate or niacin; see comments under isolated increased TG, just above.

QuickQuiz

- What are relative contraindications to niacin?
- What activities increase HDL? Lower HDL?
- What happens to the lipid panel in ACS?

- Normal LDL, normal TG, low HDL: statin first then niacin, or fibrate; probably need to treat only those with CHD/CHD equivalents.
- Clinical evidence of ASCVD, candidate for statin therapy and already on TLC, and age ≤ 75 years: high-intensity statin or moderate-intensity statin (if not a candidate for high-intensity statin).
- Clinical evidence of ASCVD, candidate for statin therapy and already on TLC, and age > 75 years or not a candidate for high-intensity statin: moderate-intensity statin.
- No clinical evidence of ASCVD, already on TLC: high-intensity statin or moderate-intensity statin (if not a candidate for high-intensity statin)
- Diabetes Type 1 or 2, age 40–75 years and estimated 10-year ASCVD risk < 7.5%: moderate-intensity statin.
- Diabetes Type 1 or 2, age 40–75 years and estimated 10-year ASCVD risk ≥ 7.5%: high-intensity statin.
- Any patient with estimated 10-year ASCVD risk ≥ 7.5%: moderate-to-high intensity statin.

Also consider adverse drug effects, drug-drug interactions, and patient preferences for statin treatment.

LIPIDS IN ACUTE CORONARY SYNDROME

Statins do more to reduce CHD mortality than just reducing LDL. They stabilize plaques, reduce inflammation and thrombogenicity, and reverse endothelial dysfunction.

Give all patients with acute coronary syndrome (ACS) a high-dose statin no matter what the LDL measures. If the patient is already taking a statin, increase the dose for the acute event. (Continuing the statin during an ACS hospitalization has been associated with an improved outcome.) Some experts specifically recommend atorvastatin based on data that high-dose atorvastatin decreases mortality during ACS, but other experts believe the benefit is a drug-class effect. (Data do not compare 2 high-dose regimens.) Exam questions probably will not ask you to pick a specific statin; more likely, they'll ask you to select a choice among different classes of drugs. Any high-dose statin regimen has more side effects (especially myalgias) than low/moderate regimens.

Remember: A recent MI or any serious illness may affect the lipid panel. These effects include decreasing LDL and HDL levels and raising or lowering triglyceride levels. So do not use the FLP drawn at admission for ACS to determine how to treat the patient. Start the statin at a high dose. Redraw the FLP 8 weeks later for a better idea of the patient's true lipid abnormalities.

GOAL LEVELS OF LDL IN PATIENTS WITH CHD

Know all of the following (based on NCEP ATP III guidelines):

Give all patients with CHD/CHD equivalents long-term statin therapy for secondary prevention, even if their LDL is in the normal range. The data indicate that patients should generally be prescribed a dosage of statin that lowers LDL at least 30–40% from the patient's baseline LDL level.

The target LDL is less well-defined, but the trend is to treat to an LDL < 70 because of data showing a reduction in "CHD event rates" (NCEP ATP III).

The 2004 NCEP update recommended a target LDL < 100 in all patients with CHD and a target LDL < 70 as "optional" in high-risk patients. However, many experts and some practice guidelines from major societies are suggesting a target LDL < 70 for those with known CHD.

Experts caution, however, that if a patient with CHD is unable to achieve an LDL < 70 with statin therapy, there is no evidence to support adding a 2nd drug.

Patients intensively treated may experience more serious side effects from the addition of a new medication than they receive benefit from further reduction in LDL.

On a Board exam, it's probably safe to assume your target LDL for these patients is < 100. Because of all the controversy, the exam is unlikely to focus on < 100 vs. < 70. Do not get distracted by the HDL and TG levels. Do what you need to do to get the LDL below target per the patient's risk assessment.

Reevaluate the lipids after initiating treatment to reduce LDL, and then consider interventions to reduce non-HDL and/or raise HDL.

DIABETES MELLITUS

OVERVIEW

The U.S. is seeing an epidemic of metabolic syndrome and diabetes mellitus that parallels the epidemic of U.S. obesity. If you were born in 2000, your risk of developing any kind of DM is 33% (males) and 39% (females)! Diabetics have twice the death rate of non-diabetics from CHD. Early initiation of excellent glycemic control reduces the risk of CHD by 50% in patients with Type 1 diabetes. Life span in diabetics is reduced by 12 years (males) and 19 years (females).

Classification of diabetes is based more on mechanism of dysfunction (Type 1 or 2) than on whether the patient requires insulin for treatment.

The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have practice guidelines for management. Fortunately, they pretty much agree on the major items!

Know these categories:

- **Prediabetes** includes both impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).
- **Type 1 immune-mediated** (T1DM, 10% of DM): previously "insulin-dependent DM" and "juvenile-onset DM." The term insulin-dependent DM (IDDM) is not used anymore.
- **Type 1 idiopathic** DM is a rare form of insulinopenia without autoantibodies and with a strong inheritance pattern. Insulin requirements often fluctuate.
- **Type 2** DM (T2DM, 90% of DM): previously "non-insulin–dependent DM" and "adult-onset DM." The term non-insulin–dependent DM (NIDDM) is not used anymore.
- **Chemical** DM: Certain drugs can induce T2DM in patients with insulin resistance or impair the action of insulin (niacin, steroids, thiazides, oral contraceptives, beta-blockers).
- **Gestational** DM.

Diabetes also is caused by endocrinopathies (Cushing's, acromegaly), and injury to the endocrine pancreas due to trauma, surgery, inflammatory disorders, or toxins.

MODY is "maturity-onset diabetes of the young" and is a rare genetic defect in the beta cell.

LADA is "latent autoimmune diabetes in adults"; a late onset of an immune-mediated course often in non-obese adults. LADA has been referred to as Type 1.5 DM! These adult patients often require insulin early in their DM due to the auto-antibodies targeting the pancreas.

DIAGNOSIS AND SCREENING

Some simple basics first. Let's say that CF = clotting factors and WP = the watery part of blood. Glucose, electrolytes, CF, and other proteins float around in the WP.

To make **serum**, let whole blood clot in a red-top tube. The clotting factors are used up when generating clot. Centrifuge the tube to remove the clot and other cells. What remains is "serum."

To make **plasma**, mix whole blood with an anticoagulant (purple-top tube), and then centrifuge it to remove only the cells. What remains is "plasma."

Therefore:

- Whole blood = (cells + CF + WP)
- Serum = WP – (cells + CF)
- Plasma = (WP + CF) – cells

Serum and plasma glucoses are basically the same, except plasma includes the clotting factors. Whole blood glucose values are about 15% less than serum/plasma values. Serum and plasma are obtained by venipuncture. (What you get depends on which tube you put the blood in.) Serum, plasma, and whole blood (venipuncture) glucose measurements can be very different from finger stick measurements.

Finger sticks obtain whole blood from capillaries. Capillary whole blood glucoses are subject to much variability. Finger sticks are acceptable for self-monitoring of known diabetics, but only plasma or serum should be used for diagnosis of diabetes. So remember: Finger stick (capillary whole blood) glucoses are not equivalent to serum/plasma glucoses.

Normal fasting plasma glucose (FPG) is < 100 mg/dL.

Diagnosis of prediabetes (use 1 of the following):

1) Impaired fasting glucose (IFG) = FPG 100–125 mg/dL.
2) Impaired glucose tolerance (IGT) = 2-hr plasma glucose of 140–199 mg/dL after a 75-gm oral glucose load; i.e., during an oral glucose tolerance test (OGTT). The OGTT is more sensitive than FPG for diagnosing prediabetes and is considered the best test by AACE, but they realize it is rather impractical in most offices—and the screening guidelines take this into account.

An HbA1c = 5.7–6.4% is supportive of prediabetes; retest patients with results in this range using the FPG or OGTT.

Diagnosis of diabetes (use 1 of the following):

1) FPG ≥ 126 mg/dL
2) Random plasma glucose ≥ 200 mg/dL with symptoms (polyuria, polydipsia)
3) A1c ≥ 6.5%
4) 2-hr plasma glucose ≥ 200 mg/dL after a 75-gm OGTT

Hyperglycemia should be confirmed by retesting at least once unless there are clear signs of metabolic decompensation (DKA, hyperosmolar coma).

When confirming the diagnosis, the recommendation is to repeat the same test that was used initially.

Know that the best test for diagnosing overt T2DM is the fasting plasma glucose. About 20% of patients screened with the HbA1c have false-negative tests, compared to using the FPG or OGTT.

Additionally, the A1c result can be misleading in some patient groups; e.g., African-Americans, those with hemoglobinopathies and thalassemias, patients with iron deficiency or hemolytic anemias, and those with hepatic or renal diseases.

AACE recommends screening the following patients for DM annually beginning at age 30 years (FPG preferred):

- 1st degree relative with diabetes
- CHD
- Acanthosis nigricans and is overweight (BMI ≥ 25 kg/m^2) or obese
- Sedentary
- Non-Caucasian race
- Hx of IGT
- HTN
- Hyperlipidemia

QuickQuiz

- What are the new categories of diabetes mellitus?
- Define prediabetes and chemical diabetes.
- Define MODY and LADA.
- When are finger stick glucoses useful? When should they not be used?
- What are the criteria for the diagnosis of prediabetes?
- What diseases can lead to a false value of HbA1c?
- What is the significance of diagnosing prediabetes?
- What autoimmune diseases are also associated with T1DM?
- What is the primary treatment for T1DM?

- Hx of gestational diabetes
- Hx of delivery of > 9-lb infant
- Polycystic ovaries
- Psychiatric disease (specifically schizophrenia)

ADA practice guidelines are slightly less rigorous, recommending screening younger patients only if they are overweight (BMI ≥ 25 kg/m^2) with any of the risk factors listed above. Without these risk factors, both ADA and AACE say to start screening at age 45.

PREDIABETES

Overview

Prediabetics have a 6-fold risk of developing overt T2DM; 1/3 of them do. 1/3 stay prediabetic, and 1/3 normalize. The condition is quite important to discover because some prediabetics develop microvascular disease. Also, overt diabetes increases a patient's risk of CHD by 50%!

Goals and Types of Treatment

Promoting a "healthy lifestyle" is your best bet for helping the prediabetic. Weight loss of 5–10% with maintenance can prevent development of overt DM; so does regular exercise (30–60 minutes, moderate intensity, 5 days/week) and a low-sodium/high-fiber diet (low in saturated and trans fats) with moderation of alcohol.

No drugs are approved yet, although metformin, acarbose, glitazones, and GLP-1 agonists have been studied, with strong evidence in their favor. Some studies say you can consider one of these drugs in high-risk prediabetics.

Lipid, blood pressure goals, and aspirin therapy should be the same as for the diabetic (see below).

AACE recommends monitoring the prediabetic with an annual OGTT (although they accept this is difficult to accomplish) and urine test for microalbuminuria. Perform twice yearly FPG, HbA1c (to assess if patient is developing overt DM), and FLP. Note: AACE has published a prediabetes algorithm that stresses lifestyle modification as well as use of medically assisted weight loss.

TYPE 1 DM

Overview

T1DM is marked by cell-mediated beta cell destruction causing absolute insulin deficiency. 90% of patients have autoantibodies against:

- islet cells,
- insulin,
- glutamic acid decarboxylase [GAD], and/or
- tyrosine phosphatases IA-2 and IA-2ß).

Anti-GAD antibody titers are generally the most clinically useful. T1DM is caused by genetic (→ immunologic) and environmental factors that are not yet entirely elucidated. Identical twins have a 30–70% concordance rate. It appears that polymorphisms in the HLA region of chromosome 6 (region that encodes the major histocompatibility complex, MHC) result in some kind of immunologic malfunction.

Quick review: The MHC directs the immune response by presenting antigen to T cells. Human leukocyte antigen (HLA) loci are part of the MHC; the alleles in these loci are defined as A, B, C, and D. DR3 and DR4 alleles are 2 in the set of D alleles.

95% of patients with T1DM have HLA DR3 or DR4. Still, in addition to MHC, there are a lot of other loci proven to contribute to T1DM. Certain environmental factors, such as viruses, may also be important.

T1DM patients are prone to ketosis, depending on how much insulin is being produced. Do not forget that T1DM is associated with other autoimmune diseases; e.g., thyroid, adrenal, celiac disease, vitiligo, B_{12} deficiency, and myasthenia).

Treatment of T1DM

Treatment of hyperglycemia in T1DM has been shown to definitively reduce micro- and macrovascular complications.

Treat with insulin. Oral hypoglycemics are ineffective. See Table 7-6 on page 7-38.

Insulin regimens consist of 3 main groups:

1) Long-acting insulin to serve as basal insulin:
   - Glargine (Lantus®)
   - Detemir (Levemir®)
2) Intermediate-acting to cover fasting and pre-meals: NPH (Humulin N®, Novolin N®)

3) Short-acting insulin to cover pre-meals:
- Regular (Humulin R®, Novolin R®)
- Lispro (Humalog®)
- Aspart (NovoLog®)
- Glulisine (Apidra®)

Premixed insulin combinations (e.g., "70/30" of NPH/R) are not recommended to treat patients with T1DM.

Fixed daily doses of each type of insulin do not always correct hyperglycemia, especially in patients whose intake of carbohydrates varies dramatically. A recent approach is to use nutritional counseling to teach patients how to effectively estimate the grams of carbohydrate in their next meal. Then, they use a pre-established carbohydrate:insulin ratio to calculate the dose of their pre-meal short-acting insulin. (For example, if using regular insulin and the patient's individualized C:I ratio is 15:1, then when the intake is estimated at 130 gm of carbs, the dose would be 130/15, or ~ 8.5 u of short-acting pre-meal). This route for dosing gives patients a little more dietary flexibility and still prevents hyperglycemia. The counseling aspect is important because both physicians and diabetic patients erroneously estimate the carbohydrate content of most meals.

Alternatively, patients also can be treated with a continuous pump that uses rapid-acting insulin to provide a basal rate, with programmed increases prior to meals. The programming is based on preprandial (before meal) blood sugars. The pumps appear to improve glucose control slightly over standard injections.

Pumps and intensive insulin regimens carry a danger of hypoglycemia, and this may be fatal if it occurs at night or is otherwise unrecognized, especially in someone with coronary artery disease. Malfunction of the pump also can result in quick ketoacidosis.

Know that nocturnal hypoglycemia is a problem, not only because it is potentially lethal, but also because episodes lead to feeling poorly the next day with marked fatigue and a measurable decrease in productivity.

Notes for T1DM

Brittle DM: Possible etiologic factors include increased growth hormone in puberty (increases resistance to insulin), gastroparesis, poor communications, and malingering. It usually reflects psychological issues.

Honeymoon effect: indicates improvement of hyperglycemia after diagnosis and institution of treatment. Sometimes, patients can be removed from medication entirely for a short while. Eventually, however, they require reinstitution of treatment. Some patients have increased insulin secretion and decreased insulin resistance in the 1st year. This additionally may be due to a decrease in the initial precipitating stress.

Table 7-6: Insulin Preparations

	Onset	Peak	Duration	Cost	Miscellaneous
Human Insulin Preparations: Peaks and duration do not simulate natural basal and post-meal insulin activity.					
Intermediate-acting					
NPH (Humulin N®, Novolin N®)	2 hours	6–10 hours	18–28 hours	$	
Short-acting					
Regular (Humulin R®, Novolin R®)	30–60 minutes	2–4 hours	5–8 hours	$	
Insulin Analogs: Result in better simulation of natural insulin activity.					
Long-acting					
Glargine (Lantus®)	2 hours	None!	20–24 hours	$$$	Less nocturnal hypoglycemia compared to NPH
Detemir (Levemir®)	2 hours	3–9 hours	6–24 hours (dose-dependent)	$$$	Less nocturnal hypoglycemia compared to NPH
Short-acting					
Lispro (Humalog®)	5–15 minutes	45–75 minutes	2–4 hours	$$$	Less hypoglycemia compared to Regular
Aspart (NovoLog®)	5–15 minutes	45–75 minutes	2–4 hours	$$$	Less hypoglycemia compared to Regular
Glulisine (Apidra®)	5–15 minutes	45–75 minutes	2–4 hours	$$$	Less hypoglycemia compared to Regular

Quick Quiz

- Explain the honeymoon effect.
- What is the difference between dawn phenomenon and Somogyi effect?
- What are the most common causes of morning hyperglycemia in DM?
- What are the mechanisms leading to development of T2DM?
- What conditions are associated with acanthosis nigricans?
- What is the 1st treatment for T2DM?

Dawn phenomenon: increased blood glucose between 4 and 7 a.m. with no preceding hypoglycemia. It also may occur in healthy people. The cause is transient, mild insulin resistance due to the normal early-morning rise in cortisol and GH.

Somogyi effect: The Somogyi effect is the theory that nocturnal hypoglycemia stimulates the adrenal to release glucocorticoids that, subsequently, increase early morning glucoses. The suggested treatment has been to decrease the evening insulin to prevent the nocturnal hypoglycemia. As stated in the Dawn phenomenon, nocturnal growth hormone secretion and hypoinsulinemia are the most common causes of morning hyperglycemia, not nocturnal hypoglycemia.

We mention this Somogyi effect only to tell you that the theory has been definitively disproven; so on a Board exam, it would be incorrect to reduce the evening NPH in patients with nocturnal hypoglycemia and morning hyperglycemia. Early morning hyperglycemia usually can be treated by delaying the evening long-acting insulin until bedtime, so that the peak (if using NPH) occurs ~ 8 hours after the dose and coincides with waking/breakfast. Alternatively, a long-acting insulin analog (glargine or detemir) can be substituted for the NPH. These insulins have a less dramatic peak and decline, compared with NPH.

TYPE 2 DM

Etiology

90% of patients with diabetes have T2DM. The disease is considered strongly hereditary (multifactorial and polygenic), but we have yet to identify any major genes. Concordance of T2DM in monozygotic twins is 70–90%. Obesity increases insulin resistance, and ~ 80% of patients with T2DM are obese. T2DM patients with a combination of central obesity, HTN, and dyslipidemia are known as having a "metabolic syndrome." Pregnancy also increases resistance due to placental hormones.

T2DM causes impaired glucose handling at many sites.

Know the defects that result in T2DM:

- Insulin resistance in muscle and fat tissues
- Gradual reduction in insulin secretion by the pancreas
- Unregulated hepatic gluconeogenesis and glucagon secretion
- Reduction in gastrointestinal incretins (glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide)

Hyperosmolar nonketotic states are a problem in T2DM, although some patients present with DKA. Hyperosmolar coma has many precipitating factors, including volume depletion, drugs (e.g., glucocorticoids), and any serious illness.

Note: Insulin resistance is also associated with acanthosis nigricans. This velvety, dark rash in flexural areas occurs in conditions associated with insulin resistance, such as PCOS, Cushing's, certain medications (e.g., niacin, corticosteroids), and acromegaly. Rapid onset of widespread acanthosis nigricans in the older patient suggests GI malignancy.

Treatment of T2DM

Overview

Therapeutic Lifestyle Changes (TLC) are still the 1st treatment (diet and exercise, weight loss). After TLC, prescribe oral hypoglycemics +/– insulin. Typically, insulin is prescribed as a "last resort" option after all other possible oral and injectable medications are tried or ruled out. This is because, in general, insulin therapy leads to weight gain over time.

No head-to-head studies of medication regimens have been done yet, so focus on knowing the mechanisms of action of each class of drugs, when the different drugs are prescribed, and the side effects/contraindications.

The medications used in treatment of T2DM:

- Oral hypoglycemics
  - Secretagogues (sulfonylureas, meglitinides)
  - Biguanide (metformin)
  - Thiazolidinediones/glitazones (rosi-, pio-)
  - α-glucosidase inhibitors (acarbose, miglitol)
- Newer agents (oral or injectable)
  - Amylin analogs (pramlintide)
  - Glucagon-like peptide-1 (GLP-1; exenatide, liraglutide)
  - Dipeptidyl-peptidase 4 inhibitors (DPP4I; sitagliptin)
  - Bromocriptine
  - SGLT-2 inhibitor (sodium glucose co-transport inhibitors; canagliflozin)
- Insulin

Oral Hypoglycemics

For general competency and for exam questions, it is important to know the mechanisms of action of each class of oral hypoglycemic drugs (Table 7-7).

Secretagogues

The sulfonylureas and meglitinides increase insulin secretion but do so by different, although similar, mechanisms of action.

Sulfonylureas: These are either 1st generation: acetohexamide, chlorpropamide, tolazamide, and tolbutamide; or 2nd generation: glipizide, glyburide, and glimepiride.

2nd generation drugs are preferred over 1st generation and are less expensive.

Even though glyburide is a 2nd generation drug, its half-life is very long, and patients (especially elderly) are at risk for severe hypoglycemia. The use of glyburide is no longer preferred by the ADA; use the other 2nd generation drugs instead.

Sulfonylureas are approved for use in combination with most other drugs except meglitinides; especially useful in patients who cannot take metformin as a preferred 1st drug.

Weight gain is a common side effect of sulfonylureas.

The half-life of these drugs is long, and hypoglycemia can persist in states of overdose or renal impairment. Severe hypoglycemia caused by an overdose of sulfonylureas mandates an admission to the hospital because the resultant persistent hypoglycemia may require days of high-dose IV glucose therapy.

Use sulfonylureas with caution in the elderly and in patients with declining renal function; glipizide has a relatively shorter half-life and is safer in these conditions.

Meglitinides: These drugs are rapid-acting with a very short half-life. Representatives are repaglinide, repaglinide + metformin (a biguanide), and nateglinide. Major effect is on postprandial glucose.

As with sulfonylureas, weight gain is also a common side effect of the meglitinides.

This class can be used in patients with chronic kidney disease.

Biguanides

Biguanides reduce hepatic glucose production.

Metformin (MET) is the only one on the market in the U.S. Other formulations are extended-release MET, MET in combination with glyburide as a single tablet, and many others. Metformin is the preferred 1st line drug for any patient with T2DM, unless the patient meets a need for immediate insulin (discussed below). Start with 500 mg bid and gradually increase to a maximum of 1,700–2,550 mg/day in divided doses.

Side effects from MET monotherapy are less than with sulfonylureas, especially no weight gain and less hypoglycemia.

Also favorable: decreases LDL and TGs.

Major side effects of MET that sometimes limit use:

- Dose-related abdominal pain and diarrhea and propensity for causing lactic acidosis.
- Contraindicated in renal dysfunction (males with serum creatinine ≥ 1.5, females with ≥ 1.4, or "abnormal" creatinine clearance [GFR < 30 cc/min is usually used in the U.S.]), decompensated CHF, and acute or chronic metabolic acidosis.
- Hold MET in acutely ill patients and in those scheduled for contrast procedures or surgery—because both might cause renal failure → lactic acidosis.

Biguanides are approved for use in a variety of combinations with other oral agents and insulin.

Thiazolidinediones (TZDs)

Also called "glitazones," TZDs enhance insulin sensitivity and may help preserve some function of pancreatic beta cells. 2 are currently approved in the U.S.: rosiglitazone and pioglitazone. Currently, the ADA does not recommend use of rosiglitazone because of questions regarding its cardiovascular risk. However, in mid 2013, following a re-adjudication of rosiglitazone safety data, the FDA concluded that rosiglitazone does not increase the risk for adverse cardiovascular outcomes and eased the prescribing restrictions in the U.S., making the drug more readily available to patients.

Pioglitazone has not been shown to have the same cardiac risks and is marketed in combination with other agents:

- Pio + metformin
- Pio + glimepiride

Table 7-7: Oral Hypoglycemic Agents

	Efficacy in Lowering HbA1c	Average Cost/Month
Metformin	1–2%	$4.00 (retail pharmacy with prescription program)
Sulfonylureas	1–2%	$4.00 (retail pharmacy with prescription program)
TZDs	0.5–1.4%	variable
Acarbose	0.5–0.8%	variable
Meglitinide	0.5–2%	variable
Exenatide	0.5–1%	$$$
Sitagliptin	0.5–0.8%	$$$
Pramlintide	0.2–0.5%	$$$
Canagliflozin	0.7–1%	$$$

QuickQuiz

- What are the mechanisms of action of the main classes of oral hypoglycemics?
- What are the metformin contraindications? Thiazolidinediones?

Favorable effects: modest reduction in blood pressure, increased HDL, and decreased TGs.

Serious adverse effects: fluid retention and increased risk of exacerbating stable heart failure, weight gain, and increased risk of fractures (definitely in women, probably in men). Pioglitazone may be associated with bladder cancer and should not be used in patients with a history of such. Monitor liver transaminases occasionally because of risk of hepatotoxicity. Hypoglycemia is a definite risk when combined with insulin.

α-Glucosidase Inhibitors (AGIs)

AGIs delay carbohydrate absorption in the gut. Representatives: acarbose and miglitol. Biggest effect is on postprandial glucose. Common side effects: flatulence, diarrhea, abdominal bloating. AGIs are approved for monotherapy and in combination with sulfonylureas.

Newer Agents

Amylin Analogs

Amylin is a hormone secreted by pancreatic beta cells along with insulin and helps to regulate glucose influx by suppressing glucagon and slowing stomach emptying.

Pramlintide is an analog that comes as an injection given before meals. It is intended to be used with prandial insulin, because it helps insulin to work more effectively.

Cut the insulin dose by 50% when initiating treatment. Gastroparesis and insensitivity to hypoglycemia are contraindications.

Glucagon-like Peptide-1 (GLP-1) Agonists

These drugs were initially called "incretin mimetics." Incretin hormones are secreted by the gut (GLP-1 is an example) and regulate glucose by stimulating insulin release, inhibiting postprandial glucagon release, slowing nutrient absorption, and accelerating satiety.

Exenatide is an injection approved for combination with MET, sulfonylureas, and TZDs as well as basal insulin.

Side effects include vomiting and diarrhea, which can be significant. Recent data associate this drug with pancreatitis (that may be hemorrhagic), but the drug has not been established as an actual cause. Extended release exenatide is available for once weekly injection.

Liraglutide injection is also available. It is currently contraindicated in patients with a family history of medullary thyroid cancer, including MEN2 syndromes, because of C-cell hyperplasia (seen only in rodents so far and not in humans).

These drugs are recommended as 1st line drugs only for patients who cannot tolerate or take potent oral hypoglycemics; e.g., metformin, sulfonylureas, or TZDs. They are add-on drugs, otherwise, and especially benefit patients with obesity who cannot tolerate an increase in insulin.

Dipeptidyl-Peptidase 4 Inhibitors (DPP4I)

These drugs slow the inactivation of natural incretins, such as GLP-1, thereby increasing its concentration. Representative drugs: sitagliptin, sitagliptin in combination with MET, and saxagliptin, vildagliptin, and linagliptin. Approved for use alone or in combination with MET or TZD.

The biggest effect is on decreasing postprandial glucose. DPP4Is are associated with fewer instances of hypoglycemia, but sitagliptin may cause pancreatitis (like exenatide) and upper respiratory infections. Occasionally, these drugs cause severe skin reactions, such as blistering, angioedema, and anaphylaxis.

Like GLP-1 antagonists, DPP4Is are reserved as 1st line drugs only for patients who are intolerant or cannot take metformin, sulfonylureas, or TZDs. They are add-on drugs, otherwise, and especially benefit patients with obesity who cannot tolerate an increase in insulin.

Bromocriptine

Bromocriptine is a dopamine agonist previously used to treat pituitary tumors, hyperprolactinemia, and Parkinson disease. It was approved in 2009 for treatment of Type 2 DM. It is rarely used because of its mild glucose-lowering effect and GI side effects.

Sodium-Glucose Co-transport Inhibitors (SGLT-2 Inhibitors)

SGLT-2 inhibitors block the co-transport of sodium and glucose in the proximal tubule, reducing glucose reabsorption and causing renal excretion of glucose. These drugs do not cause hypoglycemia, and they lead to modest weight loss. There is an increased risk of vulvovaginal infections in females.

Canagliflozin is the 1st agent in this class that works by inhibiting glucose reabsorption in the renal tubules. It is an oral agent approved as monotherapy and in combination with metformin, sulfonylureas, glitazones, and insulin. It is contraindicated in Type 1 diabetes and in patients with a GFR < 45. Common side effects are dehydration, renal impairment, urinary tract infections, and genital mycotic infections.

Insulins

The same insulins used in T1DM are used in T2DM. Know that the newer formulations (long- and short-acting) are not more effective at lowering A1c than the older NPH insulin and regular, although they often are preferred because they are easier for patients. Patients with T2DM sometimes can tolerate the fixed insulin preparations (e.g., "70/30" of NPH/regular). (See Table 7-6 on page 7-38.)

As in patients with T1DM, patients with T2DM who take insulin sometimes can benefit from using the carbohydrate:insulin ratio when determining pre-meal insulin doses.

Nocturnal hypoglycemia also may lead to poor daily functioning in patients with T2DM, just as in patients with T1DM.

According to both the ADA and the AACE, insulin should be added after oral drugs are used except in the following special situations, where insulin should be instituted early:

- Patients who have consistently high random plasma glucoses (> 300–350 mg/dL)
- A1c > 10–12%
- A1c > 9% with symptoms
- Signs of ketosis on physical exam
- Severe symptoms of hyperglycemia or history of DKA

In these groups, oral agents can be added later, after the glucoses have stabilized with insulin—and, eventually, you may be able to stop the insulin entirely.

In patients without symptoms, both the ADA and AACE suggest starting patients out on 2 or 3 medications if the A1c is > 9%.

The ADA preferred regimen for insulin is "basal-bolus" dosing, where patients are given a long-acting insulin that keeps glucoses controlled during the fasting state, and short-acting insulin is given preprandially (just before meals). Recognize that patients who are hospitalized, or are fasting for whatever reason, should not have their basal insulin discontinued simply because they are not eating. Stop the rapid-acting prandial (mealtime) insulins. But continue the basal insulin because its function is to deal with the hyperglycemia that occurs regardless of whether food is present, though it might need to be reduced by 30% to 50%.

Both the ADA and AACE suggest waiting to add insulin (meaning, use oral agents first), except in the above groups, because of the side effects of weight gain (~ 2–4 kg) and hypoglycemia associated with insulin use.

Sequence of Drug Regimens

Use the potent oral hypoglycemics first—sulfonylureas, MET, TZDs (Table 7-7 on page 7-40).

MET (with lifestyle changes) is the preferred initial treatment in all patients with T2DM unless a contraindication exists or the patient cannot tolerate it. Intensify treatment (add drugs) if the A1c is ≥ 7% (6.5% per AACE) after 3 months.

AACE management (2013) is based on degree of persistent hyperglycemia as measured by hemoglobin A1c at presentation:

- A1c < 7.5% = one drug: MET, GLP-1 agonist, DPP4I, AGI, SGLT inhibitor, TZD, insulin secretagogues
- A1c > 7.5% = dual therapy: MET + GLP-1 agonist, DPP4I, TZD, SGLT inhibitor, basal insulin, colesevelam, bromocriptine, AGI, insulin secretagogue
- A1c 7–8% = combination orals +/– insulin; choices of combinations: secretagogue + MET, secretagogue + TZD, secretagogue + AGI, TZD + MET, DPP4I + MET, DPP4I + TZD, secretagogue + MET + TZD

If the A1c is ≥ 6.5 (AACE) or 7% (ADA) after 3 months of the above therapy, add a second drug (dual therapy).

Wait another 3 months and reassess. If A1c is still ≥ 6.5 or 7%, intensify again by adding another of the potent drugs not yet used (triple therapy). Wait another 3 months, and if not at goal, proceed to or intensify insulin therapy:

- A1c > 9% without symptoms = dual or triple therapy (per regimen above).
- A1c > 9% with symptoms or >10–12% = intensive insulin. (Long-acting analogs or NPH + short-acting analogs; premixed insulins work, too. Insulin pumps are good for patients who require multiple injections. Insulins are described above in the section on treatment for T1DM.)
- ADA (2012/2013) does not suggest a hierarchy of drug choices after initial therapy with metformin, but recommends combination therapy with an additional 1–2 orals or injectable agents.

The ultimate intensive regimen would be intensive insulin + MET +/– TZD +/– GLP-1 agonist +/– SGLT inhibitor. **Intensive insulin** means combinations of long-, intermediate-, and short-acting preparations with frequent self-monitoring of blood glucoses.

For patients having trouble with their weight, know that adding a GLP-1 agonist is the best option to control blood glucoses and encourage weight loss.

GLYCEMIC TREATMENT GOALS

For both T1DM and T2DM, keep the glucose level "as close to normal as possible." Recommendations between the advisory groups differ only slightly in targets:

	FPG (mg/dL)	2-hour Postprandial (mg/dL)	HbA1c (%)
AACE	< 110	< 140	≤ 6.5
ADA	90–130	< 180	< 7.0*

*Note: Data have emerged (ADVANCE, VADT, and ACCORD studies) that show that "intensive"

QuickQuiz

- In what T2DM situations should patients be prescribed insulin early in treatment?
- What are the initial drugs used to treat newly diagnosed T2DM?
- What are the treatment goals for glucose and HbA1c?
- Describe the relationship between HbA1c and pre- and postprandial blood glucoses.
- Hyperglycemia after eating is associated with what diabetic complications?
- What antihypertensives are recommended for diabetics with hypertension?

glycemic control (compared to standard control) either has no long-term benefit or actually causes harm in some groups of patients. Therefore, the target HbA1c has been loosened to < 8% for the following groups:

- History of severe hypoglycemia
- Limited life expectancy
- Advanced complications
- Extensive comorbidities
- Long-standing DM with difficulty attaining low A1c

If the A1c remains elevated, but the FPG are controlled, start checking postprandial glucose levels.

Also know that preprandial hyperglycemia contributes more to high average blood glucose when the A1c is elevated. Once the A1c is < 7.5–8%, postprandial hyperglycemia contributes more to high average blood glucose and has been linked to macrovascular complications.

When using insulin to treat DM, consider checking the postprandial glucose periodically, even when the A1c is normal, so you do not miss periods of hyperglycemia.

Some patients who are hospitalized do worse when their blood glucoses are tightly controlled, so these are the current recommendations:

- Non-critical patients: Keep FPG < 140 and random glucoses < 180 using the patient's typical basal regimen and a titrated prandial regimen. A "corrective dose" of insulin is appropriate if needed to correct prandial hyperglycemia, but use of the "sliding scale" is discouraged.
- Critical patients: Keep glucose 140–180 using IV insulin as needed.

ANCILLARY MANAGEMENT

Hypertension

ADA recommendations say to treat first with ACEI or ARB. If additional drugs are required, add a diuretic next (loop, if the GFR is estimated at < 30 cc/min), then a beta-blocker. Non-dihydropyridine calcium channel blockers are recommended last. Goal: < 140/90 for all diabetic patients, but < 130/80 or lower without medication side effects for diabetic patients with micro- and macrovascular disease as per JNC 8.

For the rare patient with DM who is not hypertensive, use an ACEI if significant microalbuminuria or macroalbuminuria is present.

Dyslipidemia

Treat aggressively with whatever agents are suitable to target the patient's specific type of dyslipidemia.

Statins are the drug of choice for any patient with an elevated LDL.

Goals (mg/dL):

- LDL < 100 in all (some now say < 70)
- LDL < 70 in diabetics with CHD
- HDL > 40 (males) and > 50 (females)
- TG < 150

ADA goes a little further and recommends statins in all diabetics who are > 40 years of age with ≥ 1 additional risk factor for CHD, regardless of the lipid profile.

Aspirin

Aspirin use in diabetics is controversial, because we now understand that not all diabetics have the same risk for heart disease, despite DM being listed as a CHD risk-equivalent in the NCEP guidelines.

The current ADA recommendation is to use a prediction model to estimate the patient's 10-year risk for ischemic heart disease (Framingham is one; the United Kingdom Prospective Diabetes Study (UKPDS) risk engine is another that has been validated in diabetics, specifically).

Based on the 10-year risk, give ASA for primary prevention as follows:

- < 5% risk: no ASA.
- > 10% risk: give ASA.
- 5–10%: Talk to the patient and individualize your recommendation.

Diabetics with known heart disease should get a daily aspirin as secondary prevention. ASA-allergic patients can take clopidogrel.

DIABETIC COMPLICATIONS

Overview

Diabetes causes microvascular disease (eyes, kidneys, nerves) and macrovascular disease (coronary and peripheral atherosclerosis → CHD and stroke).

Postprandial hyperglycemia has been specifically associated with macrovascular complications. Tobacco greatly accelerates this process.

Prediabetes has been specifically associated with microvascular and macrovascular disease (although the process continues as long as the patient is hyperglycemic).

The following 3 microvascular complications usually appear 10–15 years after the onset of DM (but T2DM may be present 5–10 years before being diagnosed):

1) **Retinopathy** correlates with duration and control of DM. Early findings include dot hemorrhages (no additional treatment), but photocoagulation is needed if neovascularization occurs (a late finding). Retinopathy may worsen transiently with initiation of tight glycemic control. Retinopathy almost universally precedes nephropathy. If a diabetic without retinopathy develops nephrotic-range proteinuria, the patient should be evaluated for other causes of nephrotic syndrome.
2) **Nephropathy** is heralded by persistent microalbuminuria. Remember that treating hypertension with either ACEI or ARB decreases the rate of progression (by decreasing intraglomerular pressure). ADA and AACE recommend reduced protein diet (0.8–1.0 g/kg/d) in early chronic kidney disease and low-protein diet (0.8 g/kg/d) in advanced kidney disease.
3) **Neuropathy** includes autonomic neuropathy, axonal (Schwann cell) degeneration, symmetric polyneuropathy, erectile dysfunction, and gastroparesis. Both alcohol and tobacco use increase the rate of development of neuropathy. Diabetic mononeuropathy usually affects the 3rd and 6th cranial nerves, the peroneal nerve (foot drop), and the radial nerve (wrist drop). Strict glycemic control decreases the risk of developing neuropathy and improves nerve conduction. The pain associated with diabetic sensory dysfunction is difficult to treat. Recommended drugs for treatment include amitriptyline, venlafaxine, duloxetine, and pregabalin.

You should definitely know the major diabetes studies and how glycemic control affects diabetic complications:

- Microvascular complications are reduced in both T1DM and T2DM with tight control of blood glucoses. This was demonstrated for T1DM by the Diabetes Control and Complications Trial (DCCT) and for T2DM by the UKPDS and the Japanese Kumamoto study.
- Macrovascular complications: A reduction with tight control of glucose has been harder to show. Recent long-term secondary analyses of intensively treated DCCT and UKPDS patients (A1c ~ 7%) show a reduction in cardiovascular outcomes, although the reduction was not statistically significant at the time of the original studies—the significance evolved as the patients aged.

Monitoring

Patients need annual evaluations for microvascular complications (after 5 years in T1DM and immediately in T2DM).

Be sure to do the following:

- Do a urine spot albumin:creatinine as a test for nephropathy (normal < 30 mg/g). Microalbuminuria is 30–300 mg/g.
- Check creatinine and estimate GFR.
- Send them to an ophthalmologist for a slit lamp exam and rapidly refer macular edema or proliferative retinopathy. It is now acceptable to use fundus photography in clinical situations when experienced ophthalmologists are unavailable.
- Inspect the feet visually and perform a sensory evaluation using the 10-gm monofilament, pinprick, temperature, and vibration. Know that loss of vibratory sense and sensation to the 10-gm monofilament predicts foot ulcers.
- Know that asymptomatic diabetics should not be routinely screened for ischemic heart disease; outcomes are unchanged, provided that you are treating their CHD risk factors. Use of coronary CT may benefit some asymptomatic diabetics; we discuss this in Cardiology, Book 3.

HYPERGLYCEMIC STATES

Ketoacidosis

Diabetic ketoacidosis (DKA) is sometimes the initial presentation of T1DM, but it can also occur in T2DM (even in patients treated with oral meds).

It is caused by a state of complete or partial insulin deficiency leading to massive lipolysis. Lipolysis causes a release of free fatty acids and the ketone bodies—beta-hydroxybutyrate, and acetoacetate. These products cause volume depletion from massive osmotic diuresis and high anion gap acidosis (because ketones are acids).

Symptoms include nausea, vomiting, abdominal pain, polyuria, and lethargy. Ask about symptoms of infection (pneumonia, UTI)—often a precipitating condition for DKA.

On clinical exam, hypotension is noted in patients with severe volume depletion. Fruity breath and a Kussmaul respiratory pattern suggest ketoacidosis. Severe cases are marked by confusion or obtundation.

Diagnosis: DKA is diagnosed by a high anion gap acidosis and hyperglycemia. Secondary derangements include total body potassium and phosphorus deficits (even though both may be normal at presentation because of the acidosis and hemoconcentration). Serum Na^+ is usually decreased because of the osmotic shift of water from inside cells to the intravascular space caused by the hyperglycemia, a phenomenon referred to as pseudohyponatremia. Adjust the serum sodium upwards 1.6 mEq for every 100 mg/dL increase in blood glucose over 100 mg/dL before diagnosing any disease of water balance.

Treatment: Give normal saline (~ 2–3 liters), then either continue the saline or switch to 0.45% saline based on the serum sodium (corrected for hyperglycemia).

Quick Quiz

- Name 3 diabetic microvascular complications and characterize their screening and treatment.
- What microvascular complication occurs first in a diabetic, retinopathy or nephropathy?
- Discuss the major diabetes studies that show a correlation between reducing blood glucoses and subsequent micro- and macrovascular complications.
- What tests make up the annual screening for a diabetic?
- List the symptoms of DKA.
- What lab abnormalities occur in the patient with DKA?
- What is the formula used for correction of pseudohyponatremia due to hyperglycemia?
- When is bicarbonate given to treat DKA?
- What medications commonly given to diabetics are contraindicated in pregnancy?
- What is the Whipple triad?

Start IV insulin at 0.1 units/kg/hr. When glucose is < 200 mg/dL, add D5W to the 0.45% fluids. Keep the IV insulin going until the acidosis is resolved, and the anion gap is normal; the insulin is required to stop production of the ketoacids.

If the K^+ is normal at the start of treatment, give KCl immediately because there is usually a several-hundred mEq deficit. In cases of very low K^+, < 3.3 mEq/dL, hold insulin until the K^+ is ≥ 3.3. K^+ is shifted into the cells by both the reversal of acidosis and the action of insulin, further aggravating the hypokalemia and possibly leading to cardiac arrest. Also monitor the heart-wave morphology and rhythm for any K^+-associated changes.

Bicarbonate is given only for pH < 7.0, especially if the patient is having respiratory or hemodynamic collapse.

Know that the Acetest® tablets detect only acetoacetate, not the beta-hydroxybutyrate. When the patient has ketoacidosis, there can be much more of the beta-hydroxybutyrate than the acetoacetate.

If the patient is being treated for DKA and seems to be getting better but the ketones start rising, the beta-hydroxybutyrate is being converted to acetoacetate as the acidosis resolves. Follow resolution with pH and anion gap. The anion gap reflects both types of ketones.

Hyperglycemic Hyperosmolar State (HHS)

This hyperglycemic complication happens in T2DM and is caused by partial insulin deficiency and decreased intake of fluids. Usually, the patient is elderly and has a prolonged history of developing illness marked by lethargy, weight loss, and polyuria.

Exam is consistent with severe dehydration and volume depletion. These patients are not acidotic, so they do not have the fruity breath or Kussmaul respirations.

Labs show hyperglycemia and evidence of dehydration/volume depletion (Na^+ deficit—noted after correction for the hyperglycemia) and azotemia. If a high anion gap metabolic acidosis is present, it is mild and due to lactate.

Treat HHS similarly to DKA, with IV fluid resuscitation and insulin bolus + infusion. Be sure to adjust the serum sodium for the hyperglycemia to determine if a free water deficit exists, then replace it gradually over the next 24–48 hours. Potassium replacement is usually required.

GESTATIONAL DIABETES

With pregnancy in diabetic women, strict control even before conception is important. Maintain FPG < 100 mg/dL and A1c < 7%. Before conception, control of blood glucose reduces fetal malformation; during pregnancy, it reduces miscarriages, fetal anomalies/death, and newborn problems. Tight glycemic control decreases the risk of macrosomia (birth weight ≥ 9–10 lb) and shoulder dystocia in the newborn.

During pregnancy, a diabetic patient requires ~ 50% more insulin due to increased resistance from placental hormones. This increased requirement is gone immediately after delivery, so anticipate a reduction in insulin dosage of at least 33% postpartum and observe the patient carefully the day after delivery.

Know that these medications commonly employed in diabetic management are contraindicated in pregnancy:

- Statins and ACEIs are category X and should be discontinued before pregnancy.
- ARBs are category C (1st trimester) and D (later trimesters).
- Many oral hypoglycemics are category C.

C = Some adverse effect in animal studies or no controlled studies in women. Use only if potential benefit outweighs potential risk to fetus.

D = Positive evidence of human fetal risk. But may be acceptable despite the risk; e.g., life-threatening illness.

X = Causes fetal abnormalities. Do not use.

HYPOGLYCEMIA

OVERVIEW

The diagnosis of hypoglycemia is not based on an absolute blood glucose level; it requires fulfillment of the **Whipple triad**:

1) Signs and symptoms consistent with hypoglycemia
2) Associated low glucose level (< 55 mg/dL)
3) Relief of symptoms with supplemental glucose

Symptoms are autonomic (palpitations, tremor, sweating, paresthesias) and neuroglycopenic due to CNS glucose deprivation (confusion, impaired consciousness, seizures). Usually, autonomic symptoms happen first. Signs of hypoglycemia are nonspecific (pallor, sweating, anxiety).

There are 2 categories of hypoglycemia: reactive (sometimes called "postprandial") and nonreactive (sometimes called "fasting").

REACTIVE HYPOGLYCEMIA

Reactive, or postprandial, hypoglycemia develops in response to a nutrient challenge. You see it in a few patients with T2DM and in some post-GI surgical patients, when gastric contents get dumped into the small intestine too quickly with a brisk release of incretins. "Idiopathic reactive hypoglycemia" requires fulfillment of the Whipple triad to be a true diagnosis. Some patients have symptoms but normal blood glucoses; they need no further workup, in spite of their insistence. Never order an OGTT to work up this entity. On exams, OGTT is a common distractor from the correct answer.

NONREACTIVE HYPOGLYCEMIA

Nonreactive, or fasting, hypoglycemia can be further subdivided into iatrogenic (most common overall cause) and fasting/factitious.

In the fasting/factitious type, the patient is unable to maintain glucose levels with fasting. Most common causes: alcohol abuse, drugs (oral hypoglycemics, pentamidine), sepsis, and renal failure.

Causes of nonreactive hypoglycemia most commonly tested on exams:

- Factitious taking of oral hypoglycemics/insulin: common---especially suspect if the patient is in the medical field or has a family member with DM
- Hormone deficiencies: adrenal insufficiency
- Insulinoma from a pancreatic islet cell tumor
- Autoimmune etiology: rapidly changing levels of anti-insulin antibodies

4 tests are used in the workup of confirmed, nonreactive hypoglycemia brought about by a supervised fast (sometimes up to 72 hours; see Figure 7-8):

1) Serum insulin
2) Serum proinsulin
3) C-peptide
4) Urinary/Plasma sulfonylurea test

Insulin is high or inappropriately normal during the hypoglycemic episode:

- With factitious etiology, patients can have high insulin levels, sometimes > 100 μU/mL, due to self-administration.
- Patients with insulinomas usually have an insulin level > 6 μU/mL during an episode of hypoglycemia.

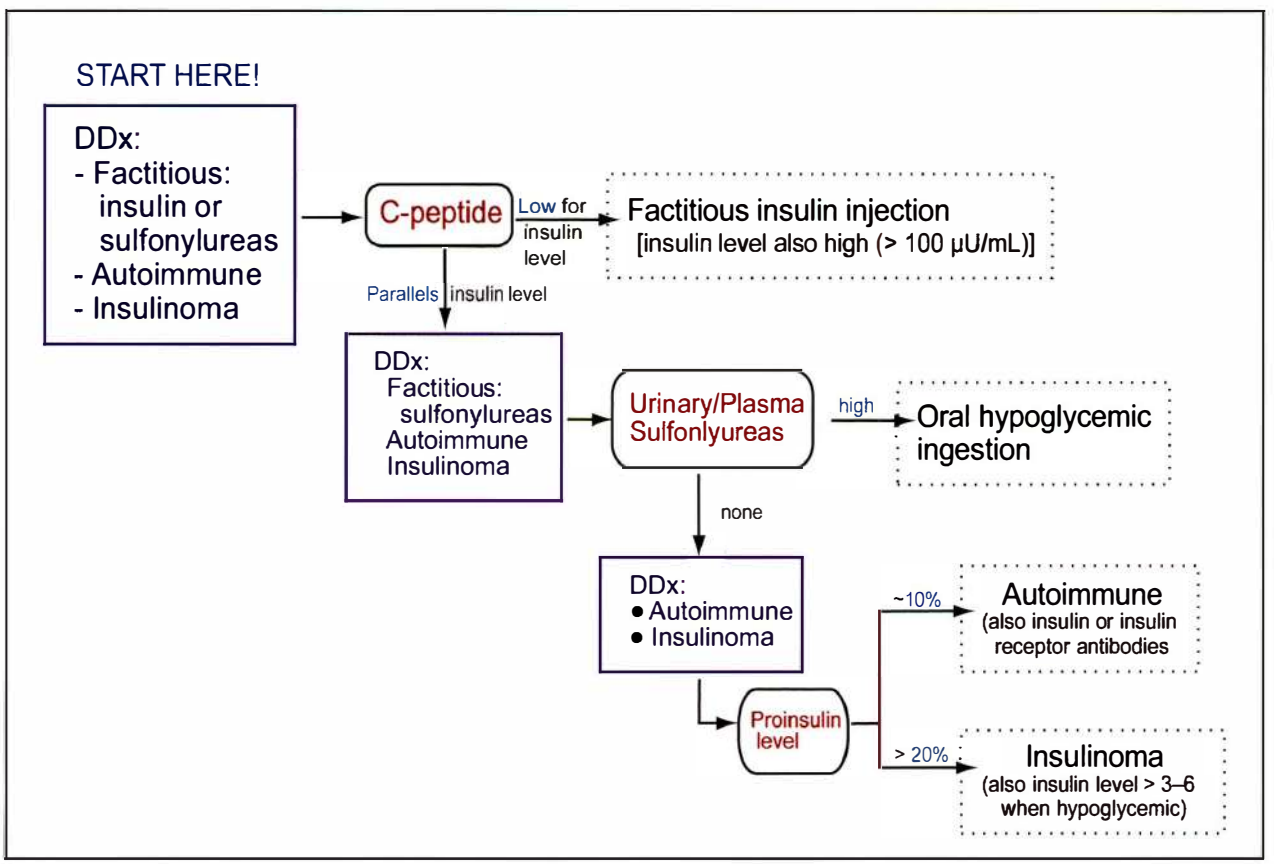

Figure 7-8: Workup of Nonreactive Hypoglycemia

QuickQuiz

- What laboratory tests help you determine if someone is factitiously self-injecting insulin to induce hypoglycemia?
- What is the classic radiographic finding on hand films of patients who have primary hyperparathyroidism?
- A normal iPTH level in the setting of hypercalcemia suggests what diagnosis?

- Autoimmune etiology also results in inappropriately high insulin levels. Antibodies to insulin and insulin receptors can be measured, but proinsulin (next) is typically done instead.

Proinsulin (the precursor of insulin): Insulinomas tend to cause a higher proportion of proinsulin in the serum. Normal level is 10% of total insulin. With insulinomas, the level is > 20%, and often 30–40%.

C-peptide is produced in a 1:1 ratio with insulin when they are both cleaved from proinsulin. Therefore, with endogenous insulin production (including sulfonylurea-induced and insulinoma), the C-peptide level parallels serum insulin values. C-peptide is low (usually not measurable) with insulin injection.

Urinary/Plasma sulfonylurea test rules in or out oral hypoglycemic use but can result in a false negative. Follow your clinical suspicions. A newer screen using mass spectrometry can detect all sulfonylureas, as well as meglitinide and repaglinide.

BONE / CALCIUM DISORDERS

NORMAL CALCIUM PHYSIOLOGY

Normal calcium physiology: Calcium is absorbed from the duodenum, stored in the bone, and excreted by the kidneys.

Increase in Serum Calcium

Two endogenous hormones increase serum calcium level: 1,25-$(OH)_2$-vitamin D and parathyroid hormone (PTH).

Vitamin D is made in the skin after a reaction with sunlight but is inert until it is sequentially hydroxylated, first in the liver (to form 25-OH-D), and then in the kidney (1,25-$(OH)_2$-D). 1,25-$(OH)_2$-D, in turn, increases Ca^{2+} and phosphorus absorption from the gut.

PTH increases calcium in the blood through the following:

- Stimulates release of bone calcium stores by indirect stimulation of osteo**c**lasts (**c** = **c**hew bone)
- Increases renal tubular Ca^{2+} resorption and renal tubular phosphorus excretion
- Increases the production of 1,25-$(OH)_2$-D by increasing activity of kidney hydroxylase

Serum free Ca^{2+} works via a negative feedback on the parathyroids. High serum Ca^{2+} decreases production of PTH, and low serum Ca^{2+} increases production.

Decrease in Serum Calcium

Calcitonin, from the thyroid parafollicular cells (C cells), can be considered a PTH antagonist. It slows down the osteoclasts, causing a decrease in bone resorption and increases renal calcium clearance.

Normal levels of glucocorticoids help maintain osteo**b**last (**b** = **b**uild bone) function, but excess decreases the bone protein matrix and cause calciuria.

Estrogen (like calcitonin) decreases bone resorption and (like glucocorticoids) may increase osteoblastic activity—so it has a double bone-building function.

HYPERCALCEMIA

Primary Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is often found incidentally after noting high serum calcium on screening laboratory studies. 80% of cases are caused by parathyroid adenomas. Natural history includes ~ 25% progression. Patients have decreased density of cortical bone (distal radius), a 2–3x increased risk of fractures, and may have complaints of bone pain.

The classic signs and symptoms in a symptomatic PHPT patient have often been described as "bones, stones, abdominal moans, and psychic groans."

Subperiosteal bone resorption (termed "osteitis fibrosa cystica"), with a moth-eaten appearance to the radial side of phalangeal cortices on finger radiographs, is the classic finding indicating prolonged PTH excess. This finding is occurring much less now than in the past, probably due to automated lab tests and earlier recognition. If an exam question shows you radiographs of a patient's hands, think about primary hyperparathyroidism.

Diagnosis of PHPT is made by finding a normal or an elevated intact PTH (iPTH) in a patient with elevated calcium. Serum phosphorus is usually low-normal to low.

Know that patients with drug-induced (lithium, thiazides) hypercalcemia and benign familial hypocalciuric hypercalcemia (FHH) may present with PTH levels above normal; and ~ 25% of patients with primary hyperparathyroidism have normal or high-normal iPTH. Even a normal iPTH is compatible with the diagnosis of primary hyperparathyroidism—because an otherwise healthy person has a suppressed iPTH in the presence of hypercalcemia.

Abdominal x-rays and measurement of 24-hour urinary calcium are no longer recommended. Also, hypercalciuria (if there is no history of stones) is no longer an indication for surgery.

Treatment of PHPT: Medically managed patients should have their serum calcium and creatinine measured yearly and bone density scans every 1–2 years. Also check their 25-$(OH)_2$-D levels and give supplementation if the level is < 20 ng/dL. Know that you should not tell patients to restrict their calcium intake; diet advice should be the same as for patients without primary hyperparathyroidism.

No specific drug is recommended by the guidelines because long-term data in these patients are scarce. However, bisphosphonates build bone in the L-spine and hips without changing serum calcium. Cinacalcet is also being investigated because it normalizes calcium levels—but does not build bone.

Symptomatic PHPT patients (e.g., nephrolithiasis or osteoporosis) go to surgery.

Asymptomatic patients are more difficult to manage. Guidelines released in 2009 from the Workshop on Hyperparathyroidism say to manage most asymptomatic patients medically, with good follow-up.

Additionally, the following PHPT patients are referred for surgery:

- GFR < 60 cc/minute/1.73 m^2 (CKD stage 3)
- T-score of –2.5 or less at L-spine, femur, hip or 33% radius
- Z-score of –2.5 or less in premenopausal women and men < 50 years
- Age < 50 years

All potential surgical candidates should have a serum calcium > 1 mg/dL above normal (at least).

Note: A urine calcium > 300 is no longer considered an indication for parathyroid surgery; however, a urine calcium (that is low) in the setting of a high serum calcium consistent with a diagnosis of FHH is needed to prevent unnecessary surgery.

Sestamibi scans and ultrasound are standard preoperative evaluations to localize the adenomas.

Secondary hyperparathyroidism is the overproduction of parathyroid hormone secondary to a chronic abnormal stimulus for its production. Typically, this is due to chronic renal failure and/or vitamin D deficiency.

Tertiary hyperparathyroidism is seen in patients with chronic secondary hyperparathyroidism and often after renal transplantation. These autonomous, hypertrophied parathyroid glands fail to return to normal and continue to oversecrete parathyroid hormone, despite elevated serum calcium levels. Often serum phosphate levels also are elevated.

Summary: Hypercalcemic patients with elevated or normal iPTH and low phosphorus = primary hyperparathyroidism. If symptomatic (e.g., kidney stones) or low bone density, do surgery. Secondary hyperparathyroidism = consider vitamin D deficiency and CKD as the cause. Tertiary hyperparathyroidism = hyperparathyroidism persisting after renal transplantation.

Other Causes of Hypercalcemia

Vitamins and Medications

Vitamin D excess, vitamin A excess (causes calcium release from bones), thiazide diuretics (decreases calcium excretion), and lithium (increases PTH threshold by requiring calcium to be at a higher level to shut off PTH production) can cause hypercalcemia.

Genetic Causes of Hypercalcemia

Benign familial hypocalciuric hypercalcemia (FHH) is autosomal dominant with normal or slightly elevated iPTH and elevated calcium—same as what can occur in patients with primary hyperparathyroidism. FHH requires no treatment, so it is important to differentiate from other causes of hypercalcemia (especially primary hyperparathyroidism). If suspected, measure calcium and creatinine in the serum and urine, then calculate the calcium:creatinine clearance ratio. If the ratio is < 0.01, the diagnosis is FHH; if > 0.02, FHH is excluded, and the diagnosis is most likely primary hyperparathyroidism. The problem is in the calcium sensor, which requires a higher calcium level before turning off PTH secretion.

Malignancy and Hypercalcemia

There are 3 groups of malignancies that cause hypercalcemia: myeloma, some solid tumors, and tumors with bone metastases. Myeloma produces several osteoclast-activating factors, causing breakdown of bone.

Some solid tumors secrete a PTH-related protein (PTHrP), in which the N-terminal (amino) end is identical to iPTH. But the mid- and carboxy-terminal portions are different, so it is not picked up by the iPTH assay. The elevated calcium causes a negative feedback on the production of PTH by the parathyroid glands.

Bone metastases account for 1/2 of all patients with elevated calcium and malignancy; they produce local osteoclast activation substances.

Several granulomatous diseases cause hypercalcemia by means of increased 1,25-$(OH)_2$-D production by the macrophages. Macrophages (and lymphocytes) have an unregulated 1α-hydroxylase, which converts 25-OH-D into 1,25-$(OH)_2$-D. These granulomatous diseases include sarcoidosis, tuberculosis, berylliosis, histoplasmosis, and leprosy. Treat with corticosteroids if it's safe (if the patient is not infected). Immobilization is a mechanical cause of elevated calcium, but only in the setting of high bone turnover—hyperthyroidism, Paget disease, and adolescence. The high calcium causes a decrease in iPTH.

Treatment of Hypercalcemia

Immediately give 3–4 L of normal saline to treat volume depletion caused by salt wasting associated with high urinary calciums. We used to add loop diuretics to

QuickQuiz

- What periodic exams do patients with primary hyperparathyroidism need if they are being medically managed?
- What are the indications for surgical treatment of primary hyperparathyroidism?
- What are the common causes of secondary hyperparathyroidism?
- Define tertiary hyperparathyroidism. When is it likely to be seen?
- What are other causes of hypercalcemia, besides primary hyperparathyroidism?
- How can you differentiate FHH from primary hyperparathyroidism?
- What malignancies are associated with hypercalcemia?
- What is the treatment for hypercalcemia?
- Why can hyperphosphatemia cause hypocalcemia?
- What is osteomalacia? How does it present and how do you screen for it?
- What is the most common cause of vitamin D deficiency?
- What lab value is used to measure vitamin D levels?

promote calciuria once volume status was corrected, but this is not done anymore because the efficacy of bisphosphonates and calcitonin outweigh the electrolyte complications of the diuretic.

Bisphosphonates interfere with bone resorption in areas of high turnover, such as sites of malignancy, and usually are used in conjunction with saline infusions and calcitonin to treat moderate-to-severe hypercalcemia.

Pamidronate and zoledronic acid are representative drugs, favored by most because of their rapid onset of action and intravenous formulation. Know that these drugs are associated with osteonecrosis of the jaw in patients with multiple myeloma and metastatic bone disease.

Give glucocorticoids for sarcoidosis and myeloma. Mobilize patients.

HYPOCALCEMIA

Overview

Low serum calcium is caused by the following:

- Hypoparathyroidism is due to decreased PTH secretion:
  - primary hypoparathyroidism,
  - thyroid surgery with loss of parathyroid glands, or
  - severe hypomagnesemia (Mg < 0.8 mEq/L; required for PTH release and its effect on target organs) due to bowel disease or alcohol abuse.
- Vitamin D deficiency.
- Loss of calcium in cases of severe, acute pancreatitis: formation of calcium "soap."
- Acute, severe hyperphosphatemia, in renal excretion of phosphorus which calcium chelates with the phosphorus.
- Pseudohypoparathyroidism (Types Ia, Ib, Ic, II) is due to increased PTH resistance. It is a rare genetic disease due to a mutation in the PTH receptor gene. These patients have an appropriately elevated PTH (in response to the hypocalcemia). In addition to hypocalcemia, patients with Type Ia have short 4th metacarpals and short stature. This phenotype of Type Ia is due to yet another mutation of the PTH receptor gene and may occur alone.

When patients with shortened 4th metacarpals and short stature have a normal biochemical profile, they have pseudo-pseudohypoparathyroidism. Very simple! Do not let this confiise you! These patients have only the mutation for the Ia phenotype but are otherwise completely normal and have normal calcium homeostasis.

Osteomalacia

Osteomalacia is a condition of demineralized bone, which occasionally presents with hypocalcemia. It is most commonly caused by vitamin D deficiency (called rickets when it occurs in youth, causing listlessness, irritability, and bowing of the legs). Older patients present with bone pain and proximal muscle weakness. Patients of all ages have diffuse demineralization. In adults, know that "bilateral symmetric pseudofractures" establish the diagnosis. If there are no fractures, you need an iliac crest bone biopsy with tetracycline double-labeling to show the mineralization defect, but usually osteomalacia is diagnosed clinically without a biopsy. Once the diagnosis is established, work up the cause (many possibilities).

The usual cause of vitamin D deficiency is inadequate intake of vitamin D and/or malabsorption. It's quite common in the elderly and in northern latitudes. Vitamin D deficiency is also more common in people who use a lot of sunscreen and/or avoid sunlight.

Studies link vitamin D deficiency with falls, fractures, increased risk of cancer, and CHD, so the Boards should have a renewed interest in your knowledge about the condition. Look for osteomalacia in the older man, hospitalized for weeks, who develops bone pain with radiographs that show hair-line fractures.

Check 25-OH-D levels if you suspect vitamin D deficiency (not 1,25-$(OH)_2$-D!).

Renal osteodystrophy and adynamic bone disease are discussed in Nephrology, Book 2. Osteoporosis is discussed under Geriatrics in General Internal Medicine, Book 5.

Table 7-8: Lab in Diseases Affecting Calcium

	PO_4	Ca^{2+}	Alk Phos	iPTH	25-OH-D	1,25-$(OH)_2$-D
Osteomalacia from Vit D def*	↓	↓	↑	↑	↓	n/a
Chronic renal failure	↑	↓	n/a	↑	normal	↓
Primary hyperparathyroidism**	n/a	↑	↑	↑	n/a	n/a
Hypercalcemia of malignancy***	n/a	↑	↑	↓	n/a	n/a

* Do not need to check 1,25-$(OH)_2$-D for osteomalacia from Vit D deficiency. If 25-OH-D is low, then 1,25-$(OH)_2$-D will be low.
** High Ca and high iPTH = primary hyperparathyroidism (elevated iPTH should not be elevated if the calcium is high; it should be suppressed).
*** Other findings for hypercalcemia of malignancy: diagnosis of myeloma or obvious bony metastases.

REVIEW OF CALCIUM-RELATED LABS

Know Table 7-8.

MULTIPLE ENDOCRINE NEOPLASIA

Multiple endocrine neoplasia (MEN, Table 7-9): All are autosomal dominant—with varying expression! These are categorized as MEN1, MEN2A, and MEN2B.

MEN1: It can have quite a variety of symptoms, but they are all caused by hyperplasia, adenomas, and/or cancers of the **p**arathyroid, **p**ituitary, or the islet cells of the **p**ancreas (think "**PPP**"). Suspect this in a patient with hypoglycemia and hypercalcemia. There is often a strong family history of peptic ulcer disease. Phenotypic expression within a family might be quite variable; one relative may have all 3 components whereas another relative may have only 1 of the endocrinopathies.

MEN2A: Medullary thyroid cancer occurs in virtually all patients with MEN2A or MEN2B and often occurs early in life. Pheochromocytoma occurs frequently; parathyroid hyperplasia occurs in 25–50%.

MEN2B is also associated with medullary thyroid carcinoma, and 1/2 have pheochromocytoma, but only rarely do they have parathyroid hyperplasia. This type is easy to differentiate from the others because of the mucosal neuromas easily seen on physical exam. Life expectancy in MEN2B is 30 years, whereas it is 60 years in MEN2A—suggesting that these are different clinical syndromes.

For MEN1, the pancreatic adenoma may functionally be a glucagonoma, which is a very rare malignant tumor of pancreatic islet cells that produces glucagon and is associated with a blistering dermatitis, diabetes, cheilitis, diarrhea, weight loss, and cognitive impairment. The skin and tongue changes are due to a glucagon-induced amino acid deficiency.

Risk factor for a glucagonoma is MEN1. Think about it in patients with a family history of MEN1 who present with a triad of mild hyperglycemia, glossitis with a "beefy red tongue," and a distinctive blistering erythematous rash that is often found in the groin region (termed "migratory necrolytic erythema"). The skin and tongue changes are due to a glucagon-induced amino acid deficiency.

Diagnose by measuring a glucagon level—one of the rare instances where it is useful to measure a random hormone! A level > 500 pg/mL is supportive (mean ~ 1,400 pg/mL). Imaging of the pancreas with a helical CT is useful in patients suspected of having the tumor because of increased glucagon levels.

In the majority, the glucagonoma has already metastasized (liver, lymph nodes, bone, adrenals, kidney, lung) at diagnosis.

Remember: Both MEN2A and MEN2B have medullary thyroid cancer and pheochromocytoma.

Look at Table 7-9 for the following:

- A causes hypercalcemia, but generally no symptoms.
- B may cause Cushing disease, but usually no symptoms unless advanced.
- C can cause a patient to present with hypoglycemic episodes or peptic ulcer disease.
- D is detected by a calcitonin level.
- E can present as hypertension but typically is asymptomatic.

If a patient with an elevated iPTH has a family history of one brother having "medullary cancer" and another having a "parathyroid tumor," what tests should you do on the patient?

Table 7-9: Multiple Endocrine Neoplasia

Type	Clinical
1	A, B, C
2A	A, D, E
2B	D, E, F

A) Parathyroid hyperplasia
B) Pituitary adenomas
C) Pancreatic islet cell tumors causing hypersecretion of either insulin or gastrin
D) From C-cell hyperplasia to medullary cancer
E) Pheochromocytoma
F) Abnormal physical appearance: marfanoid body type, multiple neuromas of the conjunctiva, lips, labia, tongue, mucosa, larynx. "Blubbery lips."

Answer: (think MEN2A) Check calcitonin and free plasma metanephrines. In an exam setting, you may see only one of these in the answer choices.

The RET proto-oncogene test for hereditary medullary thyroid cancer (MTC) can also be very useful and offers the potential for prophylactic surgical intervention prior to the development of MTC in family members who are at risk. Calcitonin elevation correlates with tumor burden and may be the first sign of recurrent persistent disease. Calcitonin doubling time has been shown to be accurate in predicting prognosis. Elevated calcitonin levels can cause symptoms such as flushing, diarrhea, and weight loss; these patients may benefit from somatostatin analogues if their disease is recurrent postoperatively.

For those with sporadic MTC, disease cannot be controlled by current therapies. Drugs that modify signaling pathways (e.g., phosphatidyl-inositol 3-kinase/Akt) and glycogen synthase kinase-3 pathways are currently in clinical trials.

FOR FURTHER READING

[Guidelines in blue]

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HEMATOLOGY

ANEMIA

NORMAL ERYTHROPOIESIS

Erythropoietin regulates red cell production. Normal erythropoiesis involves the maturation of pluripotent stem cells into proerythroblasts → erythroblasts → reticulocytes (Figure 8-1). Immature RBCs, which have lost their nucleus but retained their RNA, can be identified on a standard Wright's stained peripheral blood smear because the cytoplasmic RNA stains a gray-purple color (polychromasia). These same cells, also called reticulocytes, can be quantified by special stains or flow cytometry, yielding a reticulocyte count.

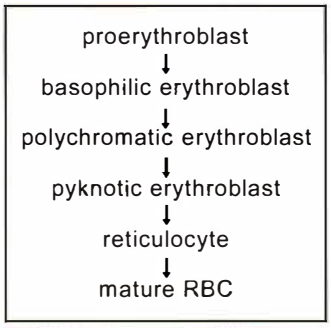

Figure 8-1: Erythropoiesis

The mature red blood cells contain no RNA and survive for approximately 120 days. Throughout their life span, RBCs pass repeatedly through the spleen, where old or damaged cells are ingested by macrophages. The hemoglobin is catabolized into its heme (protoporphyrin ring + iron) and globin components.

The porphyrin ring is metabolized into unconjugated (indirect, water insoluble) bilirubin, which, when bound to albumin (now water soluble), is then transported to the liver, where it is conjugated. Iron released from heme (or absorbed in the intestine from the diet) is transported by transferrin, the blood plasma protein, to the bone marrow and to other tissues where it is stored as ferritin and hemosiderin.

IRON

Iron is absorbed from the gut by means of ferroportin, a transmembrane protein that transports iron through the cell walls of enterocytes and macrophages and subsequently releases this iron to transferrin in the hepatoportal circulation. Ferroportin itself is controlled by hepcidin, the key regulator hormone for iron hemostasis.

Hepcidin levels are decreased in low iron states and increased in iron overload states. Hepcidin binds ferroportin, causing a decrease in the release of iron into the bloodstream. So, high levels of hepcidin cause decreased iron absorption, while low levels allow for increased iron absorption.

Hepcidin is also an acute phase protein that is increased in response to inflammatory cytokines (especially interleukin-6).

MECHANISMS OF ANEMIA

Overview

The approach to the anemic patient should be methodical. Excluding acute hemorrhage and rare sequestration, all anemias can be broadly classified as either hypoproliferative or survival defects. The etiology of most anemias is determined using the history, a physical exam, the reticulocyte count, a thoughtful evaluation of the CBC (focusing on the MCV and RDW), and the peripheral blood smear. Refer to Table 8-1 as you go through this material. Several images of normal blood smears and marrow aspirates are shown for your review on the next page (Image 8-1 through Image 8-6).

Causes and mechanisms of anemia:

1) **Production** defects result from chronic disease, acute inflammatory conditions, impaired renal function, hypometabolic states (e.g., hypothyroidism, hypogonadism, adrenal insufficiency), and bone marrow damage. Very little polychromasia and few reticulocytes are seen.
2) **Maturation** defects:
   - Cytoplasmic: All are related to impaired hemoglobin synthesis—iron deficiency, sideroblastic anemia (the inability to incorporate iron into hemoglobin: protoporphyrin deficiency, myelodysplastic syndrome, drugs, toxins), and globin synthesis deficiency (thalassemias).
   - Nuclear: DNA synthesis defects (folate and B_{12} deficiencies, myelodysplastic syndrome).
3) **Survival** defects result in premature destruction of the RBC.
   - Intrinsic (inherited): membrane cytoskeletal protein (spherocytosis, elliptocytosis), metabolic enzymes (G6PD deficiency), or hemoglobinopathies (sickle cell disease, thalassemias).
   - Extrinsic (acquired): antibody- or complement-mediated, microangiopathy, mechanical heart valves (autoimmune hemolysis, malaria, and DIC, TTP, HUS, or HELLP).
4) **Sequestration**: hypersplenism (portal hypertension, early childhood sickle cell disease).
5) **Blood loss**, with resultant iron deficiency, is the most common cause of anemia in the U.S.

Laboratory Results

Iron Studies

Free iron is produced from hemoglobin breakdown by RBC macrophages and by absorption from the duodenum. Free iron is toxic to the tissues.

Transferrin is a blood plasma protein that binds iron and transports it to the tissues. Transferrin receptors on cells bind this iron-containing transferrin and absorb it into vesicles.

Table 8-1: Summary — Causes and Mechanisms of Anemia

		Reticulocyte Count	Morphology	Etiology	Examples
1) Production defect		Decreased	Normal	1) Decreased erythropoietin 2) Bone marrow failure	1) Chronic renal disease 2) Aplastic anemia
2) Maturation defect	Cytoplasmic	Decreased	Hypochromic Microcytic	1) Impaired Hgb synthesis 2) Protoporphyrin deficiency 3) Globin synthesis deficiency	1) Fe deficiency 2) Sideroblastic anemia 3) Thalassemias 4) Myelodysplastic syndrome 5) Drugs, toxins
	Nuclear	Decreased	Megaloblastic	DNA synthesis defects	B_{12}, folate deficiencies
3) Survival defect	Intrinsic (inherited)	Increased	Specific changes; e.g., spherocytes, sickle cells, bite cells	1) Membrane cytoskeleton protein 2) Metabolic enzymes 3) Hemoglobinopathies	1) Spherocytosis, elliptocytosis 2) G6PD deficiency 3) SS disease, HbC, HbD, HbE, thalassemias
	Extrinsic (acquired)	Increased	Specific changes; e.g., spherocytes, schistocytes	1) Antibody- or complement-mediated 2) Microangiopathy 3) Mechanical heart valves	1) Autoimmune hemolysis, malaria 2) DIC, TTP/HUS 3) HELLP
4) Sequestration		Increased	Normal	Hypersplenism	Portal hypertension or early childhood sickle cell disease
5) Blood loss		Increased if iron stores are adequate	Normal or hypochromic	GI hemorrhage	Peptic ulcer disease

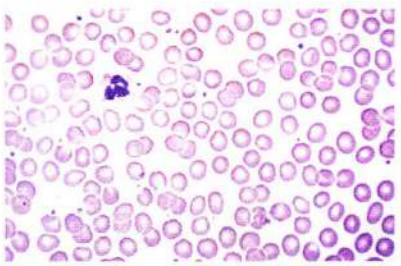

Image 8-1: Normal peripheral smear: low-power view, RBCs, platelets, and segmented neutrophil.

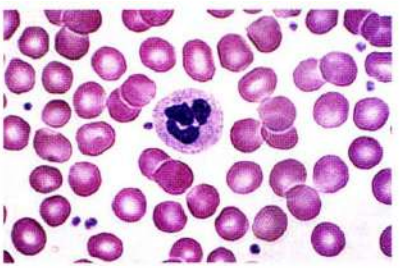

Image 8-2: Normal peripheral smear: low-oil view. Normocytic, normochromic RBCs, platelets, and normal segmented neutrophil.

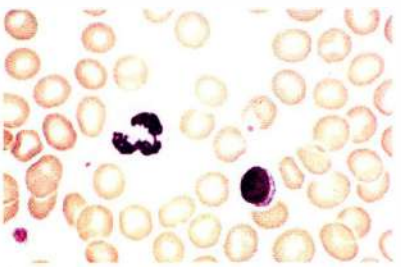

Image 8-3: Normal peripheral smear: high-dry view. RBCs, platelets, normal segmented neutrophil, and a normal lymphocyte.

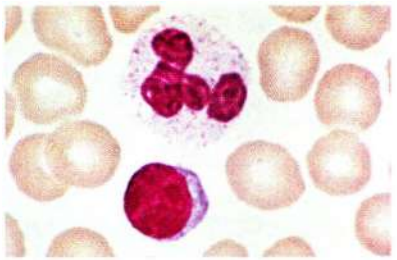

Image 8-4: Normal peripheral smear: high-oil view. Normal RBCs, segmented neutrophil, and lymphocyte. No platelets are visible in this field.

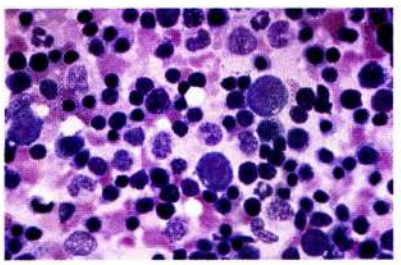

Image 8-5: Normal BM aspirate: low-power view. M:E (myloid to erythroid) ratio is usually 3:1. This field has more than the normal number of erythroid precursors. Many of the erythroid precursors have dark, condensed nuclei.

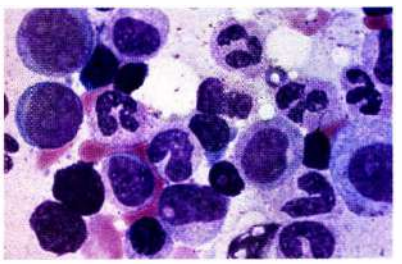

Image 8-6: Normal BM aspirate: low-oil view. Five erythroid precursors (dark condensed nuclei). Remaining cells are myeloid precursors/cells—from myoblasts to segs.

QuickQuiz

- List some extrinsic survival defects that cause anemia. (Table 8-1)
- Is reticulocytosis increased or decreased for each of these: Production defect? Maturation defect? Survival defect? (Table 8-1)
- When are Howell-Jolly bodies seen? (Table 8-2)

Soluble transferrin receptor (sTfR) concentration is elevated in iron deficiency and normal in anemia of chronic disease (ACD). It is mainly used for differentiating ACD from iron deficiency anemia.

Serum iron is a measurement of circulating iron bound to transferrin.

Total iron-binding capacity (TIBC) indirectly measures transferrin by determining the total amount of iron the blood can bind. Generally, it is not necessary to order both a transferrin level and TIBC.

The ratio of serum iron to TIBC, measured as a percentage, is called **transferrin saturation**.

Within the cell, iron is stored in protein complexes as **ferritin** or **hemosiderin**.

In equilibrium conditions, serum ferritin level is a good indicator of total iron stores. It is low in iron deficiency anemia, high-normal to high in anemia of chronic disease, and high in hemochromatosis.

Ferritin is also an acute-phase reactant and can be elevated with inflammation or chronic disease, although inflammation generally should lead to only a 3x increase in ferritin levels. A low C-reactive protein (CRP) helps rule out inflammation. Additionally, a high ferritin level is often a side effect of certain malignancies, especially hematologic cancer.

Working up Anemia

Work up anemia by analyzing the peripheral blood smear (see Table 8-2), reticulocyte count, and serum iron studies (Fe, TIBC, ferritin), then calculate the transferrin saturation (Fe/TIBC). Look at the measurements of the red cell indices for density (normochromia or hypochromia) and size (microcytosis or macrocytosis). Anisocytosis is reflected by an increase in the red cell distribution width (RDW). Finally, look at the descriptions of the red cells. Certainly, you can look at the smears yourself rather than relying on the hematology lab for measurements and descriptions. (See Image 8-7 through Image 8-12 on the following page.)

Production and maturation defects lead to low reticulocyte counts (< 2% or < 100,000), whereas shortened red cell survival, splenic sequestration, or blood loss stimulate a high reticulocyte count as new red cells are produced. Prior to interpretation, the reticulocyte count needs to be adjusted for the degree of anemia by correcting for the hematocrit and the reticulocyte maturation time (reticulocyte production index).

SPECIFIC ETIOLOGIES OF ANEMIA

Production Defects

Anemia of chronic disease ([ACD]; anemia of [chronic] inflammation) results from RBCs not functioning normally and causing impaired iron utilization, despite normal or increased iron stores.

In inflammatory states, macrophages produce IL-6, which induces the production of hepcidin by the liver. Hepcidin then inhibits iron absorption from the GI tract and decreases release of iron from macrophages.

Erythropoietin level is typically above normal but is lower than would be expected for the degree of anemia. In addition, there is no real increase in erythropoiesis in response to the higher erythropoietin level.

Table 8-2: Significance of Specific Changes in the Peripheral Smear

Finding	Meaning
RBC fragments (schistocytes)	Microangiopathic hemolytic anemia (seen in TTP, HUS, HELLP, DIC, and occasionally vasculitis), severe burns, and valve hemolysis
Spherocytes	Autoimmune hemolytic anemia and hereditary spherocytosis
Target cells	Significant liver disease, but also seen in thalassemia and other hemoglobinopathies
Teardrop cells	Classic for myelofibrosis and other infiltrating bone marrow processes Also seen with thalassemia
Burr cells (echinocytes) vs. spur cells (acanthocytes)	Burr cells (Image 8-14) are seen in uremic patients. These are distinct and different from spur cells (Image 8-13), which are seen in liver diseases.
Howell-Jolly bodies	Splenectomy or functional asplenia. Howell-Jolly bodies are the result of fragmentation of the nucleus (karyorrhexis), causing the formation of small black "pellets." This occurs normally, and the spleen efficiently removes them.
Hypersegmented PMNs	Megaloblastic anemia (pernicious anemia/B_{12} deficiency, folate deficiency)

Table 8-3: Some Laboratory Characteristics of Fe Deficiency and Anemia of Chronic Disease

	Fe Deficiency	ACD
Serum Fe	Low	Low
TIBC	High	Low
Transferrin Saturation	Low	Low to normal
Ferritin	Low	High/high-normal
Soluble Transferrin Receptor	High	Normal

The most common causes of ACD are chronic rheumatic, infectious, and neoplastic diseases. ACD and iron deficiency anemia may coexist, so it is best to work up all anemias in patients with chronic illness (Table 8-3).

Labs in ACD:

- RBCs are typically normochromic and normocytic (occasionally hypochromic microcytic) with a low reticulocyte count.
- Serum Fe and TIBC are low.
- Fe/TIBC is normal (or barely low).
- Ferritin is increased or high-normal.
- The soluble transferrin receptor test helps differentiate ACD from iron deficiency anemia and is normal in ACD (increased in Fe deficiency).

Anemia of chronic kidney disease is due to decreased erythropoietin production and is commonly responsive to recombinant erythropoietin. There may also be increased hepcidin in these patients. 20% of diabetics with stage 3 CKD have anemia. This topic is discussed more fully in Nephrology, Book 2.

Anemia of hypometabolic states can result from deficiencies in thyroid hormone, glucocorticoids, testosterone, or growth hormone and may be one of the presenting features of hypothyroidism, primary adrenal insufficiency, or pituitary disease (hypogonadism or panhypopituitarism).

Anemia from bone marrow damage includes the following:

- Aplastic anemia: pancytopenia secondary to a primary stem cell disorder, an autoimmune process, or drug.
- Pure red cell aplasia: severe anemia due to decreased RBC precursors in the bone marrow. This can be congenital due to abnormal stem cells or acquired due to viral infection, thymoma (paraneoplastic), autoimmunity, lymphoproliferative disorders, or drugs. Suspect parvovirus B19 in these severe anemia patients who also have an HIV infection or sickle cell anemia.
- Marrow infiltrative disorders: Fibrosis, granulomas, or malignancy can cause changes in the peripheral blood smear, including teardrop cells, as well as immature red and white blood cells. These leukoerythroblastic changes reflect a weakened bone marrow (myelophthisis).

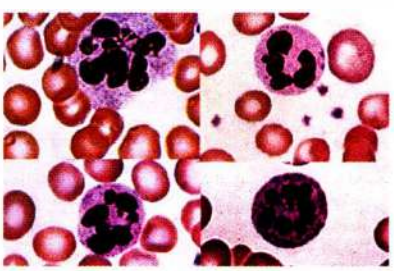

Image 8-7: Various views of hypersegmented neutrophils.

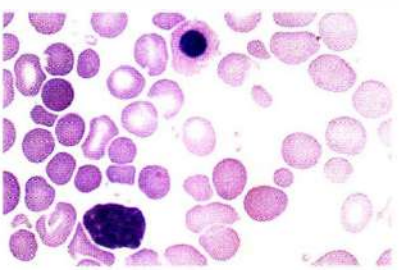

Image 8-8: This field shows hemolytic anemia with RBC fragments, a nucleated RBC, and spherocytes.

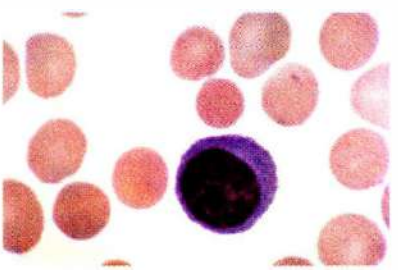

Image 8-9: Hereditary spherocytosis. Note the lack of central pallor. The normal-sized lymphocyte shows that these are microcytic spherocytes.

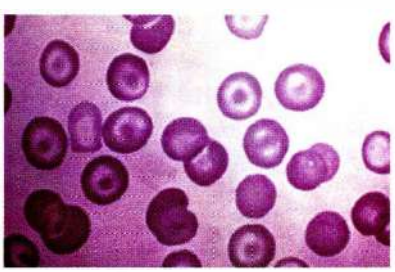

Image 8-10: Target cells. Low-oil view.

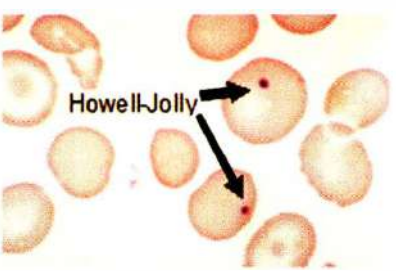

Image 8-11: Post splenectomy: Howell-Jolly bodies are the dense inclusion bodies in the RBCs. Also see target cells and a burr cell in this field.

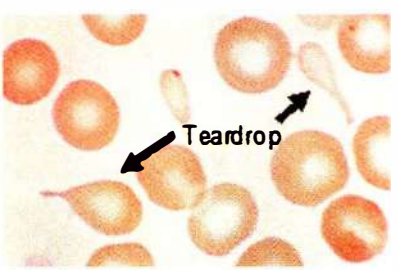

Image 8-12: Teardrop cells. This patient has myeloid metaplasia. Also seen in thalassemias and other hemoglobinopathies.

QuickQuiz

- Characterize the lab values in iron deficiency anemia vs. anemia of chronic disease.
- What are common causes of iron deficiency anemia?

Maturation Defects

Cytoplasmic Maturation Defects

Iron Deficiency Anemia

Iron is essential for the production of hemoglobin, and a deficiency leads to impaired erythropoiesis and iron deficiency anemia (IDA).

Signs and symptoms include fatigue, pallor, weakness, irritability, and poor exercise tolerance. IDA is one of the major causes of restless leg syndrome. Pica for ice (termed "pagophagia") is occasionally seen and pretty specific for IDA. Beeturia occurs in ~ 75% of patients with iron deficiency when eating beets leads to excreting red urine (also in ~ 10% of normal population).

Labs in IDA:

Red cells are microcytic (MCV < 80 mm^3) and hypochromic (decreased MCHC) with a low reticulocyte count.

Serum iron (SI) is low. Low SI causes increased production of transferrin, which is measured as total iron binding capacity (TIBC). So TIBC is elevated, and the ratio of the low SI to the elevated TIBC is usually < 10% (normal 25- 40%).

The serum ferritin level is considered the best test for assessing iron stores. In the patient with no known inflammatory or infectious disease, a ferritin level ≤ 40 ng/mL is 98% sensitive and 98% specific for IDA. When the level is < 15, the diagnosis is virtually always IDA, no matter what the disease state.

Remember that ferritin is an acute phase reactant and can increase during states of inflammation, so this test has poor sensitivity for IDA in patients who have ongoing inflammation. Soluble transferrin receptor (sTfR) concentration is normally elevated in iron deficiency and normal in anemia of inflammation.

Once you diagnose iron deficiency anemia, you must pursue the etiology:

- Chronic blood loss (most common) from either the gastrointestinal (especially PUD, malignancies) or genitourinary tracts (e.g., menorrhagia)
- Pregnancy, which can cause iron deficiency because of increased iron requirements
- Lack of dietary iron
- Malabsorption (e.g., celiac disease or gastric bypass surgery)
- Chronic low-grade intravascular hemolysis (as in paroxysmal nocturnal hemoglobinuria)

Celiac disease is a common cause of chronic, unresponsive IDA in a young person with a history of bulky, foul-smelling stools.

Thalassemias

Normal hemoglobin is a tetramer with 2 α- and 2 β-globin chains. These tetramers are covalently linked to heme, a complex of ferrous iron and protoporphyrin. A normal Hb electrophoresis pattern would be HbA ($\alpha_2\beta_2$) > 97.5%, HbA_2 ($\alpha_2\delta_2$) < 2.5%. δ and γ are β-like globins; δ is an adult form, and γ is fetal.

Thalassemias are inherited disorders characterized most commonly by absent or decreased production of either the α chain (α-thalassemia) or the β chain (β-thalassemia) leading to decreased production of hemoglobin tetramers and fewer red blood cells. In addition, there is unbalanced globin chain synthesis, and homotetramers are formed, which are insoluble and precipitate in RBCs. These precipitated chains lead to RBC hemolysis and ineffective erythropoiesis. These processes result in anemia. Mutations may be deletional or nondeletional and affect many different aspects of transcription and translation.

α-thalassemia: Chromosome 16 contains 2 copies of the α-gene at 2 different loci on each of the 2 genes. There are, therefore, 4 α-genes in normal individuals. The clinical manifestations correlate with the number of α-genes that are affected: the more loci affected, the worse the symptoms. This type is seen in African, Mediterranean, and Southeast Asian populations.

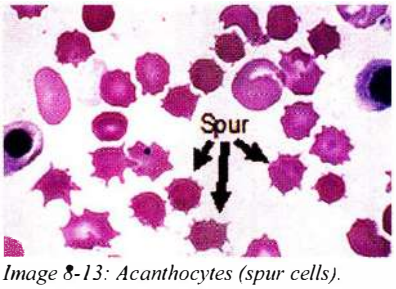

Image 8-13: Acanthocytes (spur cells). Nucleated RBCs. Spur cells are RBCs with multiple irregular projections that vary in length, width, and regularity. Usual cause is hepatic failure.

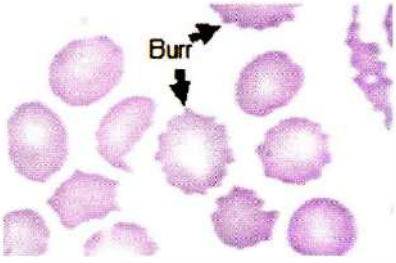

Image 8-14: Echinocytes or burr cells in uremia. These are RBCs with regular, short, spiney projections. These membrane changes disappear when uremia is corrected.

There are 4 types of α-thalassemia:

1) α-thalassemia trait: 1 locus, (αα/α-), asymptomatic, no hematologic abnormalities.
2) α-thalassemia minor: 2 loci, (α-/α-) or (αα/--), asymptomatic, MCV low, little to no anemia.
3) Hb H: 3 loci, (α-/--). Unpaired β chains form β_4 tetramers called HbH—these form inclusions in peripheral cells but not in the marrow. Clinical features are intermediate and variable and can include moderately severe hemolytic anemia but often with avoidance of transfusions until adulthood.
4) Hb Bart's: 4 loci, (--/--). No effective hemoglobin is produced beyond the embryonic stage. γ_4 tetramers (Hb Bart's) form and have such high oxygen affinity that they do not deliver any oxygen to the tissues, causing death *in utero* (hydrops fetalis).

β-thalassemia: caused by a range of mutations within the β-globin locus of chromosome 11. This type is seen in Mediterranean, Middle Eastern, and Asian populations. There are 3 categories of β-thalassemia:

1) β-thalassemia minor (heterozygotes): mild or no anemia, with a disproportionately high number of microcytes. These patients are asymptomatic and have no clinical sequelae. In most patients, this disorder has 2- to 3-fold elevations of HbA_2 ($\alpha_2\delta_2$) and slight increases in HbF ($\alpha_2\gamma_2$) on hemoglobin electrophoresis.
2) β-thalassemia major (homozygous): Patients with β-thalassemia major, termed "Cooley anemia," have essentially no β-globin production. The remaining, highly insoluble α-globin precipitates into homotetramers, or inclusion bodies, which are toxic to erythrocytes and cause them to die within the marrow. Surviving erythrocytes carry inclusion bodies that are detected by the spleen, leading to removal of the erythrocytes and chronic hemolytic anemia. The resulting severe anemia (developing over the 1st year of life) results in elevated erythropoietin levels and thus, erythroid hyperplasia. If the erythroid hyperplasia is severe, it can lead to extramedullary hematopoiesis in the liver and spleen and an expanded bone marrow with the latter, giving children "chipmunk facies." Often, patients are transfusion-dependent and develop iron overload. Bilirubin gallstone disease is common. Hemoglobin electrophoresis shows high Hb F and HbA_2.
3) β-thalassemia intermedia (homozygous): Not all patients with homozygous defects of β-globin production have the full clinical severity described above. Modulating factors are: minor qualitative defects of the β-globin; coinheritance of α-thalassemia trait, leading to decreased formation of the toxic RBC inclusion and therefore less precipitation of insoluble homotetramers and less hemolysis; and increased production of Hb F. The term "β-thalassemia intermedia" is used to convey this heterogeneity and to describe those patients who range from the asymptomatic to the transfusion-dependent states.

Know that thalassemias are often misdiagnosed as iron deficiency anemia and, subsequently, incorrectly given iron replacement. Iron therapy does not improve the microcytosis, and, even worse, it can cause secondary hemochromatosis. Remember that thalassemias can be diagnosed by excluding iron deficiency with a CBC, reticulocyte count, and iron studies (+/– soluble transferrin receptor). The microcytosis can be evaluated further with a hemoglobin electrophoresis (normal in α-thalassemia and increased A_2 component in β-thalassemia).

In clinical practice, adult patients with a microcytosis and normal iron studies are assumed to have thalassemia, and the electrophoresis is rarely ordered. Nonetheless, it is helpful to confirm the diagnosis with Hgb electrophoresis if there is some doubt.

Nuclear Maturation Defects

Megaloblastic anemias result from impaired DNA synthesis. They are often the result of deficiencies of B_{12} and/or folate but may also result from drugs that impair DNA metabolism.

Folate deficiency is caused by:

- Poor diet
- Increased demand (pregnancy)
- Alcohol use

B_{12} deficiency can result from:

- Pernicious anemia (due to autoimmune destruction of parietal cells that produce intrinsic factor)
- Strict vegetarian diet
- Alcohol use
- Inability to release B_{12} from food sources (common in the elderly, atrophic gastritis, and acid-suppressing medications)
- Malabsorption affecting B_{12} absorption in the terminal ileum (e.g., inflammatory bowel disease), bacterial overgrowth, fish tapeworm, and pancreatic insufficiency

Know that the marrow is disturbed in these nutritional deficiencies, and multiple cell lines can be affected as the deficiencies progress. The megaloblastic RBCs are destroyed in the marrow (termed "intramedullary hemolysis"), and erythropoiesis is ineffective. Surviving RBCs are macrocytic, and neutrophils are hypersegmented (defined as at least 5 lobes in 5% of neutrophils or any neutrophil with 6 lobes). Platelets can be decreased as well.

Think about a megaloblastic process in patients who present with a macrocytic anemia, pancytopenia, and slight indirect hyperbilirubinemia (from the continuous low-level intramedullary hemolysis).

In addition to anemia, deficiencies in B_{12} also produce gastrointestinal effects (smooth sore tongue, diarrhea) and neurological deficits (ranging from paresthesias to frank psychosis). B_{12} deficiency may be present without

Quick Quiz

- Characterize the CBC in patients with α-thal minor.
- What is the characteristic Hgb electrophoresis finding in patients with β-thal minor?
- How many lobes must a neutrophil have to be considered "hypersegmented"?
- Which megaloblastic anemia is associated with neurologic disease?
- What are the MMA and homocysteine levels in B_{12} and folate deficiencies?
- What general lab tests are abnormal in hemolytic states?

anemia but with serious neurologic problems. Know that folate deficiency is not associated with neurologic impairment.

Diagnose B_{12} deficiency at level < 200 pg/mL. If the level is borderline low (200–400 pg/mL), check methylmalonic acid (MMA) and homocysteine (HC). Both are elevated in B_{12} deficiency. Only the HC is elevated in folate deficiency—and the serum folate level is decreased.

Once B_{12} deficiency is diagnosed, the etiology should be pursued. For pernicious anemia (PA), the presence of anti-intrinsic factor (IF) antibodies supports the diagnosis, but sensitivity of the test is only ~ 70%. If you highly suspect pernicious anemia, but IF antibodies are absent, check the serum gastrin and pepsinogen levels. In PA, the serum gastrin is increased, and the pepsinogen I level is decreased. The ratio of pepsinogen I to pepsinogen II is also used, and it is low in PA. The Schilling test, in which the fate of radiolabeled B_{12} ingested by the patient is followed, was previously used to confirm the diagnosis but is rarely used and generally not available anymore.

Treat B_{12} deficiency with daily injections for 1 week, then weekly injections for 1 month, then monthly. Treat folate deficiency with daily oral replacement.

Survival Defects

Overview

Hemolytic anemias can be grouped by the underlying cause of premature RBC destruction.

Intrinsic:

- Molecular defect inside the cell (G6PD deficiency, hemoglobinopathies)
- An abnormality in membrane structure or function (hereditary spherocytosis)

Extrinsic: an environmental factor outside the cell (DIC, autoantibodies, TTP/HUS, HELLP).

Review of Coombs Tests

Direct antiglobulin test (DAT)—antibodies against IgG or C3 are prepared in an animal and then mixed with the patient's blood. A positive test occurs if the patient's RBCs agglutinate—meaning there is IgG (or C3) on the surface of the patient's RBCs.

Indirect antiglobulin test (IAT) is done to see if the patient's serum contains antibodies that would cause agglutination of other RBCs (i.e., with transfusion). The Rh- and ABO-compatible RBCs are mixed with the patient's serum, and again, a positive test occurs if these RBCs agglutinate.

Figure 8-2: Coombs Tests

Additionally, hemolytic anemias can be grouped as intravascular or extravascular. Hemolysis is termed "extravascular" when RBCs are outside the vascular space, trapped in the reticuloendothelial system (mainly the spleen), and engulfed by macrophages. "Intravascular" hemolysis occurs when RBCs are lysed within the lumen of the blood vessels. This can result from non-immunological mechanisms including DIC, TTP/HUS, HELLP, and severe heart valve abnormalities that shear red cells.

Supplemental Lab Tests

Haptoglobin low = hemolysis. In both intravascular and extravascular hemolysis, released hemoglobin is quickly bound to haptoglobin and then engulfed by macrophages. The resultant low level of haptoglobin can be used to diagnose hemolysis—but does not help distinguish the type.

Bilirubin. Heme loses the iron and is converted to bilirubin and cleared in the urine or stool. With excessive hemolysis of either type, more of the bilirubin is unconjugated (indirect).

Urine hemosiderin high = intravascular hemolysis. Iron is more frequently lost in the urine with intravascular hemolysis and can be detected by the urine hemosiderin test.

LDH levels elevated = intra- and extravascular hemolysis.

Coombs test positive = antibody- or complement-mediated hemolysis. The direct antiglobulin test (DAT), or direct Coombs test, can help identify antibody or complement on the red cell surface, which may mediate hemolysis (Figure 8-2).

Intrinsic Survival Defects

G6PD Deficiency

Over 400 variants of the X-linked *G6PD* gene exist—affecting over 200 million people. These result in

variable deficiencies in the reduced state of glutathione—this reduced state being a protective mechanism against oxidative stress. Common oxidative stressors are infections, medications (including dapsone, sulfa drugs, and antimalarials), fava beans, and diabetic ketoacidosis.

Hemolysis in G6PD deficiency can be mild to massive. G6PD levels normally decline over the RBC lifespan, so measured levels of G6PD may be normal during an acute hemolytic episode if young cells enrich the test population; i.e., a false-negative test is possible during acute hemolysis with brisk reticulocytosis. Measure G6PD levels 2–3 months after the hemolytic event to avoid a false-negative result. Other hematologic findings (and buzzwords) include Heinz bodies (chunks of denatured hemoglobin) on special smears and "bite cells" in peripheral blood. Coombs test is negative.

Pyruvate Kinase Deficiency

Although G6PD deficiency is more common than pyruvate kinase deficiency, the latter is more likely to result in a symptomatic hemolytic anemia. Pyruvate kinase deficiency and other enzyme deficiencies within the glycolytic pathway are subject to hemolytic crisis without exposure to oxidative stress. In fact, the mechanism of hemolysis is not clearly understood. The peripheral blood smear does not reveal characteristic RBC abnormalities, as might be seen in other types of hemolysis.

Sickle Cell Syndromes

Sickle cell syndromes result from a mutation in the β-globulin gene ($\beta^{6Glu \rightarrow Val}$), in which valine is substituted in place of glutamine. When both β-globin chains are affected, **sickle cell anemia** (**SCA**) results. The deoxygenated hemoglobin S stiffens and distorts the RBC membrane, gives the characteristic sickle shape, and prevents the cells from passing through small vessels.

Know that parvovirus B19 may cause either a pure red cell aplasia or a worsening of anemia by decreasing erythropoiesis in the face of chronic hemolysis.

Clinical manifestations of SCA are the result of small vessel blockage, downstream tissue infarction, and chronic hemolysis. Recurrent microinfarcts of the kidney lead to isosthenuria (inability to concentrate urine). Recurrent infarcts of the spleen lead to functional asplenia with increased risk of infection from encapsulated organisms, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*, and from *Salmonella*. To protect against these organisms, penicillin prophylaxis is used in children until age 5. All patients should be given pneumococcal, meningococcal, *H. influenzae*, hepatitis B, and influenza vaccines. Acute chest syndrome (chest pain and desaturation of oxygen) is thought to represent microinfarctions of the lung. The acute chest syndrome is a hematologic emergency which may require red cell exchange transfusion.

Other sickle cell syndromes can result when only 1 β-globin gene is affected:

- **Sickle cell trait** (HbS/A): Half the hemoglobin in each RBC is HbS and half HbA. Patients are asymptomatic or demonstrate renal papillary necrosis, painless hematuria, and isosthenuria.
- **Hemoglobin SC disease** ($\beta^{6Glu \rightarrow Val}\beta^{6Glu \rightarrow Lys}$): RBCs are rigid—but not sickled—and have a short lifespan. Splenic sequestration is common and can occur both in children and adults (unlike in sickle cell anemia), because the spleen does not always undergo early autoinfarction. Consider sequestration in patients with SC who present with a tender spleen and worsening of anemia. Retinal problems are also common.
- Other hemoglobin disorders may be seen in combination with HbS (double heterozygotes). They include sickle/β-thalassemia and HbS/D. Clinical features are varied.

Diagnose a sickle syndrome with hemoglobin electrophoresis. You can screen prospective parents for the carrier state and provide genetic counseling.

Treatment of SCA is largely supportive, although bone marrow transplantation is being increasingly utilized.

Exchange transfusion is sometimes required for treatment of priapism, cerebral sickling, aplastic crisis, and acute chest syndrome. Occasionally, more conservative therapy with a simple transfusion and/or supportive care treats these presentations. A partial exchange transfusion program is reserved for those with a history of stroke. Folate supplementation is important. Medications such as hydroxyurea are used to increase HbF production, which offers some protection against sickle crisis.

Hereditary Spherocytosis and Elliptocytosis

These are autosomal dominant disorders of the RBC cytoskeleton that result in loss of membrane flexibility and are associated with chronic hemolysis. These disorders are seen in Northern European populations.

Complications of spherocytosis and elliptocytosis may include cholelithiasis, due to bilirubin stones, and splenomegaly. Splenectomy is sometimes required to prolong red cell survival. Think about these disorders in patients who demonstrate evidence of hemolysis and have spherocytes or elliptocytes on their peripheral smear. Coombs test is negative.

The osmotic fragility test may assist in diagnosing hereditary spherocytosis. (The reduced surface:volume ratio makes spherocytes more susceptible to osmotic stress.) The eosin-5-maleimide (EMA) binding test is a newer rapid test that does not require much blood and gives results in 2 hours (great for newborns). Sophisticated molecular membrane studies (usually available at research institutions) can be done to make a definitive diagnosis (e.g., sodium dodecyl sulfate polyacrylamide gel electrophoresis), but it does not change management.

- What cells are seen in the peripheral blood of patients with G6PD deficiency?
- Which virus is implicated in the development of aplastic crisis or worsening of anemia in patients with sickle cell disease?
- What cells are seen on peripheral smear in patients with hereditary spherocytosis?
- What is the clinical presentation of PNH?
- What tests are used to diagnose PNH?
- Which leukemia/lymphoma is associated with autoimmune hemolytic anemia?

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is a rare acquired stem cell disorder resulting from a defective *PIGA* gene. The result is the loss of a membrane-bound protein, which, when present, anchors other proteins to the cell membrane. Some of these anchored proteins serve to protect the cell against complement-mediated lysis. Without the anchor protein, this protection is lost.

Clinical presentation includes a variable degree of intravascular hemolysis, which may lead to chronic hemoglobinuria and iron deficiency. Classic symptoms include episodic abdominal pain and chest pain due to diffuse esophageal spasms that coincide with hemoglobinuria. The other major potential complication is arterial or venous thrombosis (especially of abdominal veins; think about PNH in cases of Budd-Chiari syndrome). Rarely, transformations to aplastic anemia, acute leukemia, and myelofibrosis occur.

Diagnosis is made using specific flow cytometry assays for CD55 (decay accelerating factor) and CD59 (homologous restriction factor)—proteins that are lost from the cell membrane when the anchor protein is absent.

Definitive treatment is allogeneic bone marrow transplant. Otherwise, treat hemolysis with corticosteroids. Use anticoagulants to treat thrombotic events. Eculizumab, an antibody to C5 terminal component, has been shown to decrease hemolysis and the need for transfusion.

Extrinsic Survival Defects

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia (AIHA) is regularly caused by IgG or IgM antibodies. Antibodies that react with RBC membrane proteins are often IgG. These antibodies induce hemolysis either by stimulating macrophages and other cells in the spleen and reticuloendothelial system to gradually snip portions of membrane away (causing spherocytes) or by causing complement-mediated destruction.

IgG antibodies react best at body temperature (so-called "warm antibodies"). They may be idiopathic or secondary to neoplasm or connective tissue disease. In autoimmune hemolytic anemia, the direct Coombs (direct antiglobulin) test, which detects antibodies on the RBC surface, is positive using antibodies to IgG. Treat with corticosteroids. Splenectomy is reserved for refractory cases. The anti-CD20 monoclonal antibody rituximab is sometimes also used in difficult-to-treat patients.

IgM antibodies often bind to polysaccharides or complement. These antibodies react better at room temperature (so-called "cold antibodies"). IgM antibodies are not detected on the RBC surface by direct Coombs testing. Instead, the complement components whose binding they induce are detected with a positive direct result using antibodies to C3 (indicates ability to fix complement), not IgG (because the hemolysis is caused by antibodies to IgM). RBC clumping is often seen on the peripheral smear.

These IgM autoantibodies may be secondary to:

- neoplasm (especially CLL and lymphoma),
- infection (especially *Mycoplasma pneumoniae* and infectious mononucleosis), or
- SLE.

Treatment is best accomplished by maintaining a warm environment and identifying and treating the underlying cause. Steroids are ineffective.

Drug-Associated Hemolysis

Many drugs may cause hemolysis. Penicillin bound to red cells may elicit an antibody response that can cause hemolysis. Quinine, methyldopa, and certain cephalosporin antibiotics are also known culprits. The pattern of abnormal Coombs testing varies with the type of drug.

Sequestration

This type of anemia occurs with overactive, often enlarged spleens in a variety of disorders, especially portal hypertension where red cells, white cells, and platelets may be sequestered. In early childhood with HbS/C and HbS/β-thalassemia (before splenic infarction and fibrosis are seen), splenic sequestration may occur.

Blood Loss

Anemia from blood loss is often obvious from injuries or GU and GI tract loss, but may be less obvious in intrapulmonary, retroperitoneal, and rectus abdominis sites. And remember again, any Fe deficiency anemia is considered to be due to blood loss until proven otherwise.

Liver Disease

Anemia is common in liver disease, depending on the cause:

- Cirrhosis causes spur cell anemia (Image 8-13 on page 8-5), due to abnormal cholesterol production. Red cells change shape and are hemolyzed.
- Portal hypertension causes splenic sequestration and cytopenias.
- Alcohol abuse is associated with nutritional (megaloblastic) anemias, especially folate.
- EtOH also directly inhibits erythropoietin production and erythropoiesis.
- Viral hepatitis can cause anemia through direct inhibition of the marrow and via autoimmune hemolysis.
- GI blood loss is common, especially if the patient has esophageal varices.

Chronic Kidney Disease

Anemia in CKD is discussed extensively in Nephrology, Book 2.

Cancer Patients

Cancer patients may have coexisting causes of anemia. Consider these possibilities:

- Bone marrow infiltration by cancer cells
- Chemotherapy-induced anemia
- Infection causing bone marrow suppression
- Medications including antibiotics/antivirals
- Autoimmune hemolytic anemia (e.g., lymphoproliferative disorders such as CLL)
- Sequestration
- Anemia of chronic disease (anemia of inflammation)
- Blood loss from bleeding tumors
- Fe deficiency (especially in GI cancers)
- Malnutrition

Treatment is often supportive, with transfusions provided as needed. Erythropoietin-stimulating agents are almost never indicated except in very specific scenarios, including some cases of myelodysplastic syndrome. These agents can be considered when chemotherapy for non-curative intent causes symptomatic anemia—but even in this context, they are still controversial.

MISCELLANEOUS DISORDERS THAT AFFECT RBCs

METHEMOGLOBINEMIA

Oxidation of heme iron from the ferrous Fe^{2+} to the ferric Fe^{3+} state forms altered hemoglobin (methemoglobin), which has an impaired ability to bind oxygen. Methemoglobin gives the blood a dark color, so patients appear cyanotic despite a normal P_aO_2 on arterial blood gas. Pulse oximetry is not reliable, but co-oximetry reveals low oxygen saturation. Symptoms include headache, dizziness, dyspnea, tachypnea, tachycardia, and obtundation. Severe tissue hypoxia and death can result as levels rise. Causes are hereditary and/or acquired and may include industrial chemicals and drugs: nitrates/nitrites (nitroglycerin, amyl nitrate ["poppers"], nitroprusside—but not nitrous oxide), phenazopyridine (OTC bladder analgesic), dapsone, sulfonamides, and anesthetics (oral benzocaine, lidocaine). Treat severe cases with methylene blue.

PORPHYRIAS

The porphyrias are inherited (most) or acquired metabolic disorders in which heme biosynthetic pathway enzymes are deficient, resulting in excess accumulation and excretion of porphyrins and their precursors. Porphyria cutanea tarda (PCT), the most common of the porphyrias, is an acquired mutation.

The porphyrias are classified as either acute or cutaneous. **Acute porphyrias** affect the neurologic system causing neurovisceral abdominal pain (most common), psychiatric disorders, and other neurologic manifestations (neuropathic pain, encephalopathy). **Cutaneous porphyrias** cause either acute nonblistering or chronic blistering reactions (PCT) in sun-exposed areas.

Clinical manifestations can be extremely subtle and can mimic many other disorders.

Initial treatment in the absence of neurologic symptoms or organ failure is the administration of dextrose via intravenous infusion. Severe cases are treated with intravenous hematin. Both of these treatments decrease heme synthesis and slow the buildup of the toxic precursors.

HEREDITARY HEMOCHROMATOSIS

Hereditary hemochromatosis (HH) is an iron-overload disorder due to 1 or more mutations, with the *HFE* gene mutations being most common. These mutations cause the body's appetite for iron to be insensitive to the presence of adequate iron stores. The 2 most common *HFE* mutations are *C282Y* and *H63D*. Caucasians have the highest incidence of *C282Y* homozygosity, followed by Native Americans. Compound heterozygosity (*C282Y* with *H63D*) and heterozygosity for either *C282Y* or *H63D* are the next most common genotypes.

Other genotypic variations include mutations in genes that code for the transferrin receptor, ferroportin, and hepcidin, a peptide that plays a central role in human iron metabolism. HH is ordinarily inherited in an autosomal recessive fashion.

Clinical disease does not develop in all patients who inherit the mutations, even with *C282Y* homozygosity. The phenotype of skin pigmentation, arthropathy, cirrhosis, cardiomyopathy, and endocrinopathies that characterize fully penetrant HH may require 1 or more mutations in the *HFE* gene plus inheritance of 1 or more

QuickQuiz

- What is the most common neurologic manifestation of porphyria?
- What is the typical presentation of hereditary hemochromatosis?
- Which test is used to diagnose hereditary hemochromatosis?

of the other genetic variations and/or exposure to environmental risk factors; e.g., excessive alcohol use.

The HFE protein is expressed in the deep crypt cells of the duodenum and normally acts as a sensor of the body's iron stores, modulating the uptake of transferrin-bound iron into these cells. *HFE* mutations decrease this transferrin receptor-mediated uptake of iron into crypt cells, sending a false signal of low iron stores to the intestinal cells, causing an up-regulation of the intestinal iron transporter, DVMT, in the lumen. This unchecked absorption of intestinal iron leads to elevated levels of serum ferritin, with concomitant iron deposition into multiple organ systems, including the liver, heart, skin, gonads, joints, and pancreas.

Although classically described as a triad of cirrhosis, bronzed skin pigmentation, and diabetes mellitus, HH is now more commonly diagnosed at an earlier stage in the disease. Patients most often present in middle age with early signs and symptoms of iron overload, including (from most to least common):

- Fatigue and weakness
- Abnormal liver transaminases
- Bronzing of the skin
- Diabetes mellitus
- Joint pain +/– crystalline arthropathy (CPPD)
- Erectile dysfunction

Women may present with symptoms in their mid-to-late 50s, after menopause, because the monthly menses served as adequate phlebotomy during their younger years. All patients are at increased risk for infection with *Listeria* (because the excess iron impairs macrophage function) and with bacteria that utilize iron as a substrate (e.g., *Vibrio* and *Yersinia* species).

The most sensitive test to diagnose HH is transferrin saturation (serum Fe/TIBC x 100%). Once HH is suspected based on a transferrin saturation of > 45%, the diagnostic workup should include iron studies to further quantify iron overload. A ferritin level > 1,000 ng/mL indicates iron overload. Genetic testing can be done for the most common underlying genetic mutations. Liver biopsy, the diagnostic gold standard, now is largely used as a prognostic indicator or in cases in which laboratory and genetic testing is equivocal. MRI can detect iron in the liver, heart, joints, and pituitary (experienced facility only).

First-degree family members should also be tested for the disease, but the role for population screening for HH remains uncertain. Early diagnosis of HH is extremely important, however, because devastating consequences of the disease are easily preventable with timely treatment.

Phlebotomy remains the foundation of management of iron overload. Since it is not known who will develop cirrhosis and hepatocellular carcinoma, treatment is recommended for those with elevated liver iron content. Initially, one to two 500 mL units of blood (each containing about 250 mg of iron) should be removed weekly until the serum ferritin is 20–50 ng/mL, and the transferrin saturation is less than 30%. The typical patient requires removal of 20–25 units of blood to complete this 1st stage.

Lifelong maintenance phlebotomy, usually 2–4 times per year, is then needed to keep serum ferritin levels below 50–100 ng/mL and transferrin saturations below 50%, with regular monitoring of serum hemoglobin. Although this regimen does not reverse previously established cirrhosis or other sequelae of iron deposition, progression can be slowed, and new disease development can be prevented.

Patients should avoid uncooked seafood because of the risk of disseminated *Vibrio vulnificus*.

HEMOSTASIS

OVERVIEW

Coagulation after a vascular injury consists of 2 stages: primary hemostasis and secondary hemostasis. Primary hemostasis is the function of the platelets, whereas secondary hemostasis is dependent upon the coagulation factors.

PRIMARY HEMOSTASIS

Primary hemostasis consists of platelet plug formation, vascular spasm, and capillary endothelial adhesion, with capillaries collapsing and sticking closed when empty. This fix is temporary and lasts for only 12–24 hours. (This is why hemophiliacs often do not have a deep bleed until 12–24 hours after trauma.)

Platelet plug formation = platelet attachment → platelet activation → platelet aggregation.

After endothelial injury, platelets rapidly attach to the newly exposed subendothelial collagen. The von Willebrand factor, released from the endothelium, reacts with the platelet surface glycoprotein Ib/IX to increase "stickiness" of platelets to each other and to exposed collagen. Platelets are then activated, releasing cytokines, including ADP and arachidonic acid, which further stimulate platelet release and aggregation. Arachidonic acid is converted by cyclooxygenase into precursors of thromboxane A_2. Thromboxane A_2 recruits more platelets and exposes platelet surface glycoprotein IIb/IIIa. Thromboxane A_2 is also a potent vasoconstrictor. Fibrinogen then cross-connects the IIb/IIIa protein on platelets to form platelet plugs.

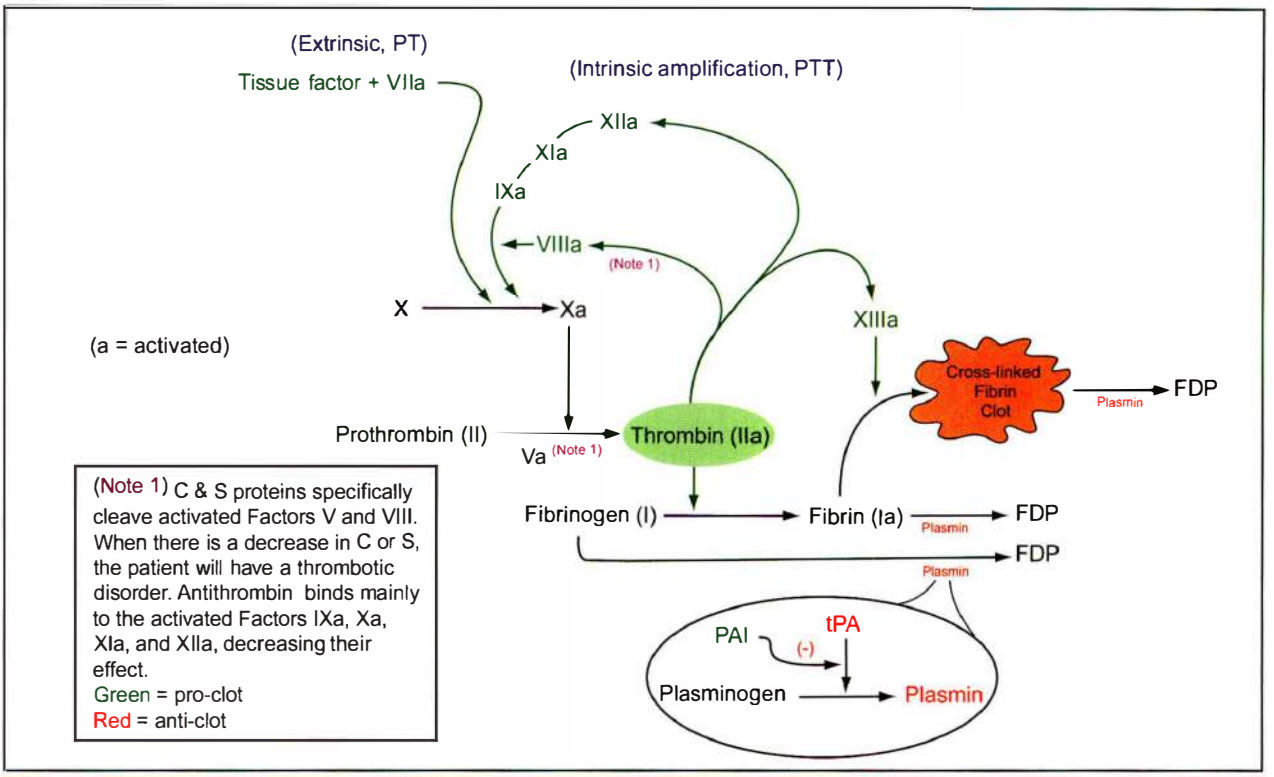

Figure 8-3: Clotting Cascade

There are several FDA-approved IIb/IIIa receptor inhibitors available. Approved indications include unstable angina and adjunctive therapy during coronary angioplasty. Aspirin irreversibly acetylates cyclooxygenase and thus decreases platelet function. Chronic ASA use of as little as 40 mg/day causes suppression of 95% of the thromboxane A_2. NSAIDs bind reversibly with cyclooxygenase; they may block the desired effect of ASA if they are administered at the same time. Clopidogrel irreversibly inhibits ADP binding to the platelet receptor, resulting in decreased platelet aggregation.

SECONDARY HEMOSTASIS

The Coagulation Cascade

All coagulation is initiated by tissue factor (released at the site of injury) interacting with Factor VII. The intrinsic pathway factors (VIII, IX, and XI) serve solely to amplify this formation of thrombin—and can do so only after a small amount of thrombin is formed by the extrinsic pathway. Tissue factor is in short supply and short-lived—so the extrinsic pathway can produce only a small amount of thrombin.

Thrombin is the key. As you can see in Figure 8-3, this little bit of thrombin immediately starts building more thrombin while it builds the thrombus.

Thrombin does the following:

- Converts fibrinogen to fibrin
- Activates Factor XIII, which causes this fibrin to cross-link and form the thrombus
- Activates Factor XII, which, in turn, activates Factor XI, which, in turn, activates Factor IX
- Activates VIII; Factors VIIIa and IXa together activate X again

So, the first 2 processes help make the thrombus while the second 2 are part of a powerful "intrinsic" amplification system that makes more thrombin.

Okay, so how does the body stop this process? Thrombus dissolution, or fibrinolysis, is initiated by tissue plasminogen activator (tPA) and released from the endothelial cells. tPA converts plasminogen to plasmin, which then breaks down fibrin and fibrinogen and limits the size of the thrombus. Proteins C and S are natural anticoagulants; they inactivate Factors Va and VIIIa. Protein C also blocks the inhibitor of tPA (plasminogen activator inhibitor-I). In healthy people, this results in fibrinolysis. In the absence of proteins C and S, thrombosis goes unchecked.

AN APPROACH TO THE PATIENT

It is often possible to differentiate between a primary and a secondary hemostatic problem at the bedside:

- **Primary hemostatic problems** (90% involve either platelet dysfunction or low platelets) result in multiple, tiny, superficial hemorrhages, causing petechiae, purpura (large petechiae), ecchymoses, and mucocutaneous bleeding.
- **Secondary hemostatic disorders**, on the other hand, such as hemophilia, develop deep tissue bleeding, including hematomas or hemarthroses.

QuickQuiz

- Explain how aspirin and NSAIDs work to decrease platelet function.
- At the bedside, how can you tell whether a hemostatic problem is primary or secondary?
- What are the 4 tests initially used to evaluate a bleeding disorder? How are they used?

Typically, 4 tests can quickly assess coagulation and platelet status:

1) Prothrombin time (PT) measures the function of extrinsic and common pathways.
2) Activated partial thromboplastin time (PTT or aPTT) measures the function of the intrinsic amplification.
3) Platelet count.
4) Platelet function tests evaluate platelet aggregation when stimulated by epinephrine, ADP, and collagen.

DISORDERS OF PRIMARY HEMOSTASIS

Overview

Disorders of primary hemostasis involve the skin and vascular endothelium as well as platelets. This review focuses on the latter, which includes both quantitative and qualitative defects.

Thrombocytopenia has multiple etiologies, which can be categorized into defects of production, sequestration, and destruction.

Pseudothrombocytopenia (i.e., artifact) occurs fairly often—so the 1st test to do after observing a low platelet count result is a repeat platelet count. A peripheral blood smear to look for platelet clumping, which is perceived by automated counters as a low platelet count, is also helpful.

You can see abnormal platelet function after aspirin ingestion and in von Willebrand disease, Bernard-Soulier (giant platelet) syndrome, Glanzmann thrombasthenia, paraproteinemia (multiple myeloma), chronic kidney disease, and connective tissue disease.

Primary Hemostasis Disorders: Thrombocytopenias

Overview

Thrombocytopenia has 3 causes: impaired bone marrow production, splenic sequestration, or decreased platelet survival (destruction).

1) Impaired production: due to bone marrow failure from toxins (including alcohol), infiltration, aplasia, sepsis, and HIV infection. Often there is concomitant anemia and/or leukopenia.
2) Hypersplenism: Thrombocytopenia is usually modest and accompanied by a reduction in the other cell lines (leukopenia and anemia).
3) Survival defects:
   - Consumptive process such as DIC, HIT (heparin-induced thrombocytopenia), TTP/HUS, and HELLP.
   - Immune thrombocytopenia (ITP; see next), either idiopathic or drug-induced. Common drug offenders include quinidine, rifampin, sulfonamide combinations, and digoxin. If the platelet count is $> 20 \times 10^9$/L, there is usually no serious spontaneous bleeding. When the count is < 10,000, the risk of serious bleeding increases and platelet transfusions are often considered. Do not transfuse platelets if you suspect HIT or TTP unless the patient has active life-threatening bleeding.

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP) is an autoimmune syndrome that occurs in children and adults. In children, it often has an acute presentation, occurs after a viral illness, and is commonly self-limited with a good prognosis. Chronic ITP generally occurs in adults and has a relapsing course. Both acute and chronic ITP are associated with IgG antibodies directed against the GPIIb/GPIIIa glycoproteins on platelets. When associated with an underlying disease in which antiplatelet antibodies are formed, patients are said to have "secondary ITP."

Underlying diseases that may be associated with secondary ITP include: viruses (e.g., HIV, hepatitis C), SLE, antiphospholipid syndrome, and CLL. Recall that many of these same diseases also are associated with autoimmune hemolytic anemias.

The adult patient with ITP usually presents with easy bruising, petechiae, and nonpalpable purpura—which differentiates this from Henoch-Schönlein purpura (HSP) in which the purpura is palpable. Patients with ITP have mucosal bleeding (gingival, menorrhagia, epistaxis). When ITP occurs in an elderly patient, the patient may present with a GI or nervous system bleed.

Platelets in patients with ITP are often hyperfunctional, and, even with severe thrombocytopenia, significant spontaneous bleeding is rare.

Primary ITP is a diagnosis of exclusion, so rule out other causes. Do not order an antiplatelet antibody test. The result is too nonspecific to be helpful!

Do the following:

- As with all cases of thrombocytopenia, repeat the platelet count.
- Examine the peripheral smear to make sure platelets aren't clumping, and that schistocytes are absent (if present, suggests TTP is underlying diagnosis, not ITP). Around 1/1,000 automated platelet counts are falsely low. Clumping is caused by platelet activation by EDTA. Collecting the sample in a citrate tube corrects this problem.

- The peripheral smear in ITP typically reveals few (but giant) platelets, and normal RBCs and WBCs.
- Patients > 60 years of age may need a bone marrow biopsy to exclude myelodysplasia before diagnosing them with ITP. In ITP, marrow cellularity is normal with evidence of megakaryocyte hyperplasia.

Treat chronic ITP only if symptomatic or if the platelet count is very low:

- Corticosteroids (prednisone 1mg/kg or equivalent daily) are 1st line treatment.
- Give IV immunoglobulin (IVIG) as a 2nd line treatment to satiate voracious macrophages, which then become less hungry for antibody-coated platelets, leading to an increase in platelet count. IVIG is useful if a rapid improvement in platelet count is desired, as in a pre-op or bleeding patient. Response, however, is regularly transient—lasting only several weeks.
- Before sending a patient for surgery, many hematologists try anti-D immunoglobulin if patients are Rh-positive and have a functional spleen. This induces a mild hemolytic state, with resultant RBC stromal release and uptake by reticuloendothelial cells. The uptake of RBC stroma (as with IVIG) interferes with the ingestion of antibody-coated platelets and results in the elevation of platelet counts. Response to IVIG predicts a good response to splenectomy.
- Splenectomy induces a complete response in 2/3 of patients, but there may be relapses.

Splenectomy is indicated in any 1 of the following:

- No response to steroids
- Frequent relapses
- Unable to taper off steroids within 3–6 months

Remember: All patients should receive vaccinations for pneumococcus, *H. influenzae*, and *Neisseria meningitidis* at least 2 weeks prior to elective splenectomy because splenectomized patients are at an increased risk of infections from these organisms.

A few drugs are available for ITP refractory to steroids, IVIG, and splenectomy:

- Rituximab is an alternative to splenectomy, particularly if there is no response to IVIG. Rituximab is a monoclonal antibody directed against CD20 present on B lymphocytes.
- Romiplostim and eltrombopag are new thrombopoietin receptor agonists now FDA-approved for refractory ITP.

Give platelet transfusions if there are signs of severe bleeding and prior to invasive procedures. While platelet counts may not rise, transfusions may be hemostatically effective. Even so, they are not effective for long-term management.

Thrombotic Thrombocytopenic Purpura

Acquired thrombotic thrombocytopenic purpura (**TTP**) and the atypical hemolytic uremic syndrome (**aHUS**) in adults were once considered variants on a spectrum of disease, although it is now understood they have different pathophysiology. In general, there are 2 types of TTP (inherited and acquired) and 2 types of HUS (atypical HUS and typical/childhood/diarrhea-associated HUS).

Inherited TTP is a defect in the *ADAMTS* gene causing a deficiency in the ADAMTS13 enzyme; it affects only newborns and children. Acquired TTP affects adults and is due to an inhibitor causing decreased activity of ADAMTS13 enzyme. This enzyme is responsible for cleaving ultra-large multimers of von Willebrand factor.

TTP is a fulminant disorder of increased platelet consumption, with high mortality, that is marked by thrombocytopenia and microangiopathic hemolytic anemia.

TTP generally affects younger adults, with a peak in the 3rd decade of life. Most commonly, TTP is idiopathic, but also is associated with:

- drug exposures (quinine, cancer chemotherapy, clopidogrel, ticlopidine),
- post-hematopoietic stem cell transplant,
- pregnancy,
- oral contraceptives,
- disseminated occult mucin-producing adenocarcinomas,
- HIV infection,
- SLE, and
- antiphospholipid syndrome (APS).

Clinical manifestations of TTP:

1) Anemia (microangiopathic hemolytic anemia with schistocytes on peripheral blood smear)
2) Thrombocytopenia
3) Neurological changes (e.g., confusion, severe headache, seizure)
4) Fever
5) Renal failure (unusual in TTP)

The dyad of thrombocytopenia and microangiopathic hemolytic anemia is sufficient to narrow the differential to TTP vs. aHUS (vs. HELLP if pregnant). TTP typically presents with neurologic involvement and minimal or no renal dysfunction. Patients infrequently present with all 5 findings.

Peripheral blood smear shows thrombocytopenia and anemia with schistocytes. Labs commonly indicate a Coombs-negative hemolysis with an elevated LDH and indirect bilirubin, +/– increased creatinine. Unlike in DIC, the PT, PTT, fibrinogen, Factor V, and Factor VIII usually are normal because the coagulation cascade is not activated in TTP.

Quick Quiz

- What are the 1st and 2nd line treatments for ITP?
- Problems with which enzyme is the cause of TTP?
- What 5 clinical manifestations occur with TTP? With aHUS?
- What is the treatment of choice for TTP? For aHUS?
- What bacterial infection is associated with diarrhea-associated HUS?
- What do the letters in HELLP syndrome stand for? In which patients does it occur?
- Does HIT Type II cause bleeding or thrombosis?

Low functional ADAMTS13 enzyme levels can be used to support a TTP diagnosis, but results are generally not available in a timely manner.

Treat TTP with plasma exchange using fresh frozen plasma or cryosupernatant (plasma from which cryoprecipitate has been removed—because the cryoprecipitate contains vWF multimers that might contribute to increased clotting). Know that there are 2 situations where plasmapheresis has not been shown to have any effect:

1) Cancer chemotherapy drugs
2) Post-hematopoietic stem cell transplant

LDH levels serve as a marker of hemolysis and platelet destruction and should be followed to gauge the effect of therapy.

Unless life-threatening bleeding is present, do not give platelet transfusions, because extra platelets will simply be consumed and cause more thrombosis. If the patient does not respond to plasmapheresis, corticosteroids and/or rituximab are additional options.

Atypical Hemolytic Uremic Syndrome

Atypical HUS (**aHUS**) is confused with TTP because aHUS has the same 5 manifestations and same labs as TTP except that renal involvement occurs and neurologic involvement either does not occur or is minimal.

There are many causes of aHUS—all related to disorders in complement regulation. ADAMTS13 enzyme levels are > 10% and generally stay within normal reference intervals.

Treatment is eculizumab, a monoclonal antibody that selectively inhibits the terminal complement cascade. Note that eculizumab predisposes the patient to fulminant meningococcal infections. For some types of aHUS, eculizumab is not effective and plasma exchange transfusion is done.

Diarrhea-Associated HUS

A childhood form of HUS exists that is often precipitated by infection with enterohemorrhagic *E. coli* (O157:H7) and is associated with a prodrome of bloody diarrhea. This presentation has been termed "diarrhea-associated HUS" or "childhood HUS" to differentiate the disease from aHUS. Treatment is supportive. Cases typically self-resolve.

HELLP Syndrome

The **HELLP** syndrome (**h**emolysis, **e**levated **l**iver enzymes, and **l**ow **p**latelets) occurs in 20% of patients with preeclampsia and in 10% of patients with eclampsia. The anemia is microangiopathic, with schistocytes on the peripheral blood smear (as with TTP and aHUS). Hepatic rupture is an uncommon, but potentially devastating, complication. Treatment is delivery of the fetus, with no role for plasma exchange. Both HELLP syndrome and TTP/HUS can occur in the peripartum period, so it is important to consider each in the evaluation. TTP/HUS additionally has fever, renal involvement, and/or neurologic symptoms.

Heparin-Induced Thrombocytopenia (HIT)

Overview

HIT Type I is a clinically insignificant, nonimmune drop in platelets after starting heparin; platelets return to normal within 2 days.

HIT Type II occurs when an antibody is formed that recognizes heparin/platelet factor 4 (heparin-PF4) complexes. The antibody activates platelets, causing clumping and thrombocytopenia within 5–10 days of heparin initiation. Previous exposure to heparin and an anamnestic response may shorten the onset to < 12 hours. Venous and/or arterial thrombosis, not bleeding, is the major complication of HIT-II. Always suspect HIT-II in a patient presenting with clot 1–2 weeks after a hospitalization, even if the platelet count is normal. (The highest risk of thrombosis occurs when platelet count has returned to normal.)

Two different clinical scoring systems, the 4 Ts and HIT Expert Probability (HEP) Score, are available to assess the clinical likelihood of HIT-II (see below).

Immunoassays that detect antibodies against platelet factor 4 complexes are of limited value; they are sensitive, but not specific. Serotonin release assay is specific and sensitive but has a long turnaround time.

The 4 Ts

This clinical scoring system includes an evaluation of 4 "Ts."

Thrombocytopenia—is it present?

- 2 points: > 50% fall but remains > 20,000
- 1 point: 30–50% fall or nadir 10,000–19,000
- 0 points: < 30% fall or falls below 10,000

Timing of the thrombocytopenia:

- 2 points: between days 5–10 of heparin exposure
- 2 points: ≤ 1 day, if anamnestic response and heparin exposure within past 30 days
- 1 point: unclear but probably between days 5–10 of heparin exposure
- 1 point: after day 10 of heparin exposure
- 1 point: ≤ 1 day, if anamnestic response and heparin exposure within past 30–100 days
- 0 points: ≤ 4 days without previous HIT-II

Thrombosis (or other sequelae):

- 2 points: new clot, necrotic skin lesion, or systemic reaction after heparin bolus
- 1 point: recurrent clot or worsening of clot, skin lesion (non-necrotic), possible clot

Thrombocytopenia---other causes?

- 2 points: no obvious other causes
- 1 point: possible other causes
- 0 points: definite other cause

Probability of HIT-II:

- High probability: 6–8 points
- Intermediate probability: 4–5 points
- Low probability: 0–3 points

HIT Expert Probability (HEP) Score

A newer scoring system based on the opinion of 26 HIT experts has, in initial tests, performed better than the above 4 Ts. HEP performed better for improved interobserver agreement and correlation with lab testing. Even non-experts used the scoring system and ended up with results consistent with expert opinion.

The HEP Score is generated from the percentage of decrease in platelets, timing, nadir, thrombosis, skin necrosis, acute systemic reaction to heparin, bleeding, and other causes. Multicenter validation is still needed.

Treatment of HIT-II

Stop all heparin exposure (including low-molecular-weight heparin [LMWH]), even though this does not fully resolve the problem. This is because once the antibodies to heparin-PF4 complex are formed, the antibodies continue to bind to PF4 alone and, thus, continue to activate platelets, causing clots. LMWH should not be substituted because of antibody cross-reactivity.

Treat this hypercoagulable state with direct thrombin inhibitors (lepirudin or argatroban) at the time of diagnosis, even in the face of thrombocytopenia, whether or not a clot is present. Continue to administer the anticoagulant until the platelet count recovers. Remember that argatroban artificially elevates the INR; goal INR during argatroban/warfarin overlap is > 4. Use lepirudin with caution in patients with renal insufficiency (requires dose reduction).

Warfarin should not be started until the platelet count returns to normal. Do not start warfarin alone, since it transiently lowers levels of proteins C and S and can contribute to clot formation. Warfarin should be continued for at least 3 months. There is no role for platelet transfusions.

Once again: Remember that TTP and HIT are thrombotic thrombocytopenic disorders. So you never give these patients platelet transfusions for the thrombocytopenia unless there is life-threatening bleeding present.

Dilutional Thrombocytopenia

Dilutional thrombocytopenia occurs when massive transfusions of platelet-poor blood products are given, typically after major trauma. Treat with platelets.

Post-Transfusion Purpura

Post-transfusion purpura is rare, occurring primarily in women sensitized by pregnancy. It occurs ~ 1 week after transfusion and can last days to weeks. The platelet count is extremely low, and the patient may present with petechiae or purpura. An anti-HPA-1a antibody (human platelet antigen-1a) is formed by alloimmunization from previous blood transfusions or pregnancies, and, inexplicably, it reacts against the patient's HPA-1a negative platelets and causes thrombocytopenia.

Unlike patients with TTP, patients with post-transfusion purpura do not have evidence of microangiopathic hemolytic anemia on the peripheral smear (no schistocytes) and no CNS or renal failure.

Treat with IVIG. Steroids and plasma exchange have also been used, but the responses are slower than with IVIG. Platelet transfusions are not very effective because the transfused platelets also are destroyed by the underlying process.

Thrombocytopenia: Quinine and Other Medications

Quinine is an important cause of thrombocytopenia. It is available over the counter and used for nocturnal leg cramps. It also was once the "tonic" in gin and tonic and, in the 1970s, this side effect was described as "cocktail purpura." Now, however, tonic water contains only a medically insignificant amount of quinine. Other drugs that may cause thrombocytopenia include sulfa combinations, rifampin, digoxin, and vancomycin.

Other Causes of Thrombocytopenia

If there is a dramatic drop in platelets from one day to the next (e.g., 300K to 5K), suspect artifact. The EDTA anticoagulant in blood collection tubes may cause platelet clumping in some patients, resulting in a reading of low platelets and "giant platelets" by an automated counter.

Clinical question: When a previously healthy patient presents with petechiae, ecchymosis, normal mental status, thrombocytopenia, and anemia, what further evaluation is required?

QuickQuiz

- What is the treatment for HIT?
- When does post-transfusion purpura occur?
- What are the 2 most common types of vWD?
- What are Factor VIII activity levels in patients with vWD?
- What are the differences between Bernard-Soulier syndrome and Glanzmann thrombasthenia?

Answer: Do a peripheral blood smear, PT, and LDH. If there are schistocytes, a normal PT, and the LDH is elevated, the patient likely has TTP. If there are no schistocytes, a normal PT, and the LDH is normal, the patient likely has ITP. This is a very important distinction because TTP is a medical emergency even if the patient is feeling fine. The patient can have a precipitous stroke or deterioration in cognition or renal function. Check renal chemistries (BUN, creatinine) to evaluate for renal dysfunction, which is seen in TTP.

Platelet Function Disorders

von Willebrand Disease

von Willebrand disease (vWD) is the most common inherited bleeding disorder. Patients typically have mucocutaneous bleeding, including epistaxis, menorrhagia, postpartum and surgical bleeding, bleeding after dental extractions, and excessive bruising.

The von Willebrand factor (vWF) binds platelets to exposed subendothelial collagen and to other platelets with the platelet receptors Ib/IX and IIb/IIIa, respectively.

vWF is also the carrier protein for Factor VIII, which is degraded in its absence.

Inheritance pattern of von Willebrand disease is usually autosomal dominant. Penetrance is variable, with some patients experiencing bleeding only after surgery or major trauma and others suffering from frequent spontaneous bleeds of the mucosal surfaces of the gastrointestinal and genitourinary tracts.

Individuals with type O blood have lower baseline levels of vWF. Levels of vWF increase during pregnancy and with estrogen use.

The PTT is often increased because of decreased levels of Factor VIII. The bleeding time is prolonged.

Classification of vWD:

1) **Type 1**: a quantitative defect and the most common type (~ 75%).
2) **Type 2**: 4 subtypes (A, B, M, N)—all qualitative defects.
   - Type **2A**: the 2nd most common type of vWD (10–15%) and the result of too little of the large vWF multimer (the same one that causes TTP).
   - Type **2B**: Mutant vWF has increased affinity for platelets, causing spontaneous binding of large vWF multimers to platelets and subsequent clearing of the complex. Causes mild thrombocytopenia. Do not use desmopressin (DDAVP®) to treat because it causes increased release of mutant vWF and increased clearance of platelet-vWF complex, exacerbating thrombocytopenia.
   - Type **2M**: decreased affinity for platelets.
   - Type **2N**: an abnormal vWF protein with impaired ability to bind Factor VIII. This leads to loss of protection for Factor VIII while in circulation and therefore increased Factor VIII clearance and decreased Factor VIII levels. Presentation is similar to classic hemophilia.
3) **Type 3**: rare and severe. Autosomal recessive. Minimal-to-undetectable levels of vWF lead to spontaneous bleeding. The presentation also resembles that of classic hemophilia.

Diagnosis of Type I is confirmed with the combination of the following:

- Abnormal platelet function tests
- Decreased vWF antigen
- Proportional decrease in Factor VIII activity
- Proportional decrease in biologic activity as measured by the ristocetin cofactor assay (rCoF)

Note that the proportional decrease in vWF antigen and Factor VIII activity indicates that the decreased activity is due to a decrease in the concentration of vWF—not dysfunctional vWF.

Patients with mild defects may have varying laboratory test results over time, often requiring repeated testing to confirm the diagnosis.

Treat mild-to-moderate cases of vWD with desmopressin (except Type 2B), which causes a release of vWF and Factor VIII from endothelial cells. For active bleeding, use Factor VIII concentrates, which typically have some vWF as well. Cryoprecipitate is almost never required.

Note: Desmopressin (DDAVP®) is a synthetic analog of antidiuretic hormone (ADH, vasopressin), which boosts plasma levels of Factor VIII and vWF. It does not have vasopressor activity and it is not effective in severe vWD or severe Factor VIII deficiency.

Desmopressin can worsen Type 2B vWD. Watch for hyponatremia when treating with desmopressin.

Other Platelet Function Disorders

In **Bernard-Soulier** syndrome, patients have severely decreased platelet adhesion because they have no glycoprotein Ib (platelets cannot bind vWF). The peripheral smear demonstrates giant platelets. These patients also have a modestly low platelet count, due to

Table 8-4: Bleeding Disorder Evaluation: PT, PTT, Bleeding Time, and Platelet Aggregation

Lab Results	Etiology
1) Elevated PT and PTT	1) Factor deficiency from common pathway 2) Multiple factor deficiency 3) Warfarin affects II, VII, IX, and X, so it can affect both PT and PTT, but PT is more sensitive to warfarin
2) Elevated PT, nl PTT	Factor VII deficiency
3) Elevated PTT, nl PT: Immediate and sustained (2 hr) correction of PTT by addition of normal plasma	Factor VIII, IX, XI, or XII deficiency
4) Elevated PTT, nl PT: PTT not corrected (or no sustained correction at 2 hr) by addition of normal plasma	Inhibitor syndrome (circulating anticoagulant): If clotting: antiphospholipid synd (esp. lupus anticoagulant) – PTT not normalized immediately If bleeding: Factor VIII inhibitor – PTT initially normalized but not normalized at 2 hrs
5) Elevated PTT, nl PT—but no clinical bleeding disorder	Factor XII deficiency
6) Normal, except elevated bleeding time: a) Elevated bleeding time with nl plt aggregation b) Elevated bleeding time with nl plt aggregation and decreased plt count c) Elevated bleeding time with abn plt aggregation	Platelet problem von Willebrand disease (has decreased plt adhesion but normal aggregation) Bernard-Soulier (giant plt) synd (absent gplb) has similar presentation as vWD except lab also shows decreased plt count Glanzmann thrombasthenia (absent gpIIb-IIIa)

accelerated platelet clearance. The inheritance pattern is autosomal recessive.

Glanzmann thrombasthenia results from deficient glycoprotein IIb/IIIa complex (so fibrinogen does not cross-connect). Platelet count is normal. The inheritance pattern is autosomal recessive.

ASA/NSAIDs: Platelet-release defects are often caused by NSAIDs and ASA, which block the synthesis of thromboxane A_2 by binding to cyclooxygenase. The effects of ASA and clopidogrel last for the lifetime of the platelets, and those of non-ASA NSAIDs are transient.

Paraproteinemia, as in MM or connective tissue disease, can cause platelet dysfunction. In these disorders, the paraprotein coats the platelets, inhibiting their function and interfering with fibrin formation.

Uremia causes platelet dysfunction. Treat with platelet transfusions (for active bleeding), conjugated estrogens, or desmopressin (pre-surgery). Conjugated estrogens have a longer effect than desmopressin in uremia.

DISORDERS OF SECONDARY HEMOSTASIS

Review the following 3 variations of the PT and PTT:

1) PT high but the PTT is normal: There is a problem with the vitamin K–dependent Factors II, V, VII, X, or with fibrinogen. (See Figure 8-3.)The most common cause is the use of warfarin (a vitamin K inhibitor). Vitamin K deficiency in the malnourished or postoperative patient also occurs (see page 8-20).
2) PT is normal but PTT is high: There is a problem with Factors VIII, IX, XI, or XII. The most common cause is heparin contaminating the blood sent to the laboratory. In the bleeding patient, think inhibitor to Factor VIII (see below). In the thrombotic patient, think antiphospholipid syndrome (discussed in Rheumatology, Book 3).
3) PT and PTT are both high: There is a defect in the common pathway or else a multiple factor deficiency involving both pathways.

Regarding #2: If there is a greatly increased PTT with a normal PT and normal platelet count, 1st check a heparin-neutralization study. If there is no correction, then do a mixing study to see if the problem is factor deficiency vs. factor inhibitor.

Review: Mixing studies are done on plasma to differentiate factor deficiency from factor inhibitor. In a mixing study, the patient's plasma is mixed 50:50 with normal plasma. If the patient's prolonged PTT is due to factor deficiency, the mixing with normal plasma provides the missing factor and corrects the problem. If the PTT is still prolonged after the 1:1 mix with normal plasma, the problem is likely to be an inhibitor, usually a lupus anticoagulant (antiphospholipid syndrome) or Factor VIII inhibitor.

Some factor inhibitors take time to react with the factor. Factor VIII inhibitors are especially likely to be time-dependent. For example, with acquired idiopathic or postpartum Factor VIII inhibitor antibodies, the PTT may initially correct to normal with the mixing study, but after incubation with the normal serum for 2 hours, the inhibiting antibody begins to bind to the added Factor VIII, and the PTT is once again prolonged.

QuickQuiz

- Characterize the PT and PTT in patients with antiphospholipid syndrome.
- What are mixing studies, and when are they used?
- What is the usual cause when a mixing study shows the PTT initially normalizing, but 2 hours later it is again prolonged?
- What determines the risk of bleeding in a patient with Factor VIII deficiency (hemophilia A)?
- When do you begin the treatment of a bleeding episode in a patient with Factor VIII deficiency?
- What is the clinical presentation of Factor XI deficiency?
- How do patients present if they have Factor XII deficiency?

The thrombin time measures the time of conversion of fibrinogen to fibrin. An increased thrombin time reflects decreased or defective fibrinogen, elevated fibrin degradation products, or heparin or heparin-like anticoagulants.

Refer to both Figure 8-3 on page 8-12 and Table 8-4 as you go through the following material.

Hereditary Coagulation Deficiencies

Factors VIII and IX Deficiencies

Hemophilia is due to a Factor **VIII** (A) or **IX** (B) deficiency. In the intrinsic pathway, activated Factor VIII accelerates by 1,000-fold the cleavage of Factor X by activated Factor IX. With either Factor VIII or IX deficiency, the PTT is increased and the PT is normal.

Clinical presentation is similar in both Factor VIII and IX deficiencies, with easy bruising, muscle and joint hemorrhages, and prolonged hemorrhage after surgery or trauma, but no excessive bleeding after minor cuts.

Both Factor VIII and Factor IX deficiencies are X-linked recessive. (Daughters with only 1 chromosome affected are carriers and exhibit no symptoms.)

In Factor VIII deficiency, the risk of bleeding correlates with Factor VIII serum levels. Patients with levels < 1% of normal have severe disease (bleeding even without trauma); patients with levels > 5% have mild disease.

Use desmopressin for mild Factor VIII deficiency. It works by causing a release of vWF and Factor VIII stores from endothelial cells. It is used as treatment for an acute hemorrhage and prophylactically for a tooth extraction in patients with Factor VIII levels > 5%.

Treat an acute bleed in a patient with a more severe Factor VIII deficiency with human Factor VIII concentrate. Previously, human Factor VIII concentrates carried a risk of transmission of hepatitis viruses and HIV. Since 1985, all plasma used to produce Factor VIII concentrate has been screened for the HIV and hepatitis C viruses, and steps that specifically inactivate these viruses are included in the production process. Recombinant Factor VIII also is an approved treatment.

Symptoms of a bleed often precede objective evidence by several days, and patients frequently inform their physician when a bleed is beginning. Early treatment delays or prevents hemophilia arthropathy, is cost effective, and can be lifesaving. Some centers advocate 2–3x weekly prophylactic Factor VIII infusions to keep levels above 1% and thus reduce bleeding risk. Prophylactic factor administration has been shown to reduce the incidence of arthropathy in adult hemophiliacs, but the product is expensive and may be associated with an increased rate of development of Factor VIII inhibitors. Avoid use of ASA in patients with hemophilia.

Factor IX deficiency is clinically indistinguishable from hemophilia A. Hemophilia B is only 1/10 as common as hemophilia A.

Manage acute bleeding episodes with either recombinant or highly purified human Factor IX concentrate. The original (less purified) human Factor IX concentrates contained trace amounts of other activated clotting factors, which could cause thrombosis.

Factor XI Deficiency

Factor XI deficiency is an autosomal recessive disorder that is less common than hemophilia A or B. The risk of bleeding depends more on the gene mutation leading to the disorder than on the actual serum level of Factor XI. The disorder is more common in certain ethnic groups, including Ashkenazi Jews.

Patients with Factor XI deficiency tend to bleed at mucosal sites (epistaxis and menorrhagia), where fibrinolytic activity is high. Surgery at sites with less fibrinolytic activity (orthopedic surgery, appendectomy) tends to have fewer bleeding complications.

Acute bleeds can be managed with fresh frozen plasma, recombinant Factor XI, or desmopressin.

Factor XII Deficiency

Patients with a decreased **Factor XII** (Hageman factor) have a normal PT and a very prolonged PTT (as with Factor VIII, IX, and XI deficiencies), but they do not have a clinical bleeding disorder and can even undergo surgery without worry of bleeding.

Factor XIII Deficiency

Factor XIII deficiency is an autosomal recessive disorder. Severe bleeding results from the inability to cross-link fibrin strands. Coagulation tests, including PT, PTT, and platelet function studies, are normal. Think about this in patients who have late postsurgical bleeding and poor wound healing.

Diagnose Factor XIII deficiency by performing a specialized clot lysis assay, in which dissolution of clot is attempted using urea. If the clot is solubilized with urea, then a Factor XIII deficiency exists. Treat with small amounts of fresh frozen plasma or specialized plasma derivative every 3–4 weeks.

And ...

As mentioned before, while people with platelet dysfunction tend to experience mucosal bleeding (bruising, nosebleeds, and menorrhagia), people with coagulation factor disorders tend to experience discrete episodes of deep tissue bleeding (hemarthroses, muscle hematomas, retroperitoneal hemorrhage). So, if platelets are absolutely required for thrombus formation, just like coagulation factors are required, why does a deficiency cause only mucosal bleeding? The answer is that early thrombus formation does not require many platelets to do the job.

What bleeding disorders may appear with a normal platelet count, PT, PTT, and bleeding time? The major disorders to consider are:

- Mild von Willebrand disease
- Mild hemophilia
- Factor XIII deficiency

Acquired Coagulation Deficiencies

DIC

Overview

Disseminated intravascular coagulation (DIC) is one of the most common acquired coagulopathies. It is always a secondary condition, so the underlying disease must be treated for the DIC to resolve.

DIC occurs in diseases that promote tissue factor release, including the following:

- Massive trauma
- Production of tumor necrosis factor, especially seen in solid tumors
- Sepsis, especially with endotoxin release
- Retained placental tissue in obstetric patients with placenta abruptio, dead fetus, or amniotic fluid embolus
- Acute promyelocytic leukemia (aPML, AML M3)

Acute (Decompensated) DIC

Large amounts of released tissue factor activate Factor VII and initiate the coagulation cascade. There is excessive thrombin and plasmin produced, resulting in both increased clot formation (via thrombin cleaving fibrinogen to fibrin) and clot breakdown (via plasmin degradation of fibrin clots). The plasmin breaks down fibrinogen and fibrin into fibrinogen/fibrin degradation products (FDPs, also called fibrin split products).

The massive depletion of coagulation factors and platelets and the increased fibrin split products (including D-dimer) may result in bleeding. Symptoms of DIC result from bleeding or microvascular thrombosis, as well as the underlying disorder.

Diagnosis of DIC:

- **PT** and **PTT** prolonged (remember, normal in TTP).
- **Thrombocytopenia** (from consumption).
- **Fibrinogen** level is decreased and trends downward during the disease process.
- **Thrombin time** is increased (due to both decreased fibrinogen and increased FDPs).
- **Schistocytes** (RBC fragments) are found in the peripheral smear in up to 1/2 of patients, which indicate microangiopathic hemolytic anemia (the fibrin strands span the small blood vessels and shear the RBCs).
- **FDP/D-dimer** increased. These are almost always elevated in DIC but also occur in many other conditions. FDP and D-dimer are therefore a sensitive, but not specific test.

Chronic (Compensated) DIC

Patients with chronic DIC can have either bleeding or thrombotic disorders. The thrombotic disorders range from migratory chronic thrombophlebitis (Trousseau syndrome) to pulmonary emboli.

Chronic DIC virtually always occurs in association with solid tumors.

With chronic DIC, a slower consumption of coagulation factors is compensated by increased synthesis of these same coagulation factors. Because of this, the lab results vary from acute DIC and all may be normal except FDP/D-dimer (elevated).

In the setting of an underlying malignancy, diagnosis of chronic DIC can be made with the finding of microangiopathic hemolytic anemia on peripheral smear and increased FDP/D-dimer.

Treatment of DIC

Treat the underlying disorder, or the DIC does not stop. With severe bleeding, give fresh frozen plasma and platelets. Heparin is not usually effective except in specific, unusual clinical situations (e.g., chronic DIC due to malignancy).

You can give cryoprecipitate if the fibrinogen level is very low, and you can use FFP to replace other coagulation factors. Platelets are given only if there is an acute bleed or to prepare a patient for surgery.

Vitamin K Deficiency

Vitamin K deficiency causes decreased production of the vitamin K-dependent factors (II, VII, IX, X) and proteins C and S.

QuickQuiz

- What special diagnostic test is used to diagnose Factor XIII deficiency?
- What disease states are associated with chronic DIC?
- How does the PT and PTT differ in DIC vs. TTP?
- How do broad-spectrum antibiotics cause vitamin K deficiency? How do certain cephalosporins cause vitamin K deficiency?
- Patients with which deficiencies are more likely to experience a venous thrombosis during initial anticoagulation with warfarin?

Causes of vitamin K deficiency include decreased dietary intake, malabsorption, antibiotic use, and decreased storage resulting from liver disease.

Especially know the probable cause of a prolonged PT in patients on either total parenteral nutrition (cause is decreased vitamin K intake) or certain cephalosporins (cause is antagonism of vitamin K by the N-methylthiotetrazole [NMTT] or similar side chains on cefotetan or cefoperazone). Other broad-spectrum antibiotics can cause vitamin K deficiency by reducing the burden of organisms in the intestine that synthesize vitamin K. The PT is prolonged, and the PTT is often normal. To further differentiate from DIC, check thrombin time and D-dimer, which are normal in patients with vitamin K deficiency.

Treat acute bleeds with fresh frozen plasma (FFP). Patients who are not bleeding can often be managed with vitamin K. Oral forms are more predictably absorbed (if the patient has a normal GI tract) than subcutaneous injections. IV vitamin K carries a very small risk for anaphylaxis. IM vitamin K should not be administered due to risk of hematoma formation. Vitamin K may take approximately 8 hours to work, so you should use FFP for immediate treatment if there is life-threatening hemorrhage.

Warfarin antagonizes vitamin K (causing an effective vitamin K deficiency). Initiation of warfarin therapy carries a theoretical increased risk of thrombosis as the levels of proteins C and S drop (the proteins with the shortest half-lives). This initial thrombotic effect may, for a short time, outweigh the antithrombotic effect on Factor VII; this is more likely with large loading doses of warfarin or if the patient is already protein C-deficient (pretreat with heparin). One-third of patients who develop warfarin-related skin necrosis have a protein C deficiency.

Any new medications or dietary changes should be reported by patients, since these may inhibit or potentiate warfarin's effect.

Primary Fibrinolysis

Primary fibrinolysis is a rare disorder often associated with prostate cancer and/or surgery. This disorder occurs when plasmin is released into the circulation in response to endothelial agents like tissue plasminogen activator (tPA). The pathophysiology differs from that of secondary fibrinolytic states, such as DIC, which occur in response to thrombi formation in the microvasculature.

Both primary and secondary fibrinolysis cause abnormalities of the PT, PTT, fibrinogen level, FDPs, and D-dimer; however, patients with primary fibrinolysis often have a normal platelet count.

Factor VIII Inhibitor

Factor VIII inhibitors are associated with:

- hemophilia,
- malignancies (CLL, adenocarcinomas),
- infections,
- pregnancy or the postpartum state,
- autoimmune disorders (SLE, RA),
- aging, and
- drugs.

However, many cases are idiopathic. Most patients who develop a Factor VIII inhibitor have never had a blood transfusion. Patients with an inhibitor present with severe bleeding, similar to hemophilia. In contrast to the lupus anticoagulant, mixing normal and patient's plasma may (initially) correct the PTT, but after a 2-hour incubation, the inhibitor antibody inactivates Factor VIII, and the PTT again becomes prolonged. Therefore, a mixing study that does not maintain a sustained normalization of the PTT suggests a Factor VIII inhibitor rather than factor deficiency.

THROMBOTIC DISORDERS

Overview

Virchow triad describes 3 factors that predispose patients to thrombosis:

1) Stasis
2) Vascular damage
3) Hypercoagulable state

Hypercoagulable states include both acquired and hereditary disorders.

Note that patients may develop a thromboembolic event only after they have multiple prothrombotic conditions. For example, a woman with a hypercoagulable state caused by *Factor V Leiden* mutation may not have her 1st deep vein thrombosis until she is pregnant or is immobilized after knee surgery.

Acquired Thrombotic Disorders

The acquired disorders include the following:

- Malignancy
- Pregnancy (especially immediate postpartum period)
- Smoking
- Estrogen use (OCPs, hormone replacement)
- Immobilization
- Major surgery
- Heparin-induced thrombocytopenia
- Myeloproliferative disorders (especially polycythemia vera and essential thrombocytosis)
- Antiphospholipid syndrome (APS)
- PNH
- Multiple myeloma

Antiphospholipid Syndrome (APS)

APS is a term used to describe the clinical relationship between a hypercoagulable state and the presence of antiphospholipid antibodies. It is discussed further in Rheumatology, Book 3.

Inherited Thrombotic Disorders

Overview

The most common inherited causes of venous thromboembolism are the *Factor V Leiden* gene mutation and the prothrombin gene mutation (*G20210A*). These mutations typically cause thrombosis before 50 years of age and more often present when other acquired risks for clotting are superimposed (e.g., pregnancy, oral contraceptives, immobility).

Although Factor V and prothrombin gene mutations are more common, patients with protein C, S, or antithrombin deficiencies are more likely to thrombose and to have recurrent thromboses. In patients > 50 years of age, think about the acquired causes of thromboembolism.

Thrombophilia means increased tendency to form thromboses.

Activated Protein C Resistance / *Factor V Leiden* Mutation

The *Factor V Leiden* mutation causes a resistance to the normally inhibitory effects of protein C, so the disease is called "activated protein C resistance" or "APC resistance." In the healthy patient, activated protein C cleaves activated Factors Va and VIIIa, rendering them inactive. Resistance to activated protein C leads to an unchecked hypercoagulable state. Heterozygosity for the *Factor V Leiden* mutation increases the lifetime risk for thrombosis 7-fold; homozygosity raises the risk 20-fold.

Prothrombin Gene Mutation

Prothrombin gene mutation is a gain-of-function mutation that results in increased levels of prothrombin (Factor II in the coagulation cascade). Heterozygous carriers of the *G20210A* mutation have 2–3x increased risk of venous, and possibly arterial, thrombosis.

Antithrombin Deficiencies

Antithrombin ([AT]; previously referred to as antithrombin III) inactivates thrombin both with and without the presence of heparin. In the presence of heparin, the antithrombin effects are accelerated roughly 4,000-fold. Antithrombin deficiencies include both quantitative (type 1) and qualitative (type 2) defects. Typically, 1st thrombotic events occur at a young age, and AT deficiencies are associated with a risk of venous thromboembolism of ~ 1%/year. Approximately 65% of patients heterozygous for AT have a thrombotic event by age 50. Homozygous AT deficiency is fatal *in utero*.

Type 1 is diagnosed by immunoassay and type 2 by functional studies (AT-heparin cofactor assay).

Protein C and S Deficiencies

Protein C and S deficiencies result in loss of the normal cleaving of Factors Va and VIIIa. The deficiencies are normally autosomal dominant. Both protein C and S are vitamin K-dependent proteins. Patients with protein C deficiency are at increased risk of developing skin necrosis while on warfarin. This is because protein C, with a very short half-life (6 hrs) compared with the other vitamin K-dependent clotting factors, is rapidly depleted with warfarin initiation, resulting in a transient hypercoagulable state.

Testing for Thrombophilia

Patients are said to be "strongly thrombophilic" if:

- 1st clot prior to age 50,
- recurrent thrombosis, or
- 1st degree family members with clots prior to age 50.

Screen these patients for all of the following:

- APC resistance (*Factor V Leiden*)
- Prothrombin *G20210A* mutation
- Protein C, S, and antithrombin deficiencies
- APS

Again, the less common deficiencies (APS, protein C, S, and antithrombin deficiencies) are more severe and have recurrent clots more often than those with APC resistance and prothrombin *G20210A* mutations.

A patient is "weakly thrombophilic" if the 1st clot occurs after age 50. In this group, an inherited thrombophilia is less likely. An acquired hypercoagulable state is most likely due to a malignancy. In most patients, a primary malignancy is already diagnosed at the time of clot. Screen for the following:

- APS, especially if the patient has any signs or symptoms of SLE

Quick Quiz

- What are the most common genetic mutations that cause venous thrombosis?
- What battery of tests is done on patients with possible inherited thrombophilia?
- What are established indications for an IVC filter in a patient with a deep venous thrombosis?

- Malignancy (solid tumors, lymphomas, myeloproliferative disorders)
- Use of certain drugs (hydralazine, procainamide, HCTZ, propranolol, phenytoin, or phenothiazines)

Remember that acute thrombosis can transiently lower levels of antithrombin, protein C, and protein S. Heparin can cause decreased antithrombin levels. Warfarin can decrease functional (and to a lesser extent, quantitative) levels of protein C and S and can (albeit rarely) raise antithrombin levels. In addition, warfarin yields a false-positive test for lupus anticoagulant. So wait to test for C, S, and antithrombin deficiencies until 2 weeks after completion of the initial 3–6 months of anticoagulation.

Management of Thrombosis

An extensive discussion of deep venous thromboses and pulmonary emboli (DVT/PE) is included in Pulmonary Medicine, Book 2.

Acceptable drugs for treatment of an established thrombosis include low-molecular-weight heparin (LMWH), unfractionated (UF) heparin, and fondaparinux. Recently, the oral Factor Xa inhibitors rivaroxaban and apixaban were approved to treat symptomatic venous thromboembolism. Caution is advised with renal failure. While the oral direct thrombin inhibitor dabigatran is approved for stroke reduction in nonvalvular atrial fibrillation, its use in venous thromboembolism is considered off-label. UF heparin is more expensive due to the need for monitoring of the PTT, but the infusion is easily titrated to meet the needs of an unstable patient. Thus, UF heparin usually is recommended in unstable patients.

Treatment of isolated calf vein thrombosis is guided by whether or not the patient is symptomatic. Options include anticoagulation or observation only, with serial ultrasound over the next 2 weeks to determine whether the clot is extending proximally.

LMWH and fondaparinux are not recommended in patients with low creatinine clearance (GFR < 30 cc/min). UF heparin is recommended in this group. LMWH is recommended, except in the unstable and in those with low creatinine clearance, because of mortality benefits and lower cost.

Be sure to monitor the platelet count in any patient taking a heparin product because of the possibility of HIT-II.

Warfarin can be started simultaneous with the heparin product or fondaparinux. Both drugs should be continued for at least 5 days with subsequent discontinuation of heparin/fondaparinux after the INR has been therapeutic for at least 48 hours.

Thrombolytic therapy is reserved for patients who are unstable due to a pulmonary embolism or a massive ileofemoral thrombus.

Duration of anticoagulation is somewhat controversial for certain patient groups, but general guidelines include the following:

- If the patient has a provoked thrombosis with transient risk factor (OCP use, surgery, immobilization, HIT-II): anticoagulate with goal INR 2–3 for at least 3 months.
- An unprovoked thrombosis: Anticoagulate with goal INR 2–3 for at least 3 months. The ACCP recommends indefinite anticoagulation be considered and benefits weighed against the risks.
- Recurrent thromboses, one unprovoked life-threatening thrombosis, one spontaneous thrombosis with APS: indefinite anticoagulation.
- A thrombosis in the setting of pregnancy or active malignancy: LMWH is more effective for preventing future thrombosis and for treatment of an acute thrombosis. Remember that warfarin is contraindicated in pregnancy because it is teratogenic and causes fetal bleeding. Unfractionated heparin is an alternative, but it is considered least favorable because of the need to use an increased dose during pregnancy and to monitor the PTT, in addition to the long-term risk of bone demineralization.

Consider an IVC filter in the following situations:

- When anticoagulation is contraindicated
- When there is a failure of anticoagulation
- In the presence of severe cardiopulmonary comorbidities, making a new PE life-threatening

Prior to surgery, consult the latest recommendations by the ACCP for discontinuation and resumption of anticoagulation therapy.

FIBRINOLYTIC TREATMENT

Urokinase and streptokinase cause a systemic lytic state. tPA is more specific; it increases the conversion of plasminogen to plasmin in the presence of fibrin, so most of the plasmin made is localized to the fibrin clot.

However, tPA also results in systemic lysis. These drugs are occasionally used to lyse a life-threatening pulmonary embolism (very specific situations) or an acute stroke or MI.

TRANSFUSION MEDICINE

RBC Transfusions

Whole blood is rarely used. Exceptions include major hemorrhage from trauma or from pediatric cardiac surgery. A donated unit of whole blood is normally separated into platelets, plasma, and packed RBCs. Alloimmunization can be a problem in multiple-transfused patients. In absence of ongoing losses, 1 unit of packed RBCs should increase the hemoglobin by 1 g/dL.

Platelet Transfusions

Wait to transfuse most patients with thrombocytopenia if they are not bleeding. A low platelet count that is > 10 x 10^9/L is acceptable for nonbleeding patients with acute leukemia. Platelet counts of 50 x 10^9/L are adequate for most interventional procedures (higher number often used for neurosurgical procedures). Patients with ITP almost never require platelet transfusions, even with very low platelet counts. Their younger platelets seem to work better, and transfusion does not result in an appreciable rise in the platelet count but may be hemostatically effective.

Know that platelet transfusions should not be given to patients with HIT or TTP/HUS unless there is life-threatening bleeding, because of increased risk of thrombosis.

WBC Transfusions

WBC transfusions are only rarely performed. G-CSF or GM-CSF is used instead to increase the neutrophil count—most commonly in patients receiving myelosuppressive chemotherapy.

Plasma and Cryoprecipitate Transfusions

Fresh frozen plasma (FFP) is transfused to replace coagulation factors. Use it to reverse anticoagulation in the context of dangerous bleeding when the PT and/or PTT are supratherapeutic.

Cryoprecipitate is a plasma component enriched in fibrinogen. It is used in conditions like DIC to replace fibrinogen (indicated when fibrinogen < 100 mg/dL).

Transfusion Reactions

Acute hemolytic transfusion reaction is a medical emergency caused by rapid, intravascular hemolysis, commonly due to an ABO incompatibility—and most often a result of a clerical error.

The initial signs may be only fever and chills. So, if a patient receiving a transfusion develops fever and chills, stop the transfusion immediately—prognosis worsens as more blood is given. Provide supportive care, including normal saline infusion.

Diagnostic tests include Coombs testing, serum-free hemoglobin, hemolysis labs (indirect bilirubin, haptoglobin, LDH), urine for hemoglobin testing, and repeat type and cross on transfused RBCs, as well as any blood left in the transfusion bag. Plasma is pink and peripheral smear shows schistocytes.

Alert the blood bank immediately because another patient may also be receiving the wrong blood.

Delayed hemolytic transfusion reaction is caused by extravascular hemolysis associated with Rh incompatibility or minor antigen mismatches. Patients present approximately 7 days after transfusion with anemia, mild fever, and mild unconjugated bilirubin elevation.

No treatment is necessary in the absence of brisk hemolysis. Future transfusions should be matched appropriately.

Febrile transfusion reactions. Fever and chills after a transfusion are common and represent nonhemolytic reactions to leukocytes in the blood product. A normal peripheral smear differentiates this mild, benign reaction from the more dangerous acute hemolysis.

Stop the transfusion and assess for hemolysis by sending off the same labs in the "acute hemolytic" category above. If the Coombs is negative, the symptoms are probably due to anti-HLA antibodies against the WBCs, which are transfused along with the component blood product.

Give antipyretics. Filters are used to remove WBCs in the transfused product (leukocyte-depletion) to minimize this reaction. But filters do not remove cytokines, which can also cause the reaction.

Post-transfusion purpura is discussed on page 8-16.

Transfusional hemosiderosis is iron overload from chronic repeat transfusions, usually in patients with sickle cell disease, thalassemia, or transfusion-dependent myeloproliferative or myelodysplastic disorders. Each 250 cc of packed RBCs contains approximately 250 mg of iron. Patients can become symptomatic after as few as 20 units. After 100 units (20–25 grams of iron), patients almost always show some symptoms of iron overload, which include:

- Glucose intolerance
- Cirrhosis
- Cardiomyopathy
- Hypogonadism

Diagnosis of transfusional hemosiderosis is established by an elevated ferritin and an iron-laden liver biopsy. As with hemochromatosis, MRI can detect iron in the liver, heart, joints, and pituitary (experienced facility only). Start iron chelation treatment (deferoxamine) before symptoms appear, because symptoms are typically not reversible. Consider chelation after 20–25 units of packed red cells (approximately 5 grams of iron) if transfusions are ongoing.

Transfusion-related acute lung injury (TRALI) is a severe pulmonary reaction caused by antibodies present in transfused FFP. The timing of TRALI is typically

Quick Quiz

- Which patients, except in the case of life-threatening bleeding, should not be given platelet transfusions, regardless of the degree of thrombocytopenia?
- What is the most common reason for an acute hemolytic transfusion reaction? What is the clinical presentation?
- What types of transfusions are most associated with transfusion-related bacterial infections? Why?
- What are the lab findings in a patient with aplastic anemia?

during or shortly after transfusion (1–2 hours), but TRALI can be more delayed, occurring up to 6 hours after transfusion. Clinically, there is sudden onset of respiratory distress. This may include alveolitis, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome (ARDS). Treatment is supportive and may include mechanical ventilation. Stop the transfusion and never use blood products from that donor again!

Pre-transplant alloimmunization can occur if transfusions are given before transplant. To reduce risk:

- Do not use family members as donors.
- Use leukocyte-poor irradiated blood components.
- Use single-donor platelets if needed.

Allergic reactions to transfused blood: Simple urticaria and anaphylaxis can occur. Know that recipient IgA deficiency leads to anti-IgA antibody formation, and donor blood with normal IgA levels can provoke anaphylaxis. IgA-deficient donors should be used for such recipients.

Infectious complications are most likely to occur with platelet products because they are stored at room temperature. Skin flora and gram-negative bacteria (*E. coli*, *Yersinia*, and *Pseudomonas*) are the usual organisms. Blood banks now screen for the most common infectious agents as follows:

- HIV-1 and -2: EIA antibody screen and nucleic acid amplification, with confirmation of positive results using Western blot or immunofluorescence test; window of risk for undetectable infection now only 11 days; risk of contracting HIV-1 or -2 from U.S. blood supply is 1 in 2 million.
- HTLV-1 and -2: qualitative antibody screen. Risk is < 1 in 2 million.
- HCV: EIA antibody plus nucleic acid testing; window of risk is 8–10 days; risk of contracting HCV from U.S. blood supply is 1 in 1.3 million.
- HBV: EIA for anti-HBc; risk of contracting HBV from U.S. blood supply is 1 in 200,000–500,000.
- West Nile virus: nucleic acid testing.
- *T. pallidum*: syphilis-specific antibodies using agglutination.
- *T. cruzi*: Trypanosomiasis is of particular concern in South America. Many U.S. blood banks are implementing universal screening using an EIA test for *T. cruzi* antibody, with a confirmatory radioimmunoprecipitation assay (RIPA).
- CMV: EIA for antibody; only CMV-negative blood is transfused in CMV-negative transplant patients, and leukocyte-depleted blood is used to further reduce risk.
- Less common organisms also can cause disease: *Babesia* and malaria (these are rare).

Hypotensive reactions can be seen in patients on ACE inhibitors, whose blood is filtered through coils, such as those used to filter out WBCs. Kinin activation is the probable cause. Prestorage filtration eliminates this problem.

Graft vs. host (GVH) reaction. Immunocompromised patients may develop GVH from lymphocytes in transfused blood. Also in immunocompetent patients, 1st degree relative donations carry some risk because they may be HLA-haploidentical, and lymphocytes may engraft. Order irradiated blood in both circumstances in order to ensure that the potentially harmful lymphocytes have been destroyed.

DISORDERS OF THE BONE MARROW

APLASTIC ANEMIA

Aplastic anemia is an absence of hematopoietic stem cells that results in pancytopenia and a hypocellular marrow. It can be acquired or inherited. The etiology of acquired aplastic anemia is unknown in most cases.

Dose-related causes include benzene and other industrial chemicals, pesticides, and radiation. Idiosyncratic drug causes include sulfa, carbamazepine, valproate, phenytoin, gold, chloramphenicol, and nifedipine.

Aplastic anemia is occasionally associated with viral infections with parvovirus B19, hepatitis viruses, and HIV. Other associated illnesses include thymoma, paroxysmal nocturnal hemoglobinuria, and systemic lupus erythematosus.

The presentation is determined by which cell lines are affected most: fatigue and weakness, if anemia; infections, if neutropenic; bleeding, if thrombocytopenic.

Aplastic anemia presents with pancytopenia, decreased reticulocyte count, and a hypocellular marrow (< 20%) with normal maturation of the cell lines. Differential diagnosis includes other causes of pancytopenia, such as B_{12} or folic acid deficiency, primary hematologic malignancies, MDS, infiltration of bone marrow with neoplastic cells, or fibrosis.

Aplastic anemia is classified as "severe" if:

- Marrow cellularity is < 25% of normal, or
- If the marrow is hypocellular and < 30% of the cells are hematopoietic, and at least 2 of the following 3 conditions are met:
  - ANC < 500/mm^3
  - Platelets < 20,000/mm^3
  - Reticulocytes < 1% corrected for hematocrit

Classification is "very severe" if "severe criteria" are met but ANC < 200/mm^3. A low absolute neutrophil count has poor prognostic significance. Younger age and higher cell counts are predictive of a better response rate to treatment.

Definitive treatment of aplastic anemia is with bone marrow transplantation for patients who are young and have an HLA-matched family member (10-year survival > 80%).

If there is no suitable donor or the patient is > 45 years of age, immunosuppress using either antithymocyte globulin or antilymphocyte globulin in combination with corticosteroids and cyclosporine. The complete response rate is 65%, although relapses are common.

Hematopoietic growth factors are undergoing evaluation and are not yet recommended treatment.

For all patients, treatment includes withdrawal of any possible offending medications. In addition, if thymoma is found, surgical excision is indicated.

Know that patients with aplastic anemia are at increased risk of developing acute leukemia.

THE ACUTE LEUKEMIAS

Overview

The acute leukemias are clonal disorders of early hematopoietic stem cells.

Normal hematopoiesis begins with pluripotent stem cells, which, in addition to reproducing themselves, are capable of differentiating into cells of either the myeloid lineage (granulocytes, monocytes, erythrocytes, and megakaryocytes) or the lymphocyte lineage (B or T cells).

Acute leukemias occur when cells of either the early myeloid (AML) or early lymphoid (ALL) lines lose their ability to differentiate, while retaining their ability to replicate. These blast cells accumulate in the bone marrow and crowd out normal hematopoiesis. The blast cells often spill out into the peripheral circulation but may be contained within the marrow.

Suspect acute leukemia when blasts (immature cells) are seen in the peripheral blood smear, without mature cells. Note that chronic leukemias have overproduction of 1 or more developing cell lines but not of blasts.

Patients present with symptoms related to cytopenias (infections, fatigue, mucosal bleeding).

Diagnosis and prognosis are made using morphologic analysis, cytogenetic studies (karyotype), cytochemical analysis (PAS, peroxidase, esterase, Sudan black), molecular markers, and cell surface markers (flow cytometry and immunophenotyping for CD markers).

Treatment for most acute leukemias involves an induction phase, where all hematopoiesis is suppressed with high-dose chemotherapy, with the hope that normal hematopoiesis returns without the leukemic clone. Successful induction involves a prolonged period of pancytopenia, during which the patient is highly susceptible to infection.

Myeloid growth factors are often used to shorten the time spent in a neutropenic state. Though these agents may reduce the length of hospitalization and decrease the incidence of infection, they have not been proven to increase survival (with the exception of a single study in the elderly). Supportive care with blood and platelet transfusions also is given during this time.

Once remission is achieved and cell counts have recovered, consolidation therapy is used to prolong remission and survival.

Gene expression profiling, utilizing DNA microarrays, is becoming an increasingly important tool to assist with prognosis and to guide therapy.

Acute Myelogenous Leukemia (AML)

During normal hematopoiesis, myeloid blast cells (Image 8-15 and Image 8-17) differentiate into granulocytes, monocytes, erythrocytes, or megakaryocytes. AML is a clonal disorder of the early myeloid cells where there is overproduction of myeloblasts with reduced production of red cells, platelets, and mature granulocytes. The blast forms accumulate in the peripheral blood, marrow, and, sometimes, lymphoid tissues.

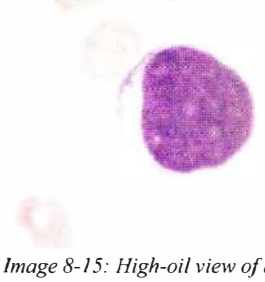

Image 8-15: High-oil view of a normal myeloblast. Few cytoplasmic granules. Several nucleoli.

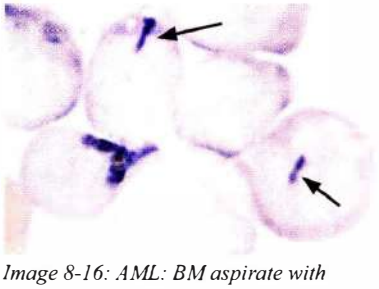

Image 8-16: AML: BM aspirate with peroxidase-positive blasts and 2 peroxidase-positive Auer rods.

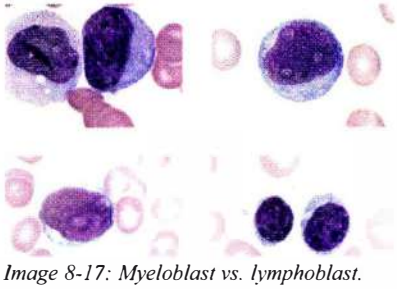

Image 8-17: Myeloblast vs. lymphoblast. UL: young mono and a myeloblast. UR: myeloblast. LL: lymphoblast. LR: normal lymphocytes are smaller.

QuickQuiz

- How can you tell the difference between acute and chronic leukemias?
- What is the treatment for leukemic patients who have hyperviscosity symptoms due to a large number of circulating blasts?
- What percentage of marrow blasts defines AML?
- What is a characteristic peripheral blood finding in a patient with AML?

The disorder can develop from exposure to chemicals such as benzene and certain chemotherapeutic agents. It may also arise after transformation from myeloproliferative disorders, myelodysplastic disorders, aplastic anemia, and PNH. Typically, these secondary leukemias have a worse prognosis than *de novo* AML.

Symptoms related to disordered hematopoiesis result in patients seeking medical care, but bone pain is uncommon. When fever is present, it's usually from infection; this leukemia rarely involves the CNS.

[Know.] Large numbers of blasts in the peripheral blood (> 100,000 cells/mm^3) can increase blood viscosity and cause end-organ disease such as brain ischemia and hemorrhage (presents as altered sensorium) and sludging in the pulmonary vasculature (presents as respiratory distress). This leukostasis is a medical emergency, and urgent treatment includes leukapheresis or hydroxyurea.

Thrombocytopenia predisposes to hemorrhage, especially in the presence of a high blast count. Qualitative and quantitative WBC problems predispose to serious infection of all kinds. Concurrent anemia requires RBC transfusions.

Diagnose AML by bone marrow biopsy if blasts are seen in the peripheral blood: Marrow blasts ≥ 20% is acute leukemia. Commonly, the blasts of AML and ALL look alike, and you cannot tell the type of leukemia by observation alone, so cytochemical tests, immunophenotyping, and chromosomal analysis are performed on marrow cells. Know, however, that finding Auer rods inside peripheral blood blast cells (Image 8-16) makes the diagnosis of AML. Auer rods are azurophilic needle-shaped crystals found in the cytoplasm of AML blasts.

AML can be categorized using the older French-American-British (FAB) classification (Table 8-5) or the newer (2008) World Health Organization (WHO) system. FAB contains classes M0–M7 with categories ranging from poorly differentiated to megakaryocytic. WHO classifies AML based on cytogenetics, clinical disease, and immunophenotype, with categories ranging from "AML with recurrent cytogenetic abnormalities" to "AML, not otherwise specified."

Except for 1 category (FAB M3, acute promyelocytic leukemia [aPML]), the specifics of both systems are not important for the general internist. aPML, however, is important because these patients have cytogenetic abnormalities that carry a favorable prognosis when the patient is treated with an ATRA drug (discussed next). So, remember the subset of AML that is treated with an ATRA drug: M3, acute promyelocytic leukemia, aPML.

Currently, several factors are used to establish AML prognosis. Cytogenetic findings represent one of the most powerful prognostic indicators. The karyotype can be used to classify patients into different risk groups:

- **Favorable** karyotype → t(8;21), t(15;17), or inv(16)
- **Intermediate** karyotype → normal karyotype or t(19;11)
- **Unfavorable** karyotype → inv(3), 5/del(5q), monosomy 7, or a more complex karyotype (3 or more aberrations)

Other unfavorable prognosticators for AML include:

- Age > 60
- Poor performance status
- WBC count > 100,000/mm^3
- Prior disease of the bone marrow (myelodysplasia or myeloproliferative disorder)
- Mutations in FLT3 (a receptor tyrosine kinase), found in 20–30% of patients with AML

Mutations in nucleophosmin (*NPM1*) gene, found in approximately 25% of patients with *de novo* AML and up to 50% of patients with normal karyotype *de novo* AML, are associated with a favorable prognosis (unlike *FLT3* mutations—and as long as no *FLT3* mutation is present).

CEBPA gene mutations are also associated with a favorable prognosis. Know that the molecular diagnostic field of AML is rapidly evolving with new favorable and unfavorable mutations continuously being discovered.

Table 8-5: French-American-British Classification of Acute Myeloid Subtypes with Some Distinguishing Characteristics

M0	Acute myeloblastic, poorly differentiated	5–10%
M1	Myeloblastic, without maturation	5–10%
M2	Myeloblastic, with maturation; associated with t(8;21) (favorable cytogenetics)	25–30%
M3	Acute promyelocytic leukemia, favorable prognosis, t(15;17), associated with DIC	3–15%
M4	Myelomonocytic, associated with inv(16) (favorable cytogenetics)	15–30%
M5	Monocytic	10–20%
M6	Erythroleukemia, poor prognosis	3–7%
M7	Megakaryocytic, associated with marrow fibrosis, unfavorable prognosis	3–6%

Acute promyelocytic leukemia (aPML; AML M3 type) is characterized by a translocation between chromosomes 15 and 17, involving the promyelocytic leukemia gene and retinoic acid receptor α gene (PML-RARα).

Treatment of aPML differs from treatment of other types of AML. Prognosis for aPML is very favorable, and therapy is associated with a remission rate of > 80% and a cure rate of > 70%. These rates are much better than with other forms of AML. Treatment includes all-trans retinoic acid (ATRA), which is used to induce differentiation, along with daunorubicin.

Know that "differentiation syndrome" (formerly "ATRA syndrome") is an adverse effect of ATRA therapy and clinically presents as fever, volume overload with pleural and pericardial effusions, respiratory distress, and hypotension. It can be life-threatening. Treat with high-dose dexamethasone and withhold ATRA if necessary.

Patients with aPML are also at increased risk for developing DIC due to release of procoagulants from cytoplasmic granules. The diagnosis of aPML needs to be made quickly because DIC can change aPML from a curable disease into a fatal one within hours.

An important distinction in AML is whether the disease is *de novo* AML or CML in degenerated blast crisis. CML in blast crisis arises because of the presence of the Philadelphia chromosome (*BCR-ABL* gene translocation) and is vulnerable to treatment with a tyrosine kinase inhibitor such as imatinib.

Standard induction therapy for AML (non-aPML) is a combination of 7 days of cytosine arabinoside (ara-C) and 3 days of daunorubicin ("7 + 3"). Consolidation therapy can take the form of further chemotherapy with the same agents as above. With standard therapy, for patients > 60 years of age, remission is achieved in ~ 40–50%, but long-term, event-free survival is achieved in < 10%. For patients < 60 years of age, long-term survival, on average, is 20–30%.

Allogeneic stem cell transplantation is an important treatment option in patients with AML. It is typically reserved for patients < 60 years of age. Morbidity and mortality are reduced if a histocompatible sibling donor is utilized rather than a matched unrelated donor. Over the last decade, a new technique called nonmyeloablative stem cell transplant has been developed. The difference, compared to standard allogeneic transplant, is that the pre-stem cell rescue chemotherapy is very modest in dosing. This technique has decreased immediate transplant mortality.

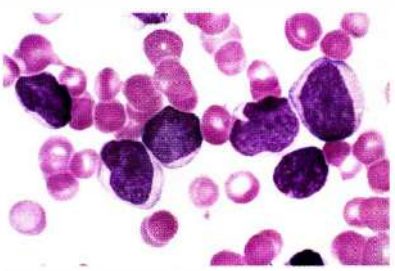

Image 8-18: ALL: many lymphoblasts. Note how large the blasts are compared to RBCs.

However, it is still associated with GVH. For patients < 60, considerations for transplant should include comorbid conditions, relapse/remission status, and cytogenetics.

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is a clonal disorder of early lymphocytic precursors. The blasts of ALL may be of B- or T-cell lineage (see Image 8-18). While ALL is primarily a disorder of children, there is a bimodal age distribution with increased incidence also in older patients. ALL represents ~ 20% of adult leukemias.

The WHO classification divides ALL into 3 categories: precursor B-cell (frequency 70–75%), precursor T-cell (frequency 20–25%), and mature B-cell ALL (Burkitt lymphoma/leukemia, frequency 5%). Among the precursor B and T-cell types, the groups are further delineated into either ALL (if the marrow contains > 25% blasts) or lymphoblastic leukemia (LBL, if mediastinal or other mass is present and marrow contains < 25% blasts). ALL and LBL are essentially the same disease process. The T-cell neoplasm more often presents as LBL, with > 50% of the cases involving a mediastinal mass.

Clinically, patients often present with cytopenias; constitutional symptoms; symptoms of CNS involvement (e.g., cranial nerve and/or retinal abnormalities and symptoms of meningeal irritation); and enlargement of the liver, spleen, lymph nodes, and testicles due to extramedullary deposits of blast cells.

The peripheral blood smear may show leukopenia or leukocytosis with blast counts above 100,000/mm^3. Definitive diagnosis and important prognosticators are made by immunophenotyping and chromosomal analysis of the leukemic cells.

Unfavorable prognostic factors in ALL:

- Age > 60
- WBC > 100,000/mm^3
- Mature B- or early T-cell types
- Persistent minimal residual disease, as detected by flow cytometry after remission is achieved
- t(9;22) translocation = Philadelphia chromosome (unlike in CML, where the translocation is favorable)
- t(4;11) = *MLL-AF4* fusion gene

Treatment is with multiple chemotherapy agents used in induction, consolidation, and maintenance phases. Prednisone, vincristine, and daunorubicin form the foundation, and cyclophosphamide + L-asparaginase are often added (may increase response). Complete response rates are in excess of 80%.

Post-remission therapy in ALL includes CNS chemoprophylaxis (with or without cranial radiation), consolidative therapy, and 2–3 years of maintenance therapy.

For patients without unfavorable prognostic factors, chemotherapy alone results in a 60% long-term, disease-free

QuickQuiz

- Characterize the AML M3 type genetic translocation, and describe how it affects treatment. What is the prognosis for aPML?
- Which FAB category of AML is associated with DIC?
- What physical findings do patients with ALL often present with?
- What ALL cytogenetic abnormality is associated with a poor prognosis?

survival. For patients with 1 or more unfavorable prognostic indicators, consider bone marrow transplantation.

Supportive care is an important component of treatment. In addition to the effects of cytopenias, patients often have hyperuricemia, hyperphosphatemia, and hypocalcemia—all secondary to the high cell turnover.

MYELODYSPLASTIC SYNDROME

Myelodysplastic syndrome (MDS) includes clonal stem cell disorders characterized by ineffective blood cell production and variable progression to acute leukemia. MDS occurs *de novo* or secondary to previous chemotherapy. While both MDS and the myeloproliferative disorders (see below) are clonal stem cell disorders, only patients with MDS exhibit cytopenias and inadequate (dysplastic) maturation of blood cells.

MDS presents with symptoms secondary to cytopenias (weakness, infection, bleeding). Platelets may be dysfunctional and result in bleeding out of proportion to the degree of thrombocytopenia. Patients who have MDS with > 20% blasts are now considered to have AML.

Unfavorable prognosticators for MDS:

- High percentage of bone marrow blasts
- Number of "cytopenias"
- Cytogenetic abnormalities, especially chromosome 7 anomalies
- Increasing age

Favorable prognosticator: the deletion of chromosome 5q or 20q.

The World Health Organization separates MDS into 8 groups, which incorporate the known prognostic factors:

1) Refractory anemia (RA)
2) RA with ringed sideroblasts (RARS; ringed sideroblasts are nucleated RBCs with iron granules in the cytoplasm) (See Image 8-19 and Image 8-20.)
3) Refractory cytopenia with multilineage dysplasia (RCMD)
4) RCMD with ringed sideroblasts (RCMD-RS)
5) RA with excess blasts1 (< 5% blasts) (See Image 8-21.)
6) RA with excess blasts2 (5–19% blasts)
7) MDS-unclassified
8) MDS with del(5q) ("5q- syndrome"): occurs more frequently in women and is associated with thrombocytosis and a more favorable prognosis

Differential diagnoses include B_{12}/folate deficiency, aplastic anemias, and myelofibrosis. Bone marrow biopsy reveals a hypercellular marrow (peripheral cytopenias are due to ineffective hematopoiesis) and dyserythropoiesis.

The International Prognostic Scoring System (IPSS) helps risk stratify patients and predict survival. Points are assigned based on percentage of blasts (the most important prognostic indicator), number of cytopenias, and karyotype. (Good cytogenetics includes 5q- and 20q-; poor cytogenetics includes chromosome 7 anomalies.)

Median survival approximates 5 months for high-risk scores compared to 5.7 years for low-risk scores.

Treatment depends on patient age, comorbidities, and aggressiveness of disease. Treatment is supportive, although allogeneic bone marrow transplant is considered in young patients who are high-risk or have evolving disease. Azacitidine and decitabine are hypomethylating agents with activity in patients with MDS. Mortality in MDS is usually a result of cytopenias or progression to AML.

Know 5q- syndrome: Patients with the favorable 5q- deletion have refractory anemia and thrombocytosis.

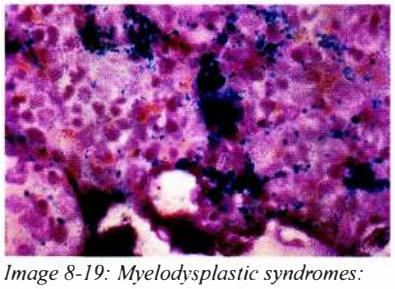

Image 8-19: Myelodysplastic syndromes: This patient has refractory anemia with ringed sideroblasts (RARS). Low-power view of bone marrow aspirate stained for iron shows increased iron stores (dark blue).

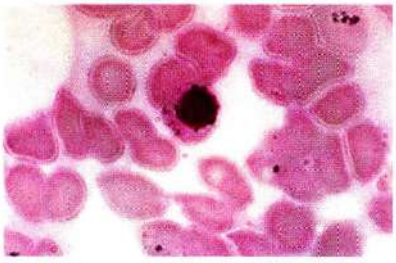

Image 8-20: Myelodysplastic syndromes: A ringed sideroblast is seen in this patient with RARS. Note: The sideroblast is the erythroblast with a perinuclear "string of pearls" formed by intramitochondrial granules of iron.

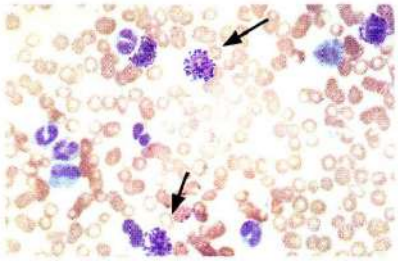

Image 8-21: Increased basophils. Common finding in the myeloproliferative syndromes.

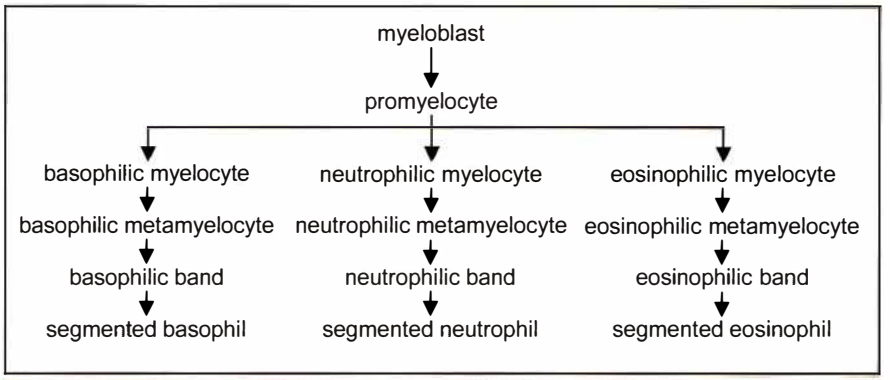

Figure 8-4: Granulopoiesis

Know that these patients generally respond to lenalidomide therapy and have prolonged survival with decreased risk of transformation to AML.

Chronic myelomonocytic leukemia (CMML) is now classified as an overlap myelodysplastic/myeloproliferative disorder. Patients are older with a poorer prognosis. Peripheral blood shows monocytosis with increased myeloid/erythroid precursors. Bone marrow is hypercellular with dysplasia (as in MDS). Patients with CMML should be checked for the t(5;12)(q33;p13) oncogenic product. (The *PDGFRB* gene [platelet-derived growth factor-b] moves adjacent to the *TEL* gene.) These patients may respond to imatinib therapy (tyrosine kinase inhibitor).

MYELOPROLIFERATIVE DISORDERS

Overview

The myeloproliferative disorders (MPDs) are clonal malignancies of early hematopoietic stem cells, characterized by loss of the regulation of cell proliferation. The result is the overproduction of the entire pyramid of maturation of granulocytes, erythrocytes, and platelets (see Image 8-22 through Image 8-23). (Contrast this with acute leukemia, marked by maturation arrest and proliferation of blasts.) MPDs variably progress to acute leukemias or myelodysplasia (Figure 8-4). There appears to be some familial pattern of inheritance, but we do not yet know the mechanism.

The 4 most common MPDs:

1) Chronic myelogenous leukemia (CML)
2) Essential thrombocythemia (ET)
3) Polycythemia vera (PV)
4) Primary myelofibrosis ([MF]; the rarest of these 4 MPDs)

JAK2 (Janus kinase, a tyrosine kinase) is an intracellular signaling molecule that is coupled to cell surface hematopoietic growth factor receptors (like the erythropoietin receptor). A *JAK2* gene mutation causes constitutive activation of the JAK2 kinase domain, inducing unregulated erythrocytosis. The mutation is found in almost all patients with PV and ~ 50% of those with ET or MF. There is no known prognostic significance. Inheritance of this mutation does not appear to be the mechanism for the familial clustering of disease.

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a clonal stem cell disorder of myeloid cells. The clinical hallmark is one of uncontrolled production of mature but dysfunctional neutrophils. Most patients present in the chronic phase with an elevated white blood cell count and a predominance of granulocytes. There is often an elevated basophil count and a low leukocyte alkaline phosphatase (LAP) score. The expanded myeloid pool may lead to organ infiltration, causing hepatosplenomegaly.

The diagnosis of CML is dependent on detection of the Philadelphia chromosome, t(9;22), or its products: BCR-ABL fusion mRNA or the BCR-ABL protein, which is a tyrosine kinase. Over 90% of patients demonstrate this abnormality at the time of diagnosis.

Uncontrolled replication of the myeloid stem cells as the disease progresses inevitably leads to further genetic errors. The myeloid cells begin to lose their ability to differentiate from their blast stages, and the disease degenerates into acute leukemia (AML or ALL). This 2nd, or accelerated, phase of CML is characterized by increasing numbers of blasts and basophils and a declining platelet count.

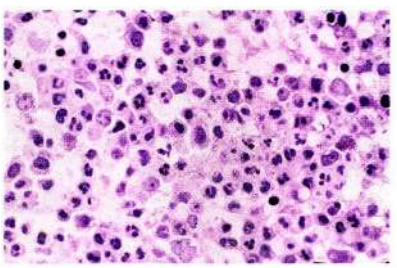

Image 8-22: Myeloproliferative syndromes: CML. Hypercellular marrow. Low power. Myeloid elements are clearly more abundant than the normal 3:1 myeloid:erythroid (M:E) ratio.

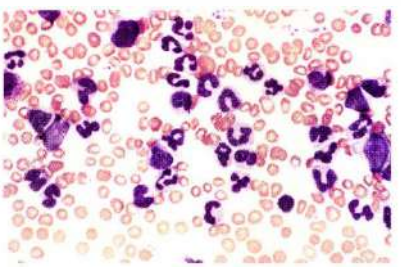

Image 8-23: Myeloproliferative syndromes: CML. Peripheral smear with the pyramid of maturation of granulocytes: promyelocytes, myelocytes, metamyelocytes, bands, and segmented neutrophils.

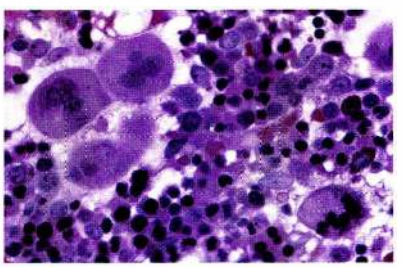

Image 8-24: Myeloproliferative syndromes: Polycythemia. BM Bx shows increased megakaryocytes and greatly increased erythroid precursors (with black condensed nuclei) and a decreased M:E ratio.

Quick Quiz

- What is 5q- syndrome?
- What is the main difference between the MPDs and acute leukemia?
- What are the 4 most common MPDs?
- JAK2 is found in what disease states?
- CML is associated with which cytogenetic abnormality in > 90% of cases?
- What is the current standard of care for treating CML?
- What side effects are associated with imatinib?
- What symptoms necessitate treatment in patients with ET?

The patient is considered to be in the blast phase once the percentage of blasts has progressed to > 20%. Survival is greatly diminished once this "blast crisis" has occurred.

Most (85–90% of patients) present in stable chronic phase while 10–15% may present in accelerated or blast phase. Fewer patients are now progressing to blast phase because of improvements in treatment during the chronic phase.

A tyrosine kinase inhibitor (TKI; imatinib, nilotinib, and dasatinib) is 1st line treatment of CML in chronic phase. The new 2nd generation TKIs, dasatinib and nilotinib, also are approved for frontline treatment of CML. These agents provide faster hematological and cytogenetic responses than imatinib. It is unclear thus far if this corresponds to improved overall survival. Dasatinib and nilotinib should be used in disease resistant to imatinib.

Side effects of TKIs include edema, exacerbation of congestive heart failure, and worsening of LV dysfunction, hepatotoxicity, cytopenias, and hemorrhage. Also, TKIs are teratogens and should not be used in women of childbearing age.

Allogeneic hematopoietic stem cell transplantation remains the only proven curative therapy for CML and is considered in patients who develop TKI resistance or complications. Dasatinib causes pleural effusions and cytopenias. Nilotinib is known to cause GI and liver toxicity as well as cytopenias.

Essential Thrombocythemia

Essential thrombocythemia (ET) is the least aggressive of the myeloproliferative disorders. Suspect ET when a high platelet count is noted on a routine CBC. Although patients with ET have a normal life expectancy, they are at risk for thrombosis (venous and arterial) and hemorrhage.

Risk factors for clot with ET:

- Age > 60
- Previous history of thrombosis

Diagnosis requires exclusion of causes of secondary thrombocytosis (e.g., infection, inflammation, tissue injury, trauma, ischemia, post-splenectomy, surgery, and especially, iron deficiency anemia).

Clinical presentation includes symptoms related to microthrombi (e.g., headaches, visual disturbances, and erythromelalgia), as well as symptoms referable to larger clots (including miscarriages) and bleeding. **Erythromelalgia** is paroxymal vasodilation of small arteries of the feet (mainly) and hands, causing burning pain, swelling, and erythema.

Treatment for ET should be limited to patients with significant erythromelalgia—managed with aspirin—and those at high risk for thrombosis (i.e., age > 60 or history of thromboembolism):

- High-risk patients: Cytoreductive therapy with hydroxyurea; goal is to reduce the platelet count below 400,000/mm^3.
- Everyone else: Prescribe aspirin to prevent thrombosis (especially if erythromelalgia is significant).

For surgical patients with ET, there is a high perioperative risk of thrombosis and bleeding complications. Very high platelet counts preoperatively should be reduced prior to surgery (with platelet pheresis if urgent surgery is required).

Like PV, ET can progress to myelofibrosis and acute leukemia. It is not known if treatment with hydroxyurea accelerates leukemic conversion. Treatment with JAK2 inhibitors remains in the clinical trials phase.

Polycythemia Vera

Polycythemia vera (PV) is characterized by an increased red cell mass in the absence of erythropoietin and in association with the *JAK2* mutation. (See Image 8-24.)

An increased red cell mass most often results from erythropoietin stimulation, which may result from a primary or secondary disorder. Common secondary causes of increased red cell mass include hypoxemia (obstructive sleep apnea, COPD, smoking, right-to-left cardiac shunts, high altitude, carbon monoxide poisoning), tumor secretion of erythropoietin (renal cell carcinoma, hepatocellular carcinoma), and androgens.

Patients with PV often present with an increased hematocrit with leukocytosis and thrombocytosis, the latter often causing erythromelalgia (see above). Other common symptoms are headache, weakness, and dizziness, which are thought to be secondary to hyperviscosity from the elevated hematocrit. Patients with PV often complain of pruritus (perhaps secondary to increased histamine levels) after a hot bath or shower. Gout can result from rapid cellular turnover. Splenomegaly is common.

Increased mortality in patients with PV is related to thrombosis (venous or arterial)—an elevated hematocrit is prothrombotic. Mortality also results from conversion to AML and myelofibrosis.

There is no consensus on an exact diagnostic protocol. The proposed WHO criteria are:

Major criteria:

- Hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume
- Presence of *JAK2* V617F or other functionally similar mutation such as *JAK2* exon 12 mutation

Minor criteria:

- Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
- Serum erythropoietin level below the reference range for normal
- Endogenous erythroid colony formation *in vitro*

Diagnosis requires the presence of both major criteria and 1 minor criterion or the presence of the 1st major criterion together with 2 minor criteria.

Treatment of PV is phlebotomy to a goal hematocrit of < 45% (to induce an iron-deficient state), which reduces mortality but may transiently increase the rate of thrombosis.

Low-dose ASA lowers the risk of thrombosis during this period. Cytoreduction therapy with hydroxyurea lowers this thrombotic risk but may accelerate the leukemic transformation. Once again, JAK2 inhibitor therapy remains in the clinical trials phase.

Primary Myelofibrosis

Primary myelofibrosis (MF) is a clonal stem cell disorder of unknown cause that results in hyperplasia of atypical megakaryocytes. These megakaryocytes stimulate a nonclonal proliferation of fibroblasts, which then go on to cause fibrosis of the bone marrow. Secondary marrow fibrosis may result from transforming PV and ET.

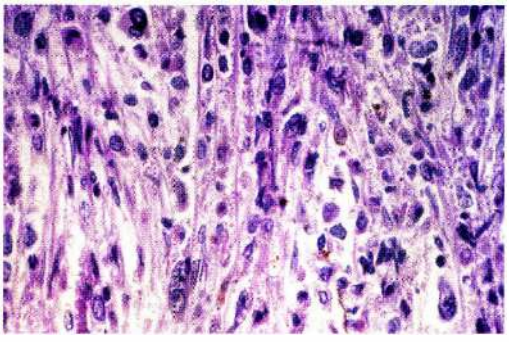

Image 8-25: Myeloproliferative syndromes: Myelophthisis (replacement of bone marrow by a disease process)—in this case, myelofibrosis (replacement by reticulin).

The most common symptom is fatigue. Early satiety and abdominal fullness also are common, attributable to hepatosplenomegaly. Screening labs show marked anemia and variable changes in white cells and platelets, with cytopenias developing as disease progresses. Serum LDH may be increased.

The peripheral blood smear often shows teardrop cells—a finding that is common to diseases that infiltrate the marrow (metastatic cancer, TB, fungal infections). (See Image 8-25.) Marrow aspirate often results in a "dry tap."

Allogeneic hematopoietic stem cell transplantation remains the only chance for cure, but this therapy is limited to younger patients. For the vast majority of patients, treatment is primarily supportive, including splenectomy for severe splenomegaly. The oral JAK2 inhibitor ruxolitinib is approved to treat primary myelofibrosis. Studies show significant improvement in weight loss, fatigue, and splenic volume, but no trial so far has shown an improvement in survival.

LYMPHOPROLIFERATIVE DISORDERS

OVERVIEW

These disorders range from slow-growing asymptomatic tumors to the most aggressive malignancies. Some present mainly as lymphomas (solid tumors) and others more like leukemias (involving blood and bone marrow). Others present with features of both.

OVERVIEW OF NON-HODGKIN LYMPHOMA

The term non-Hodgkin lymphoma (NHL) encompasses a group of disorders characterized by clonal proliferation of lymphocytes—B, T, or natural killer cells. See Table 8-6 for prevalence of cell-type neoplasms. The term lymphoma is used when the neoplastic cells grow as a solid mass in the lymph nodes, spleen, bone marrow, or solid organs. The term leukemia is used when the neoplastic cells are found in the blood. It is not unusual to see overlap of these 2 entities. For example, patients with chronic lymphocytic leukemia (CLL) often have a solid component to their disease, termed small lymphocytic lymphoma (SLL). When present, the combined diagnosis of CLL/SLL is used. In other words, many lymphomas have small components of leukemia to them, and some leukemias have a component of lymphoma.

NHL is associated with Epstein-Barr virus (EBV), human T-cell lymphotrophic virus 1 (HTLV-1), and human herpesvirus 8.

Patients with NHL often present with palpable adenopathy and constitutional symptoms (e.g., weight loss, fever, night sweats).

Nodal growth may also occur in nonpalpable areas as well, resulting in hepatosplenomegaly.

QuickQuiz

- What peripheral blood finding is seen in patients with myelofibrosis?
- What is the common physical finding on initial presentation of NHL?
- An NHL that produces an IgM monoclonal gammopathy, and is associated with hyperviscosity, is termed what?
- What are the 2 general types of NHL?

Airway obstruction or superior vena caval syndrome can result from nodal growth in the mediastinum; bowel or ureter obstruction may result from growth in the mesentery or retroperitoneum.

Some lymphomas produce an IgM monoclonal gamma globulin that can lead to hyperviscosity (Waldenström macroglobulinemia) or autoimmune cytopenias (Coombs + anemia and/or thrombocytopenia), while others (CLL/SLL) cause agammaglobulinemia that leads to frequent infections. Cytopenias also may develop from hypersplenism and from bone marrow infiltration.

Diagnosis of lymphoma is made by an excisional biopsy of a lymph node, which allows the pathologist to observe both the appearance of the cells and the architecture of the lymph node. Immunohistologic stains and flow cytometry also are performed. If there is a sizable leukemic component to the lymphoma, as in CLL/SLL, the diagnosis can be made by flow cytometry of the peripheral lymphocytes, looking for characteristic cell surface markers.

Once the diagnosis is made, staging is carried out using physical exam and CT scans of the neck, chest, abdomen, and pelvis. A bone marrow biopsy can be helpful to determine the nature of cytopenias if present.

Positron emission tomography (PET) scanning can be integrated into initial diagnostics and used in follow-up after treatment. PET uses radiolabeled glucose to image glycolysis *in vivo*. Areas that are relatively metabolically active (brain, heart, kidneys) "take up" the glucose and image brightly. Active malignancies also take up the tracer and become "PET" or "FDG avid" (FDG = 18-fluorodeoxyglucose). Patients with NHL often have persistent masses seen on CT scan after treatment. These masses usually represent either residual lymphoma or fibrous scar tissue. A mass that does not fully resolve with treatment and is FDG avid would represent persistent disease, while a lack of avidity would represent remission or cure.

NHLs fall broadly into 2 groups: indolent and aggressive (Table 8-7).

Indolent lymphomas have a long clinical course, measured over years. They are seldom cured with conventional chemotherapy, and early treatment has never been shown to improve survival over delayed treatment. Treatment is ordinarily held until symptoms develop—a "watch and wait" strategy. Treatment controls symptoms by placing the lymphoma in a temporary remission or decreasing the overall disease burden.

Aggressive NHLs grow more quickly—often becoming symptomatic early in the disease course. If left untreated, they lead to death within months. These rapidly growing lymphomas respond well to chemotherapy, and, while many ultimately relapse, an increasing number are being cured.

An individual patient's prognosis with NHL depends primarily upon characteristics of the lymphoma: the subtype, the Ann Arbor stage (same as that for Hodgkin disease), and the LDH (a marker for tumor burden). Prognosis is also dependent on characteristics

Table 8-6: REAL / WHO Classification of the Most Common NHLs and Leukemias

Types	Freq %
B-Cell Neoplasms	
Diffuse large B-cell lymphoma	33
Follicular lymphoma	22
Extranodal marginal zone B-cell lymphoma	8
CLL/B-cell SLL	7
Mantle cell lymphoma	6
Burkitt lymphoma	2
Nodal marginal zone B-cell lymphoma	2
Lymphoplasmacytic lymphoma	1
Precursor B-cell neoplasms, B-cell prolymphocytic leukemia, splenic marginal zone B-cell lymphoma, hairy cell leukemia, plasma cell myeloma	< 1% each
T-Cell Neoplasms	
Mature (peripheral) T-cell neoplasms	8
Precursor T-lymphoblastic leukemia/lymphomas	2
Primary systemic anaplastic large cell lymphoma	2

Adapted from Evans LS and Hancock BW. Non-Hodgkin lymphoma. *Lancet.* 2003 Jul 12;362(9378):139–146.

Table 8-7: Types of NHL

Indolent Lymphomas	Aggressive Lymphomas
CLL/SLL	Diffuse large B cell
Follicular lymphoma	Burkitt
Marginal zone (MALT, nodal, splenic)	Precursor T-lymphoblastic
Mycosis fungoides	B-lymphoblastic
	Mantle cell

of the patient: age and performance status at the time of diagnosis.

The International Prognostic Index (IPI) is commonly utilized, and uses the following 5 factors to help predict outcome:

1) Age
2) Serum LDH
3) Ann Arbor stage
4) Performance status
5) Number of extranodal disease sites

More recently, molecular and genetic markers of prognosis have been introduced.

Know that there is growing use of monoclonal antibodies in the treatment of NHL.

Rituximab is a chimeric antibody directed against CD20, a surface marker found on many B-cell lymphomas. The binding of antibody to the neoplastic cell causes cell death by complement-mediated lysis, cellular cytotoxicity, and directly by apoptosis. Rituximab is well tolerated even in elderly patients and can be used alone against indolent lymphomas or in combination with traditional chemotherapy against aggressive disease.

Ofatumumab is a fully human anti-CD20 monoclonal antibody also used in the treatment of refractory CLL.

Alemtuzumab is a monoclonal antibody directed against CD52, a cellular marker often found in CLL. This antibody can control otherwise refractory CLL, although its use comes at the price of immunosuppression because CD52 also is found on normal B and T cells.

INDOLENT NON-HODGKIN LYMPHOMAS

Follicular Lymphoma

Follicular lymphoma is the most common of the indolent non-Hodgkin lymphomas (NHLs). Patients are often elderly and present at a late stage with diffuse adenopathy. Patients are often asymptomatic at presentation. The hallmark is overexpression of the anti-apoptotic protein BCL-2 caused by a t(14;18) translocation. As with other indolent lymphomas, follicular lymphoma is commonly slow growing and incurable (except in very early-stage disease in which it sometimes can be cured with local radiation therapy).

Treatment is not indicated in asymptomatic patients. Younger patients may receive combination therapy with the goal of prolonged (though not permanent) remission. Older patients can be treated with gentler, single-agent therapy, such as rituximab. If in early-stage disease, radiation therapy alone is an option. In relapsed or refractory disease, the radioimmunoconjugates tositumomab and ibritumomab, anti-CD20 monoclonal antibodies bound to radioactive iodine and yttrium-90 respectively, may be used. The role of these agents in 1st line treatment, particularly with rituximab, is still under investigation.

Patients progress over time to develop cytopenias and die from infection or complications of anemia. Approximately 10% of follicular lymphomas undergo a transformation to a more aggressive lymphoma---diffuse large cell lymphoma. Transformed diffuse large cell lymphoma is more resistant to chemotherapy than its *de novo* counterpart, and such a transformation is often a sign of a rapidly fatal outcome.

Marginal Zone Lymphoma

Marginal zone lymphoma (MZL) is an indolent lymphoma that in part develops from chronic antigenic stimulation. It is separated into **mucosa-associated lymphoid tissue** ([**MALT**]; extranodal), **nodal**, and **splenic** marginal zone lymphoma. Unlike many indolent lymphomas, MZLs are often found at an early stage. The most common location is the gastric or intestinal mucosa (referred to as a MALT lymphoma), and the most common antigenic stimulant is chronic *H. pylori* infection. MZL also can occur in bronchial mucosa and salivary glands, and splenic MZL may arise from chronic HCV infection.

When MZL is diagnosed, rule out infectious causes (*H. pylori* and HCV).

Early-stage gastric MALT lymphoma may be treated with antibiotics alone to eradicate *H. pylori* or with added radiation if the initial treatment fails. Early treatment of the other types of MZL with lung lobectomy and splenectomy can result in a prolonged symptom-free remission.

CLL / SLL

CLL/SLL is an indolent disease characterized by the clonal proliferation of mature but poorly functioning B-cell lymphocytes (see Image 8-26 through Image 8-28.)

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are the same B-cell lymphocyte

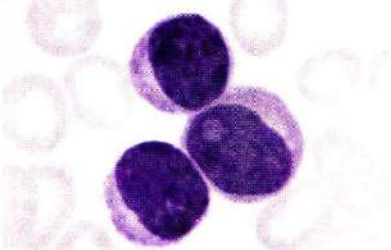

Image 8-26: CLL/SLL: High-oil view. 3 leukemic lymphocytes.

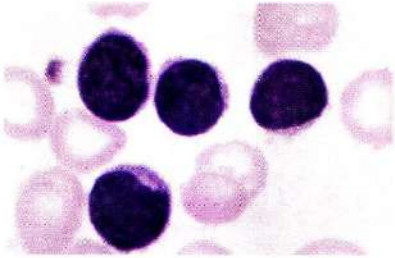

Image 8-27: CLL/SLL: More leukemic lymphocytes.

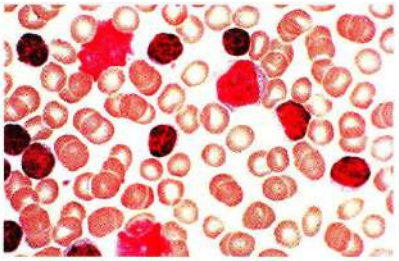

Image 8-28: CLL/SLL: Smudge cells.

Quick Quiz

- NHL prognosis depends on what 2 patient-specific factors?
- What drug is now incorporated into treatment for most cases of NHL—whether indolent or aggressive?
- What is the treatment for asymptomatic follicular lymphoma?
- Marginal zone lymphoma is associated with what chronic infection?
- What is the difference between CLL and SLL?
- What does rapid enlargement of previously stable lymph nodes in a patient with CLL/SLL suggest?
- What is the treatment for CLL/SLL without symptoms?
- What is the clinical presentation of hairy cell leukemia?

disease, with different manifestations depending on where the abnormal cells are found.

Typically, there is an initial leukemic phase (cells in the blood: CLL) that progresses to a lymphoma phase (cells in the lymph nodes: SLL).

Clinically, the majority of patients with CLL/SLL are diagnosed at an asymptomatic stage with a high lymphocyte count found on a routine CBC. Suspect CLL with the appearance of a high lymphocyte count and smudge cells on the peripheral blood smear. Of note, only 5,000 B cells of a monoclonal origin (noted on flow cytometry) are required to diagnose CLL. Characteristic markers on the cell surface can differentiate CLL/SLL from other lymphomas with leukemic components.

Prognosis has largely been based on the Rai staging system. Other favorable prognostic findings:

- Mutated Ig heavy chain variable region
- 13q deletion
- Low ZAP-70 and CD38 levels

Poor prognostic cytogenetics:

- 17p deletion
- 11q deletion

A staging system unique to CLL/SLL, the Rai system, is shown in Table 8-8, along with the Binet system that also is used. Asymptomatic patients with only high WBC are stage 0 and have a near-normal life expectancy.

With disease progression, the lymphoma element begins to dominate, and patients develop symptoms secondary to lymphadenopathy (stage I), hepatosplenomegaly (stage II), anemia (stage III), and thrombocytopenia (stage IV). The cytopenias are due to bone marrow infiltration by leukemic cells, splenic sequestration, and antibody-mediated destruction.

CLL/SLL is characterized by a disordered immune system. Frequent autoantibodies directed against red cells and platelets develop, leading to immune-mediated hemolytic anemia and thrombocytopenia. The resultant cytopenias can be managed with prednisone. Paradoxically, CLL/SLL also is characterized by hypogammaglobulinemia. When patients with CLL/SLL and low immunoglobulin levels develop frequent infections (especially pneumococcus, *Staphylococcus*, *H. influenzae*, and herpes), they can be managed with monthly IVIG infusions.

As with follicular lymphoma, approximately 10% of patients with CLL/SLL transform to diffuse large cell lymphoma ("Richter transformation")—a transformation often heralded by fever, rapid enlargement of previously stable nodal disease, and a rising LDH.

Treatment of CLL/SLL is mainly a "watch and wait" strategy like other indolent lymphomas. Several treatment options are available, however:

- Young patients: multiple agents (fludarabine and rituximab) with the goal of a prolonged remission (risks immunosuppression). Stem cell transplant is under investigation.
- Elderly patients: chlorambucil (gentle, single-agent therapy) and rituximab with goal of symptom palliation. Bendamustine (an alkylating agent) is gaining increased use in both elderly and younger patients.

Hairy Cell Leukemia

Hairy cell leukemia is a rare indolent NHL with components of both lymphoma and leukemia. Patients often present with splenomegaly and complications of

Table 8-8: Staging Systems for B-cell Leukemias

Stage	Clinical Findings	Risk Level	Median Survival (Years)
Rai System			
Stage 0	Lymphocytosis	Low	12
Stage I	Lymphocytosis + adenopathy	Mid	9
Stage II	Lymphocytosis + hepatosplenomegaly	Mid	7
Stage III	Anemia	High	1–2
Stage IV	Thrombocytopenia	High	1–2
Binet System			
A	< 3 sites involved	Low	10
B	> 3 sites involved	Mid	5
C	Anemia and/or thrombocytopenia	High	3

cytopenias. The peripheral smear can show characteristic cytoplasmic "hairy" projections on the lymphocytes' cell surface (see Image 8-29 and Image 8-30).

The disorder responds well to chemotherapy, and remissions can be prolonged. Purine analogs are used with cladribine (2-CDA), which are preferred over pentostatin because of equally good results (> 80% remission)—with less toxicity and only 1 cycle of treatment needed.

Waldenström Macroglobulinemia

Waldenström macroglobulinemia (lymphoplasmacytic lymphoma) is an indolent B-cell lymphoma characterized by the clonal expansion of lymphocytes with plasma cell properties that produce monoclonal IgM. Clinical presentation includes:

- **Hyperviscosity syndrome** (headache, dizziness, vision disturbances) secondary to high levels of IgM (look for "sausage-link veins" on funduscopy, which are tortuous veins caused by the hyperviscosity)
- **Constitutional** symptoms, oozing blood at mucosal surfaces, lymphadenopathy, and/or splenomegaly

Acute hyperviscosity syndrome should be treated with plasmapheresis. Prognosis depends upon age and the presence of anemia. As with other indolent lymphomas, treatment should be initiated only after symptoms develop. Therapy is typically rituximab-based chemotherapy.

Teaching point: Note that hyperviscosity symptoms can occur with polycythemia vera (PV), leukocytosis > 100,000/mL, WM, MM, and cryoglobulinemia. When the hyperviscosity and associated symptoms are due in immunoglobulins (WM, MM, cryoglobulins), it is called "hyperviscosity syndrome." When it is due to WBCs, it is called leukostasis.

AGGRESSIVE NON-HODGKIN LYMPHOMAS

Diffuse Large Cell Lymphoma

This is the most common aggressive lymphoma. It may develop *de novo* or arise from a previously indolent lymphoma. While diffuse large cell lymphoma (DLCL) is predominantly a disease of the lymph nodes, it may also develop in extranodal sites such as the lung or liver. If left untreated, life expectancy is measured in months.

Treat with the standard chemo regimen: R-CHOP (rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone). Localized DLCL can be treated with 3 cycles of R-CHOP, followed by involved field radiotherapy. Advanced disease gets 6–8 cycles of R-CHOP.

Almost all patients respond to this treatment, and 40–50% get long-term disease control. Half of these become refractory—or the lymphoma recurs soon after completing therapy. Treat recurrence in young patients with further chemotherapy and refer for autologous stem cell transplant. Treat older patients with palliative chemotherapy.

Burkitt Lymphoma

Burkitt's is the most aggressive of the NHLs and presents in the context of endemic EBV infection (Africa), sporadic occurrence (U.S. and Europe), and immunodeficiency (especially HIV/AIDS).

The genetic hallmark is translocation of the *C-MYC* oncogene, which results in aggressive cell turnover with rapid growth.

Know that for patients with HIV, the development of a Burkitt lymphoma is an AIDS-defining illness regardless of the CD4 count.

Presentation typically is an enlarging abdominal mass, and the rapid cell turnover may be associated with spontaneous tumor lysis syndrome. Dissemination to the CNS is common, and treatment with intrathecal chemotherapy is standard. Treatment consists of prolonged high-dose chemotherapy as well as treatment or prophylaxis for CNS involvement.

Mantle Cell Lymphoma

Mantle cell is a subtype of NHL that combines the least desirable characteristics of both classes of NHL. Like indolent NHL, it is incurable with standard chemotherapy; and like aggressive NHL, it progresses rapidly with median survival ≤ 3 years. There is typically bone marrow, peripheral blood, and spleen involvement; and patients often present with cytopenias and splenomegaly.

Extranodal involvement is common, especially in the GI tract, and there is often a leukemic component. Hallmark is overexpression of *BCL-1* gene product cyclin D1 due to the t(11;14) translocation. Initiate treatment early with the goal of inducing a temporary remission.

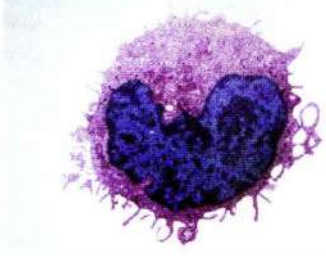

Image 8-29: Hairy cell (electron microscope).

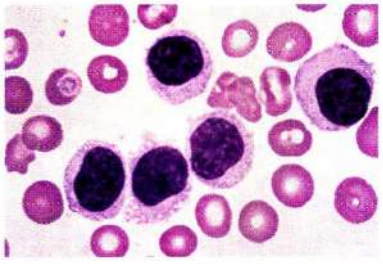

Image 8-30: Hairy cell leukemia.

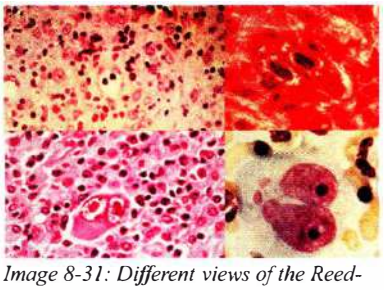

Image 8-31: Different views of the Reed-Sternberg cell as seen in Hodgkin disease.

QuickQuiz

- What is the standard chemo regimen for DLCL?
- Characterize the clinical presentation of Burkitt's. What cytogenetic abnormality is associated?
- What diseases are seen after radiation therapy to the chest during treatment of Hodgkin disease?

T-CELL NON-HODGKIN LYMPHOMAS

T-cell NHLs are classified in a similar fashion as B-cell NHLs: indolent and aggressive.

The peripheral T-cell lymphomas are a group of disorders that includes mycosis fungoides/Sézary syndrome. Early disease is limited to the skin, but later disease develops in lymph nodes. The disorder can be controlled in the early stages with photochemotherapy. As with other indolent lymphomas, the goal of treatment is control rather than cure.

The aggressive forms of T-cell NHL include a T-cell variety of DLCL, which is treated with CHOP (no rituximab as with B-cell DLCL).

HODGKIN DISEASE

Hodgkin disease (HD) is primarily a disease of the young (unlike NHL), with average age of 30 years at time of diagnosis. HD is also a far more curable illness than NHL, with cure rates of 95% in early stages and 65% in advanced stages. Patients with HD often present with an enlarged, painless lymph node.

Diagnosis is made by excisional biopsy (not fine needle aspiration [FNA]). Although the Reed-Sternberg cell (a B cell that resembles "owl's eyes") is the classic and specific histological finding, the diagnosis is aided by immunohistochemical staining. (See Image 8-31.)

In the WHO classification, these lymphomas are categorized as follows:

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classic Hodgkin lymphoma (most common)
  - Nodular sclerosis (most common)
  - Lymphocyte-rich
  - Mixed cellularity
  - Lymphocyte-depleted

These 4 subtypes of classic lymphoma are similar and are typically treated in the same fashion. Accurate staging is critical in HD so as to avoid both undertreatment and overtreatment (Table 8-9).

Staging: H&P; CXR; CT of neck, chest, abdomen, and pelvis; and bone marrow aspiration and biopsy. PET scan is used both for initial staging and to monitor response to treatment. Always restage after treatment.

Treat with **ABVD** (**A**driamycin® [doxorubicin], **b**leomycin, **v**inblastine, and **d**acarbazine:

- Early-stage disease (Ann Arbor stage I or II without bulky disease or B symptoms): 2–4 cycles ABVD + radiation to disease sites.
- Advanced disease (stage III or IV, bulky stage II, or B symptoms): 6–8 cycles ABVD + radiation to any bulky sites.
- Relapsed or refractory disease: high-dose chemotherapy + autologous stem cell transplant.
- Relapsed disease after transplant or multiple lines of chemotherapy: brentuximab vedotin, an anti-CD30 monoclonal antibody-drug conjugate that releases its antimitotic agent upon binding to CD30 positive cells present in HL.

ABVD is less likely than previous treatments to cause sterility (but still may), and it can cause cardiac and pulmonary toxicities from the doxorubicin and bleomycin, respectively.

Radiation to the chest is associated with increased risk of future solid tumors, including lung and breast cancer. Women who receive radiation to the chest should have mammograms starting 10 years after treatment. Also, remember to watch for cardiovascular complications and hypothyroidism.

Table 8-9: Cotswold Modification of Ann Arbor Staging System for Hodgkin Disease

Stage	Definition
I	1 node region or lymphoid structure (e.g., spleen, thymus) or 1 extralymphatic site
II	2 or more lymph node regions on same side of diaphragm (or hilar nodes on both sides)
III	III: Both sides of diaphragm involved III_E: If also contiguous localized involvement of one extranodal site III_S: If involvement of the spleen; if both extranodal and spleen = III_{ES}
IV	Disseminated

The following apply to all stages:
A = Asymptomatic.
B = Symptoms: Fever > 38° C, drenching night sweats, unexplained loss of > 10% body weight within preceding 6 months.
X = Bulky disease (a widening of the mediastinum by more than 1/3 of the size of a nodal mass—this nodal mass having a max dimension > 10 cm).
E = Involvement of a single extranodal site that is contiguous or proximal to the known nodal site. If the extranodal site is the spleen, then S = spleen is used.
The number of anatomic regions involved is also indicated by a subscript.

LYMPHOMA AND IMMUNOSUPPRESSION

Overview

Patients with both congenital and acquired immunodeficient states are at increased risk for lymphoma. In adults, the 2 most common immunodeficient states are HIV/AIDS and iatrogenic immunosuppression after solid organ transplant.

Lymphoma and HIV

The majority of HIV-associated lymphomas are aggressive NHLs, with DLCL and Burkitt's predominating. Whether or not antiretroviral therapy (ART) has impacted the incidence of NHL in HIV/AIDS is unclear. ART seems to have reduced the incidence of lymphoma in patients with CD4 < 50/mm^3, but Burkitt's is increasing in incidence in patients with higher CD4 counts. Patients with HIV also are at increased risk for Hodgkin disease, and control of the infection has not altered this risk.

Primary CNS lymphoma (DLCL limited to the CNS) is universally associated with EBV in patients with HIV/AIDS. Primary effusion lymphoma (PEL) usually presents as ascites or pleural effusion and is associated with HHV-8. HIV/AIDS-associated HD presents more often with extranodal disease and B symptoms.

Treatment is similar to that given to patients without HIV, except that rituximab may not show benefit in HIV-positive patients with DLCL and CD4 counts < 50/mm^3 due to the increased risk of death from infection.

Lymphoma and Post Transplant

Post-transplant lymphoproliferative disorders occur in approximately 5% of patients with solid organ transplants. The risk of lymphoma is highest in the 1st year after transplant. The lymphoma is often composed of nonclonal B cells. Over 90% of early lymphomas are EBV-positive. When disease occurs, it is often at a late stage with extranodal manifestations.

Treatment consists of lowering the degree of immunosuppression—allowing anti-EBV immunity to attack the lymphoma cells. If this is not tolerated, attempt treatment with chemotherapy.

Quick Review

Remember these diseases that are associated with an increased risk of lymphoma:

- Chronic autoimmune thyroiditis (Hashimoto's)
- Sjögren syndrome
- Celiac disease
- Chronic *H. pylori*
- HIV/AIDS

PLASMA CELL DISORDERS

Multiple Myeloma

Multiple myeloma (MM) is a neoplasm of B cells that results in a clonal expansion of plasma cells. These cells produce an M (monoclonal) component, which may be intact immunoglobulin or fragments of heavy or light chains. Any immunoglobulin subclass (IgG, IgA, IgD, IgE, and IgM) may appear as the "M" component. Waldenström macroglobulinemia (page 8-36) is a B-cell lymphoma that secretes monoclonal IgM. It presents differently from MM. These paraproteins, together with the cells producing them, cause many clinical problems.

In MM, bone pain is the most common symptom—often localized in the back or ribs. Tumor cells invade bone and release osteoclast-activating factor, creating punched-out lytic lesions that are seen on radiographs but not on bone scans—because there is no associated new bone formation. Pathologic fractures are common.

Frequent infections result from a diffuse hypogammaglobulinemia. While total immunoglobulin levels are elevated, normal immunoglobulin production is suppressed, and catabolism of immunoglobulin is accelerated.

Renal failure can result through a multitude of mechanisms, including hypercalcemia, amyloid deposition, tubular obstruction, and direct toxic effects of the paraproteins.

Additional clinical symptoms secondary to hypercalcemia, anemia, and neuropathy develop. Plasmacytomas (plasma cell tumors) can cause local symptoms, depending on their location, including spinal cord compression.

Think about myeloma when you see:

- Bone pain
- Symptoms of hyperviscosity
- Recurrent bacterial infections

Plus a combination of the following labs:

- Rouleaux formation on peripheral blood smear
- Hypercalcemia
- Increased creatinine +/– proximal (Type 2) renal tubular acidosis
- Normocytic/normochromic anemia
- Elevated T protein but decreased albumin with decreased anion gap (due to increased positively charged paraprotein)

Diagnose with a serum (SPEP) and urine immunoelectrophoresis (UPEP) to detect the monoclonal protein, but know that the plasmacytoma variant may not have an M spike. Furthermore, myelomas that produce only light chain immunoglobulins do not have an M spike.

Measure serum viscosity if the M-protein concentration is > 5 g/dL (or if the patient has symptoms, such as headache).

QuickQuiz

- Primary CNS lymphoma in patients with HIV/AIDS is associated with which virus?
- Which virus is associated with post-transplant lymphoma?
- What diseases are associated with an increased risk of lymphoma?
- What are the typical symptoms of multiple myeloma? The lab findings?
- Characterize the differences between MGUS, smoldering myeloma, and multiple myeloma.

A skeletal survey helps identify lytic lesions.

Bone marrow biopsy assists with definitive diagnosis (> 10% plasma cells in BM sample).

Measurement of serum β_2-microglobulin helps predict survival and is used in the ISS staging system (see below). β_2-microglobulin is a protein that is associated with MHC class I heavy chains—found on the surface of nucleated cells. An increase in its amount tells you that extra lymphocytes are circulating.

Multiple myeloma must be distinguished from the vastly more common MGUS and from smoldering myeloma. See Table 8-10.

Staging for MM includes the Durie-Salmon system (which utilizes level of anemia, hypercalcemia, presence of lytic lesions, and level of paraprotein) and a much simpler International Staging System ([ISS], Table 8-11).

Initiate treatment when symptomatic (i.e., lytic lesions appear) or the M component rises above 5 g/dL.

Table 8-10: Monoclonal Gammopathies

MGUS (monoclonal gammopathy of undetermined significance)	Serum monoclonal protein < 3 g/dL Bone marrow plasma cells < 10% and Absence of end-organ damage
Smoldering myeloma (asymptomatic myeloma)	Monoclonal protein ≥ 3 g/dL or Bone marrow plasma cells ≥ 10% and Absence of end-organ damage
Multiple myeloma	Bone marrow plasma cells > 10% or biopsy-proven plasmacytoma and Presence of monoclonal protein (in urine or serum) and Evidence of end-organ damage (i.e., lytic bone lesions, anemia, hypercalcemia, renal insufficiency attributable to the plasma cell disorder)

There are many effective therapies, including thalidomide and dexamethasone, and newer therapies, including a thalidomide-like agent, lenalidomide (Revlimid®) and the proteosome inhibitor, bortezomib (Velcade®), to induce remission. Stem cell transplant is then used for remission prolongation. Older patients can be managed with alkylating agents (melphalan or cyclophosphamide) plus prednisone. Treat plasmacytomas with local radiation.

Monoclonal Gammopathy of Uncertain Significance

Both MM and monoclonal gammopathy of undetermined significance (MGUS) have an association with previous heavy exposure to pesticides. MGUS is seen in 1% of people age > 50 years and 10% of people age > 75.

Patients with MGUS have:

- a bone marrow plasmacytosis < 10%,
- no bony lesions, and
- M components < 3 g/dL.

Any immunoglobulin subtype may be seen (IgG, A, M, D, E). Urinary light chains are absent. There is no increased risk of infection, renal failure, or anemia.

A risk stratification model including M-spike > 1.5 g/dL, non-IgG subtype, and an abnormal serum free light-chain ratio is useful for predicting progression. Depending upon these 3 things, 5% (no risk factors) to 58% (all 3 risk factors) progress to multiple myeloma at 20 years.

There is no role for preemptive therapy with MGUS.

Follow-up for patients with MGUS includes a repeat SPEP q 6 months x 13 years and, if stable, annually thereafter.

Patients with smoldering myeloma (asymptomatic myeloma) do not require treatment either but should have more involved follow-up, including a CBC, creatinine, calcium, and SPEP/UPEP every 3–6 months along with annual skeletal survey.

Table 8-11: International Staging System for MM

Stage	Definition	Median Survival (Months)
I	β_2MG < 3.5 mg/L Albumin ≥ 3.5 g/dL	62
II	Neither I nor III	44
III	β_2MG ≥ 5.5 mg/L	29

ONCOLOGY

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia due to cancer occurs most frequently in patients with the following malignancies:

- Squamous cell carcinomas arising in the lung or head and neck
- Multiple myeloma
- Breast carcinoma
- T-cell lymphoma
- Renal cell carcinoma

Symptoms include fatigue, constipation, anorexia, nausea, polyuria, polydipsia, and alteration in mental status. Patients often present with profound hypovolemia. Obtundation and dysrhythmias can occur in severe cases. Symptom severity is associated with the rate of rise in calcium and the ionized calcium level.

Causes of hypercalcemia of malignancy:

- Increased osteoclastic activity induced by local bone metastasis
- Ectopic production of a parathyroid-related protein (PTHrP)
- Overproduction of 1,25-$(OH)_2$-D (active form)

PTHrP is the usual cause of malignancy-associated hypercalcemia in patients with squamous cell carcinomas. The receptor-binding area for PTHrP is similar to PTH, which results in increased calcium resorption from the bones and increased calcium resorption in the distal tubules. Given the high incidence of concomitant hyperparathyroidism in patients with malignancy, evaluation should include PTH, PTHrP, and 1,25-$(OH)_2$-D.

Albumin binds calcium and, with hyperalbuminemia, you may have a high total calcium level but a normal free calcium level. When a lab result shows hypercalcemia, first check the albumin level. For any increase in albumin above the normal upper limit, decrease the patient's total calcium lab result by 0.8 x that increase. If the result now falls in the normal range for calcium, the free calcium level is normal. (Same in reverse for hypocalcemia in the setting of hypoalbuminemia.)

ECG changes indicating hypercalcemia are a short QT interval due to a shortened ST interval. With levels > 16 mg/dL, the T wave widens.

Know management: The most important step in the management of hypercalcemia is vigorous hydration with IV normal saline. Once euvolemia is established, furosemide (if volume overload is an issue) can be given to force diuresis and calciuresis. If furosemide is given prior to euvolemia, it may exacerbate the hypercalcemia and hypovolemia. Volume expansion helps treat hypercalcemia but does not maintain calcium levels in the normal reference interval. It is important to administer a bisphosphonate. (Zoledronic acid 4 mg IV over 15 minutes is preferred because of its increased potency and decreased infusion time, but you need to be careful if there is concomitant renal failure.)

Prolonged treatment with pamidronate is associated with sclerosis of glomeruli and nephrotic syndrome.

Osteonecrosis of the jaw (ONJ) is an uncommon adverse effect seen with IV doses and prolonged use of bisphosphonates. ONJ presents as pain, infection, and sometimes fracture of the mandible. There may be exposed bone along the gum line. Patients receiving long-term bisphosphonates should have necessary dental work performed prior to taking the drugs. (Or, if possible, defer the work until the drugs are discontinued.) Counsel such patients that any emergent dental work should be as conservative as possible; e.g., preserve the dental root when possible, in lieu of extraction. X-rays, CT, and MRI can diagnose severe disease but reveal nonspecific findings only in early disease. Treatment of ONJ is still being determined. The bisphosphonate is stopped and a conservative approach with minimal debridement, antibiotic therapy, and oral rinses is usually followed.

Definitive treatment of hypercalcemia of malignancy is treatment of the underlying tumor. See Endocrinology, Book 4, for more on hypercalcemia.

SVC SYNDROME

Superior vena cava (SVC) syndrome occurs most commonly in patients with lung cancer (especially small cell), lymphoma (Hodgkin's and non-Hodgkin's), and mediastinal germ cell tumors.

Classic symptoms:

- Swelling of the face, neck, and arms (typically worse after the patient is supine)
- Cough
- Dyspnea
- Hoarseness (due to laryngeal edema)
- Headaches (due to increasing intracranial pressure)

Physical examination findings:

- Periorbital and upper extremity edema
- Facial plethora
- Elevated jugular venous pressure
- An increased number of collateral veins covering the anterior chest wall
- Abnormal pulmonary exam due to airway compression (i.e., stridor)
- Altered mental status secondary to cerebral edema

Diagnose by CT venogram of the chest, which typically shows a large mediastinal and/or right hilar mass with SVC occlusion.

Although SVC syndrome was previously thought to require emergent treatment, there is often time to establish a diagnosis prior to treatment. A tissue diagnosis prior to therapy is recommended in those without a

QuickQuiz

- Hypercalcemia occurs most commonly in which type of lung cancer?
- How do you initially manage acute hypercalcemia?
- What are the most common causes of SVC syndrome? What is the treatment?
- Name the cancers that commonly metastasize to bone.
- What is the urgent treatment when you suspect spinal cord compression due to bone metastasis?
- What treatment option is available to patients with 3 or fewer small brain mets?

known malignancy. Immediate treatment to shrink the tumor is required for signs of airway compromise and increased intracranial pressure. Radiation therapy, once the mainstay of treatment, is now limited to those tumors that do not respond rapidly to chemotherapy. Chemotherapy is used as initial therapy for most small cell lung cancer, germ cell tumors, and lymphoma. Also, endovascular stents can be used for emergent relief. Use of corticosteroids is controversial, except in cases of a steroid-responsive malignancy (i.e., lymphoma).

BONE METASTASES

Bone metastases are most commonly associated with cancer of the lung, breast, prostate, and kidney—and also with multiple myeloma and non-Hodgkin lymphoma.

Pain is the usual presenting symptom. The large bones with bone marrow: pelvis, vertebral body, sternum, ribs, and femur are most commonly affected.

Confirm the diagnosis by technetium uptake on a bone scan. Note: Lytic only lesions, as commonly seen in multiple myeloma and less commonly in breast and renal cancer, are not evident on the bone scan but can be diagnosed by plain radiographs, CT scan, or MRI.

Radiotherapy is the most common treatment to provide pain relief and prevent fractures. Opiate analgesics along with NSAIDs are often necessary to control symptoms. **Bisphosphonate** therapy may reduce skeletal-related events, as can the RANK ligand inhibitor, denosumab, in solid tumors. Radiopharmaceutical agents such as **samarium** and **strontium** may help palliate painful osteoblastic metastases, which are commonly experienced in prostate cancer. Other developing therapies include radiofrequency ablation (**RFA**), especially in previously irradiated regions, and **vertebroplasty** for vertebral metastasis leading to painful compression fractures. When a lytic lesion occurs in a weight-bearing long bone or the humeri with significant cortical bone destruction, orthopedic intervention is typically indicated to prevent or stabilize a pathologic fracture.

SPINAL CORD COMPRESSION

Spinal cord compression is a dreadful oncologic complication that can lead to paralysis if not recognized promptly and managed effectively. Back pain and localized tenderness are ordinarily the 1st symptoms and may precede neurologic deficits by days to months. The pain is often worse with activity but typically continues with rest. Radiation of pain in a radicular manner is common. Escalating narcotic needs for a patient's baseline pain can be a warning sign of impending cord compression.

All cancer patients with new-onset or worsening back pain should be evaluated promptly with a careful history and neurologic exam looking for paresthesias, paralysis, and pain. The MRI is the diagnostic procedure of choice for the spine. You must conduct a spinal screen of all levels (cervical, thoracic, lumbar, and sacral), since occult, incipient structural problems are often revealed.

As soon as you suspect spinal cord compression due to bone metastases, give dexamethasone at 4–8 mg q 6 h. **Radiotherapy** is the treatment of choice for spinal cord compression due to multiple myeloma or lymphoma. **Surgical** intervention is recommended for most solid tumors, for any patient with progressive neurologic decline, those with no tissue diagnosis, and those who have had previous radiotherapy in the involved region.

BRAIN / LUNG / LIVER METASTATIC DISEASE

Brain metastases can cause significant morbidity. If neurologic abnormalities are present, then treat with intravenous dexamethasone to lessen tumor-associated edema. If the metastatic lesion is solitary and the systemic disease is well controlled, consider neurosurgical resection. Prophylactic antiepileptics are not recommended for patients with no previous seizure history.

Stereotactic radiosurgery is an option for patients with ≤ 3 brain metastases that are all < 3 cm in size. In many patients, the best option is to proceed with whole brain radiotherapy for palliation. Malignancies commonly associated with brain metastasis include lung cancer, breast cancer, renal cell cancer, malignant melanoma, and gastric cancer. On the other hand, malignancies such as prostate cancer and colon cancer are rarely associated with brain metastasis.

The lungs and liver are common sites for metastasis in most malignancies. Surgical resection of liver and lung metastases is reserved for patients with single-organ involvement and low tumor burden. Radiofrequency ablation is a useful modality to palliate painful liver metastasis.

MALIGNANT EFFUSIONS

PLEURAL EFFUSIONS

Malignant pleural effusions have 2 major causes:

1) Exudative reactions due to metastases to major lymphatic structures or pleural surface
2) Chylous effusions due to lymphatic/thoracic duct obstruction

Lung cancer, by far, is the most common cause of exudative malignant effusions. However, as with most sites of metastases, many malignancies can spread to the pleura. Chylous effusions are more commonly seen in patients with non-Hodgkin lymphoma.

Evaluation includes a thoracentesis with appropriate studies to calculate Light criteria (exudative vs. transudative; see Pulmonary Medicine, Book 2, Pleural Effusions), and the fluid should be sent for cytologic evaluation as well. Repeated thoracentesis with cytologic evaluation is worthwhile if the initial cytology is non-diagnostic. You can perform thoracoscopic pleural biopsies in patients when the diagnosis is uncertain.

In patients with symptomatic (dyspnea, chest pain) malignant effusions, drainage is indicated. Most effusions quickly recur if effective treatment of the underlying malignancy with systemic therapy is not achieved. In these patients, consider chest-tube placement with talc pleurodesis or placement of PleurX® catheter with repetitive drainage.

PERICARDIAL EFFUSIONS

Malignant pericardial effusions are caused by either local disease extension into the pericardium or by hematogenous spread to the pericardium. The most commonly associated malignancies are lung cancer, breast cancer, and non-Hodgkin lymphoma.

Closely monitor patients with suspected malignant pericardial effusions for signs and symptoms of tamponade (hypotension with muffled heart sounds, pulsus paradoxus, and JVD; more in Cardiology, Book 3, Pericardial Diseases). Echocardiography is highly recommended. It not only confirms the presence of the effusion, but it gives an immediate determination of degree of hemodynamic compromise. If the effusion presents a risk for tamponade, perform a pericardial window procedure.

ASCITES

Malignant ascites is due to peritoneal seeding of the malignancy. This often presents in patients with ovarian cancer. All gastrointestinal cancers, breast cancers, and non-Hodgkin lymphomas can cause malignant ascites. Paracentesis can be both diagnostic and therapeutic. In refractory cases, peritoneal catheters are placed for palliative therapy.

TUMOR LYSIS SYNDROME

Tumor lysis syndrome is the metabolic derangement caused by release of cellular components into the blood after rapid lysis of malignant cells. It can occur spontaneously in cancers with a high cell turnover (e.g., Burkitt's), in response to cytotoxic therapy or radiation if a large tumor burden is present, or if the cancer is highly sensitive to treatment (e.g., non-Hodgkin lymphomas, ALL, AML).

Lysis results in hyperuricemia +/– acute kidney injury due to uric acid precipitation in renal tubules. Malignant cells have high levels of phosphorous—rapid release of PO_4 stores can cause hyperphosphatemia and hypocalcemia. Calcium phosphate then can precipitate in the kidneys, also contributing to kidney injury. Potassium release causes hyperkalemia. Clinical manifestations of tumor lysis include arrhythmias, acute kidney injury, and seizures—and sometimes death.

In 2008, the American Society of Clinical Oncology (ASCO) published risk-stratification guidelines and recommendations for tumor lysis prophylaxis. For patients who are at high risk for hyperuricemia, add rasburicase to initial supportive management of aggressive hydration. Intermediate-risk patients can be managed with hydration only, with the addition of rasburicase if hyperuricemia develops.

Allopurinol prevents formation of the uric acid but does not decrease pretreatment uric acid levels. It can also increase serum levels of the relatively insoluble purine precursor, xanthine, which can precipitate in the kidneys and cause obstructive uropathy.

Rasburicase (recombinant urate oxidase) oxidizes uric acid to the more soluble allantoin, which decreases pretreatment uric acid levels and avoids the risk of xanthine precipitation seen with allopurinol.

BREAST CANCER

NOTE

Know breast cancer perfectly. It is the most common malignancy in women and the second leading cause of death in women (after lung cancer). 12% of women born today develop breast cancer at some point in their lives. There are ~ 200,000 new cases diagnosed annually; ~ 40,000 women die from breast cancer each year in the U.S. The incidence of breast cancer has been increasing at 2% per year for the past 50 years, and the deaths-per-year index is only just now decreasing slightly—likely due to earlier detection and better treatment.

Quick Quiz

- What malignancies are associated with pericardial metastases?
- Rasburicase is used in the management of what condition?
- List the factors associated with an increased risk for breast cancer.
- What cancers are associated with *BRCA* mutations?

RISK OF BREAST CANCER

Increased risk:

- The most significant risk factors for breast cancer are a personal history of previous breast cancer, female sex, and increased age.
- 1st degree relatives of breast cancer patients—3x normal, especially if the involved member was premenopausal and had bilateral breast cancer.
- Genes: In 1994, the first breast cancer gene was identified (*BRCA1*). It was localized to chromosome 17q21. It is present in 5% of women and is associated with a 50–85% lifetime risk of developing breast cancer, with a 50% chance of occurrence before age 50. This compares to a 12% lifetime risk in the general population. Male breast cancer is rare, but many men with breast cancer carry *BRCA* mutations.
- *BRCA* also is associated with a 40% lifetime risk of developing ovarian cancer—and accounts for most patients with familial ovarian cancer, which compares to a 1.5% lifetime risk in the general population. *BRCA1* also is associated with colorectal and prostate cancer. *BRCA2* (13q12-13) is associated with a similarly high risk of breast cancer and a 10–20% risk of ovarian cancer. *BRCA2* also is associated with melanoma, pancreatic cancer, and prostate cancer. Although only about 5% of breast cancer cases are attributable to a specific genetic abnormality, together, alterations of the *BRCA1* and *BRCA2* genes account for 30–50% of all inherited breast cancer. In patients with a *BRCA* mutation, bilateral mastectomies may decrease the incidence of breast cancer by up to 90%. Bilateral oophorectomies may decrease the risk of ovarian cancer by up to 90% and can decrease the risk of breast cancer for premenopausal women.
- Atypical ductal hyperplasia in breast biopsy samples ---4x normal.
- DCIS or LCIS (ductal/lobular carcinoma *in situ*)—10x normal. LCIS is associated with increased risk of cancer in either breast. LCIS is a marker for invasive carcinoma, while DCIS evolves into invasive carcinoma.
- Also: early menarche, late menopause, late 1st pregnancy or nulliparity, obesity, moderate-to-heavy alcohol ingestion, and mantle field radiation therapy.

In normal postmenopausal women, conjugated estrogens cause a slightly increased risk of breast cancer after 5 years of use. They definitely increase the risk of endometrial cancer if given without progestins.

A trial of combined estrogen plus progestin (the Women's Health Initiative) was stopped early because overall risks, including invasive breast cancer, exceeded benefits.

The oncologic risks of postmenopausal estrogen replacement therapy (ERT) were thought to be offset by the benefits: decreased incidence of hip fractures, sexual dysfunction, and cardiovascular disease; however, the 1998 HERS trial showed that estrogens with progestin are associated with an increased risk of secondary cardiac events in the 1st year of treatment, and it also showed no cardiovascular benefit at 7-year follow-up. Also noted was an increased risk of thromboembolism and biliary tract surgery in those on long-term estrogen/progestin replacement therapy. Due to the results of this trial, this therapy has fallen out of favor. Breast cancer survivors should not be treated with estrogen replacement therapy because data have shown it to be associated with breast cancer recurrence and worsened mortality.

SCREENING FOR BREAST CANCER

Overview

The following paragraphs are summaries of the current breast cancer screening guidelines. Many of these guidelines are at odds with one another. Thus, suggestions on how to handle the discrepancies are provided.

Mammography is less sensitive in women with dense breasts and those who have used estrogen replacement therapy or oral contraceptives (which delay the transition of breast tissue from dense to fatty). Being postmenopausal increases the sensitivity of mammography.

ACS Screening Guidelines

The American Cancer Society (ACS) guidelines recommend yearly mammography starting at age 40 and continuing as long as the woman is in good health. Existing data suggest that digital mammography is superior to film mammography in women younger than age 50 with dense breasts—but digital mammography offers no benefit over film in any other groups of women.

Clinical breast exam (CBE) is recommended every 3 years between ages 20 and 40 and yearly after age 40. Breast self-exam (BSE) is an option for women once they reach age 20.

USPSTF Screening Guidelines

The U.S. Preventative Services Task Force (USPSTF) 2009 guidelines recommend biennial (q 2 years) mammography screening between the ages of 50 and 74. Biennial screening prior to age 50 is an individual decision. There are insufficient data to recommend screening in women > 75 years of age.

There are insufficient data to recommend for or against CBE, digital mammography, or MRI screening. USPSTF recommends against BSE.

ACP Screening Guidelines

The American College of Physicians (ACP) panel had difficulty similar to the USPSTF in making recommendations for women 40–50 years of age. The ultimate ACP guideline recommends that mammography risks and benefits be discussed with the patient.

Putting It Together

The vagueness of the USPSTF and ACP guidelines arise because their recommendations are "data driven" or "evidence based"—not "expert driven," like the ACS guidelines. Thus, if only limited data exist for or against an intervention, then the USPSTF and ACP won't make a definitive recommendation for or against.

Most practicing physicians are recommending BSE and CBE for women > 40 years of age (or earlier in patients with significant family histories). But, again, this is not an evidence-based decision.

But what do you learn for the Boards? We recommend you focus on where the guidelines agree. Guidelines agree in the recommendation to screen women with mammography from ages 50 to 74 (most say yearly, but the USPSTF says every 2 years). There are opposing stances in the guidelines on the use of breast exams (BSE and CBE), so they shouldn't appear on the Boards.

Breast MRI

Breast MRI is being used for screening in select women, usually young women with dense breast tissue at high risk of developing breast cancer. It has a high sensitivity but limited specificity. The procedure requires injection of gadolinium contrast and is significantly more expensive than mammography. The ACS supports breast MRI screening for the following high-risk women only:

- *BRCA1*- or *BRCA2*-positive status
- 1st degree relatives with *BRCA1* or *BRCA2* and the patient untested
- Lifetime risk of breast cancer ≥ 20–25%
- Radiation to the chest between ages 10 and 30 years
- Carrier of, or 1st degree relative with, the TP53 (Li Fraumeni syndrome), *PTEN* mutation (Cowden syndrome), or hereditary diffuse gastric cancer syndrome

PHYSICAL FINDINGS

Patients often find breast cancer, either incidentally or during a self-exam. Over the last 10 years, an increasing proportion has been diagnosed by mammography. Breast cancer may be any shape or size. Typically, it forms a hard, well-defined "**dominant mass**," in contrast to diffuse fibrocystic changes.

Work up **asymmetric eczema** of the nipple in a non-breastfeeding woman for Paget disease of the breast. This is done by a nipple scraping for cytology or a nipple punch biopsy. Note that allergic eczema is a symmetric disease.

Inflammatory breast cancer is very aggressive and can present as a mastitis with **warmth**, **redness**, and **swelling**. There can be a peau d'orange (skin of the orange) appearance and nipple inversion. Mastitis in a non-lactating woman is rare, so initiate a workup for inflammatory breast cancer in non-lactating women with this presentation. Inflammatory breast cancer is very aggressive. Mammograms pick up 63% of minimal breast cancers that are not otherwise detectable.

Nipple discharge that is not milky and bilateral is always considered abnormal. **Bloody** discharge is commonly due to a papilloma but can be a sign of breast cancer. **Greenish** discharge is an indication of a draining cyst. **Clear** discharge may also be caused by breast cancer. Cancer is less likely when the discharge occurs from both breasts.

WORKUP FOR BREAST CANCER

What workup to do for a suspicious breast finding:

1st: mammogram, ultrasound, +/– MRI.

2nd: aspiration (FNA)/biopsy.

3rd: Determine receptor and *HER2/neu* status.

4th: Treat as indicated.

1st: **Mammography** is required for all suspicious breast lesions (e.g., for mastitis not associated with lactation; for eczematous nipple—see Physical Findings above).

Suggestive findings of concern for malignancy on the mammogram:

- Clusters of irregular microcalcifications (most clusters are benign)
- Densities with irregular borders (stellate or spiculated lesions)
- Distorted architecture

Ultrasound the mass to determine whether it is cystic or solid. If the mass is a simple cyst, consider fluid aspiration and analysis. Ultrasound cannot differentiate solid malignant from solid benign tumors—so, if the mass is solid by ultrasound, refer for biopsy.

The impact of a breast MRI during the initial evaluation is evolving. Nearly all invasive breast cancers enhance with

QuickQuiz

- Mammography, either yearly or every 2 years, should definitely be recommended as a screening tool for women at what ages?
- Clinical mastitis in a woman who is not breastfeeding should make you consider what diagnosis?
- What is the sequence of actions used in the workup of a suspicious breast mass? Explain in detail.
- What are the indications for breast-conserving therapy for treatment of DCIS?

gadolinium. MRI also is helpful in evaluating both the ipsilateral and contralateral breasts for occult lesions once malignancy has been established. Finally, MRI is the best modality to assess the breasts for an occult primary tumor in a woman with adenocarcinoma of unknown primary site involving the axillary lymph nodes.

2nd: **Biopsy** to confirm the diagnosis of breast cancer by FNA and core needle biopsy. At this time, the ultrasonographer also looks in the axilla for enlarged lymph nodes.

Also, biopsy any palpable non-cystic masses—even if the mammogram is negative—because the sensitivity of mammography for identifying malignancy is only 75–80%.

3rd: If the biopsy shows invasive cancer, evaluate estrogen and progesterone **receptor status**, *HER2/neu* status, and grading of the cancer.

4th: **Treat** (discussed later). See Table 8-12 for staging and survival rates.

CARCINOMA *IN SITU* (LCIS AND DCIS)

Overview

We now review 2 types of carcinoma *in situ* ([CIS]; noninvasive cancer) and then invasive breast cancer.

2 types: Lobular (**LCIS**) and ductal/intraductal (**DCIS**). Both are associated with risk of breast cancer (10x N). Both types are benign and curable with resection, but both can be associated with multifocal involvement of the involved breast and also bilateral breast involvement. LCIS is frequently bilateral (30%).

LCIS appears to be a marker indicating that either breast is at risk of developing an invasive carcinoma but, by itself, does not evolve into an invasive carcinoma. Rather, it is an "innocent bystander," seen in about 2–3% of biopsies.

DCIS is more common (20% of all new breast cancers) than LCIS. It is frequently associated with distinct microcalcifications on mammogram, and it is usually confined to a lobule. The calcifications are often clustered and rod-shaped or angulated. DCIS is divided into low-, intermediate-, and high-grade types. The high-grade type is comedocarcinoma, which has a high risk of becoming invasive. DCIS evolves into an invasive carcinoma at the rate of 1% per year.

Treatment of LCIS

LCIS is a benign lesion and more appropriately managed with observation. However, because of the increased risk of breast cancer, and because the disease is frequently multifocal and bilateral, some patients opt for a bilateral mastectomy (occurs less often now). This is an extreme approach, but might be given more consideration in the woman whose mammograms show very dense breast tissue and are thus difficult to evaluate.

In the 1998 NSABP-P1 prevention trial, tamoxifen—an estrogen receptor modulator—was shown to reduce invasive breast cancer in LCIS patients by 56%. However, there are risks with tamoxifen therapy (venous thromboembolism, endometrial cancer), and you should carefully discuss these risks with the patient before beginning such treatment.

Treatment of DCIS

Treat DCIS with surgical excision: either simple mastectomy or (preferably) local excision with adequate margins, also known as breast-conserving therapy (BCT).

The majority of women with DCIS are candidates for BCT as long as certain criteria are met:

- Negative margins should be achieved, with the optimal margin being ≥ 10 mm.

Table 8-12: Breast Cancer Staging and Survival

Breast Cancer — Do not memorize, just review!					
Stage	**Definition**	**TNM Classification**			**10-yr survival**
Stage 0	Carcinoma *in situ*	Tis	N0	M0	Most
Stage I	< 2 cm, no nodes	T1			75%
Stage II	2–5 cm or axillary node positive	T < 4	N0–1		50%
Stage IIIa	> 5 cm or fixed nodes		N2		
Stage IIIb	Ca spread to chest wall or skin or Spread to internal mammary nodes	any with T4 or any with N3			27%
Stage IV	Distant metastases	any T and N		M1	< 10%

- The resection should lend itself to a cosmetically acceptable result. This is dependent on the size and number of lesions in relation to breast size. Multifocal disease often requires a simple mastectomy.

Important prognostic factors include grade of lesion (high-grade lesions, such as comedo subtype, are more likely to recur than low-grade lesions, such as cribriform subtype) and resection margin width.

For patients who elect BCT, local radiation therapy (RT) reduces risk of in-breast recurrence by 50%. However, the addition of RT has not shown any survival benefit.

The NSABP-24 trial examined the role of tamoxifen in patients with DCIS. All patients underwent excision and RT and subsequently were randomized to placebo or tamoxifen. In DCIS, tamoxifen reduced the absolute risk of an ipsilateral breast event by 3.3% at 5 years. However, the addition of tamoxifen has not shown a survival benefit.

INVASIVE BREAST CANCER

Types

Most invasive breast cancer is the invasive ductal type (> 80%). Next is invasive lobular (10%); then medullary (5%).

Prognosis for Localized Invasive Breast Cancer

[Know:] The most important prognostic factor is the presence or absence of lymph node metastases. The more nodes involved, the worse the prognosis. More than 1/2 of breast cancer patients have negative axillary nodes at the time of diagnosis.

More recently, a technique using "sentinel nodes" has been used. Sentinel nodes are the 1st nodes that the tumor drains into, and they are determined by the injection of a radioactive substance around the tumor or into the biopsy cavity. These sentinel nodes then are identified and removed by probe-guided resection. The majority of breast cancers drain to nodes in the axilla. The positive or negative status of the sentinel nodes is 97% accurate in reflecting the positive or negative status of all the axillary nodes. If the sentinel node is negative, no further sampling is required. If the sentinel node is positive, a full axillary dissection must be performed.

The next most important prognostic factor is the size of the primary tumor. If the tumor is < 1 cm and axillary nodes are negative, the 5-year relapse rate is around 10%; if > 2 cm, the 5-year relapse rate is 20%. If axillary nodes are at all positive, 5-year relapse rates rise to 50–80%.

Overexpression of the *HER2/neu* oncogene occurs in ~ 25–30% of breast cancers and is associated with increased likelihood of distant metastases, as well as with a more aggressive cancer. Overexpression of the *HER2/neu* oncogene is predictive of a benefit from adjuvant chemotherapy (now includes 1 year of trastuzumab), but is associated with less benefit from adjuvant hormonal therapy.

Positive estrogen receptors (ER+) and positive progesterone receptors (PR+) are favorable prognostic indicators because they predict a benefit from adjuvant hormonal therapy (tamoxifen or aromatase inhibitor).

Genomic technologies are increasingly being applied to breast cancer specimens to refine prognosis. Oncotype DX® is a RT-PCR testing for 16 gene panels on paraffin-embedded tissue. It has been evaluated retrospectively in node-negative breast cancer patients. In this analysis, gene profiling has been able to risk-stratify patients into groups with low-, intermediate-, and high-risk recurrence scores when treated with endocrine therapy. High-risk patients benefit from adjuvant chemotherapy, while there is no benefit in low-risk patients. It is still unclear which patients in the intermediate-risk group benefit from treatment, and the decision should include patient preferences.

An aggressive histologic grade and the presence of nodal metastases are also poor prognostic factors.

Overall, the most powerful prognostic factor is stage of disease—indicated by lymph node status and size of tumor. The presence of distant metastasis indicates incurable disease.

Initial Treatment of Invasive Breast Cancer

Management of invasive breast cancer is determined by the following:

- Presence or absence of lymph node involvement
- Size of the primary lesion
- *HER2/neu* status
- Hormone receptor status (HR+ or HR–)
- Presence or absence of metastasis
- Whether the patient is pre- or postmenopausal
- Patient preferences

Note that, except for the last 2, these are the same factors used to determine prognosis. Review and learn Table 8-12 on page 8-45 and Table 8-13 on page 8-48.

Primary treatment for invasive breast cancer is broken down into 2 parts:

1) **Local** control: This entails removal of the tumor, whether by modified radical mastectomy or a breast-conserving therapy ([BCT]; lumpectomy). When lumpectomy is performed, it is always followed by radiation therapy to the breast (BCT + RT).
2) **Systemic** control: While lumpectomy and radiation decrease the risk of the cancer returning to the affected breast, they do not prevent the cancer from recurring at distant sites. For this, adjuvant therapy is given. There are 3 types of adjuvant therapy: hormonal, chemotherapy, and biologic therapy.

Quick Quiz

- What is the most important prognostic indicator for localized invasive breast cancer? How important is the size of the tumor?
- What is the significance of *HER2/neu* oncogene overexpression?
- What is the significance of positive estrogen and progesterone receptors?
- What factors influence the type of adjuvant therapy selected for a breast cancer patient?
- Which drugs, when given concomitantly, decrease the efficacy of tamoxifen?
- What are the significant risks of tamoxifen therapy?
- What is the role of aromatase inhibitors in the treatment of breast cancer?

Note on local and systemic control: Local control with a modified radical mastectomy is often the surgery of choice when the tumor is > 4 cm or the breast is comparatively small, because good cosmetic results are difficult to achieve with BCT.

A second and increasingly popular option is to give systemic chemotherapy in the preoperative setting. This neoadjuvant approach addresses the systemic risk of relapse and provides some shrinkage to the primary tumor, thus increasing the chance that local control can be achieved with lumpectomy and RT. To date, this technique has not shown a survival benefit.

Adjuvant Chemo / Hormonal / Biological Therapy Options for Invasive Breast Cancer

Overview

The types of adjuvant therapy used for systemic control depends on the following factors:

- **Size of tumor** and **nodal status**: Chemotherapy is generally reserved for patients with a high risk of relapse. This includes patients with tumors > 1 cm in size or those with positive lymph nodes. Oncotype DX analysis can help distinguish which woman with T1 (< 2-cm) tumors that are node-negative benefit from adjuvant chemotherapy.
- **Hormonal status** of the tumor: Using tissue from the initial core biopsy, the pathologist determines if the tumor expresses receptors for estrogen and progesterone. If the tumor is hormone receptor-positive (HR+), the patient benefits from adjuvant hormone therapy (tamoxifen or aromatase inhibitor).
- **Gene expression**: Women with > 2-cm tumors and/or node-positive disease whose tumors overexpress the *HER2/neu* gene benefit from trastuzumab (Herceptin®).

Chemotherapy

Chemotherapy decreases risk of recurrence in many patients. It is generally given in drug combinations that follow these general rules:

- Each agent is effective.
- Each agent has a different mechanism of action.

Common combinations are:

- **CMF** (**c**yclophosphamide, **m**ethotrexate, **f**luorouracil)
- **TAC** (docetaxel [**T**axotere®], doxorubicin [**A**driamycin®], **c**yclophosphamide)
- **AC** (doxorubicin [**A**driamycin], **c**yclophosphamide)
- **AC + T** (**AC** followed by paclitaxel [**T**axol®])

The most common regimens in use today are:

- AC for node-negative breast cancers, and
- AC + T for node-positive cancers.

The AC + T is often given in a "dose-dense" fashion, meaning the patient receives AC chemotherapy every 2 weeks instead of the more traditional 3-week schedule. The increased efficacy of this schedule is offset by the increased toxicity to the bone marrow, so growth factor support with G-CSF is used.

Hormonal Therapy

Tamoxifen is a selective estrogen receptor modulator. It is effective only in HR+ patients (both pre- and postmenopausal) in which its overall effect is comparable to chemotherapy.

Know that tamoxifen is converted to its active metabolite, endoxifen, by CYP2D6. Enzyme inhibitors (mainly SSRIs) and/or genetic variation can lead to decreased efficacy of tamoxifen. If a patient needs an SSRI (for depression or hot flashes) while on tamoxifen, venlafaxine is considered the best choice because it does not inhibit CYP2D6.

Tamoxifen's principal adverse effects include hot flashes, weight gain, increased risk of thromboembolic events, and a slight increased risk of endometrial cancer.

Recent data suggest that some patients may benefit from treatment longer than 5 years, but the risks of thromboembolic disease and patient tolerance of the drug need to be assessed.

Letrozole, **anastrozole**, and **exemestane** are aromatase inhibitors. These agents markedly suppress estrogen levels in postmenopausal women by inhibiting the enzyme responsible for synthesizing estrogens from androgenic substrates. Aromatase inhibitors cannot be used in premenopausal women since they do not block ovarian estrogen production.

Data from a randomized trial revealed that the addition of an aromatase inhibitor (letrozole) after 2–5 years of adjuvant tamoxifen improved disease-free survival by 6% (93% vs. 87%) at 4 years. Meta-analysis data support a lower rate of recurrence with aromatase inhibitor over

tamoxifen. Women with a contraindication to tamoxifen (history of DVT/PE or endometrial cancer) can be treated with an aromatase inhibitor alone for 5 years.

Aromatase inhibitors are not associated with an increased risk of thromboembolic events or endometrial carcinoma. However, arthralgias, myalgias, and osteoporosis are more common with these agents. Breast cancer survivors who were treated with aromatase inhibitors should be screened with DXA.

Fulvestrant is an estrogen receptor antagonist without any agonist features. It is given as a monthly intramuscular injection.

Biologic Agents

Trastuzumab (Herceptin®) is a newer biologic agent. It is a monoclonal antibody that targets a growth factor receptor on the surface membrane of breast cancer cells. Around 25–30% of breast cancers have an overexpression of the *HER2/neu* gene, which leads to an increase in the amount of growth receptor protein. This, in turn, leads to an increase in cell proliferation. Trastuzumab has been approved for advanced metastatic cancer with evidence of overexpression of the *HER2/neu* gene. Recent trials have shown a 50% decrease in recurrence when the drug is used as an adjuvant for high-risk (> 2-cm or node-positive) tumors.

Let's review treatment again from a slightly different perspective.

Adjuvant Therapy for the Node-Negative Patient

See Table 8-13. If the tumor is < 1 cm, adjuvant chemotherapy is typically unnecessary because the risk of recurrence is < 10%. Exceptions include young women with high-risk Oncotype DX® scores. Women are often placed on hormonal therapy if the tumor is HR+.

If the tumor is > 1 cm, adjuvant chemotherapy with AC is recommended. Give adjuvant hormonal therapy to women with HR+ tumors. Tamoxifen is used for premenopausal women; an aromatase inhibitor can be used alone or sequentially after tamoxifen for postmenopausal women. The use of adjuvant biologic therapy for node-negative tumors < 2 cm is being investigated. In tumors > 2 cm that are *HER2/neu*+, give adjuvant trastuzumab after chemotherapy.

Adjuvant Therapy for the Node-Positive Patient

Chemotherapy is recommended for node-positive patients. The preferred regimen is dose-dense AC + T. If the tumor overexpresses the *HER2/neu* gene, give patient 1 year of trastuzumab therapy. Give premenopausal women with HR+ tumors adjuvant tamoxifen. Aromatase inhibitor can be used alone or sequentially after tamoxifen for postmenopausal women.

Give all patients radiation therapy after lumpectomy. Contraindications include pregnancy and previous radiation therapy to the same breast for prior breast cancer. Relative contraindications include connective tissue disorders affecting the skin, tumors > 5 cm, and women ≥ 35 years with a *BRCA* mutation. Give radiation after chemotherapy is completed and before hormonal therapy is started.

Prophylaxis / Prevention of Breast Cancer

Tamoxifen is FDA-approved for the prevention of breast cancer in both pre- and postmenopausal women. According to the NSABP Breast Cancer Prevention Trial (terminated early in 1998), which followed 13,388 high-risk women for 6 years, 175 on placebo vs. 89 on tamoxifen developed invasive breast cancer, a relative risk reduction of 38%. Tamoxifen prophylaxis for a duration of 5 years is now considered for women at high risk for invasive breast cancer (defined as a 1.67% 5-year risk of developing breast cancer, or the risk present in an average 60-year-old woman). There is an increased risk of endometrial cancer with the use of tamoxifen; it is the same risk as in postmenopausal women taking single-agent estrogen replacement therapy. Also increased is the risk of DVT (about 1.5x N) and pulmonary embolism (about 3x N).

Table 8-13: Treatment of Node-Negative Invasive Breast Cancer

Size of Tumor	< 1 cm	1 cm to < 4 cm	≥ 4 cm
Type of Surgery	BCT + radiotherapy	Modified Radical Mastectomy or BCT + radiotherapy	Modified Radical Mastectomy
Adjuvant Therapy?	No adjuvant chemotherapy	† Adjuvant chemotherapy for all premenopausal and HR– postmenopausal patients also if ... HR+: add tamoxifen x 5 yrs	
What if node-**positive**? Treatment follows the same basic guidelines as above, except the adjuvant therapy (†) is given for all tumor sizes. Also for postmenopausal HR+ women with more than 1 node involved, both chemotherapy and hormonal therapy are often used.			

Quick Quiz

- What is the role of tamoxifen in the prevention of breast cancer? For which women is it considered?
- What are the established risk factors for cervical cancer?
- What patient populations are approved for receipt of the HPV vaccine?
- At what age and with what test results is it appropriate to stop screening for cervical cancer?

Raloxifene is FDA-approved for breast cancer prevention in postmenopausal women and has a lower risk of endometrial cancer and DVT compared to tamoxifen.

Recurrent Breast Cancer

If there is local recurrence of breast cancer, the patient undergoes the diagnostic protocol again and is retreated based on the same criteria, except for the drugs that are used. Many oncologists consider an anthracycline or paclitaxel for recurrences.

Metastatic Breast Cancer

Although there is no curative therapy for metastatic disease, effective palliation and survival extension is possible with the implementation of active agents. There are many newer chemotherapy agents that are effective in metastatic breast cancer.

In patients with HR+ disease, initiating or changing hormonal therapy is often effective. Aromatase inhibitors are more effective than tamoxifen for the initial treatment of metastatic disease in postmenopausal women.

Bisphosphonate therapy can effectively reduce bone pain and fractures due to skeletal metastasis.

Denosumab is a RANK ligand inhibitor that also decreases the risk of skeletal-related events.

Radiation therapy is useful in providing palliation and local control to symptomatic regional disease, brain metastasis, skeletal metastasis, and soft tissue metastasis.

CERVICAL CANCER

INCIDENCE

Since the introduction of the Papanicolaou (Pap) smear in 1947, mortality due to cervical cancer in the U.S. has dropped by 70%. Still, despite effective screening, there will be 10,000 cases of cervical cancer diagnosed in the U.S. this year.

RISK OF CERVICAL CANCER

The major risk factor for cervical carcinoma is HPV (human papillomavirus) infection. Other risk factors reflect the risk of exposure to HPV: early onset of coitus, number of sexual partners, smoking, and history of other sexually transmitted diseases. In addition, patients with chronic immunosuppression are at increased risk of developing HPV infection (e.g., HIV/AIDS is a risk factor).

HPV isolates are found in 85–90% of cervical carcinomas, especially types 16 and 18. HPV is thought to express E7 protein, which binds to the RB (retinoblastoma) protein, inactivating the RB tumor suppressor gene. HPV is the cause of the cervical intraepithelial neoplasia (CIN) dysplasia, and 65% evolve into CIS over a period of 10 years. Without treatment, 30–70% of CIS lesions evolve into an invasive carcinoma over 10–12 years.

A significant medical advancement has been the development of the quadrivalent HPV 6/11/16/18 virus-like particle vaccine (Gardasil®). The safety and efficacy of this vaccine has been established in 4 placebo-controlled randomized trials. The FUTURE II trial revealed the vaccine to be 100% effective in preventing CIN grade 1–3 in HPV-susceptible women. The vaccine is approved for use in both females (to prevent cervical, vulvar, and vaginal cancer) and males (to prevent genital warts), ages 9 to 26 years.

SCREENING AND WORKUP OF CERVICAL CANCER

Pap smears are used as a screening method to find cancerous or precancerous cervical lesions. Because most atypia and cancer form in the transformation zone between the endocervix and exocervix, it is crucial to get a good sample from this area.

The American Congress of Obstetricians and Gynecologists (ACOG) released new guidelines for cervical cancer screening in 2012, which advocate beginning to screen at age 21 and every 3 years thereafter in women ages 21–29. Women 30 and older with 3 consecutive negative screens (and no history of CIN 2 or CIN 3, HIV-negative, no immunocompromise, and no *in utero* DES exposure) can be screened every 5 years if there is co-testing of HPV and cytology, or every 3 years if done with cytology alone.

Liquid-based and conventional methods are both acceptable for screening. Patients who have had a total abdominal hysterectomy for benign conditions can discontinue screening. Stop screening at age 65 if patient has had adequate screening (3 or more negative cytology test results in a row or 2 consecutive negative co-tests in the past 10 years with the most recent within the past 5 years). Whatever the age, continue screening for 20 years after treatment for a high-grade precancerous lesion.

Testing for HPV DNA and cytology is appropriate in women ≥ 30 years of age. Low-risk women 30 and older,

with both negative cytology and HPV testing, can be screened every 3 years. All guidelines apply to women who have received the vaccine.

Remember: The Pap smear is only a screening test; a biopsy is required for diagnosis of CIN or invasive carcinoma.

The Bethesda classification is the most common method to communicate the grade of atypia or dysplasia found on Pap smears. It has 3 categories:

1) ASCUS (atypical squamous cells of undetermined significance)
2) LGSIL (low-grade squamous intraepithelial lesion), which usually reflects CIN 1, but occasionally 2 or 3
3) HGSIL (high-grade squamous intraepithelial lesion), which is due to CIN 2, 3, or invasive carcinoma

ASCUS can be evaluated with colposcopy-guided biopsy or DNA testing for high-risk viruses with colposcopy reserved for cases where viral DNA is identified. A third option is to treat any underlying infection and repeat the Pap smear in 3 months.

Both LGSIL and HGSIL require colposcopic-guided punch biopsies for the diagnosis of CIN or cancer. Colposcopy is also recommended for all visible cervical lesions—even if the Pap smear is normal. If the entire transitional zone cannot be visualized, perform endocervical curettage (ECC).

Biopsy results: The premalignant and malignant lesions of the cervix are termed either:

- cervical intraepithelial neoplasia (CIN), or
- invasive cancer.

CIN is further divided into CIN 1 (slight dysplasia), CIN 2 (moderate dysplasia), and CIN 3 (severe dysplasia). CIN 1 may resolve spontaneously, whereas CIN 2 and 3 require treatment.

TREATMENT OF CERVICAL CANCER

Most CIN is treated with ablative therapy, normally consisting of loop electrosurgical excision procedure (LEEP) or cold-knife conization (CKC). Follow-up after treatment for CIN is reexamination and cytology at 6 months. If this follow-up smear is normal, screening can resume, depending on the patient's age and level of immunosuppression.

Treat local, invasive cancer with various combinations of hysterectomy, pelvic node dissection, and radiation, along with chemotherapy.

OVARIAN CANCER

OVERVIEW

Ovarian cancer is the 4th leading cause of cancer deaths in women. It is the 7th most common malignancy in women; 1 out of 70 women develop this type of cancer. The incidence increases with age, and 1/2 of affected patients are > 65 years of age. Ovarian cancer is the most common cause of an ovarian mass in postmenopausal women.

Most (85%) ovarian cancers are epithelial cell cancers, and most of these are serous and mucinous; but they also may be endometrioid, clear cell, Brenner, or undifferentiated. The next most common cause is germ cell (5%). Most ovarian germ cell tumors are benign, however.

Again, know the following. Epithelial cell (85%) and germ cell (5%), and:

- **Epithelial cell** tumors are more common among postmenopausal Caucasian patients.
- **Germ cell** tumors typically occur in young women (10–30 years of age).

Germ cell cancers account for 95% of testicular cancers but only ~ 5% of ovarian cancers.

RISK OF OVARIAN CANCER

Increased risk:

- Positive family history
- Nulliparity
- *BRCA1*- or *BRCA2*-positivity
- Lynch syndrome

Decreased risk:

- Oral contraceptive use
- Tubal ligation
- Breastfeeding
- Early age of 1st pregnancy
- Multiparity (10% decrease in risk with each pregnancy)

BRCA1 (17q21) is associated with a 40% lifetime risk of ovarian cancer. This compares to a 1.5% lifetime risk in the general population. *BRCA1* accounts for most cases of familial ovarian cancer. *BRCA2* (13q12-13) is associated with a 10–20% risk of ovarian cancer. Remember: *BRCA1* and *BRCA2* also are associated with increased risk of breast cancer.

Lynch syndrome (or hereditary nonpolyposis colon cancer) is caused by a germline mutation in a mismatch repair gene and is associated with a 12% lifetime risk of ovarian cancer.

BIOLOGIC MARKERS IN OVARIAN CANCER

CA-125 levels are often increased in ovarian cancer; so include this test when working up possible ovarian cancer. CA-125 also is beneficial in monitoring the effects of therapy.

Recent data show that treatment at a CA-125 relapse does not impact survival. Routine screening for ovarian cancer with either CA-125 or transvaginal ultrasound, or both, is of no benefit and is not recommended.

Quick Quiz

- What is the appropriate procedure to follow up an LGSIL Pap smear result?
- Which type of ovarian cancer is usually benign? In what age group do you typically find these cancers?
- What is the lifetime risk of ovarian cancer in a woman with *BRCA1*? With *BRCA2*?
- What are the risk factors for testicular cancer?
- What biologic markers are used for testicular cancer, and how are they used?
- What is the significance of finding AFP elevation in a patient with a testicular mass?

Alpha fetoprotein (AFP) and hCG are not elevated in epithelial cancers. Both may be elevated in the less common germ cell cancer. Choriocarcinoma, one of the germ cell cancers, produces large amounts of hCG.

STAGING OF OVARIAN CANCER

I. Confined to the ovary

II. Extended to adjacent pelvic structures

III. Spread to peritoneal surfaces, including liver and diaphragmatic surfaces, or to lymph nodes

IV. Distant metastases

Staging is often performed with CT scans of the chest, abdomen, and pelvis. Large intraperitoneal metastases can be seen by CT, but small peritoneal studding may be missed. For this reason, patients are often determined to have a higher than expected stage at the time of laparotomy.

TREATMENT OF OVARIAN CANCER

Treatment for stages I, II, and III consists of surgically removing all visible tumor from the peritoneal surfaces. This debulking or cytoreduction surgery includes a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) and often removal of sections of small bowel, colon, and bladder. The goal is to leave < 1 cm of residual disease. Systemic chemotherapy and, increasingly, intraperitoneal chemotherapy are used in the treatment for stage II and III disease. Optimally, start chemotherapy 4–6 weeks after surgery to allow for adequate post-surgical healing. 5-year survival is 65% for stage II disease and 40% for stage III disease. In stage III disease, optimal cytoreduction is a significant prognostic factor. Also manage Stage IV with chemotherapy (and debulking, in certain situations).

If diagnosed and treated while the cancer is still localized, the 5-year survival rate is 90%, but only 23% are found in this stage. Overall, the 5-year survival rate is 42%.

TESTICULAR CANCER

OVERVIEW

Testicular cancer is the most common solid malignancy affecting men 15–35 years of age. Testicular cancer is one of the most curable cancers, with the 5-year survival rates between 90% and 95%.

Patients usually present with a painless mass in the testicle. If a testicular mass is palpated, then a scrotal ultrasound should be obtained to determine if it is solid. If the mass is solid, inguinal orchiectomy is the preferred next step. Needle biopsy should not be performed because of risk of seeding the biopsy tract. 95% of testicular carcinomas are germ cell tumors (GCTs: seminoma and nonseminoma). The remaining 5% consist of sex cord-stromal tumors, adenocarcinoma of rete testis, mesothelioma, carcinoid, lymphoma, and gonadoblastoma. Testicular cancer also can occur in extragonadal primary sites (retroperitoneum and mediastinum).

Risk factors for testicular GCTs include cryptorchidism (undescended testes), a personal or family history of testicular cancer, infertility, and HIV infection (relative risk for seminoma is 21!). Cryptorchidism increases the risk of testicular cancer in both the undescended and normal testes. The risk increases with delayed orchiopexy. Isochromosome 12p is present in 70–80% of testicular GCTs; however, its role in familial GCTs is unknown. Klinefelter syndrome is a risk factor for primary mediastinal germ cell tumors.

Management of testicular cancer is determined by the type of germ cell tumor. Nonseminoma is the more aggressive type, so when there are elements of both types, follow management of nonseminoma.

BIOLOGIC MARKERS IN TESTICULAR CANCER

Biologic markers include α-fetoprotein (AFP) and hCG. Tumor markers have several important functions:

- Staging and prognosis
- Monitoring for disease relapse
- Monitoring for efficacy of therapy

These markers should be checked prior to surgery, after surgery, and during follow-up. See Figure 8-5 on page 8-52.

AFP is never produced by seminomas. If morphology from a specimen suggests a pure seminoma but the AFP is elevated, the testicular cancer is classified as a nonseminoma. AFP is secreted by all yolk sac tumors and less frequently by embryonal cell carcinoma. The half-life of AFP is 5 days. AFP is also produced by hepatocellular carcinoma, other GI tract tumors, and is elevated in chronic liver disease.

hCG is secreted by all choriocarcinomas, many embryonal cell carcinomas, and 15% of seminomas.

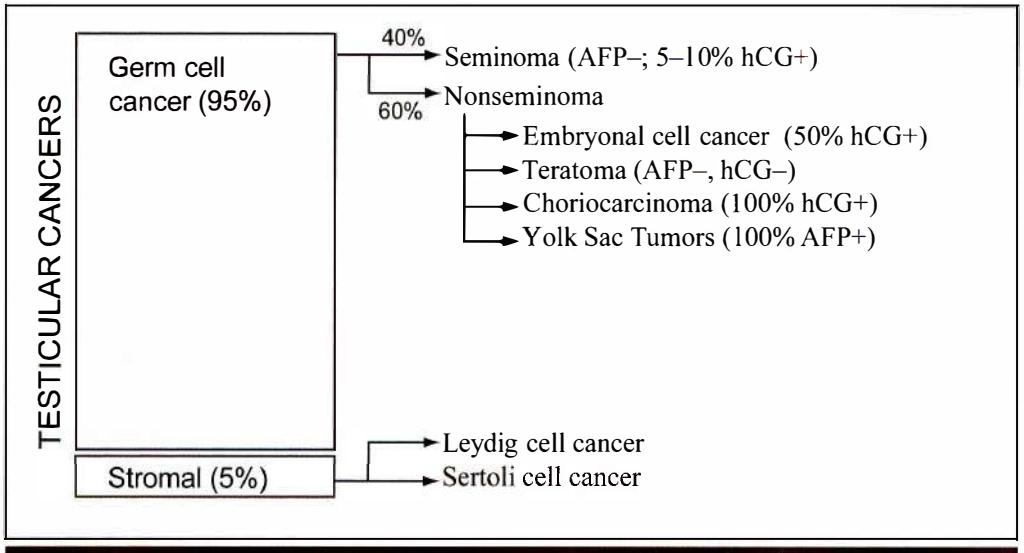

Figure 8-5: Testicular Cancers and the Associated Biologic Markers

Syncytiotrophoblast cells produce hCG in pure seminomas; thus, it is possible to have a pure seminoma with an elevated hCG. False-positive hCG values can occur in hypogonadal states and with marijuana use. The half-life of hCG is 18–36 hours.

STAGING OF TESTICULAR CANCER

Testicular cancer follows a predictable course of metastasis. Stage I disease is limited to the testicle. Stage II disease involves the retroperitoneal nodes, and stage III disease includes more distant metastatic disease—often to the lung. Note that there is no stage IV classification for testicular cancer.

The staging process includes CT of the abdomen and pelvis, as well as tumor markers and LDH. See Table 8-14 for the TNM classification of germ cell tumors.

TREATMENT OF TESTICULAR CANCER

Seminomas are highly radiosensitive. Standard therapy includes orchiectomy followed by radiation to the retroperitoneal lymph nodes, chemotherapy, or surveillance. Radiation can be used on nodes up to 5 cm in size. If nodes are > 5 cm, or there is metastatic disease elsewhere, chemotherapy is used. In small, good-risk tumors, surveillance is an option. Note that there is no poor-risk seminoma, so even metastatic disease is curable.

Table 8-14: TNM Classification of Germ Cell Tumors

I	Confined to testes with normal or abnormal serum tumor markers
II	Lymph node involvement with LDH < 1.5 x N, β-hCG < 5,000, and AFP < 1,000
	IIA: Lymph node or lymph node mass < 2 cm IIB: Lymph node or lymph node mass 2–5 cm IIC: Lymph node or lymph node mass > 5 cm
III	Distant metastases or lymph node metastasis with tumor markers above levels listed for stage II

Treatment of **nonseminomas** is complicated, and only a general approach is reviewed here. The initial management always includes inguinal orchiectomy. Patients with disease limited to testes (negative abd/pelvic CT for adenopathy and negative tumor markers post-orchiectomy) can be managed with observation (20% relapse rate but salvage chemotherapy 90% successful), or with nerve-sparing retroperitoneal lymph node dissection (RPLND). A short course of adjuvant chemotherapy also is an option, especially when the poor prognostic feature of lymphovascular invasion is present. Patients with persistently elevated tumor markers after orchiectomy should always be treated with chemotherapy.

Stage II disease can be treated with either chemotherapy or RPLND. Adjuvant chemotherapy is used after RPLND, when bulky nodes are removed. Stage III disease is treated with chemotherapy. Patients sometimes have residual masses in the chest or the abdomen with normal tumor markers after chemotherapy. These masses often are mature teratomas and should be surgically excised since local growth and malignant transformation is possible.

PROSTATE CANCER

OVERVIEW

Prostate cancer is the most common cancer and the 2nd leading cause of cancer death (after lung cancer) in men in the U.S. Prostate cancers have been detected more frequently due to the availability of the prostate specific antigen (PSA).

QuickQuiz

- What is the association between benign prostatic hypertrophy and prostate cancer?
- What is the normal level of PSA in men 60–64 years of age?

95% of prostate cancers are adenocarcinomas. The major risk factors for prostate cancer are increased age, race (African-Americans > Caucasians > Asians) and family history. Diet (increased risk with fats) and high testosterone levels may also pose a significant risk.

Benign prostatic hypertrophy (BPH) is not a risk factor for prostate cancer.

SCREENING

Screening remains controversial. A European study (ERSPC) showed a 20% decrease in prostate cancer mortality in the PSA screening group. However, 1,410 men needed to be screened to prevent 1 death over 9 years. A U.S. study (PLCO) showed no decrease in mortality with screening, but in that study, more than 50% of the patients in the control group had at least 1 PSA during the study.

The American Cancer Society recommends that men have a discussion with their physician about the risks and benefits of screening. PSA and DRE should be done in those men older than 50 who chose to be screened if they have a life expectancy > 10 years.

The USPSTF guidelines released in 2012 recommend against screening for prostate cancer regardless of age, suggesting that harm outweighs benefit. They do qualify this statement by saying the use of PSA for screening is outside the scope of the USPSTF.

The American Urologic Association (AUA) released new guidelines in 2013 recommending against screening men < 40 years of age and recommended against routine screening for average-risk men between the ages of 40 and 54, men older than 70, or those with a life expectancy < 10 years.

Some primary care physicians and oncologists chose to screen African-American men who are outside the recommendation ranges of the ACS or AUA, given that the risk of prostate cancer is higher in this population. Men with multiple 1st degree relatives with prostate cancer also fall into this category.

The normal level of PSA varies with age. One study revealed that normal PSA levels were:

- 3.7 ng/mL for men 50–54 years of age
- 4.0 ng/mL for 55–59 years of age
- 5.4 ng/mL for 60–64 years of age
- 6.2 ng/mL for 65–69 years of age
- 6.6 ng/mL for men 70–74 years of age

If the rectal exam is suggestive, and/or the PSA is > 4 ng/mL (or > age-specific normal values), transrectal ultrasound-guided needle biopsies (12 cores) are performed for diagnosis.

STAGING OF PROSTATE CANCER

The TNM staging system (Table 8-15) is the most widely utilized. The TNM system is able to distinguish disease confined to the prostate (T1–T2) from disease that extends outside the gland (T3–T4). A limitation of the TNM system is its failure to predict organ-confined disease in patients diagnosed with prostate cancer due to an elevated PSA with clinical T1 or T2 disease.

A combination of pretreatment tumor stage, PSA level, and tumor grade (better known as the Gleason grade) can predict pathologic stage and risk of prostate cancer

Table 8-15: TNM Staging of Prostate Cancer

Tumor Stage	Substage
T1 Clinically inapparent tumor neither palpable nor visible by imaging	T1a: tumor incidental histologic finding in 5% or less of tissue resected
	T1b: tumor incidental histologic finding in more than 5% of tissue resected
	T1c: tumor identified by needle biopsy (e.g., because of elevated PSA)
T2 Tumor confined within the prostate	T2a: tumor involves 1/2 of lobe or less
	T2b: tumor involves more than 1/2 of lobe but not both lobes
	T2c: tumor involves both lobes
T3 Tumor extends through the prostate capsule	T3a: extracapsular extension (uni- or bilateral)
	T3b: tumor invades the seminal vesicles(s)
T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall	
N Regional lymph nodes assessed	NX: not assessed
	N0: no regional lymph node
	N1: metastasis in regional lymph node
M Distant metastases	M0: no distant mets
	M1: distant mets present
	M1a: non-regional lymph nodes
	M1b: bone(s)
	M1c: other site(s) with or without bone disease

Adapted from AJCC Cancer Staging Manual, Sixth Edition (2002).

ONCOLOGY

recurrence after radical prostatectomy. The Gleason grade is an additive scoring system between 2 (least aggressive) and 10 (most aggressive) used to describe the 2 most prevalent histologic patterns of the prostate cancer.

Pretreatment staging of prostate cancer includes a bone scan and CT scan of the pelvis because the bone and lymph nodes are by far the most likely sites of metastasis. In patients who elect surgery, lymph nodes are often sampled at the time of surgery.

TREATMENT OF PROSTATE CANCER

All treatments for prostate cancer can have serious side effects (such as impotence and urinary incontinence). For this reason, active surveillance (PSA q 6 months; digital rectal exam q 12 months; repeat prostate biopsy q 12 months) is often appropriate for older patients and patients with early-stage, low-risk disease. Patients with asymptomatic metastatic disease or PSA elevation after primary therapy also can be observed, with therapy (androgen deprivation) delayed until rapid PSA doubling time or symptom development.

Radical prostatectomy (RP) is reserved for patients with clinical T1–T2cN0M0 disease with a life expectancy of > 10 years. Radiation therapy (RT) can be offered to patients with clinical T1–T3bN0M0 with an acceptable life expectancy. Data support the use of androgen deprivation therapy along with radiation in patients with Gleason 7–10 disease.

Also remember that pretreatment PSA, tumor stage, and Gleason grade are helpful in predicting extracapsular spread. For example, patients with T1–T2 lesions with a high pretreatment PSA (> 10–20 ng/mL) or high Gleason grade (8–10) are less likely to have organ-confined disease and are more suitable for RT.

Hormonal therapy consists of androgen deprivation. This is achieved by a LHRH agonist (leuprolide, goserelin) combined with an androgen receptor antagonist (flutamide, bicalutamide) or orchiectomy. Hormonal therapy was once thought of as benign treatment, but there are significant adverse effects: weight gain, osteoporosis, gynecomastia, loss of muscle mass, anemia, sexual dysfunction, hot flashes, and an increased risk of diabetes. In retrospective analysis, hormonal therapy has been associated with a 5–8% increased risk of cardiac mortality. Hormonal therapy can be appropriately offered to several categories of prostate cancer patients:

- Those with metastatic disease (best reserved for symptomatic patients or patients with a rapidly rising PSA)
- Those with a PSA-only recurrence after primary therapy with a short PSA doubling time (< 6–10 months)
- Those with N+ disease discovered after RP: adjuvant therapy for 36 months
- Those undergoing RT (adjuvant therapy for 4–24 months in those with Gleason 7–10 disease)

Eventually, most patients with metastatic disease become refractory to hormonal therapy. This is referred to as androgen-independent prostate cancer (AIPC).

Treatment options for AIPC include:

- Alternative hormonal therapy: corticosteroids, ketoconazole, estrogens, and abiraterone (inhibits the enzyme CYP17, which is required for the formation of the testosterone precursors DHEA and androstenedione).
- Immunotherapy with sipuleucel-T for patients with little to no symptoms from metastasis has been shown to prolong overall survival. In this therapy, autologous antigen-presenting cells from the patient are collected, activated with GM-CSF and prostate acid phosphatase, and then reinfused.
- Chemotherapy: taxanes (specifically docetaxel and the semi-synthetic taxanes cabazitaxel because each has shown survival benefit), mitoxantrone, estramustine.
- Palliative RT to painful bone disease.
- Radiopharmaceuticals.

Bisphosphonates are useful in decreasing bone pain from metastases and decreasing osteoporosis associated with hormonal therapy. Once again, denosumab is available to prevent skeletal-related events.

PROSTATE CANCER PREVENTION

Based on a recent randomized trial, ASCO recommends having a discussion with patients regarding the potential 25% decreased risk of prostate cancer with use of finasteride, a 5-α-reductase inhibitor, for 7 years. Since patients in the treatment arm had a higher percentage of high-grade prostate cancers, patients need to be warned about that potential risk.

HEAD & NECK CANCER

Head and neck cancer: 90% of patients are smokers and 75% abuse alcohol; thus, most are preventable. There is increased head and neck cancer with smoking, alcohol, chewing tobacco, and HPV 16/18 infections. 95% of head and neck cancers are squamous/epidermoid.

If a suspicious cervical node is present, diagnose with FNA, and, if positive for squamous cell carcinoma with unknown primary, most recommend doing CT and/or MRI staging of the head/neck. This is commonly followed by panendoscopy.

In early stage disease, there is a real potential for cure with surgery and/or radiation therapy. Effort should be made to preserve function. Recent clinical trials have demonstrated that the addition of chemotherapy or biologic therapy (cetuximab, an EGFR inhibitor) with RT as primary therapy improves outcomes in head and neck cancer. If the disease is metastatic, treatment is palliative,

Quick Quiz

- Where are the likely sites of metastases in patients with prostate cancer?
- Name the side effects of androgen-deprivation treatment.
- What drug has been shown to actually decrease the risk of prostate cancer when used long-term?

ordinarily with cisplatin, 5FU, taxanes, or cetuximab. Patients who have HPV-positive tumors respond better to treatment.

CANCER OF UNKNOWN PRIMARY

These account for 4–5% of all invasive cancers. In all cases, immunohistochemistry and imaging with CT and/or PET scan may be helpful. Classification by histologic group determines further workup and treatment:

- Adenocarcinoma: accounts for 70% of cases. In a woman with isolated axillary nodes, consider breast MRI and treat as stage II breast cancer. Often, occult primary tumors may be found at mastectomy. In a woman with peritoneal carcinomatosis or ascites, treat as a stage III ovarian cancer. Men with blastic bone metastases or an elevated PSA may respond to treatment for prostate cancer.
- Poorly differentiated carcinoma: accounts for 20% of cases. Consider germ cell tumors. Elevated LDH, AFP, and/or β-hCG may suggest extragonadal germ cell tumor, especially if retroperitoneal or mediastinal site of disease, and should be treated as a stage III germ cell tumor.
- Neuroendocrine tumors: high-grade neuroendocrine tumors are aggressive and typically respond to chemotherapy, although the response is usually short-lived. Determining the primary site is not commonly of great importance because all forms of aggressive neuroendocrine cancer are treated with the same chemotherapy regimens (treated like small cell lung cancer with a platinum agent and etoposide).

MISCELLANEOUS

For cancers of the colon, lung, kidney, endocrine system, and CNS, see, respectively: Gastroenterology, Book 1; Pulmonary Medicine, Book 2; Nephrology, Book 2; Endocrinology, Book 4; Neurology, Book 5.

One quick note to remember: An isolated supraclavicular node has a high risk of malignancy, and its primary depends on which side it arises. If it's on the left—look for an abdominal tumor (GI, GU); on the right—suspect mediastinum, lungs, or esophagus.

CARCINOID

Carcinoids are neuroendocrine tumors that generally occur in the appendix (50%), small bowel, or rectum. These tumors are usually asymptomatic—especially the rectal carcinoids—until they have metastasized to the liver or lungs. Carcinoids are seen in MEN1. Hormone-secreting carcinoids produce serotonin, bradykinins, GH, ACTH, calcitonin, and prostaglandins, resulting in the "carcinoid syndrome."

Carcinoid syndrome consists of a triad:

1) Flushing
2) Valvular heart disease
3) Diarrhea

These symptoms are especially prominent in hormone-secreting carcinoids. Initial evaluation should include a urinary 5-hydroxyindoleacetic acid (5-HIAA) level and a serum chromogranin A level.

Treatment: Surgical resection is done for localized disease (< 1 cm rarely has metastases). There is an 80% cure rate for localized carcinoid. If the carcinoid has metastasized, the treatment is typically symptomatic. Even metastatic carcinoid is a slowly progressive and fairly benign disease, and often can be managed with symptomatic therapy for many years with little difficulty (e.g., using an antidiarrhea medication, avoiding offending foods and alcohol). The somatostatin analog, octreotide (Sandostatin®), can help control symptoms and is now available as a monthly injection.

CARCINOGENS

Agents and processes that can cause cancer, and what they typically affect:

Tobacco: lung, bladder, head and neck, and esophagus. Tobacco is related to 30% of U.S. cancer-related deaths.

Alcohol: liver, head and neck, and esophagus.

Tobacco + alcohol: synergistic effect on the development of head and neck and esophageal cancers.

Asbestos: lung, mesothelioma of the pleura, and abdominal peritoneum (much increased risk if combined with tobacco use).

Estrogens: uterine, vaginal, and breast cancers. Both birth control pills and postmenopausal estrogens appear to have a slight increase in risk after 5 years of use; however, the NCI is currently conducting a national study to evaluate this risk.

Nitrites: stomach.

Animal fat: colon, breast, and prostate.

Ionizing radiation: leukemia and thyroid. There is a slightly increased risk of breast cancer in Hodgkin patients who received radiation therapy. Generalized, high-dose exposure to radiation (e.g., nuclear bomb) is associated with an increased risk of all malignancies except CLL.

Ultraviolet radiation: skin (basal cell, squamous cell, and melanoma).

Radon gas: lung.

Viruses:

- HHV 8 (human herpesvirus 8): Kaposi sarcoma, primary effusion lymphoma
- Hepatitis B and C: liver cancer
- HPV (human papillomavirus): cervical, anal, and oropharyngeal cancers
- EBV: Burkitt lymphoma, nasopharyngeal carcinoma, and 30–50% of AIDS-related lymphomas (and 100% of AIDS-related primary CNS lymphoma)
- HIV: Kaposi sarcoma, non-Hodgkin lymphoma
- HTLV-1: adult T-cell leukemia

CHEMOTHERAPY AND BIOLOGIC THERAPY

NOTE

See Table 8-16 and Table 8-17 on the following pages. The main things to know are the major toxicities of the drug or drug classes.

CHEMOTHERAPY DRUG HIGHLIGHTS

Capecitabine (Xeloda®) is an oral chemotherapeutic agent approved for the treatment of colon cancer and advanced breast cancer. It is activated/converted by the malignant cell into 5-fluorouracil. Diarrhea can lead to life-threatening volume loss. Affects warfarin metabolism leading to labile INRs and bleeding risk.

Rituximab (Rituxan®) is a chimeric monoclonal antibody with significant activity in low-grade lymphomas. The antibody is directed against the CD20 antigen, which is found on the surface of almost all B lymphocytes of the low-grade lymphomas and normal, circulating B lymphocytes. CD20 is important because it regulates early steps in the activation process for cell-cycle initiation and differentiation. Rituximab is approved as 1st line therapy for low-grade and high-grade B-cell lymphomas in combination with chemotherapy. Ofatumumab is another anti-CD20 monoclonal antibody used for refractory CLL.

Brentuximab is an anti-CD30 monoclonal antibody bound to an antimitotic drug conjugate. Binding to CD30 internalizes the molecule and activates the drug conjugate. It is used in refractory Hodgkin lymphoma and other CD30+ lymphomas.

Denileukin diftitox (Ontak®) is a unique compound that binds to the IL-2 receptor (CD25) on T cells. After binding, the diphtheria toxin is introduced into the cell, which then inhibits protein synthesis. It is used in patients with cutaneous T-cell lymphomas. It is associated with hypersensitivity reactions.

Imatinib mesylate (Gleevec®) binds to tyrosine kinase and prevents downstream signaling for cellular proliferation. It is approved for use in CML and gastrointestinal stromal tumors (GIST). Also approved for CML are 2 additional tyrosine kinase inhibitors, **dasatinib** and **nilotinib**.

Trastuzumab (Herceptin®) is a monoclonal antibody directed at the receptor on the surface of the breast cancer cell. It is exciting because its development was based on our knowledge of the molecular biology of the breast cancer cell. *HER2/neu* is an oncogene, which is overexpressed in some breast cancers. This drug is approved for patients with tumors known to be associated with overexpression of *HER2/neu*. Cardiotoxicity is the main side effect. It causes a usually reversible cardiomyopathy that may be asymptomatic or present as heart failure.

Interferon-alpha is effective against Kaposi sarcoma in AIDS patients if the CD4 count is > 200/mL. There is evidence that adjuvant therapy with high-dose interferon in high-risk melanoma delays recurrence.

Interleukin-2 has been approved for the treatment of renal cell carcinoma. IL-2 occasionally produces complete remissions in these patients! It also may be of benefit in malignant melanoma.

IL-2 and GM-CSF can cause capillary leak syndrome. This syndrome occurs when there is increased capillary permeability, leading to extravasation of the intravascular fluid, which then leads to hypotension, decreased organ perfusion, organ failure (such as liver or kidney failure), cardiac arrest, and intestinal perforation.

Ipilimumab is an anti-CTLA4 monoclonal antibody that enhances T-cell activation and proliferation approved for metastatic melanoma. It carries a significant side effect profile, including hypophysitis and colitis due to its immune effects.

Retinoids are differentiating agents. There have not been many uses found. Two uses are cis-retinoic acid for cutaneous T-cell lymphoma and all-trans-retinoic acid (ATRA) for acute promyelocytic leukemia.

Carboplatin, like cisplatin, is used for ovarian, testicular, and lung cancer (and may be used for head and neck cancer). Dosing requires calculations that take into account the patient's creatinine clearance.

Compared to cisplatin, it has less nausea and vomiting and less nephrotoxicity. Carboplatin has a stronger myelosuppressive effect; its main toxicity is thrombocytopenia, which is dose-related; a nomogram is available that shows dose vs. expected platelet level. Hypersensitivity may develop after multiple doses.

Oxaliplatin is another platinum agent. It has superior activity in colorectal cancer when combined with 5-fluorouracil. Similar to carboplatin, it produces less

Quick Quiz

- Which cancers are associated with a history of radiation therapy?
- Know these unique chemotherapy drugs: rituximab, imatinib, trastuzumab, ATRA, paclitaxel, and lenalidomide. (Also, tamoxifen from the breast cancer section.)
- Know the following associations:
  - Cyclophosphamide and hemorrhagic cystitis
  - Platinum compounds and ototoxicity
  - Doxorubicin and cardiomyopathy
  - 5-FU and sun sensitivity
  - Hydroxyurea and leg ulcerations
  - Rituximab and infusion reactions, including bronchospasm
  - α-interferon and flu-like illness
- What is the dose-limiting toxicity of vinblastine? Vincristine?
- Which agent causes magnesium wasting?

nephrotoxicity, nausea, and vomiting than cisplatin. However, it is associated with peripheral neuropathy that is exacerbated by exposure to cold temperatures. Additionally, hypersensitivity may develop after multiple doses.

Idarubicin is an anthracycline analog that is used for acute myeloid leukemia (AML).

Paclitaxel (Taxol®) is derived from the bark of the Western yew tree. It is approved for use in ovarian, breast, and lung cancer. It can cause anaphylactic infusion reaction.

Docetaxel (Taxotere®) is a synthetic taxane approved for treatment of breast, prostate, and lung cancers.

Irinotecan (Camptosar®) is an inhibitor of topoisomerase I, an enzyme involved in DNA replication. It is approved for the treatment of metastatic colon cancer. Severe diarrhea can result.

BCG bladder installation improves disease-free survival in superficial bladder cancer.

2-CDA (2-chlorodeoxyadenosine; cladrabine) is an extremely interesting drug used in hairy cell leukemia, CLL, and low-grade lymphomas. It induces apoptosis, the normal programmed death of cells. Cells in such diseases as hairy cell leukemia, CLL, and low-grade lymphomas are thought to "lose" their programming for maturation and to stay young and immortal while still dividing. 2-CDA essentially re-programs that portion of the cell's gene to function normally and to go on to die naturally. 2-CDA is sometimes curative for hairy cell leukemia.

Fludarabine and **pentostatin** are other drugs that appear to work similarly to 2-CDA. They are used to treat low-grade lymphomas and CLL.

Vinorelbine is an agent with activity in breast cancer and lung cancer.

Pemetrexed (Alimta®) is an antimetabolite used in combination or as a single agent for the treatment of adenocarcinoma of the lung. It is ineffective in the squamous cell subtype of non-small cell lung cancer. It also is approved for the treatment of mesothelioma. Vitamin B_{12} and folate replacement are necessary to avoid excess toxicity.

Bendamustine is a nitrogen mustard derivative alkylating agent that also has a purine ring. It is used in indolent lymphomas, particularly CLL and follicular lymphoma, as either single agent therapy or in combination with rituximab.

Cetuximab (Erbitux®) is a monoclonal antibody against the epidermal growth factor receptor (EGFR) that is FDA-approved for refractory colon cancer and head and neck cancer. It is likely to have activity in other cancers that express EGFR. It can cause an acne-like rash.

Erlotinib (Tarceva®) is an oral agent that also binds to the EGFR. It is used in lung cancers that express a mutation in the EGFR and in refractory lung cancer. It can cause an acne-like rash.

Bevacizumab (Avastin®) is a monoclonal antibody directed against the vascular endothelial growth factor (VEGF) receptor, preventing tumor-associated angiogenesis. It is FDA-approved for use in metastatic colon cancer, glioblastoma, non-squamous non-small cell lung cancer, and metastatic renal cell cancer.

Thalidomide (Thalomid®) is a unique agent with a unique history. It is an agent that is associated with severe birth defects and was removed from circulation several decades ago. Thalidomide has significant activity in multiple myeloma, but its mechanism of action is not understood. Nevertheless, it has regained FDA approval for multiple myeloma. It can still cause severe birth defects, so patients need to undergo a comprehensive education program before the drug is prescribed. It also is associated with peripheral neuropathy.

Lenalidomide (Revlimid®) is an antineoplastic agent with similarities to thalidomide. It is approved for the treatment of multiple myeloma and the 5q- myelodysplastic syndrome. Lenalidomide also can cause birth defects similar to thalidomide.

Bortezomib (Velcade®) is part of a new class of agents: proteasome inhibitors. Inhibition of proteasomes prevents targeted proteolysis that affects intracellular signaling cascades. This agent also is used for multiple myeloma and mantle cell NHL.

Sorafenib (Nexavar®) and **sunitinib** (Sutent®) are biologic agents that target intracellular signaling pathways. Both have proven activity in renal cell cancer.

Table 8-16: Common Chemotherapy Agents (Table 1 of 2)

CLASS / ACTION	Agents	Major Dose-Limiting Side Effects	Other Side Effects
ALKYLATING AGENTS Interfere with cross-linking of DNA Class side effects: • Dose-limiting myelosuppression • Azoospermia, which may be permanent • Amenorrhea • Secondary leukemias	Cyclophosphamide	Myelosuppression, hemorrhagic cystitis	Amenorrhea and male sterility
	Ifosfamide	Less myelosuppressive but more hemorrhagic cystitis than cyclophosphamide	
	Melphalan	Myelosuppression (esp. platelets)	Most secondary leukemia Amenorrhea and male sterility No hemorrhagic cystitis
	Busulfan	Strong myelosuppression	Interstitial pneumonitis Progressive pulmonary fibrosis
	Mechlorethamine (nitrogen mustard)	Myelosuppression	Amenorrhea and male sterility Phlebitis N/V
	Chlorambucil	Myelosuppression (usually mild)	Amenorrhea and male sterility
	Nitrosoureas (the CNUs: BCNU and CCNU)	Myelosuppression	Pulmonary fibrosis, N/V
	Platinum compounds: Cisplatin Carboplatin Oxaliplatin	Neurotoxicity, including ototoxicity Nephrotoxicity	Myelosuppression, N/V Alopecia
TOPOISOMERASE INHIBITORS Interfere with topoisomerase I or II, causing distortion of DNA cross-linkage	Topotecan (topo-I) Irinotecan (topo-I)	Neutropenia	Anemia, dyspnea, fever, neutropenia, thrombocytopenia
	Etoposide (topo-II) Teniposide (topo-II)	Leukopenia	Fever, hypotension, bronchospasm
	Anthracyclines (topo-II): Doxorubicin (Adriamycin®) Daunorubicin (Doxil®) Idarubicin	Myelosuppression Mucositis Cardiomyopathy	Alopecia, N/V

Sorafenib also is approved for hepatocellular carcinoma. Patients have a significant chance of developing arterial thrombolic events (ATEs) and hypertension.

Vemurafenib (Zelboraf®) targets the BRAF intracellular pathway. It is approved for metastatic melanoma.

Temsirolimus is a mammalian target of rapamycin (mTor) inhibitor approved for renal cell cancer.

Abiraterone (Zytiga●) was approved in 2011 for castrate-resistant prostate cancer and is a 17-alpha hydroxylase inhibitor. Its major side effects include edema, hypertriglyceridemia, and transaminitis.

Cabazitaxel (Jevtana●) is approved to treat metastatic prostate cancer, and its major toxicities include significant myelosuppression along with diarrhea.

MAIN SIDE EFFECTS OF CHEMOTHERAPEUTIC AGENTS

Know all the following:

Alkylating agents and procarbazine are very toxic to the germinal cells of the testes; MOPP (mechlorethamine, vincristine, procarbazine, prednisone), a previously used treatment for Hodgkin lymphoma, caused permanent sterility in > 90% of males > age 25.

Alkylating agents are leukemogenic.

Bleomycin can cause irreversible pulmonary fibrosis.

Vinblastine: Myelosuppression is dose limiting.

Vincristine: Neurotoxicity is dose limiting. Virtually all patients lose deep tendon reflexes, develop paresthesias of the digits, and, over time, develop

Table 8-17: Common Chemotherapy Agents (Table 2 of 2)

CLASS / ACTION	Agents	Major Dose-Limiting Side Effects	Other Side Effects
ANTIMETABOLITES Serve as false substrates for biochemical reactions or interfere with enzymes involved with these reactions	Pyrimidine-analog agents: Fluorouracil (5-FU) Cytarabine (Ara-C) Gemcitabine	Mucositis, some myelosuppression 5-FU: plus cerebellar ataxia	Alopecia, N/V 5-FU: plus sun sensitivity
	Purine-analog agents: Fludarabine (Ara-A) Cladribine (2-CDA) Pentostatin 6-mercaptopurine (6-MP) 6-thioguanine (6-TG)	Myelosuppression	N/V Opportunistic infections Hemolytic anemia
	Other: Hydroxyurea	Moderate leukopenia	N/V Hyperpigmentation Leg ulcers
	Other: Methotrexate	Myelosuppression, mucositis, neurotoxicity	Alopecia Liver and lung damage Diarrhea
ALKALOIDS Derived from plants	Vinca Alkaloids: Vincristine Vinblastine Vinorelbine	Neurotoxicity Myelosuppression	Vincristine: muscle weakness; SIADH in kids; more neurotoxic than myelosuppressive Vinblastine and vinorelbine: bone pain; more myelosuppressive than neurotoxic
	Taxanes: Paclitaxel (Taxol®) Docetaxel (Taxotere®)	Myelosuppression, esp. neutropenia	Hypersensitivity reactions (esp. with paclitaxel) Fluid retention (docetaxel) Alopecia (both)
BIOLOGICALS	Monoclonal antibodies: Trastuzumab (Herceptin®) Rituximab (Rituxan®)		Trastuzumab: infusion reaction, CHF Rituximab: infusion reaction, hypersensitivity reaction (including bronchospasm)
	Interferon-alpha		Flu-like syndrome, N/V, skin rash, diarrhea, myelosuppression
	Interleukin-2 (IL-2)		Capillary leak syndrome contributing to liver or kidney failure, cardiac arrest, intestinal perforation

muscle weakness—especially of the quadriceps in adults. Children develop footdrop. Taxanes, cisplatin, oxaliplatin, bortezomib, and thalidomide also commonly cause peripheral neuropathy.

Cisplatin causes magnesium wasting, neurotoxicity, nephrotoxicity, and also is one of the most emetogenic chemotherapy agents.

Anthracyclines are associated with dose-dependent cardiomyopathy. **Trastuzumab** also causes cardiomyopathy.

Taxanes, **monoclonal antibodies**, and **carboplatin** are most frequently associated with significant infusion-related hypersensitivity reactions.

Anthracyclines, **mitomycin**, and **nitrogen mustards** are vesicants. Extravasation can lead to severe skin and tissue damage that may require surgical intervention. Consider central intravenous access in these agents.

EGFR inhibitors (cetuximab, erlotinib) commonly cause an acne-like skin rash.

Many targeted **biologic agents** (e.g., bevacizumab, sorafenib, sunitinib) are associated with an increased risk of vascular events and hypertension.

USE OF GROWTH FACTORS

Erythropoietin has 2 forms: epoetin (Epogen®) and darbepoetin, a long-acting form. Remember to keep iron stores > 100 with oral iron, as needed.

Erythropoietin is indicated for the treatment of the following:

- Chemotherapy-induced anemia with Hgb < 10. Remember that there is a risk of thrombosis, especially if given when hemoglobin > 12 g/dL.
- Anemia of chronic renal failure.
- Anemia in HIV patients taking zidovudine (AZT).

Erythropoietin is not for use in anemia due to cancer, because it may worsen survival, especially in head and neck and breast cancers.

Thrombopoietin agonists (romiplostim and eltrombopag) are approved for the treatment of chronic ITP that have an insufficient response to corticosteroids or IV IgG.

Table 8-18: Uses of Bone Marrow Transplant (BMT)

		Disorders	Effectiveness / Notes
Malignant Diseases		AML	40–70% cure if done during 1st complete remission.
		ALL	Normally no benefit over chemo but useful in 1st remission of Ph+ ALL. Also done in 2nd remission if 1st remission is short.
		CML	Treatment of choice for CML in accelerated phase, blast phase, or imatinib failure.
		Myelodysplastic synd.	Useful in certain cases.
	†	CLL	Autologous and allogeneic BMTs have been used in young patients with CLL. Short-term follow-up reveals 50% disease-free.
	†	Non-Hodgkin lymphoma	May be used as primary Tx in some patients (60–90% disease-free survival at 2–3 yrs). Autologous.
	†	Hodgkin lymphoma	Not the normal therapy but shows promise! Autologous appears better than allogeneic. One trial: 90% disease-free survival at 3 years.
	†	Multiple myeloma	Autologous BMT has a much lower mortality rate than allogeneic BMT. Moderately successful.
	†	Breast cancer	Awaiting treatment recommendations for breast cancer.
	†	Testicular cancer	Disease-free survival in 10–20% with severe disease suggests much better results if done earlier.
Nonmalignant Diseases		Thalassemia	75% 1-year disease-free survival.
		Sickle cell anemia	Potentially curable with BMT.
		Aplastic anemia	> 50% disease-free survival after BMT for severe aplastic anemia.
		Genetic disorders	Most genetic immunologic or hematopoietic disorders are potentially curable.

Note: All BMTs require an HLA-identical donor.

† Autologous BMTs. All others are allogeneic.

Granulocyte colony-stimulating factor (G-CSF) is indicated for the treatment of the following:

- Neutrophil recovery after treatment for AML or post-bone marrow transplant
- Mobilization of stem cells for use in stem cell transplantation
- Neutrophil recovery after myelosuppressive chemotherapy regimens (does not improve survival, but does decrease the number of days of hospitalization due to febrile neutropenia)
- Severe chronic neutropenia (cyclic, congenital, or idiopathic).

There are 2 forms of G-CSF: filgrastim (Neupogen®) and pegfilgrastim (Neulasta®), which is longer-acting.

BONE MARROW TRANSPLANTATION

Table 8-18 reviews the indications for bone marrow transplantation.

Allogeneic bone marrow transplantation is from one person to another. If these people are identical twins, it is more specifically called a syngeneic transplantation.

Autologous BM transplantation is the use of the patient's own bone marrow.

For information on post-transplant infection risks, see Solid Organ Transplantation in Infectious Disease, Book 1.

FOR FURTHER READING

HEMATOLOGY AND HEMATOLOGIC MALIGNANCIES

[Guidelines in blue]

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THE IMMUNE SYSTEM

OVERVIEW

The Innate Immune System

The innate immune system is rapid-acting, nonspecific, and has no memory. It has many components, which include complement, macrophages, and natural killer (NK) cells. It is the first line of defense after the skin.

The Adaptive Immune System

The adaptive immune system is much slower than the innate to get started, but is very specific and has memory.

It consists of T and B cells, as well as immune globulins (Igs), and is a second line of defense that is activated by the innate immune system.

The adaptive immune system can be divided into humoral and cell-mediated components:

- **Humoral**: B cells, plasma cells, and immunoglobulins
- **Cell-mediated**: T cells, activated macrophages, and activated NK cells

Innate vs. Adaptive Immunity

The innate immune system is the foundation on which the more sophisticated adaptive immune system rests. The innate system not only protects the body while the adaptive immune system gears up, but it also helps direct the response. The innate immune system, in general, needs messages to prevent it from killing, while the adaptive immune system needs messages (usually from the innate immune system) to allow it to kill.

The key difference between the 2 systems can be found in their respective receptors:

- **Innate** immune system receptors are generic, germline-encoded receptors (e.g., Toll-like receptors). They allow a quick but non-specific response—one that is very rapid but recognizes only a limited number of microbial patterns rather than a large variety of specific pathogens. Think of the innate immune system as the "first responders" to a new attack.
- **Adaptive** immune system receptors are highly specific receptors (T-cell receptors [TCRs], B-cell receptors [BCRs], and immunoglobulins [Igs]), which are refined to be as precise as possible for the pathogen. This system has the ability to recognize a seemingly infinite variety of pathogens. Once these highly specific receptors have served their purpose, the body keeps a few of them around in case it needs them again in the future—so it can react much more quickly next time (memory).

Innate and Adaptive Overlap

It is important to understand that there is significant overlap between the innate and adaptive immune systems. For example, macrophages and NK cells initially function as part of the innate system. However, after being activated by T cells, they then act as part of the adaptive immune system. Similarly, the "classical pathway" of the complement system uses antibody (Ig) to initiate its activity. Antibody involvement in the complement system is an example of how the adaptive immune system provides memory.

Overlap is again demonstrated by a group of innate-like cells of the adaptive immune system that are more rapid acting and less specific.These innate-like immune cells include:

- γ:δ T cells and natural killer T cells
- B-1 cells (an innate-like version of B cells)

CELLS OF THE IMMUNE SYSTEM

Cells in the immune system are divided into 2 categories: lymphoid and myeloid cells. We'll outline the types here and discuss the need-to-know points.

Lymphoid cells:

- Lymphocytes (B and T cells):
  - B cells:
    - B-1 cells (innate-like)
    - B-2 cells (what we typically call "B" cells)
    - Marginal B cells (innate-like)
  - T cells:
    - α:β T cells: consist of CD4 and CD8 T cells
    - γ:δ T cells (innate-like)
    - Natural killer T (NKT) cells
- Natural killer cells (different from the similarly named NKT cells!)

Myeloid cells:

- Granulocytes:
  - Neutrophils
  - Eosinophils
  - Basophils
- Professional antigen-presenting cells:
  - Monocytes/Macrophages
  - Dendritic cells
- Other:
  - Mast cells
  - Erythrocytes
  - Platelets

HLA ANTIGENS

The major histocompatibility molecules are required by the body to differentiate self vs. non-self material. The major histocompatibility complex (MHC) of genes is located on chromosome 6. The human MHC is called human leukocyte antigen (HLA). There are 3 classes of HLA antigens (I, II, and III).

Class I HLA antigens (HLA-A, -B, and -C) are on most nucleated cells. They present non-self material to CD8+ T cells and play a role in transplant rejection, neoplasms, and viral infections.

Class II HLA antigens (HLA-DP, -DQ, and -DR) are on antigen-presenting cells, which include monocytes/macrophages, Langerhans cells, dendritic cells, and B cells (so these cells have both class I and class II HLA antigens). They mediate the reaction between macrophages, T cells, and B cells. The CD4+ T cells recognize material presented only by the class II antigens.

Class III HLA antigens consist of a few cytokines, like TNF and lymphotoxin, and several complement component structures.

LYMPHOID CELLS

LYMPHOCYTES

T Cells

Overview

Review: "Clusters of differentiation" (CD) markers are like "name tags" and allow one to "differentiate" one immune cell from another. For example:

T cells are CD2+ and CD3+. T cells also usually have either a CD4 or CD8 protein on their surface (more on this below).

Mature B cells are CD19+ and CD20+. Natural killer cells are CD16+ and CD56+.

Functions of T cells:

- Destroy intracellular and other bacteria (especially gram-negative), viruses, fungi, parasites, and mycobacteria
- Regulate antibody production by B cells

All T cells have receptors (T-cell receptor = TCR), which are antigen-specific binding sites composed of 2 subunits (the majority being alpha and beta and a minority being the innate-like gamma and delta). The TCR is always associated with a CD3 complex, which allows for intracellular signaling.

Again: T cells recognize antigen only if it is presented in the context of an MHC molecule. This is the key concept of MHC restriction! CD8+ T cells recognize antigen only if it is presented with a class I HLA antigen, whereas CD4+ T cells recognize antigen only if it is presented with a class II HLA antigen. (A nice way to remember this: CD8 x MHCI = 8, CD4 x MHCII = 8.)

CD4+ T Cells

CD4+ T cells are the primary defense against exogenous antigens. The CD4+ T cells are divided into several subsets:

1) **TH1**—activates CD8+ T cells and leads to cell-mediated immunity.
2) **TH2**—activates B cells to produce antibody and leads to humoral immunity.
3) **TH17**—plays a role in immunity against fungi and bacteria, and in autoimmune disorders (including RA, MS, and IBD).

Again: Class II antigens appear only on professional antigen-presenting cells such as monocytes/macrophages, Langerhans cells, dendritic cells, and B cells.

How does CD4+ T cell activity get induced? An antigen-presenting cell such as a macrophage ingests a foreign particle or microorganism. The foreign particle is processed and presented along with the class II HLA antigen to CD4+ T cells. These T cells, after being activated, induce B cells to convert to plasma cells and produce specific antibodies against that foreign particle.

HIV targets all CD4+ cells, including CD4+ T cells and other cells that express CD4, such as macrophages, monocytes, and microglial cells. By targeting and attacking CD4+ cells, HIV weakens the immune system, allowing opportunistic infections to occur.

CD8+ T Cells

The CD8+ cells are cytotoxic T cells. They are important in the defense against viruses and neoplastic cells. They are activated by neoplastic antigens and other antigens presented in association with class I HLA antigens. So most cell types can present antigen to CD8+ T cells!

T Regulatory Cells

T regulatory cells are a specialized subpopulation of T cells that modulate the activity of the immune system. This can be a confusing group of cells since it is made up of several different types of T cells (usually CD4+ but also CD8+ and others). The expression of the transcription factor FOXP3 controls the development and function of T regulatory cells. These cells regulate the immune response by secreting immunosuppressive cytokines like IL-10 and TGF-β. T regulatory cells help maintain tolerance to self-antigens, and genetic mutations in FOXP3 leads to overwhelming systemic autoimmunity.

NKT Cells

(Name alert! Don't confuse with "natural killer cells"—the innate lymphoid cells with a very similar name!)

Natural killer T cells have a twist on the concept of MHC restriction. They are restricted to a type of MHC-like molecules called CD1, which recognizes primarily lipids and glycolipids. They are so named because they share several features with natural killer cells, such as granzyme production and CD16 and CD56 expression.

B Cells

Some B cells, upon stimulation, become plasma cells (antibody-producing cells). B cells are surface membrane immunoglobulin positive (SmIg+); i.e., they have IgM and IgD on their surfaces, which distinguish them from T cells, B-cell precursors, and plasma cells. B cells are the most specific antigen-presenting cells. Mature B cells are CD19+ and CD20+.

Quick Quiz

- Explain the differences between innate and adaptive immunity.
- What are class II HLA antigens, and where are they located?
- What are the different functions between CD4+ and CD8+ T lymphocytes?
- What immunoglobulins are present on the surface of mature B cells?
- Characterize the various immunoglobulins: G, A, M, E, and D.

B cells can be stimulated to convert to plasma cells by either antigen alone or activated CD4+ T cells. Plasma cells produce specific antibodies. The specific antibodies can coat the surface of a foreign organism. The coating either identifies it as edible to the macrophages (opsonization) or initiates the complement cascade (complement activation). Specific antibodies can also neutralize bacterial toxins and viruses.

B cells, like monocytes/macrophages, have class II HLA antigens on their surfaces, so they also can present foreign antigens to CD4+ (helper) T cells. The activated T cells can then induce other B cells to convert to plasma cells and produce antibody.

NATURAL KILLER CELLS

(Name alert! Don't confuse with "natural killer T cells"—the similarly-named innate-like CD4+ T cells).

Natural killer (NK) cells are lymphoid cells that play a major role in the immune system response to tumors and viruses. They express CD16 and CD56 but not TCR or its associated CD3 molecules (an important difference between them and natural killer T cells!).

They are called natural killers because they are always in kill mode, and the cells they encounter must present themselves appropriately in order to not be killed. For example, all cells (except mature RBCs) must display class I HLA-E antigens on their cell surface in order to not be killed by natural killer cells.

Natural killer cells are an important component of the immune system because some viruses have evolved to reduce class I HLA expression on the host cell, protecting them from recognition and destruction by T cells. With natural killer cells, it is precisely this absence or reduction of class I HLA expression that causes the natural killer cell to kill (usually by inducing apoptosis) the infected cell.

In comparison, natural killer T cells, like all other T cells, require the antigen to be presented in association with an HLA antigen before they can become activated to kill.

MYELOID CELLS

Granulocytes: white blood cells with identifiable granules in their cytoplasm.

Neutrophils = polys = PMNs = segs (mature) and bands (immature). PMNs phagocytize microorganisms, especially those coated with antibodies. If PMNs are absent, patients get overwhelming pyogenic infections.

Eosinophils: involved in the pathology of allergic reactions but also in the immunologic defense against parasites.

Basophils are discussed under Immediate Hypersensitivity Reactions (page 9-6).

Professional antigen-presenting cells: Cells expressing both MHCI and MHCII. This is an exclusive group of cells consisting of 3 cell types:

1) B cells are the most specific, antigen-presenting cells.
2) Monocytes/macrophages eat opsonized microorganisms, process and present antigens, and secrete interleukin-1 (IL-1), which stimulates T cells.
3) Dendritic cells are scavengers that, when they ingest a pathogen, change conformation, travel to a lymph node, and activate lymphocytes.

Other:

- Mast cells are discussed under Immediate Hypersensitivity Reactions (page 9-6).
- Erythrocytes are covered in Hematology, Book 4.
- Megakaryocytes/platelets also are discussed in Hematology, Book 4.

ANTIBODIES

All antibodies (immunoglobulins) have the same basic structure (Figure 9-1 on page 9-4). Each monomer is composed of 2 heavy and 2 light chains that are held together by disulfide bonds. There are 5 immunoglobulin isotypes: G, A, M, E, and D. These isotypes are determined by differences in the structure of the constant regions of the heavy chains. All antibodies have 1 of 2 types of light chains, kappa or lambda.

Remember the following:

IgG is the main antibody in serum, and it is the major antibody in the immune response. It readily crosses the placenta. It has 4 subclasses (IgG1, IgG2, IgG3, and IgG4). IgG can activate complement.

IgA is the main Ig in secretions and is usually a dimer (2 immunoglobulins) with the J chain and a secretory component, which is actually just a piece of the epithelial or liver cell receptor attached to locally produced IgA. It is the main Ig secreted in breast milk. IgA does not activate complement.

IgM is the 1st Ig subtype produced in an infection. It is a monomer on the cell surface but is secreted as a pentamer (5 immunoglobulins), in which each monomer is

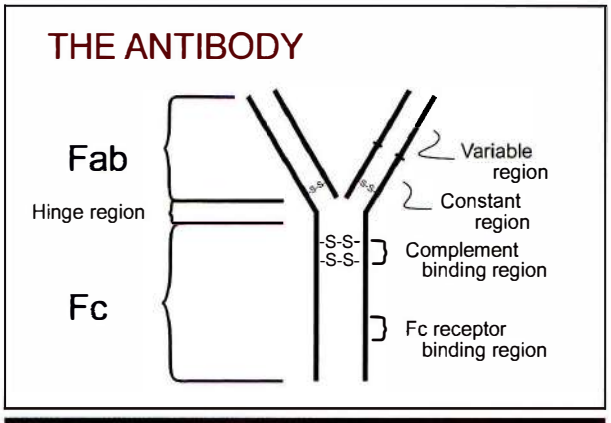

Figure 9-1: Antibody Structure

connected by a J chain. IgM is useful in diagnosis of a recent illness and can help distinguish acute vs. chronic infection. Because IgM is a pentamer, it is the best antibody for complement activation.

IgE is the Ig with the lowest concentration in normal serum but is a major factor in many allergic conditions, including asthma, allergic rhinitis, atopic dermatitis, and food allergies.

IgD is found in trace amounts on adult B cells, and its function is as yet undefined.

The variability in antibody specificity is due to the rearrangement of several regions within the antibody gene. Most of the variability is located in the complementarity determining regions (CDRs), also known as hypervariable regions.

Immunoglobulins (antibodies) bind specific antigens in the Fab region and then activate either cells or complement (discussed next), by means of the Fc region, to destroy the antigen-bearing material.

COMPLEMENT CASCADE

OVERVIEW

The 3 Complement Pathways

First, a brief review of the complement system. See Figure 9-2.

The complement system is a group of about 30 known plasma factors important in host defense and destruction of microorganisms. It is now known to have 3 main pathways: classical, lectin, and alternative. Through different mechanisms, they all perform the same function-—opsonizing target cells with C3b and then forming the "membrane attack complex."

Classical Pathway

The immunoglobulins (usually IgG and IgM) activate the classical pathway. The C1 complex (with q, r, and s subunits) initiates the response when a C1q subunit attaches to antibody in an antigen-antibody complex.

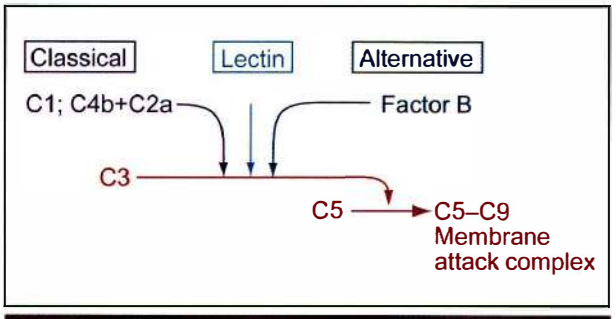

Figure 9-2: Summary of the Complement Cascade

C1q binds to the Fc portion of at least 2 IgGs (or 1 IgM pentamer), or it binds to the surface of the pathogen itself. Binding changes the conformation of the C1q. This activated C1 cleaves many C2 and C4, subcomponents of which (C2a and C4b) combine and form C4b2a ("C3 convertase"), which in turn activates many C3s.

Again: 1 IgM pentamer can initiate the classical pathway, but it generally takes at least 2 IgGs.

Lectin (or Mannose-Binding) Pathway

Lectins (mannose-binding lectin [MBL]; also called mannose- or mannan-binding proteins) bind mannose on the surface of pathogens. Then associated proteases cleave C2 and C4, and further steps are similar to the classical pathway. These MBLs are produced by an acute-phase response and are fairly nonspecific.

Alternative Pathway

C3 also is activated by the alternative pathway. C3 combines with a factor "B." This complex then activates more C3 and factor B, causing a cascade, which is normally kept under control by the inhibitory regulatory proteins "H" and "I." Both gram-positive and gram-negative cell walls directly activate the alternative pathway by spontaneous cleavage of C3.

A C3b-coated circulating bacterium is recognized, removed, and destroyed by Kupffer cells in the liver.

Common Terminal Pathway — Membrane Attack Complex

C3, when combined with either C4b2a or factor B, activates C5, which causes the formation of a C5-6-7-8-9 membrane attack complex (MAC). The MAC can poke holes in bacterial cell membranes and cause the bacteria to lyse.

HEREDITARY COMPLEMENT DEFICIENCIES

Hereditary Angioedema

Hereditary angioedema (HAE) is an autosomal dominant disorder caused by a decrease in C1 inhibitor (C1-INH) function. C1-INH normally inhibits the activity of the

QuickQuiz

- What is the cause of hereditary angioedema? What is the clinical presentation?
- Terminal complement deficiency is associated with which infection?
- What does the CH50 assay measure, and when is it used?

Cl complex (classical pathway) and MBL complex (lectin pathway). Lack of C1-INH function allows for increased complement activation resulting in a secondarily decreased C4 (because of ongoing consumption). Patients can have either a decreased C1 inhibitor enzyme level (85%, Type I) or a non-functioning C1 inhibitor enzyme (15%, Type II). Bradykinin is thought to be the key mediator in the angioedema attacks.

Patients have recurrent nonpitting edema with each episode, lasting 1–3 days. Unlike angioedema/urticaria caused by immediate hypersensitivity reactions, hereditary angioedema does not cause urticaria or itching.

Even minor trauma from dental procedures can precipitate attacks! Attacks may include laryngeal obstruction and very often affect the GI tract, causing severe abdominal pain.

Diagnosis: Screen by checking C4 levels (low). Then, check a C1-INH functional assay:

- If the C1-INH level also is low, then it is **Type I HAE**.
- If the C1-INH level is normal, it is due to a nonfunctioning C1-INH enzyme, and it is **Type II HAE**.

Treatment: Epinephrine is not effective. Fresh frozen plasma can be helpful when given before trauma, such as dental surgery. Androgens (danazol) increase C1-INH levels and decrease swelling episodes. Until recently, this was the only available preventive medication. New available therapies include plasma-derived C1-INH to prevent and treat attacks. A kallikrein inhibitor (ecallantide) and a bradykinin receptor antagonist (icatibant) are available for acute attacks.

C1, C2, and C4 Deficiencies

C1, C2, or C4 deficiency causes decreased activation of complement via the classical pathway. Most of the complement proteins are inherited as autosomal recessive genes. Although the alternative pathway takes up some of the slack, these patients still have recurrent sinopulmonary infections (and ear infections when young) with encapsulated bacteria. In patients with 1 abnormal gene, complement blood levels are about 1/2 normal. In these patients, there is an increased incidence of rheumatoid diseases—especially SLE!

C2 deficiency is the most common complement deficiency in North American Caucasians; thus, consider it in patients with early-onset SLE. This is because complement proteins are either important in removing immune complexes, or their genes are physically associated with genes that control the immune response.

C3 Deficiency

C3 deficiency (complete absence) results in severe pyogenic (bacterial) infections.

C5–C9 Deficiency

C5–C9 MAC deficiency is also called terminal complement deficiency. It results in increased *Neisseria* meningococcal/gonococcal infections (especially meningitis or septicemia). Screen for terminal complement deficiency with CH50. Specific diagnosis is made by assay of these complement components.

CH50

The CH50 assay measures the total complement hemolytic activity of the classical pathway. A normal test shows that all factors of the classical pathway (C1–C9) are present. Know that a CH50 assay still can be normal even if C3 or C4 are significantly lower than normal because normal levels of C3 and C4 are far higher than required. CH50, C3, and C4 are sometimes used to follow disease activity of SLE. The CH50 is a good screen for complement deficiencies. If the CH50 is very low, check individual complement components (C1 through C9 levels) for specific deficiencies.

IMMUNE COMPLEXES

Immune complexes ([ICs]; i.e., antigen-antibody complexes) form during normal, day-to-day immune surveillance, and then are removed from the serum. As they form, complement usually is activated and a C3 component (C3b) attaches to the complex.

This C3b-IC entity is recognized by, and attaches to, the complement receptor. The main complement receptor is CR1, which is found in abundance on RBCs.

The immune complexes are scrubbed off the RBCs by the Kupffer cells in the liver. (Remember that Kupffer cells also remove and destroy C3-coated gram-positive and gram-negative bacteria—see above.) If there are any defects in this elimination process, immune complexes increase in the serum, as in the following conditions:

- **Hepatic vein thrombosis** (Budd-Chiari syndrome) and cirrhosis result in decreased clearance.
- **Paroxysmal nocturnal hemoglobinuria** (PNH) results in decreased binding.
- **SLE** results in a decreased amount of CR1 on the RBCs.

So, each of these disorders causes increased immune complexes in the serum.

Immune complexes activate complement to form C3b, which attaches to the Fc portion of the IgG. This

maintains the solubility of the complexes in the serum and prevents them from cross-connecting and precipitating. IgA does not activate the classical complement pathway and, therefore, may be more susceptible to precipitation; this causes immune complexes to deposit in small blood vessels and tissues when high levels build up.

More under Immune Complex Hypersensitivity (page 9-8).

HYPERSENSITIVITY REACTIONS

OVERVIEW

Hypersensitivity reactions reflect immune-mediated tissue injury, resulting in a variety of outcomes: allergies, autoimmune disease, and other inflammatory diseases.

There are 4 types of hypersensitivity reactions (per Gell and Coombs):

Type I: IgE-mediated—immediate (anaphylactic, atopic)

Type II: IgG- or IgM-mediated---cytotoxic

Type III: Immune complex (antibody-antigen) mediated

Type IV: Cell-mediated—delayed type

TYPE I: IMMEDIATE HYPERSENSITIVITY REACTION

Allergies

The "classic" allergies are Type I hypersensitivity reactions. Examples: hives/urticaria, allergic rhinitis, allergic asthma, reaction to insect stings, drugs (PCN, etc.), and foods (peanuts, eggs, shellfish, etc.).

Type I: Acute Response

The acute phase of immediate hypersensitivity reactions occurs within 1 hour after exposure—usually within minutes. Mast cell degranulation (especially producing histamine) is the cause of the symptoms. This reaction is IgE-mediated. These IgE antibodies are antigen-specific and occur only in response to previous exposure to the same allergen.

The base (Fc portion) of IgE antibodies binds to a receptor on mast cells. This receptor is not specific, so there are many IgEs (each with its own antigen specificity) bound to a mast cell. No reaction occurs when IgE binds to the mast cell.

So what really happens in Type I allergic reactions? An allergen interacts with the allergen-specific receptor on the Fab portion of IgE, and, when the same antigen reacts with more than 1 IgE—thereby interlinking the 2—the mast cell is stimulated to degranulate and release histamine and also begin synthesizing and secreting other mediators (leukotriene C_4, PGD_2, and cytokines). Histamine is responsible for most of the acute symptoms. Mast cells also release other products that have chemotactic effects, and some of them are enzymes (chymase and tryptase). We measure tryptase levels to confirm anaphylactic reactions, and diagnose mast cell disorders. See Mastocytosis on page 9-11.

Review: Histamine interacts with 4 receptors—H_1, H_2, H_3, and H_4.

- **H_1** receptor activation causes the wheal and flare, bronchoconstriction, and pruritus.
- **H_2** receptor activation results in increased gastric acid secretion.
- **H_3** activation causes decreased histamine synthesis and release (negative feedback).
- **H_4** has immunomodulatory effects and affects eosinophil and mast cell recruitment.

Type I: Late-Phase Response

The late-phase response (LPR) occurs 3–12 hours after the acute response and can last hours to days. The LPR is caused by the initial, immediate IgE reaction stimulating the synthesis of cytokines and the subsequent cellular recruitment of eosinophils and basophils. This results in an eosinophilic inflammatory infiltrate. The probability of a LPR increases with the severity of the acute reaction.

In the skin, there is induration that is erythematous, burning, and occasionally pruritic. In the airways, the LPR is one of the causes of nonspecific airway hypersensitivity seen in asthmatic patients.

Type I: Anaphylaxis

Anaphylaxis is usually an extreme IgE-mediated form of immediate hypersensitivity reaction, but it also can be caused by the by-products of activated C3, 4, and 5 (anaphylatoxins), which, like IgE, cause the release of the cytoplasmic granules from mast cells (+/– basophils). The released cytoplasmic granules cause an immediate hypersensitivity reaction.

ASA/NSAIDs, physical stress, and certain chemicals (sulfites that cause asthma, opiates) are causes of non-IgE–mediated anaphylaxis.

The most common causes of IgE-mediated anaphylaxis are drugs, foods, and insect stings. Persons with asthma or heart disease are at greater risk for fatal anaphylaxis. Penicillin allergy is a common cause of drug-related anaphylaxis. Peanuts, tree nuts, and shellfish are common causes of food anaphylaxis. Bees, wasps, and yellow jackets are common culprits of insect sting anaphylaxis. Any insect sting can occasionally cause a large local reaction. This does not increase the risk of anaphylaxis, and further workup is not necessary. However, systemic reactions (generalized hives or anaphylaxis) from insect stings do require further evaluation with venom skin testing and serum venom specific-IgE.

Remember that hypotension is not always required for the diagnosis of anaphylaxis! See Table 9-1.

Quick Quiz

- What mediates immediate hypersensitivity reactions?
- When does the late phase of Type I hypersensitivity reaction occur? Why does it occur?
- Know the causes of and how to treat anaphylaxis—both mild and severe.
- Which antihypertensive medication is relatively contraindicated in someone at risk for anaphylaxis? Why?

Note that ASA-induced anaphylaxis is a separate syndrome from ASA-induced urticaria, and both of these are separate from ASA-induced asthma, which is often associated with rhinosinusitis and nasal polyps due to cyclooxygenase inhibition and leukotriene production.

Type I: Treatment

Treatment for immediate hypersensitivity diseases: **a**voidance of the allergen, and give **a**ntihistamines (occasionally steroids) and **a**llergen-specific immunotherapy (3 **A**s). The immunotherapy may take up to 6 months to show an effect. Patients at high risk for anaphylaxis, such as beekeepers, should get an epinephrine auto-injection kit. Effective immunotherapy causes an increase in T regulatory cell secretion of IL-10 and blocking antibodies of the IgG isotype, among many other effects. Only reactions that are IgE-mediated benefit from immunotherapy treatment.

Treatment for anaphylaxis:

- Give epinephrine (1:1,000) 0.2–0.5 cc IM (maximum dosage 0.5 mg, 0.5 cc of 1:1,000 = 0.5 mg; do not give IV); repeat every 10–20 minutes as needed. If the cause is antigenic material injected into an extremity (e.g., bee sting), place a tourniquet proximal to the site.
- H_1 and H_2 antagonists (usually diphenhydramine and cimetidine, respectively) also may be given.
- Inhaled albuterol may be given if bronchospasm develops.
- Steroids may help prevent the delayed (late-phase) reactions.
- For significant hypotension, give epinephrine (1:10,000) 5 cc IV q 5–10 min (5 cc of 1:10,000 = 0.5 mg), a normal saline bolus, and (lastly) dopamine as needed.
- IV steroids are not effective for acute cases but may abort or decrease the delayed response.

Epinephrine is 1st line treatment for all causes of anaphylaxis! The failure to recognize the symptoms of anaphylaxis, and to administer epinephrine promptly, has led to preventable fatalities.

Table 9-1: Anaphylaxis Diagnosis

Anaphylaxis is diagnosed when any 1 of the following 3 criteria is fulfilled.

1) Sudden onset with involvement of the skin/mucosal tissue and either:
   - Sudden respiratory symptoms, or
   - Hypotension
2) 2 or more of the following that occur suddenly after exposure to a likely allergen:
   - Skin/mucosal tissue involvement
   - Respiratory involvement
   - Hypotension
   - GI symptoms
3) Hypotension after exposure to known allergen

Epinephrine affects the alpha and beta adrenergic systems, resulting in bronchial relaxation, vasoconstriction, and decreased vascular permeability. The effect of epinephrine is blunted in patients on beta-blockers, so these are relatively contraindicated in patients at risk for anaphylactic reactions. Glucagon or vasopressin injections may be used in patients with anaphylaxis on beta-blockers after epinephrine has already been administered. Again: Epinephrine is always 1st line!

TYPE II: CYTOTOXIC HYPERSENSITIVITY

Type II reactions occur when an IgG or IgM antibody binds to a fixed tissue antigen or cell receptor. These are autoantibodies.

Binding of the antibody results in target cell destruction by various means:

- Complement activation may cause cells to be lysed by the membrane attack complex (MAC, discussed on page 9-4).
- Complement activation may result in opsonization from the production of C3b. Phagocytes have a receptor for C3b.
- Phagocytes also have a receptor for the Fc portion of the antibodies and therefore may attack antibody-coated cells.

Examples of target cell receptors:

Target Cell	Disease
Platelets	Thrombocytopenia
RBCs	Autoimmune hemolytic anemia
WBCs	Leukopenia

Examples of target fixed tissue antigens:

Target Antigen	Disease
Component of the basement membrane (kidney and lung)	Goodpasture's
ACh receptor on muscle cells	Myasthenia gravis

TYPE III: IMMUNE COMPLEX HYPERSENSITIVITY

Anytime you see a vasculitis, think of Type III hypersensitivity reaction. Type III reactions are also seen in Ig autoimmune diseases and reactions to drugs. Immune complexes (ICs) form when antibodies combine with an antigen (self or foreign). A hypersensitivity reaction occurs when antibody (usually IgG) reacts with a target antigen to form ICs, which precipitate and activate complement with subsequent small vessel inflammation and necrosis.

Remember: Just because an antibody reaction occurs and ICs are formed, it does not necessarily mean there is precipitation. Significant precipitation occurs only when there is slight antigen excess in relation to the antibody.

When the antibody response initiates, there is a huge excess of antigens compared to antibodies (Ag:Ab >> 1). The ICs that are formed are small, soluble, and quickly cleared.

Within 1–2 weeks, as exceedingly more antibodies are produced, a point is reached when there is only slight antigen excess, and the ICs interlace and become bigger and less soluble. These precipitate in the small vessels and activate complement, which starts a cascade causing the release of more cytokines and the gathering of more inflammatory cells. This process ultimately results in necrosis of the small vessels. The pathologic hallmark skin sign is leukocytoclastic vasculitis (hemorrhagic, indurated lesions).

As the antigen is cleared, there comes a point when there is antibody excess. The formed ICs are large and quickly cleared by circulating phagocytes (macrophages).

There are 2 animal models for what happens clinically:

1) Serum sickness (a systemic reaction): A large amount of antigen is injected into a nonimmunized animal, and within 1–2 weeks, you see a necrotic vasculitis similar to the one just discussed.
2) Arthus reaction (a local reaction): The animal is first hyperimmunized, so there are many circulating IgG antibodies, and then given a small intradermal injection of the target antigen. All reaction occurs at the injection site, where there are many ICs made—inducing the complement cascade and inflammation. Within 4–12 hours, a painful indurated lesion appears and may progress to a sterile abscess.

Type III reaction plays a part in the following conditions—autoimmune diseases (and associated antigen[s]):

- SLE (nuclear materials such as dsDNA, Smith antigen, and many others)
- Hashimoto thyroiditis (thyroglobulin)
- Pernicious anemia (intrinsic factor)
- Rheumatoid arthritis (rheumatoid factor)

External antigens:

- Hepatitis-antigen–associated serum sickness
- Tetanus and diphtheria immunization
- Local insulin reactions

Serum sickness and Arthus Type III hypersensitivity reactions are generally self-limited, and patients usually recover fully. Occasionally, corticosteroids are given.

Treatment of autoimmune diseases is covered in other sections, particularly Rheumatology, Book 3.

Treat external antigen reaction by stopping the exposure to the antigen.

TYPE IV: CELL-MEDIATED HYPERSENSITIVITY

Previously sensitized T cells interact with an antigen, causing an inflammatory reaction. The reaction peaks in 24–72 hours—hence the common name: delayed-type hypersensitivity.

Tuberculin sensitivity and contact dermatitis caused by poison ivy are examples of delayed-type IV hypersensitivity reactions. Don't confuse "delayed-type" IV hypersensitivity reaction with the "late phase" of Type I!

TYPE V: AUTOIMMUNE STIMULATORY HYPERSENSITIVITY

The term Type V hypersensitivity reaction is used by some to indicate when the autoimmune IgG has a stimulatory effect on a receptor (as distinguished from Type II, which is destructive). It is not part of the Gell and Coombs classification. An example is Graves disease, where an IgG stimulates the TSH receptor.

OTHER URTICARIA

There are also several non-allergen–mediated causes of urticaria:

- **Acquired cold urticaria** is usually mediated by either cryoglobulins or IgE. Shock may occur if the patient is immersed in cold water! Test with a 5-minute skin ice-cube challenge.
- **Familial cold urticaria** is an autosomal dominant, inherited inflammatory disease characterized by urticaria, myalgias, fever, and joint pain after cold exposure.
- **Cholinergic urticaria** is precipitated by heat (e.g., hot shower, hot day, exercise). Usually presents as punctate lesions that are very pruritic.
- **Immediate pressure urticaria** is seen with severe dermatographism and may develop around the waistline.
- **Delayed pressure urticaria** typically causes swelling and burning (not itching) of palms and soles several hours after carrying a load for a while or walking long distances.

Quick Quiz

- Which diseases are mediated by Type III immune complex hypersensitivity reactions?
- A tuberculin test is an example of which type of hypersensitivity reaction?
- What is the difference between a Type II and a Type V hypersensitivity reaction?
- What causes cholinergic urticaria?
- Distinguish between chronic urticaria and urticarial vasculitis.
- What is rhinitis medicamentosa? How is it treated?
- What is atrophic rhinitis? How is it treated?
- Why is it important to avoid 1st generation antihistamines in the elderly?
- Which class of medication should be avoided for the treatment of allergic rhinitis in pregnancy?

- **Autoimmune urticaria** occurs when autoantibodies to the IgE receptor on mast cells link the receptors and cause degranulation.
- **Chronic urticaria** occurs when hives last > 6 weeks. Most often the underlying cause is unknown. In some patients, thyroid disease can cause chronic urticaria, so remember to check for thyroid function and thyroid autoantibodies.
- **Urticarial vasculitis** can clinically resemble chronic urticaria. However, patients report hives lasting ≥ 24 hours in a fixed location (in contrast to acute urticaria, which resolves in minutes to hours or migrates to other areas). Other red flags include residual ecchymosis, purpura, or petechiae. Diagnose with skin biopsy.

RHINITIS

Allergic rhinitis—may be:

- seasonal, provoked by seasonally present pollens, or
- perennial, usually provoked by dust mites, molds, or animal dander.

Once initiated, patients have nonspecific hypersensitivity to many irritant stimuli. Eosinophils appear on nasal smear only if the patient is symptomatic. Patients with perennial (year-round) allergic rhinitis have a high eosinophil count in secretions year-round!

NARES: **n**on-**a**llergic **r**hinitis with **e**osinophilia **s**yndrome typically occurs in the middle-aged. Symptoms are similar to allergic rhinitis, including rhinorrhea, sneezing, and occasionally loss of smell. Nasal eosinophilia is also found in secretions. However, patients do not demonstrate sensitization to allergen, either by skin prick test or RAST test (See Skin Testing vs. RAST on page 9-11).

Vasomotor rhinitis: This is an interesting reaction to neurogenic/vagal stimuli. Patients have sneezing attacks, followed by nasal congestion on exposure to cold, sunlight, food, or various other stimuli.

Rhinitis medicamentosa is rebound congestion caused by prolonged use of vasoconstricting nasal drops (phenylephrine or oxymetazoline). Treat by stopping the drug.

Atrophic rhinitis is characterized by (you guessed it!) atrophy of the nasal mucosa, crusting, dryness, fetor, and loss of smell. Patients are typically younger and from warmer climates. Some are colonized with *Klebsiella ozaenae*. Secondary causes include excessive nasal/sinus surgery, granulomatous disease, and exposure to radiation. Treat with nasal saline lavage.

Other possible causes of chronic nasal congestion include deviated septum, foreign body, tumors, and drug reactions (especially with propranolol and alpha-methyldopa). Persistent nasal symptoms may accompany pregnancy, hypothyroidism, or testosterone deficiency (hormonal rhinitis).

Treatment: H_1 antihistamines are 1st line therapy for allergic rhinitis. However, intranasal steroid sprays are the most effective medicine for allergic rhinitis. Intranasal steroid sprays are effective in all types of rhinitis; cromolyn only in the allergic type.

Early-generation antihistamines (diphenhydramine, chlorpheniramine, and hydroxyzine) have the major side effect of sedation. This is due to the ability of these drugs to cross the blood-brain barrier and interact with dopamine, serotonin, and acetylcholine receptors in the brain. The interaction with acetylcholine receptors also results in blurry vision, dry mouth, and urinary retention. Therefore, 1st generation antihistamines should be avoided in the elderly. 2nd generation antihistamines (cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine) do not cross the blood-brain barrier as much and cause less sedation.

Considerations in pregnancy: [Know!] For pregnant patients, use chlorpheniramine, tripelennamine, or diphenhydramine. If sedation is an issue, use 2nd generation antihistamines such as loratadine and cetirizine (pregnancy category B).

Cromolyn and montelukast are considered safe in pregnancy. If an intranasal steroid spray is needed, budesonide is preferred (pregnancy category B). Allergy shots are not started during pregnancy, but if a woman who is already on allergy shots becomes pregnant, she can continue without dose escalation.

Avoid oral decongestants in pregnancy! May cause congenital malformations such as gastroschisis and atresia of the small intestine.

ASTHMA

The etiology of exercise-induced asthma is uncertain. The early response may be due to mast cell degranulation in the airways or excessive cooling. The late response causes a dramatic increase in inflammatory cells (often eosinophils) in the airways.

Sulfites can exacerbate or precipitate symptoms in susceptible patients.

In the 2007 guidelines, the 2 major components to assess for asthma control are impairment (symptoms) and risk (exacerbations).

Apply one of the following categories of control at each visit:

1) Controlled
2) Not well controlled
3) Very poorly controlled

To simplify and summarize the important points briefly: Monitor and follow control using the rule of **2**s!

Step-up therapy for any of the following:
- Asthma symptoms during the day > **2**x/week
- Night time awakenings > **2**x/month
- ED visits/admissions for asthma > **2**x/year

If patients are not controlled, intensify treatment. This can include treating contributory comorbid conditions like rhinitis and gastroesophageal reflux. Reevaluate new patients and those requiring step-up in therapy in 2–6 weeks. Follow stable patients at longer intervals.

Asthma is also covered in Pulmonary Medicine, Book 2.

DRUG ALLERGY

OVERVIEW

See Hypersensitivity Reactions on page 9-6.

The timing and type of reaction provide clues to which type of reaction is elicited. If a drug is given intravenously and an immediate reaction with urticaria develops within minutes to an hour, a Type I immediate IgE-mediated reaction has occurred.

If a reaction is delayed up to 24–72 hours, a delayed hypersensitivity reaction is likely. An exanthematous (maculopapular or morbilliform) eruption also suggests a delayed hypersensitivity reaction.

More severe skin manifestations include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS syndrome (more on this later). These manifestations usually appear > 72 hours after exposure to the drug.

Besides skin manifestations, other problems can occur, including fever, arthritis, and vasculitis, as well as GI, neurologic, and pulmonary findings. Prior exposure to the drug is necessary for an immunologic reaction to occur.

Laboratory testing is generally not helpful. Peripheral blood eosinophilia is suggestive but not conclusive of a drug allergy. Penicillin skin testing may be helpful if you suspect an IgE-mediated mechanism (i.e., Type I hypersensitivity reaction).

BETA-LACTAM ANTIBIOTICS

Beta-lactam antibiotics are the most common cause of drug allergy. Penicillin is composed of benzylpenicillin, which is 95% of the tissue-bound penicillin. Benzylpenicillin is known as the major determinant of penicillin. The minor determinants (benzylpenicilloate and benzylpenicilloic acid) are responsible for most of the anaphylaxis due to penicillin allergy. Therefore, it is important to include both the major and minor determinants for penicillin-allergy testing. Also note, a negative allergy test does not rule out a delayed (non-IgE mediated) hypersensitivity reaction. Remember: Allergy skin testing (PCN testing included) checks only for IgE-mediated reactions!

Treatment: For any drug causing an allergic reaction, the key is to stop the drug. If anaphylaxis is occurring, use epinephrine, antihistamines, and corticosteroids if necessary. See treatment for anaphylaxis on page 9-7.

Know about PCN cross-reactivity: Penicillin cross-reacts with cephalosporins at a rate of 1–3%. Cross-reactivity between beta-lactams and carbapenems is very low. Aztreonam does not cross-react with other beta-lactams except for ceftazidime (both share a common R group side chain).

DRUG DESENSITIZATION

Also known as induction of tolerance, drug desensitization allows for a temporary state of tolerance to the drug as long as the person continues to take the specific drug.

Know: Desensitization is necessary if the drug is the only clinically effective therapy. Otherwise, use alternative drugs if available.

Desensitization is likely to be effective only if the drug reaction is due to an immediate hypersensitivity mechanism (i.e., IgE-mediated). Desensitization is contraindicated for serious non-IgE–mediated reactions such as SJS, TEN, or DRESS.

Scenarios:
- A pregnant woman with syphilis who has a penicillin allergy
- A person with neurosyphilis who has a penicillin allergy

Both require penicillin, so both require desensitization. In these two cases, penicillin is the only effective therapy and there are no alternatives. Also, remember that desensitization works only for that particular episode, and future administrations require repeat desensitization.

Quick Quiz

- What are the 2 major components to assess for asthma control?
- When is drug desensitization indicated? Give two examples of when penicillin desensitization is required.
- What is DRESS syndrome? Name a few drugs commonly associated with this reaction.
- Describe the difference between Stevens-Johnson syndrome and toxic epidermal necrolysis.
- What does a RAST test measure?
- What physical finding is pathognomonic for urticaria pigmentosa?

DRESS SYNDROME

DRESS syndrome: **d**rug **r**ash with **e**osinophilia and **s**ystemic **s**ymptoms. Patients typically develop (you guessed it!) a nonspecific drug rash, peripheral eosinophilia, and systemic symptoms, including fever, lymphadenopathy, and multi-organ involvement (liver, kidney, cardiac, etc.). Usually occurs 2–8 weeks after exposure to the offending drug, typically with aromatic anticonvulsants, minocycline, and allopurinol. Reactivation of human herpesvirus 6 has been implicated. Treat by stopping the drug. Paradoxically, symptoms may worsen or persist even after stopping the drug. Glucocorticosteroids and IVIG are beneficial.

STEVENS-JOHNSON SYNDROME (SJS) & TOXIC EPIDERMAL NECROLYSIS (TEN)

SJS and TEN are part of a single disease spectrum. Mortality is high. Diagnosis depends on the extent of epidermal detachment according to body surface area (BSA):

- SJS = epidermal detachment < 10% BSA
- Overlap syndrome = 10–30% BSA
- TEN = epidermal detachment > 30% BSA

There is severe sloughing away of the skin, equivalent to a 3rd degree burn! Mucosal involvement of the eyes, mouth, and lips almost always occurs. Nikolsky sign refers to removal of the epidermis with slight tangential pressure. Treat with supportive care in a burn unit. Of course, the offending drug is stopped. IVIG may be beneficial. Glucocorticosteroids are contraindicated.

PNEUMONITIS & ABPA

Hypersensitivity pneumonitis is immune complex-mediated and cell-mediated (Types III and IV). **Acute bronchopulmonary aspergillosis (ABPA)** is IgE- and immune complex-mediated (Types I and III). Both respond to glucocorticoids.

In neither one of these would you give allergy injections. Why? Because:

- Hypersensitivity pneumonitis is not IgE-mediated.
- ABPA can be worsened by allergy injections—they could induce production of more *Aspergillus*-immune complexes.

Both are discussed in more detail in Pulmonary Medicine, Book 2.

SKIN TESTING vs. RAST

In vitro tests for antigen-specific IgE in serum include radioallergosorbent test (RAST) and fluorenzyme immunoassay (CAP-FEIA). Skin testing is quicker, more sensitive, and more cost effective, so use blood testing only if skin testing cannot be done, as when the patient has:

- extensive skin disease,
- dermatographism,
- anaphylactic sensitivity to the allergen, or
- ongoing antihistamine use (these depress the skin test response), which cannot be withheld for 1–2 weeks.

MASTOCYTOSIS

Mastocytosis is a rare disorder characterized by abnormal mast cell proliferation and accumulation in various organs. The degree of involvement determines the extent of the disease.

There are cutaneous, systemic, and malignant types of mastocytosis:

- **Cutaneous mastocytosis** results from increased mast cells only in the dermis. There are characteristic brownish macules called urticaria pigmentosa. Formation of a wheal upon gentle stroking of the macule (Darier sign) is pathognomonic.
- **Systemic mastocytosis** is caused by increased mast cells in tissues, organs, and skin. So patients have generalized symptoms, depending on the degree of involvement, in addition to urticaria pigmentosa.
- **Malignant mastocytosis** causes severe systemic symptoms, but often no skin changes. Signs include hepatosplenomegaly and lymphadenopathy.

Diagnosis: Positive screen is with elevated tryptase > 20. Remember mast cells secrete tryptase. So if you have a lot of mast cells, the tryptase levels are high. Diagnose with biopsy.

Treatment: Stay away from cold, heat, alcohol, ASA, and opiates. Oral cromolyn may help for GI symptoms. Various chemotherapy regimens have been used in the treatment of systemic and malignant mastocytosis. Unfortunately, chemotherapy has not been particularly successful.

HLA DISEASES

There are many diseases associated with certain HLA antigens. This makes sense because the HLA complex is the backbone of immune surveillance. Autoimmune disease arises when there is immune dysfunction. Many rheumatic disorders are associated with HLA-B27, especially ankylosing spondylitis, acute anterior uveitis, reactive arthritis, psoriatic spondyloarthropathy, and juvenile rheumatoid arthritis—but not adult rheumatoid arthritis. (RA is associated with the DR4 and DR2 antigens—see Rheumatology, Book 3.)

CONGENITAL IMMUNODEFICIENCY

IMMUNOGLOBULIN DEFICIENCIES

See also Hereditary Complement Deficiencies on page 9-4.

Congenital agammaglobulinemia (= "Bruton" = "X-linked" = XLA): Patients have increased susceptibility to pyogenic and encapsulated organisms (*Staphylococcus*, *Streptococcus*, meningococcus, *Haemophilus*). Hence, they have recurrent sinopulmonary and ear infections. They usually have normal resistance to fungi, gram-negative organisms, and viruses. The only exception is that XLA patients are susceptible to enteroviral infections and *Giardia*.

Diagnosis: Ig assay shows very low or no immunoglobulins at all (no Igs). There also are no B cells (i.e., no SmIg+ cells or CD19+ cells).

Prognosis is good if the condition is caught early. Check all of the patient's brothers and male cousins on the mother's side.

Treat by replacing immunoglobulins with exogenous IVIG or SQIG. Prophylactic antibiotics may be required for some patients.

Common variable immunodeficiency (CVID): deficiency of IgG +/– IgA, and/or IgM. Like XLA, patients have increased susceptibility to encapsulated organisms (*S. pneumoniae*, *H. influenzae*). They have recurrent sinopulmonary infections and bronchiectasis. They also tend to get giardiasis and enterovirus. They usually have normal resistance to fungi, gram-negative organisms, and viruses.

Unlike XLA, there is an increased incidence of autoimmune disease and malignancy.

Diagnosis: Ig assay shows low IgG +/– low IgA, and/or IgM. Unlike XLA, CVID patients have mature B cells present (CD19+).

Treat by replacing immunoglobulins with exogenous IVIG or SQIG. Monitor for signs of disease-associated autoimmune complications and malignancy.

IgA deficiency: the most common Ig deficiency. Its incidence is as high as 1/300! Fortunately, most patients are asymptomatic. There is only a slightly increased incidence of associated autoimmune disease. Some patients with IgA deficiency have recurrent sinopulmonary infections, recurrent giardiasis, and an association with multiple autoimmune diseases, such as celiac disease and Hashimoto thyroiditis. Most, however, have no symptoms.

For these patients with recurrent infection, treat with prophylactic antibiotics. (This is discussed more in Infectious Disease, Book 1.)

Wiskott-Aldrich syndrome: low IgM and elevated IgA and IgE. The triad of findings is **e**czema, **i**mmunodeficiency, and **t**hrombocytopenia. Remembering that it is **X**-linked makes for a nice mnemonic ("Wisk through the **EXIT**"). You can treat successfully with bone marrow transplantation.

CELL-MEDIATED DEFICIENCY

DiGeorge syndrome (congenital thymic hypoplasia) is a T-cell deficiency due to an early intrauterine malformation of the embryo that can affect several tissues, including the thymus, parathyroids, heart and great vessels, and face. Infants may present with hypocalcemic tetany! A mnemonic for these findings is "DiGeorge **CATCH-22**" (**c**ardiac, **a**bnormal facies, **t**hymic hypoplasia, **c**left lip, **h**ypocalcemia, chromosome **22**).

There is a wide range of symptoms and variable decrease in T-cell function related to the variable decrease in thymic tissue. In many patients, a microdeletion in 22q11 can be demonstrated. For the most severely affected infants (with no thymus or T cells!), treating with thymus transplantation is under investigation.

COMBINED DEFICIENCIES

Severe, combined immunodeficiency: a deficiency in numbers or function of both T and B cells; either autosomal recessive or X-linked; always fatal unless treated. Treat with bone marrow transplantation.

Ataxia-telangiectasia is an autosomal recessive disorder causing both cellular and Ig deficiency. This results in recurrent sinopulmonary infections, bronchiectasis, and progressive telangiectasias. These patients also have a progressive neurologic deterioration of uncertain etiology, characterized by cerebellar ataxia and progressive mental deterioration.

QuickQuiz

- Which rheumatologic disorders are associated with HLA-B27?
- Which immune deficiency has no mature B cells? What are its symptoms?
- What is the most common immunoglobulin deficiency? What are its symptoms?
- What is Wiskott-Aldrich syndrome?
- For which types of cancer is interleukin-2 approved to treat?

CANCER IMMUNOTHERAPY

Know the following:

- **Interferons**, in general, are cytostatic (not 'cidal) and often cause symptoms similar to a severe viral syndrome. Alpha-interferon has been effectively used in hepatitis C and hairy cell leukemia.
- **Tumor necrosis factor** is produced by activated macrophages. It attracts PMNs and causes vasodilation.
- **Monoclonal antibodies** are antibodies from cells originating from one clone and are therefore monospecific. They can be used to carry chemotherapy agents or isotopes to the tumor.
- **Interleukin-2** is a lymphokine that activates the natural killer T cells; it is approved for treating melanoma and renal cell cancer.

FOR FURTHER READING

[Guidelines in blue]

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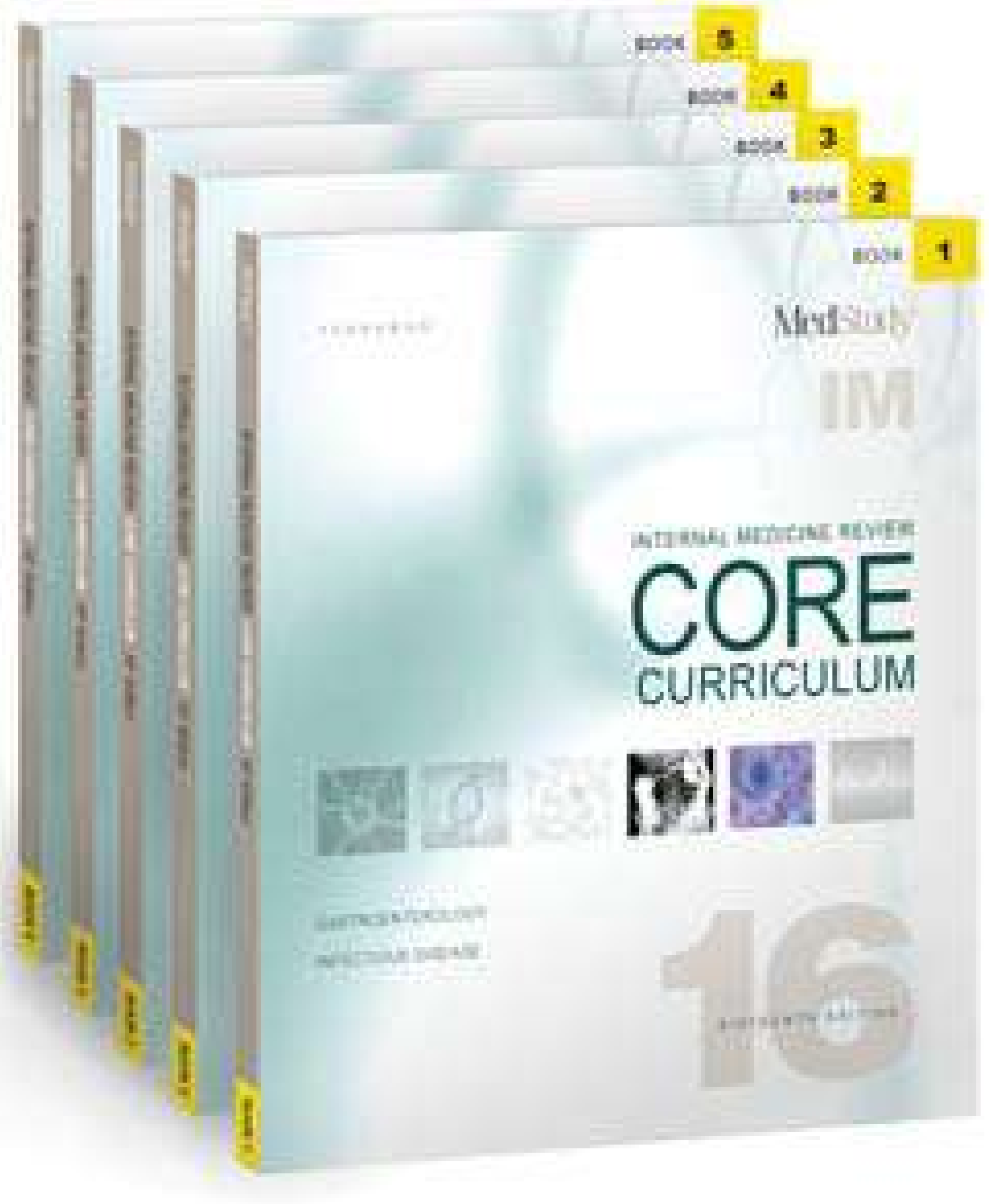
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General Internal Medicine

PHARMACOLOGY

PHARMACOKINETICS

Absorption

First-pass effect: Oral drugs are absorbed from the GI tract, pass through the portal vein, and then enter the liver. Drugs metabolized by the liver then undergo "first-pass" metabolism. These drugs require a much higher oral dose to be as effective as a parenteral dose of the same medicine because of this first-pass metabolism. Common drugs that undergo first-pass effect:

- Opiate-related: meperidine, morphine, and naloxone
- Calcium antagonists: nifedipine, verapamil, and diltiazem
- Some beta-blockers: labetalol, metoprolol, and propranolol
- Tricyclic antidepressants
- Benzodiazepines (BDZs)
- Anticonvulsants: valproic acid and phenytoin
- NSAIDs: ibuprofen, ketoprofen, naproxen, and indomethacin
- Other: cyclophosphamide, theophylline, warfarin, and metronidazole

Some drugs require an acidic environment for absorption—especially the azole antifungals (except fluconazole and voriconazole), iron, and thyroid hormone. If used with H_2 blockers or proton pump inhibitors (PPIs), dose adjustment may be needed; giving the medication with acid (e.g., vitamin C or orange juice) may help. PPIs can also decrease calcium absorption.

Important! The ingestion of cations (e.g., calcium and iron supplements or antacids containing magnesium and aluminum) can interfere with the absorption of thyroid hormone or quinolones.

Distribution

Volume of distribution (V) [Know]: This is the effective volume for determining the total amount of drug in the body and for determining the loading dose. The total amount of drug in the body (D_T) is equal to the volume x concentration:

$$D_T = V (C_p)$$

So the volume of distribution is:

$$V = D_T/C_p$$

V = the volume of distribution. This is the apparent volume into which the drug is dispersed. $\mathbf{C_p}$ is the concentration of the drug in the plasma. If the tissues hold more drug than the plasma at equilibrium, "V" is large.

Rule of thumb: If the drug is dosed at each half-life, the total amount of drug (D_T) is double the maintenance dose. Note that the loading dose does not depend on excretion capability! The loading dose in a patient with renal failure is the same as that in a healthy patient; but if the drug is cleared by the kidney, the subsequent maintenance dose is very different.

Excretion

Drugs excreted mainly by the liver include all of those mentioned above under first-pass effect.

In a person with cirrhosis, the decreased first-pass effect increases the effective bioavailability of the above drugs. Clearance is also decreased, so the effective dose of a drug may be very small.

Meperidine is metabolized by the liver to normeperidine, which is an active metabolite causing CNS stimulation (including seizures); therefore, in liver disease, there is less first-pass effect. Normeperidine is cleared by the kidney. So, carefully watch a patient with hepatic or renal dysfunction when on meperidine!

Michaelis-Menton Pharmacokinetics

[Know:] Michaelis-Menton consists of both zero-order and first-order in Michaelis-Menton pharmacokinetics. As a drug's plasma concentration increases, the rate of drug elimination assumes the familiar hyperbolic curve with a plateau reached when all enzyme systems are saturated. Most medications are metabolized in linear fashion (rate of drug metabolism increases in proportion to drug plasma concentration) because drug plasma concentration is well below available enzyme active sites. Medications may assume zero-order pharmacokinetics when the drug concentration far exceeds the therapeutic range, saturating all enzyme systems (rate of drug metabolism no longer changes in proportion to its plasma concentration). These facts are incorporated in the Michaelis-Menton equation.

First-Order Kinetics

First-order kinetics: The rate at which a drug is cleared is dependent on (proportional to) the drug concentration. That is, the rate of drug clearance increases as the plasma concentration of the drug increases when you plot rate of drug metabolism against drug plasma concentration (it is actually linear) when the available enzymatic sites far exceed the substrate molecule. After one half-life, the drug level in the body is only half of the initial level. It is possible to determine the half-life by checking 2 blood levels at a certain interval (between doses).

As seen in Table 10-1, 5 half-lives after a patient is started on a first-order drug without a loading dose, the drug level is 97% of steady state. Also, if a first-order drug is stopped, a plot of plasma drug concentration against time is a downward non-linear curve. The drug is 97% gone after 5 half-lives. So, when starting patients on a medication with no loading dose, usually wait 3–5 half-lives before rechecking the blood level to see if you need to adjust the dosage.

Table 10-1: Half-lives

# of Half-lives	Percent of Steady State
1	50
2	75
3	87.5
4	93.75
5	96.875

Zero-Order (Saturable) Pharmacokinetics

Zero-order clearance processes are non-linear and occur when all the metabolizing enzyme system sites are saturated and the maximum rate of metabolism is achieved (Vmax). At this point, the rate of drug clearance is independent of (not proportional to) the drug plasma concentration (that is, it is non-linear). That means the drug concentration builds up and may cause toxic effects because rate of drug metabolism is constant. Steady-state drug serum concentrations increase in disproportion to dose changes. If you plot drug plasma concentration against time after a zero-order drug is stopped, the curve is a downward linear curve. Because clearance is dose- or concentration-dependent, half-life changes as the concentration/dose of the drug changes.

Because steady-state serum concentration is often well below the saturability of enzyme systems, linear pharmacokinetics are the norm for most medications.

Drug Interactions

Note: There are thousands of drug interactions, but several are very serious—and thus frequently on exam questions. We cover some of the most serious and common ones here.

Warfarin Interactions

Table 10-2 outlines the most important warfarin interactions that result in increased INR (international normalized ratio). Especially know that trimethoprim/sulfamethoxazole (TMP/SMX) can markedly raise the INR within the first few days of therapy. TMP/SMX displaces warfarin from protein-binding sites and decreases warfarin metabolism. However, any antibiotic can affect the INR without affecting warfarin metabolism by decreasing vitamin-producing bacteria in the intestine.

Table 10-2: Warfarin Interactions (Increased INR)

Most Severe	Possible
TMP/SMX	Quinolones
Erythromycin	Omeprazole
Amiodarone	Clarithromycin
Propafenone	Azithromycin
Azole antifungals	Prednisone
Metronidazole	Acetaminophen (> 1.5 g/d)

Two studies show that increased INR with warfarin + acetaminophen: > 9,100 mg/week leads to 10x risk of having INR > 6.

Natural products with the potential to enhance the anticoagulant effect of warfarin include glucosamine, ginkgo, garlic, feverfew, and dong quai.

Drugs that Cause Hyperkalemia

ACE (angiotensin-converting enzyme) inhibitors, ARBs, (angiotensin receptor blockers), spironolactone and other potassium-sparing diuretics, and heparin can cause severe hyperkalemia. The risk is far greater when several of these drugs are combined (as seen in the treatment of heart failure). Trimethoprim can cause hyperkalemia by blocking amiloride-sensitive channels in the renal tubule. The risk is greatest in the elderly and with use of high-dose TMP/SMX.

Statin Interactions

The most common statin side effect is myalgias. The most life-threatening reaction is rhabdomyolysis. Combining statins with drugs that slow their metabolism increases the risk of drug toxicity.

Statins are metabolized by the liver's cytochrome P450 system, except for pravastatin, which is metabolized by the kidney. Fibrates, erythromycin, cyclosporine, azole antifungals, protease inhibitors, verapamil, diltiazem, and amiodarone affect statin hepatic metabolism.

Grapefruit juice also markedly raises the blood levels of some statins by inhibiting initial hepatic metabolism. Lovastatin and simvastatin are most affected; pravastatin is least affected (because it is metabolized by the kidneys).

Other Interactions / Side Effects to Know

[Know:]

- Rosiglitazone and pioglitazone cause edema, worsening congestive heart failure (CHF), and weight gain.
- Dihydropyridines (nifedipine, amlodipine) cause peripheral edema and constipation.
- SSRIs cause hyponatremia, sexual dysfunction, and may cause platelet dysfunction.
- Topiramate causes non-anion gap acidosis and kidney stones.
- Hydrochlorothiazide causes low K^+, high Ca^+, low Na^+, and high uric acid.
- St. John's wort increases metabolism of statins, cyclosporin, some HIV/AIDS drugs, and oral contraceptives (--→ treatment failure).
- NSAIDs increase risk of symptomatic CHF in patients at risk for coronary artery disease (CAD).
- Bisphosphonates can cause muscle and joint pain.

QuickQuiz

- Define first-order kinetics.
- How long should you wait before rechecking a blood level for a drug that follows first-order kinetics?
- You have invented a test that is 90% sensitive and 95% specific for screening of breast cancer. If you tested 100 women with known breast cancer, how many would the test say have breast cancer (true positives)?
- Be able to fill in a 4 square and quickly determine sensitivity, specificity, PPV, and NPV.

- Oral contraceptives increase risk of DVT/PE and hypertension.

STATISTICS

SENSITIVITY AND SPECIFICITY

The Bayesian 4 Square

Note: T = true, F = false, P = positive, N = negative

[Know statistics perfectly!]

To make sense of the 4 square used in answering sensitivity and specificity questions, we go over Figure 10-1. Let's assume we have a group of cattle being tested for a deadly disease. They go through the testing station on the left and are directed to either the upper corral if their test is positive or the lower corral if their test is negative. All cattle are then driven across the corral to the right; but this disease is so deadly, all the diseased cattle die before they get to the far right of the corral. So we are left with 4 sets of cattle. The 4 square is very useful in determining sensitivity, specificity, and positive and negative predictive values.

Sensitivity and Specificity

Sensitivity and specificity try to account for those with (sensitivity) the disease and those without (specificity) the disease.

Sensitivity takes into account only those who have the disease. Sensitivity = true positives (# of patients with disease who test positive) divided by the total # of patients with disease (those who test positive plus the false negatives).

Sensitivity = TP/(TP + FN) (Figure 10-1)

Note that (1.0 – sensitivity) = false-negative rate. This implies that among patients with disease, there are some who test negative. Hence the mnemonic "**SNOUT**" (**SeN**sitive tests help rule **OUT** disease because the false-negative rate is low).

A good screening test should try to approach 100% but typically does not because there are some patients who have the disease but do not test positive (false negatives). SNOUT!!

Specificity takes into account only those who do not have the disease. Specificity = true negatives (# of patients without the disease who test negative) divided by the total # of patients without the disease (those who test negative plus the false positives).

Specificity = TN/(TN + FP)

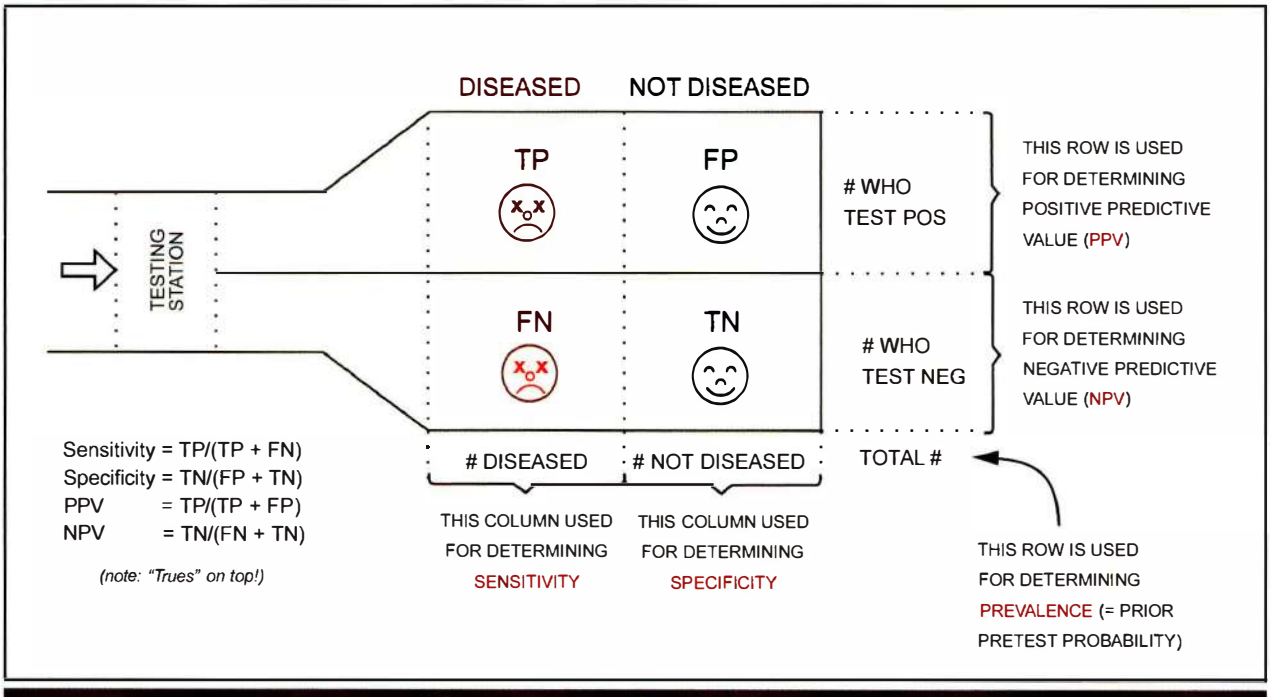


Figure 10-1: The Bayesian 4 Square

Note that (1.0 – specificity) = false-positive rate. This implies that among patients without disease, there are some who test positive. Hence the mnemonic "**SPIN**" (**SP**ecific tests help rule **IN** disease because the false-positive rate is lower).

A good confirmatory test should try to approach 100% but often does not succeed—because some without the disease test positive (false positives). SPIN!!

To help remember: Note that sensitivity takes into account only those who have the disease, and specificity takes into account only those who do not have the disease. This means that sensitivity and specificity are independent of the prevalence (percentage) of the population with the disease! Sensitivity and specificity are properties of the test itself.

Positive and Negative Predictive Value

The **positive predictive value** (**PPV**) of a diagnostic test is the probability of disease in a patient given a positive test.

$$PPV = P(\text{disease} \mid \text{positive test})$$

To figure this, you take into account the numbers of both the true positives and the false positives. This combination does take prevalence into account. The positive predictive value is generally higher with conditions that are more prevalent (common) than with conditions that are less prevalent (rare), given the same sensitivity and specificity of a test. The formula is:

$$PPV = TP / (TP + FP)$$

This makes sense: true positives divided by all those who test positive! If a disease is rare, even if the sensitivity and specificity are high, the false positives may greatly outnumber the true positives, making the chance of having the disease with a positive test (PPV) much less. This is one of the main factors used to determine whether a screening program is feasible.

The **negative predictive value** (**NPV**) of a diagnostic test is the probability of not having a disease given a negative test:

$$NPV = P(\text{no disease} \mid \text{negative test})$$

Using the 4 square, the formula is:

$$NPV = TN / (TN + FN)$$

NPV, like PPV, takes into account the disease prevalence. The negative predictive value is generally higher with conditions that are less prevalent (rare) than with conditions that are more prevalent (common), given the same sensitivity and specificity of a test.

Tips:

- Note that in all the above (sensitivity, specificity, PPV, NPV), the "Trues" go in the numerator (on top).
- PPV deals with nothing but positives; NPV deals with nothing but negatives (in terms of test results).
- Sensitivity deals with positives; specificity deals with negatives (in terms of disease status).

The prevalence (or prior/pre-test probability) is merely the fraction of the population who has the disease. This is:

$$\text{Prevalence} = (\text{Total with disease}) / \text{Total}$$

or

$$\text{Prevalence} = (TP + FN) / [(TP + FN) + (FP + TN)]$$

Not all the data may be given in a question asking you to find sensitivity, specificity, PPV, NPV; it is very useful to use Table 10-3 in its stripped-down form (Table 10-4). You insert the given values and then calculate for the blank spaces!

The "givens" in the following example are filled in. When all the spaces are filled in, the question is easily answered. Know this stuff!

Example: The prevalence of cancer in a population is 1/200. In a test under consideration, if sensitivity = 99% and the frequency of abnormal tests in the population is 1.3%, what is the ratio of false positives to true positives—and is this a good screening test? To solve, first draw Table 10-4 and fill in the given numbers. This gives us Table 10-5.

If the population is not given, assume 1 million. 1/200 incidence gives 5,000 total persons with cancer. 0.013 x 1 million gives 13,000 total abnormal tests. Then just subtract to find the number without cancer

Table 10-3

	Disease	No Disease	Total
Abn tests	TP	FP	TP + FP
NI tests	FN	TN	FN + TN
Total	TP + FN	FP + TN	

Table 10-4

I. Sketch this first:

	With	Without	Total
Abn tests			
NI tests			
Total			

Table 10-5

II. Based on the given information:

	With	Without	Total
Abn tests	1	3	13,000
NI tests	2	4	987,000
Total	5,000	995,000	1,000,000

Note that the 5,000 and 995,000 are the denominators in the sensitivity and specificity equations!

QuickQuiz

- Which of the following take into account disease prevalence: sensitivity, specificity, PPV, NPV?
- Define positive and negative likelihood ratios in terms of sensitivity and specificity.

(995,000) and the number of normal tests (987,000). Note that the 5,000 and 995,000 are the denominators in the sensitivity and specificity equations!

Then we find the other blanks in the order shown 1, 2, 3, and 4. Blank 1 is the only one requiring thought:

$$\text{Sensitivity} = TP / (TP + FN) \text{ or } 0.99 = TP/5{,}000$$

$$\text{So: } TP = 4{,}950$$

The others are found by subtraction (Table 10-6).

Once you have the entire matrix filled in, you can solve any problem, provided there is enough information. In this example, PPV = TP/(TP + FP) = 38%—not a good percentage for a screening test! If data given to solve the problem are insufficient, it becomes apparent when you are unable to fill in all the blanks.

Table 10-6

III. Calculations

	With	Without	Total
Abn tests	4,950	8,050	13,000
NI tests	50	986,950	987,000
Total	5,000	995,000	1,000,000

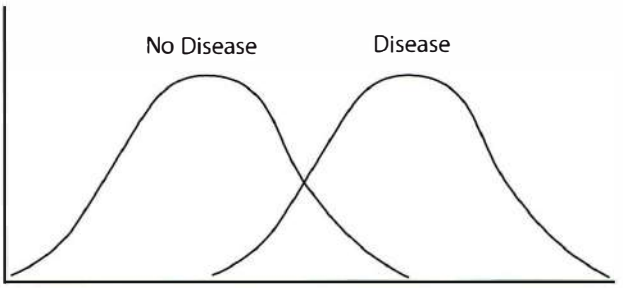
Changing Normal Limits

What happens if you change the criteria for what is called a normal test? If you increase the range for what is normal, you get more negative tests—both true negatives and false negatives. This decreases the sensitivity while increasing the specificity.

Why is this? Assume we did this for the previous example. Because the numbers of people with and without the disease (prevalence) remain the same, the denominators in the sensitivity and specificity equations remain the same—but the numerators change. In the sensitivity equation, the numerator decreases (decreased TP due to increased FN), so sensitivity decreases; i.e., fewer of those with the disease are found by the test. In the specificity equation, the numerator increases, so specificity increases; i.e., those testing negative are less likely to have the disease.

As disease prevalence and incidence decrease, the number of false positives increases while the number of false negatives decreases—so the ratio of false positives to false negatives increases. This occurs because there is no change in the sensitivity or specificity of the diagnostic test.

Sensitivity, specificity, PPV, and NPV can also be interpreted from diagrams such as these:



This graph shows test performance for a diagnostic test in 2 populations, 1 with the disease and 1 without.

Remember that sensitivity = True positive / (True positives + False negatives). Point A would have no false negatives, since all of the group with the disease would have a value greater than A. Thus, Point A has the best sensitivity. Point A also has the best false-negative value. Point E has no false positives and would have the best specificity and the best positive predictive value.

Likelihood Ratios

The last thing we'll deal with here is positive and negative likelihood ratios:

$$\text{Positive likelihood ratio} = \text{Sensitivity} / (1 - \text{Specificity})$$

The positive likelihood ratio is used with positive test results; i.e., the probability of a patient who has the disease testing positive divided by the probability of a person not having the disease testing positive. For example, if the presence of peripheral edema has a sensitivity of 80% and a specificity of 40% for the presence of cirrhosis, what is the likelihood ratio if a patient has edema? Plugging in the numbers:

$$(.8) / (1 - .4) = (.8) / (.6) = 1.33$$

Since it is the ratio of true positives to false positives, it is essentially the odds of disease given a positive test result (1.33 for to 1 against).

$$\text{Negative likelihood ratio} = (1 - \text{Sensitivity}) / (\text{Specificity})$$

Use this when you have a negative test result and you are looking to see how much less likely something is with a negative test. For example: If the absence of peripheral pulses has a sensitivity of 90% for PAD and a specificity of 95%, what is the negative likelihood ratio for PAD if a patient has peripheral pulses? Plugging in the numbers:

$$(1 - .9) / (.95) = (.1) / (.95) = .105$$

This is the ratio of false negatives to true negatives. So, it is essentially the odds of disease given a negative result.

Pre-test probability and post-test probability may be calculated in terms of odds using likelihood ratios. The results should be the same as the example above to arrive at positive and negative predictive value.

If the prevalence of cancer is 1/200, the odds of cancer are 1 for to 199 against. If the sensitivity of a test is 99%, and the specificity is 99.2%, then the true positive rate is 99% and the false positive rate is .8%. Positive likelihood ratio (True positives to False positives) is 99 to .8; the negative likelihood ratio (False negatives to True negatives) is 1 to 99.2.

To arrive at the post-test probability given a positive test result, multiply the pre-test odds times the odds of disease given a positive test result (Positive likelihood ratio):

1/199 x 99/.8 = .622 odds

To convert these post-test odds to a probability, use the formula odds/(1 + odds):

.622/1.622 = .384 or about 38%
(which is the positive predictive value)

The same calculation applies in the setting of a negative test result using a negative likelihood ratio (ratio of False negatives to True negatives):

1/199 x 1/99.2 = .00005 odds of disease or .0049%
(.00005/1.00005) probability of disease

This translates into a negative predictive value of 99.995% (100% – 0.0049%).

Hence, post-test odds of disease = pre-test odds of disease x odds of disease given a test result (the likelihood ratio).

The advantage of using likelihood ratios and pre-test odds is that the effect of prevalence of disease is easy to visualize and understand. With increasing prevalence of disease, post-test probability of disease increases whether you test positive or negative. Notice that positive predictive value increases with pre-test probability (prevalence) of disease but the negative predictive value goes down (and vice versa). This is simply due to the definitions of positive and negative predictive value. Notice also that likelihood ratios are unaltered by prevalence of disease since they are a function of sensitivity and specificity. This explains why a negative HIV test in a high prevalence setting can have a vastly different negative predictive value than in a low prevalence setting. It also helps explain why a negative stress test is unhelpful in the setting of a patient with a high pre-test probability of coronary disease.

RESEARCH AND STUDY DESIGN

Study Designs

There are 2 primary categories of study design: observational and randomized.

Observational trials correlate exposures (such as smoking) with outcomes (such as lung cancer), but do not assign patients to one group or another. Most observational trials are either:

- cohort trials, in which a group of individuals are followed over time to see which exposures cause disease (e.g., the Framingham Heart Study), or
- case-control trials, in which people with disease are compared to those without, to identify relevant exposures in the past.

Randomized trials split a single group of patients randomly into different study groups, usually an intervention (e.g., a drug) vs. a control (e.g., a placebo). The strength of random assignment is that it reduces the risk of confounding variables that frequently arise when patients choose treatments themselves. For example, women who chose to take estrogen after menopause also presumably made other healthy lifestyle choices, leading to an apparent benefit for estrogen in prevention of cardiovascular disease. Randomized trials show that there is no benefit to estrogen—it is actually harmful.

Although observational trials have advantages—they are less expensive than randomized trials and are able to study exposures that we cannot ethically randomize (smoking, carcinogens, etc.)---the randomized trial is less susceptible to error and is usually considered the "gold standard" study.

P Value

The p value is a way of expressing a study's statistical significance. Suppose a randomized trial compares 2 drugs and concludes that drug A is better than drug B. The smaller the p value, the more confident we can be that drug A really is better than drug B—and that this is not simply a chance occurrence. Thus, if a study has a p value of 0.05, the likelihood that the results are due to chance is only 1 in 20 (= 5%; or $p = 0.05$). P values of less than 0.05—such as 0.01 or 0.001—imply even greater statistical significance. A p value ≤ 0.05 is considered statistically significant—this is probably all they expect you to know on an exam!

Type 1 and Type 2 Errors

These relate to statistical hypothesis testing. There is a null hypothesis, and then there is an alternate hypothesis. (The null hypothesis is not true.)

Type 1 error = concluding that there is a difference (rejecting null hypothesis) when there is no difference. In other words, it is the chance of a false positive result. This chance is typically expressed by the p value. This reflects the willingness of the investigator to declare a benefit when there is none. You can think of this as similar to the argument for specificity of a study and how it can be used to rule in a true effect. (Remember SPIN.)

QuickQuiz

- You read that a study shows a new treatment for lung cancer improves survival by 60% and the *p* value for the study is 0.2. With these results, would you recommend this treatment based on statistical significance?
- What is the cutoff *p* value that is considered statistically significant?

Type 2 error = concluding that there is no difference (accepting null hypothesis or, more correctly, failing to reject the null hypothesis) when one exists. In other words, this is the chance of a false-negative result. This is the likelihood that the trial misses a true difference between the two test groups.

The **power** of a study (1 minus the type 2 error value) is similar to the argument for sensitivity of a study. It tells you the likelihood of ruling out a true effect. (Remember SNOUT.)

Suppose a study shows no difference between experimental groups. If the power is set at the typical 80% level, the chance of type 2 error is 20%. In other words, you'll be wrong 1 out of every 5 times the same study is done. If you increase the power of the study to 95%, the false-negative rate is now 5%. This gives you a little more confidence in the negative result because it is less likely to be falsely negative, but requires the study use more patients, longer follow-up, or (usually) both.

Meta-Analysis

Meta-analysis is the retrospective analysis of many studies (essentially a mathematical systematic review) concerned with the same topic. It generally involves the aggregation of data to try to find a statistically significant "answer" from multiple studies that have conflicting or nonsignificant results. By combining the results of different studies on the same topic, we can better understand the collective effects of an intervention.

There are several methodological flaws and biases involved with meta-analyses, as well as several severe statistical constraints. Compiling studies with differing type 1 and type 2 errors is difficult. Other areas of difficulty include ages of participants and assumptions of the magnitude of differences expected among the experimental groups. These factors, which lead to methodological heterogeneity, can result in statistically significant heterogeneity in the results. Unfortunately, the absence of statistically significant heterogeneity is not necessarily evidence of the absence of heterogeneity, because methodological heterogeneity may not be detected using the surrogate of statistical heterogeneity testing.

Confidence Interval Charts

Confidence interval (CI) charts are frequently used in meta-analyses—which are when results from all available relevant studies are analyzed together for greater statistical power.

A CI of 95% is essentially the same as a $p = 0.05$. A CI of 99% is similar to $p = 0.01$. In the first case, it reflects the spread of 95% of the data points measured. In the second, it reflects 99% of the spread of the data points. A consistent result that falls outside the confidence interval of 95% is "statistically significant." A CI of 99% is even more significant.

Look at the charts (A–D) in Figure 10-2 through Figure 10-5. Pay attention to the **vertical** dotted line, which always means no effect. In charts A and B, the vertical dotted line represents no response to treatment. In C and D, the vertical dotted line is equal to an odds ratio of 1 (again, no effect). In other representations, the vertical line may be given a specific number that represents the mean from the entire population or from controls.

Each plotted solid **horizontal** line on these charts represents the 95% confidence interval from one study.

The **null hypothesis** (no difference in treatment outcomes) is being tested in each chart. If the difference between treatment *x* and treatment *y* is assumed to be zero, but 95% of the time the difference is less than (or greater than) zero, then there must be a difference in treatment outcomes that cannot be ignored—that is, statistically significant.

The null hypothesis can also be expressed as a ratio, in which case, because treatment outcomes are assumed to be the same, the ratio between treatment group *x* and treatment group *y* is 1 (no difference). In this case, the vertical line is shown with a value of 1.

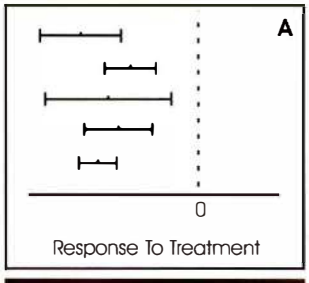


Figure 10-2

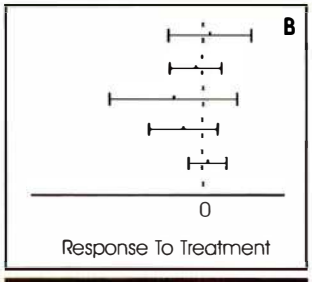


Figure 10-3

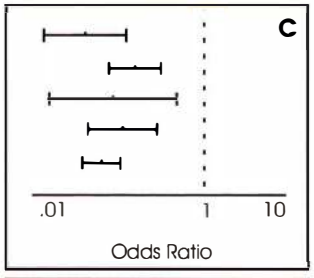


Figure 10-4

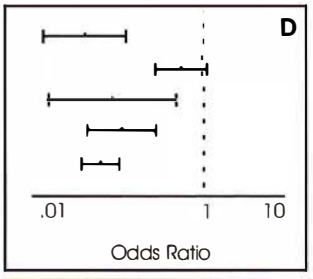


Figure 10-5

So, if the "95% confidence interval" does not cross the vertical line (representing no effect), then the results are considered significant. For example, if you are reviewing a trial looking at response to treatment (i.e., vertical line = 0) and see that the 95% confidence interval is 0.5 to 1.9, you know the study shows a significant response. However, if the 95% confidence interval is –0.7 to 1.6, then it is a nonsignificant result!

Let's go over these charts so you know at a glance how to interpret them:

- Chart A is a meta-analysis with each study showing a significant response to treatment.
- Chart B shows a similar meta-analysis in which not even 1 of the studies shows a significant response to treatment.
- Chart C shows a significantly different odds ratio in all studies reviewed. Odds ratio is a way of comparing whether the probability of an event is the same for 2 groups—usually comparing a control group and the study group (1 = same odds).
- Chart D shows 1 study with non-significant results but 4 others with significant results; therefore, the meta-analysis shows an overall significant result.

Number Needed to Treat

This helps us make the leap from statistical significance to clinical significance.

The **number needed to treat** (**NNT**) is the number of people who need to be treated for a period of time to prevent 1 event. NNT is calculated by taking the inverse of the absolute risk reduction between intervention and control groups.

Example: A new drug is studied to see if it can reduce heart failure mortality. Mortality in the treatment arm (active drug) was 10/100, while mortality in the placebo arm was 30/100 during a 4-year follow-up with a p value of < .001. So, this is statistically significant. Clinically, you want to know how useful this is going to be for patients.

$$NNT = 1/(30/100 - 10/100) = 1/(0.3 - 0.1) = 1/0.2 = 5$$

This means 5 patients must be treated for 4 years to prevent 1 death.

Alternatively, **NNH** means **number needed to harm**. It is the number of patients who get a drug or intervention for each patient harmed.

Also note the difference between relative risk reduction and absolute risk reduction. This drug has a relative risk reduction of 66.7% (0.2/0.3) and an absolute risk reduction of 20%. Both reflect clinical significance, but relative risk is sometimes used preferentially. If the treatment and mortality numbers were to be changed to 1/100 and 3/100 respectively, the NNT would change from 5 to 50 because the absolute risk reduction is now 2% instead of 20%. But the relative risk reduction is still 66.7%!

Similar logic is applied to studies looking at screening tests (number needed to screen).

OSTEOPOROSIS

OVERVIEW

Osteoporosis is decreased bone strength predisposing patients to bone fractures. One-half of all postmenopausal women suffer an osteoporosis-related fracture during their lifetime. Most fragility fractures occur in those without a prior radiographic diagnosis of osteoporosis.

Primary prevention of osteoporosis is controversial. As of 2013, the USPSTF concluded that for the primary prevention of fractures, the current evidence is insufficient to assess the balance of the benefits and harms of:

- Combined vitamin D and calcium supplementation, in premenopausal women or in men
- Daily supplementation with greater than 400 IU of vitamin D_3 and greater than 1,000 mg of calcium, in noninstitutionalized postmenopausal women

For postmenopausal women, the common practice of supplementation with a combination of 1,000 mg of calcium, and 400 IU of vitamin D was found to have no effect on the incidence of fractures. Supplementation at this level was found to increase a woman's risk of developing kidney stones. For these reasons, the USPSTF recommends against daily use of low dose calcium (1,000 mg) and vitamin D (400 IU) in postmenopausal women. At present, evidence is lacking for support of higher doses of supplemental calcium and vitamin D supplements in these women.

In contrast to the USPSTF, the 2010 National Osteoporosis Foundation guidelines recommend vitamin D and calcium supplements to prevent fractures in all adults ≥ 50 years of age. The Institute of Medicine report issued in 2010 also calls for dual supplementation.

Vitamin D does appear to play a role in preventing falls in the elderly. In a separate statement, the USPSTF recommends use of vitamin D supplementation (along with exercise or physical therapy) in community-dwelling adults ≥ 65 years of age.

From a Board standpoint, it is reasonable to accept that vitamin D supplementation is recommended to prevent falls in the elderly and that evidence is insufficient at present to recommend for or against vitamin D and calcium supplementation for primary prevention of osteoporosis.

RISK FACTORS

Osteoporosis is common in the elderly and is generally suspected by clinical presentation. (Fragility fracture is a clinical diagnosis if postmenopausal.)

Quick Quiz

- A study shows a newer treatment for lung cancer improves survival by 5%, and the 95% confidence interval for the study is 1.6 to 4.9. Assuming treatments have the same side effects, would it be worthwhile to consider the new treatment?
- Be able to calculate the NNT.
- What are the risk factors for osteoporosis?
- How do you screen for osteoporosis?
- How are the Z-score and T-score used in the evaluation of osteoporosis?
- What are the recommendations for all patients with osteoporosis?
- Which patients should be treated with drug therapy for osteoporosis?

There are many risk factors for primary osteoporosis, but these have the highest known risk:

- Age
- Personal history of fragility fracture (no trauma or from fall less than standing height)
- History of fragility fracture in 1st degree relative
- Weight less than 127 lbs or BMI < 21
- Alcohol intake of 2 or more drinks/day
- Menopause before age 40
- Current or previous use of glucocorticoid therapy: > 3 months at a dose of > 5 mg/d of prednisone
- Cigarette smoking

SCREENING

The National Osteoporosis Foundation Guidelines of 2010 recommend screening all women age 65 or older and all men 70 or older with DXA scans and selectively screening women and men > 50 years if they have any osteoporosis risk factors, particularly those listed above. The USPSTF 2011 Guidelines are the same for women, but they do not promote screening in men, stating that the evidence is insufficient for assessing the balance of risks and benefits in men. Evidence for the optimal interval for repeat screening is lacking. Recent data suggest that the degree of osteopenia found on the initial scan should dictate appropriate screening intervals.

Consider screening patients with the following conditions regardless of age and gender:

- GI diseases (UC, Crohn's, celiac, gastric bypass, malabsorption)
- Endocrine disorders (hyperparathyroidism, Cushing syndrome, hypogonadism, hyperthyroidism)
- Medications (glucocorticoids, thyroxine over-replacement, lithium, phenobarbital, phenytoin, cyclosporine)
- Rheumatoid arthritis, SLE
- Anorexia nervosa
- Prolonged bed rest or wheelchair bound
- Multiple vertebral compression fractures noted on x-ray (2/3 of vertebral fractures are painless)

Dual energy x-ray absorptiometry (DXA) is the preferred method for screening. It is quick (about 15 minutes), inexpensive, and quite accurate.

Bone mineral density (BMD) reports usually have 2 results, the T-score and the Z-score:

- The **T-score** compares results with normal, young, healthy bone; a T-score of –1.0 means the BMD is 1 standard deviation (SD) less than normal—about 10% low. A T-score of –2.5 or lower is the definition of osteoporosis (about 25% below normal), whereas those between –1 and –2.5 suggest osteopenia.
- The **Z-score** compares the BMD result to age- and sex-matched controls and is now recommended for use in men and women < 50 years of age. The Z-score is not used for treatment but rather to see if there is accelerated osteoporosis, which would suggest secondary factors—such as drugs—might be involved.

Bone mineral density by DXA is an excellent predictor of fracture risk, but it does not take into account other risk factors. In 2008, the World Health Organization (WHO) developed a more comprehensive risk assessment tool called FRAX. FRAX is a well-validated tool that incorporates both BMD and clinical risk fractures and calculates one's 10-year risk of developing a fragility fracture. These fracture probabilities require calculations at www.shef.ac.uk/FRAX.

TREATMENT

Universal recommendations for all patients (regardless of age or risk factors) with osteoporosis:

- Dietary calcium of 1,200–1,500 mg/day (include supplements if necessary, but higher amounts are not recommended due to increased risk of kidney stones and cardiovascular disease)
  - RDA for those without osteoporosis (up to age 70 get 600 IU vitamin D/day; > 70 years of age: 800 IU vitamin D/day)
- Regular weight-bearing exercise
- Fall prevention
- Avoid tobacco
- Avoid excess alcohol use (< 2 drinks/day)

The 2010 National Osteoporosis Foundation guidelines recommend that drug therapy should be considered in postmenopausal women and men > 50 years of age presenting with these findings:

- A hip or vertebral fracture (clinical or radiographic)
- T-score between –1.0 and –2.5 with other prior fractures (not hip or vertebral)

- T-score < –2.5 (remember, this means a score like –3.0, –2.7, etc.; we are dealing with "less than" and negative numbers)
- T-score between –1.0 and –2.5 and secondary causes associated with high risk of fracture (steroid use or total immobilization)
- T-score between –1.0 and –2.5 and a 10-year probability of hip fracture > 3% or a 10-year probability of any major osteoporosis-related fracture > 20% based on the U.S.-adapted WHO algorithm FRAX calculation

Drug Therapy for Osteoporosis

All drugs that increase bone density do so by their effects on bone remodeling. They can either increase buildup (stimulate osteoblasts) or decrease breakdown (inhibit osteoclasts). A categorization of the drugs, which is based on these effects on bone remodeling, is anabolic vs. anticatabolic. Anabolic agents stimulate both osteoblasts and osteoclasts but stimulate the osteoblasts more, leading to a net increase in bone building and increased bone density. Anticatabolic agents inhibit osteoclasts, thereby decreasing the resorptive process.

Anabolic agents (stimulate osteoblasts): The parathyroid hormone, teriparatide, is currently the only one available. Teriparatide can be used for only 2 years because of cumulative increased risk of osteosarcoma, and, once it is discontinued, patients need to use a bisphosphonate.

Anticatabolic agents (inhibit osteoclasts) include the rest of the osteoporosis drugs:

- Bisphosphonates
  - Oral bisphosphonates: alendronate (Fosamax®), ibandronate (Boniva®, also available in IV form, see below), risedronate (Actonel®)
  - Injectable bisphosphonates: ibandronate and zoledronate (Reclast®)
- Denosumab (Prolia®)
- HRT (hormone replacement therapy)
- Raloxifene (Evista®)
- Calcitonin salmon

A few notes on these treatments:

Teriparatide is the only anabolic agent currently available. Parathyroid hormone causes both an increase in bone buildup and an increase in bone resorption—but the net effect is to build more bone than it breaks down.

HRT may prevent or reverse the development of osteoporosis, but its use in the peri- and postmenopausal woman is a two-edged sword. Most recommend not using HRT as 1st line therapy! See HRT on page 10-16.

Bisphosphonates are analogs of pyrophosphate and, like estrogen and other anticatabolic agents, inhibit bone resorption. Bisphosphonates and HRT appear to have an additive effect. They effectively act as antagonists of parathyroid hormone, which causes resorption—a release of calcium from the bone into the serum.

Bisphosphonates, especially IV, have been associated with osteonecrosis of the jaw. Use caution if using these drugs in patients who are having extensive dental surgery. Another very important side effect is severe muscle/joint/bone pain. Atypical fractures of the long bones (midshaft of the femur) have been reported in patients receiving bisphosphonates.

Notes on the bisphosphonates:

- Alendronate is an option when a patient is uncomfortable with HRT or HRT is contraindicated. Alendronate is poorly absorbed and rarely causes severe esophagitis (although this is less of a problem with weekly dosing). The patient must carefully follow the recommendations to take it with a full glass of water on an empty stomach and not eat or lie down for 30 minutes after ingestion.
- Risedronate was FDA-approved in April 2000 for the prevention and treatment of postmenopausal osteoporosis. It has the same clinical effect as alendronate but may have fewer GI side effects. Even so, take the same dosing precautions as with alendronate.
- Ibandronate is the first once-monthly medication approved for postmenopausal osteoporosis.
- Zoledronic acid is given by IV once a year. In addition to reducing fracture risk, zoledronic acid improved survival when given within 90 days of a hip fracture.
- Denosumab is a monoclonal antibody that inhibits the RANK receptor, preventing pre-osteoclasts from maturing into osteoclasts, decreasing bone resorption.

Calcitonin nasal spray at 200 mg/d increases bone mineral density and decreases risk of vertebral fractures. It is also helpful for acute pain associated with vertebral fracture. There is no evidence that it decreases hip fracture risk. While less potent than bisphosphonates for osteoporosis, calcitonin appears to be an effective analgesic in the setting of osteoporotic vertebral fractures.

Raloxifene: During the development of anti-estrogens, it was discovered that some substances that block the effect of estrogen on some tissues actually mimic estrogen on others! These are called selective estrogen receptor modulators (SERMs). Examples are tamoxifen and raloxifene. The effect of raloxifene on bone and lipid levels is similar to, but less than, estrogen; however, it exerts estrogen-antagonistic effects on the breast and uterus and may be less likely to cause cancer than traditional HRT. Raloxifene is FDA-approved for both prevention and treatment of postmenopausal osteoporosis.

There is no consensus on the appropriate duration of drug therapy for osteoporosis. Alendronate has shown efficacy for reducing fracture risk out to 10 years. Some experts recommend a drug holiday of 1 to 2 years for low-risk patients who have completed 5 years of therapy.

QuickQuiz

- A patient on alendronate presents with difficulty swallowing. What is the likely etiology?
- What is the most serious consequence of osteoporosis?
- How do you diagnose "frailty"?
- What assessments should be done periodically in elderly patients?

FRACTURES

Fractures are the most serious consequence of osteoporosis. There are 1.5 million fractures per year due to osteoporosis, with 300,000 of those due to hip fracture. Mortality due to hip fractures is about 20% within the 1st year! Femoral neck and intertrochanteric fractures account for 97% of hip fractures.

Femoral neck fractures are intracapsular and occur below the femoral head but above the trochanters.

- Displaced femoral neck fractures often disrupt the blood supply to the femoral head and result in osteonecrosis and/or nonunion; therefore, the treatment of choice is either femoral head replacement or total hip arthroplasty.
- Nondisplaced femoral neck fractures have a low incidence of osteonecrosis and nonunion, so these are usually treated with internal fixation using pins or screws.

Intertrochanteric fractures are extracapsular and are usually treated with internal fixation with a "sliding hip screw."

In both types of fracture, the main goal is to achieve mobility and function as soon as possible, thereby avoiding the morbidity and spiraling complications due to poor mobility.

Deep vein thrombosis (DVT) occurs in 48% of hip fracture patients without anticoagulants. With anticoagulation, DVT occurs in 24% and 27%, respectively, for those on warfarin or subQ low-molecular-weight heparin.

Other complications of hip fractures are pressure ulcers, constipation, and fecal impaction.

GERIATRICS

DEMOGRAPHICS

Life expectancy correlates with race and gender. Caucasian women live the longest. African-American women and Caucasian men tie for 2nd place. African-American men have the shortest life spans. Generally, women live longer than men, are less likely to remarry, lack money to take care of all their needs, and are more often disabled as they age.

60–84% of patients > 65 years old have hypertension, and roughly 20% have diabetes. Cancer is now the leading cause of death in adults younger than 85 years (followed by heart disease and stroke). Many studies show that elderly patients are not offered the same life-saving procedures as younger patients with the same disease states, even though age has no adverse effect on outcomes of the interventions. Know that age alone is not enough of a reason to withhold an intervention.

If a patient lives to be 75 years old, he is most likely to live to age 86. Those who live to 85 years are likely to live to age 91.

ASSESSMENT

Frailty affects a large number of elderly patients. It can be caused by comorbid illnesses and/or disability but not necessarily so. Frail patients are more likely to fall, become disabled, or die. Make a diagnosis of "frailty" if ≥ 3 of the following are present:

1) Unintentional loss of ≥ 10 lbs/1 year
2) Exhaustion due to lack of endurance
3) Decreased hand strength
4) Walking slowly
5) Reduced activity

All geriatric patients should have a specific interval assessment of "function" because functionality is related to longevity. Functional assessment evaluates several components:

- Activities of daily living (ADLs)
- Instrumental activities of daily living (IADLs)
- Cognition
- Hearing
- Vision
- Gait and balance
- Nutrition (discussed separately)
- Driving ability

Start by assessing ADLs: Can the patient dress, bathe, feed, use the bathroom, and move around without help? IADLs are those activities that connect the patient with the community: Can the patient manage their money, take their own medication, manage transportation, make phone calls, do the shopping and housework, and make their own meals?

Assessment of cognition looks for evidence of dementia and delirium:

- Assessing dementia: A quick way is to use the Mini-Mental State Exam (MMSE) or the Mini-Cog (easier to remember) to assess dementia. To perform the Mini-Cog, ask the patient to remember 3 words, and then ask them to draw a clock showing a specific time. After drawing the clock, ask the patient to recite the 3 words. Score by giving 1 point for each word remembered correctly and 2 points for an accurate clock (0–2 = dementia). The Montreal Cognitive

Assessment (MoCA) test is more sensitive for mild cognitive impairment than the MMSE or Mini-Cog.

- Assessing **delirium**: The best tool to assess delirium is the Confusion Assessment Method (CAM; 94–100% sensitive; 90–95% specific). See Table 10-7. Delirium is present when the patient has features 1 and 2 with either 3 or 4.

More on delirium and dementia on page 10-16 and page 10-17.

Hearing and **vision** are assessed using traditional instruments such as the whisper test and the Snellen eye chart. The whisper test is performed by covering the ear that is not being tested, then whispering a question while standing about 2 feet away. If the patient responds correctly, then no more testing is required. Give the patient 6 tries. Refer for further audiometric testing if the patient answers 3 or more questions (out of 6) incorrectly.

Gait and **balance** is assessed by observing gait, and by watching the patient get up from a chair, walk across the room, turn around, walk back, and sit down (the "**Get Up** and **Go** test"). The "timed" Get Up and Go test is not particularly accurate in functional elders.

Know that elderly (and teens) have more driving violations compared to the general population. Usually, patient performance on the vision, hearing, and gait assessment gives you an adequate assessment of a patient's ability to operate a vehicle. Formal assessment is offered for the elderly through departments of motor vehicles.

NUTRITION

We become less active as we age, and we lose muscle and body fat (more muscle than fat). Nutritional requirements are reduced, so generally, older people eat less. Malnutrition is still an issue, though, because of declining abilities and comorbid systemic disease.

Malnutrition is diagnosed in any of the following circumstances:

- Unintentional weight loss of ≥ 10 lbs/6 months
- BMI < 22
- Albumin < 3.8 g/dL
- Cholesterol < 160 mg/dL
- Any vitamin deficiency

When malnutrition is diagnosed, thoroughly assess for modifiable risks; e.g., decreased access to nutritious food, denture or teeth problems, untreated medical illness, inability to perform IADLs such as grocery shopping.

The age-related decline in appetite and energy needs is naturally associated with dietary replacement of carbohydrates with fats. Counsel geriatric patients to increase their daily fluid and fiber intake and to eat healthy fats (monounsaturated and omega-3s) such as olive oil, nuts, avocados, and fish. Vitamin supplements are useful in those with poor oral intake, because this age group is especially vulnerable to deficiencies of vitamin D, B_{12}, and calcium.

For those older than age 65, the National Institute on Alcohol Abuse and Alcoholism and the American Geriatrics Society recommend no more than 2–3 drinks/day and/or 7 drinks/week, with lower amounts for people taking meds with alcohol-potentiated side effects.

MOBILITY AND GAIT

Falling

Age is associated with **increased instability and falls**. 50% of patients age 80 and older fall each year! The elderly have a stiffer, less agile gait with decreased position reflexes. 5% of falls result in fractures and, if the patient cannot get up, possibly hypothermia and dehydration.

Aging is associated with decreased proprioception and baroreceptor reflexes, so orthostatic hypotension and swaying are common. There is also an increased incidence of **postprandial falls** in the elderly—probably due to hypotension from ingestion of carbohydrates.

The major **predictor** for fracture from a fall is **osteoporosis**.

Risk factors for falls:

- Age
- Female gender
- Past history of falls
- Rugs, untidiness, and dim lighting in the home
- Poor vision
- Orthostatic hypotension
- Unsteady gait
- Cognitive impairment

Table 10-7: Delirium Assessment Tool — Confusion Assessment Method

Feature 1	Acute onset and fluctuating course: Is mental status acutely changed from baseline, and does the change fluctuate throughout the day?
Feature 2	Inattention: Is there a problem focusing attention (e.g., easily distracted)?
Feature 3	Disorganized thinking: Is conversation rambling or irrelevant? Are ideas illogical in flow?
Feature 4	Altered level of consciousness: Is the patient alert (normal state), hyper-alert, drowsy but easily aroused, difficult to arouse, or unarousable?

QuickQuiz

- What are the major features of delirium, using the Confusion Assessment Method?
- What are the criteria that diagnose malnutrition?
- Which factors, associated with aging, predispose patients to imbalance and falls?
- What are risk factors for falls in the elderly?
- How does immobilization affect serum calcium levels?
- What factors are associated with development of decubitus ulcers?
- What is the role of wet-to-dry dressings in decubitus ulcer treatment?

- Musculoskeletal disease
- Cardiovascular disease (e.g., syncope)
- Psychotropic drug use

The drugs most commonly implicated are benzodiazepines, antidepressants, neuroleptic agents, and blood pressure medications. Know that use of physical restraint increases the risk of serious falls and injuries, so avoid physical restraints when possible.

Fall-risk assessment in the elderly includes 5 quick office tests:

1) Timed Get Up and Go test
2) Gait speed (slower = ↑ risk)
3) Tandem (heel-to-toe) walk
4) Visual acuity
5) Calf circumference (smaller = ↑ risk)

Workup for the patient with falls includes a good history and physical exam, with emphasis on a multidisciplinary assessment and evaluation for a cardiovascular cause. Do a syncope workup if the patient does not remember the fall or if the history is suggestive. Also think about weakness associated with osteomalacia as a cause—especially in nursing home patients who are bedridden and never get in the sunshine. Check 25-$(OH)_2$-D if you suspect osteomalacia, and treat deficiency if found because treatment decreases fall risk.

Anticipatory guidance for falls may include restriction of certain activities, improving the lighting at home (use night lights), decreasing hazards (remove rugs and loose carpets), and placing extra supports (bars in the shower). Exercise (especially focused on balance and resistance training) is very important in helping patients maintain mobility and strength, reduce falls, and prolong survival.

Immobility

Patients adapt to bedrest; and the longer a patient is immobilized, the harder it is to ambulate again. Immobilization causes decreased ADH secretion → diuresis → decreased blood volume → orthostatic symptoms. Also, immobilization causes muscle atrophy. The heart continually deconditions after 2 days of bedrest. The elderly are more affected by bedrest because they have less reserve than young people. Treat with rehabilitation.

Know that prolonged immobility is associated with development of hypercalcemia (although this is more common in teens and young adults after traumatic immobilization). The hypercalcemia improves with mobilization.

Decubitus Ulcers

Pressure ulcers occur most commonly on the heels, trochanter, sacrum, and iliac crest. The main etiology is sustained pressure over a prominent bone. Shearing and friction tear the skin and cause necrosis with ulceration. Moist environments (notably, urinary incontinence) and malnutrition (≥ 10-lb weight loss in past 6 months) also increase the risk for developing ulcers.

Know that decubiti in nursing home patients increase their mortality (usually from osteomyelitis and bacteremia/sepsis).

There are 4 stages of decubitus ulcerations:

- Stage 1 is nonblanching erythema (reddish macules).
- Stage 2 is partial-thickness skin loss (small superficial ulcer).
- Stage 3 is full-thickness skin loss.
- Stage 4 is loss of tissue down to the muscle, tendon, or bone.

Bed-bound patients should be rotated from side to side (30-degree angle) every 2 hours. This prevents contact against bony prominences mentioned above. Special mattresses and heel/elbow pads also help, but it's controversial whether most interventions actually prevent ulcers.

In established ulcers, keep pressure off the area; and if an eschar exists, remove it for proper staging. Then determine whether any arterial or venous insufficiency exists, treat infection if present, and maintain a "clean" ulcer.

Effective healing requires debridement of necrotic tissue back to healthy granulation tissue, using either "chemical" topical treatments or a scalpel.

Next, the wound has to be cleaned and dressed properly. Know that saline cleansing is best because it is gentle on growing tissue, and that iodines or peroxides kill tissue if used repeatedly. The choices for wound dressings are wide and variable. Follow the advice given by the wound care therapist. Know that as a means for debriding wounds, wet-to-dry dressings have fallen out of favor because too often they damage friable new tissue.

Give antibiotics, in addition to local wound care, if the patient is systemically ill. Use deep wound cultures to guide your choice.

Wounds do not heal in malnourished patients, so strictly follow the recommendations of the nutritionists to provide adequate increased nutrition.

[Know:] Wounds that develop in the setting of arterial or venous insufficiency do not heal unless the local blood flow is corrected—most often via surgical intervention. Sometimes this is feasible, sometimes not, depending on the patient's comorbidities.

Stage 1 and 2 ulcers heal quickly, but stages 3 and 4 usually take months.

IMMUNITY

There is an age-related decrease in immunity. Total T- and B-cell numbers stay the same, but the number of CD4 T cells increases with age, while the number of CD8 T cells decreases with age. Also, only half of the T cells remain competent, which is why herpes zoster and reactivation tuberculosis are often seen in the elderly.

PHARMACOLOGY

The elderly are very sensitive to drugs for the following reasons:

- Pharmacokinetics change with aging (affecting absorption and metabolism), causing increased drug concentrations.
- The volume of distribution for a drug increases because of the proportional increase of body fat compared to muscle.
- Excretion decreases, consistent with age-related decreases in renal and hepatic function.
- Pharmacodynamics of aging → increased effects of drugs, especially opioids and benzodiazepines.

General rules for medications in the elderly:

- Start meds at a low dose—usually about 1/2 the dose required for the general population and gradually titrate up to the normal therapeutic dose. ("Start low and go slow.") If the patient gets into trouble at the therapeutic dose, try reducing the dose gradually—many elderly patients get satisfactory responses with subtherapeutic doses.
- Any adverse event should be assumed to be drug-related until proven otherwise.
- Always look to see if a prescribed drug is the cause of new symptoms before prescribing a new drug to symptomatically treat the new symptoms.
- Look at an elderly patient's medicine record for prescription of an atypical antipsychotic (see Delirium on page 10-16) if the patient is institutionalized and falling. These are the most common causes of falls in nursing homes.
- Errors in self-administration increase dramatically once a patient is prescribed 3 or more medications. Elderly patients get very confused with pills that look alike and with distinguishing between generic and brand names.

Some elderly patients are dependent on low-dose benzodiazepines (BDZs) or narcotics. For these patients, attempt a slow withdrawal of these medications. These have often been misprescribed as treatment for anxiety, insomnia, depression, chronic pain, and drug withdrawal. Slowly taper following these general principles: Taper BDZs over 3–6 months after switching to an equivalent dosage of a water-soluble BDZ, such as oxazepam (slower onset, less addictive potential). With narcotic dependence, first determine the cause of pain (if any) and treat it with a non-narcotic drug (NSAID, acetaminophen). Avoid long half-life narcotics in treating geriatric pain.

Know that up to 75% of the elderly population in some studies use herbal supplements. Many do not divulge this information unless you ask directly.

ENDOCRINE

The only specific hormonal change that occurs with aging is ovarian failure: The average age of menopause is 51. The hypothalamic-pituitary-gonadal axis is also disturbed in men, but not as predictably as in women. In both sexes, the adrenal zona glomerulosa declines in synthesis of DHEA, and the pituitary secretion of growth hormone wanes (and subsequently, also levels of IGF-1). Many other hormones are normal in the amount produced but do not function as well.

Many of these hormone perturbations are felt to be associated with the aging process, but none are conclusively linked. Growth hormone reduction appears to be associated with loss of muscle mass and strength; supplementation is not encouraged because it is associated with too many side effects.

The pineal gland's melatonin production is disrupted with aging. This may cause poor sleep and insomnia. Melatonin supplementation may help some patients.

Aging patients have a reduction in the clearance of thyroid hormone, so thyroid replacement for hypothyroidism, can be started at a lower dose. TSH increases with age, especially in women (see Endocrinology, Book 4); so at this time, a rising TSH without an accompanied decrease in T_4 does not merit treatment for hypothyroidism.

Testosterone production decreases in the aging male, but the effect is variable. However, the rate of sperm production is stable from ages 20 to 70 years! FSH and LH also decline but disproportionately compared to the more drastic decline in testosterone. The low testosterone production is most likely due to declining testicular function and not to hypothalamic disease.

Low testosterone is believed to be related to the following, although direct causation has not been proven:

- Decreased sexual function
- Decreased bone mineral density
- Decreased muscle mass (and increased fat)

Quick Quiz

- What should you do for an elderly woman who is on chronic low-dose benzodiazepines for "nerves"?
- What is the average age of menopause?
- What is "andropause"?
- What is the typical presentation of Paget disease?
- What complications are geriatric patients specifically at risk for developing as they are being treated for diabetes?
- Metformin should not be given to patients with estimated GFR below what calculation?

- Decreased muscle strength
- Decreased mentation

The collection of the above, in association with reduced free testosterone, has been called "andropause." The Endocrine Society set forth guidelines (2006) for treatment of certain males with andropause who have symptoms and a serum testosterone < 200 ng/dL, with a treatment goal of 300–400 ng/dL. In spite of this recommendation, there are no good studies that prove a treatment benefit. Do not screen elderly men and do not treat men with low levels if they do not have symptoms. Testosterone promotes red cell proliferation and is trophic to prostate tissue. Men receiving testosterone therapy need to have periodic monitoring of their blood for polycythemia and rapid rises in PSA.

Vitamin D deficiency is common because of decreased intake, decreased absorption, reduced sun exposure, and poor conversion of the storage to active form of vitamin D. As discussed in the section on osteoporosis, vitamin D supplementation in the elderly is controversial for prevention of osteoporosis, but appears to play an important role in prevention of falls. Calcium supplementation in elderly without osteoporosis is likewise controversial (see page 10-8 and page 10-9 on Osteoporosis).

Bone

Osteoporosis

The majority of women > 80 years of age have osteoporosis. According to current guidelines (see Osteoporosis on page 10-8), women 65 years of age and older should be screened with a DXA scan at least once. If the patient has any risk factors for vitamin D deficiency (especially poor diet or lack of sun exposure), check stores by measuring 25-(OH)-D.

Paget Disease

Paget disease of bone occurs in about 1% of people > age 40 in the U.S. It is usually diagnosed after discovering an isolated elevation of alkaline phosphatase in an asymptomatic person. The disease results from a mismatch of osteoclast and osteoblast activity (remodeling), causing changes seen on x-ray, bone scan, CT, or MRI in localized areas. The bones are more brittle, vascular, and larger—leading to arthritis, high-output heart failure, and nerve compression, respectively.

Etiology: There is a clear genetic predisposition; some hypothesize a viral trigger, but that remains controversial.

Diagnosis is strongly suggested by bone scan results. Patients with Paget disease have focal areas of marked increased uptake.

Treatment is not required in the majority of patients and is not curative but may be needed if heart failure, bone pain, nerve compression, or hearing loss develops.

Drugs used: Bisphosphonates (etidronate, pamidronate, and alendronate) given orally or IV are effective in the treatment of Paget disease. SQ or IM calcitonin has also been shown to be effective.

Diabetes

With aging, there is decreased carbohydrate tolerance, with a slight increase in fasting glucose. Both insulin sensitivity and production decline. Elderly patients with diabetes get the same micro- and macrovascular complications as younger patients, but the elderly have to be specifically watched for life-threatening hypoglycemia, hypotension, and drug-drug interactions.

Hypoglycemia more often presents as cognitive impairment in the elderly, rather than tremulousness and sweats. The most likely causes of hypoglycemia are insulins and the insulin secretagogues (sulfonylureas and meglitinides). Glyburide has about twice the incidence of hypoglycemia in the elderly compared to glipizide (27% vs. 14%!) and is no longer recommended for use as a 1st line sulfonylurea by the American Diabetes Association (ADA).

Be cautious with metformin use in the elderly because of the high prevalence of renal insufficiency in this population and the increased risk of lactic acidosis. Assess the estimated glomerular filtrate rate (eGFR) prior to use of metformin in patients > age 80, and do not give the drug to any patient with an eGFR < 60, regardless of age.

Rosiglitazone is no longer recommended by the ADA. Also avoid pioglitazone in the elderly, due to the risk of edema and precipitation of CHF. The jury is still out on whether these drugs are associated with an increased risk of cardiac events and stroke.

Remember to adjust the insulin doses downward, as renal function declines with age, especially as GFR drops below 50 cc/min.

Hyperthyroidism

Those > 60 years of age with thyroid disease are more likely to have vague symptoms that could indicate either hyper- or hypothyroidism. Features of classic hyperthyroidism, such as hyperreflexia, heat intolerance, tremor, nervousness, polydipsia, and increased appetite, are often absent in elderly persons. Apathetic hyperthyroidism can be seen in elderly patients and presents as apathy, fatigue, anorexia/weight loss, and tachycardia.

Atrial fibrillation and anorexia can occur in older patients with hypothyroidism; we rarely see these symptoms in hypothyroid younger patients.

Hormone Replacement Therapy (HRT)

Estrogen replacement is the best option for alleviating vasomotor and other menopausal symptoms and can be used safely for short periods.

The most substantial data we have on HRT are from the Women's Health Initiative (WHI), published in 2002. Prior to this study, common practice (based on observational data) had been to prescribe HRT to postmenopausal women to protect their bones and prevent coronary disease. The WHI data, however, show that HRT (estrogen only) is ineffective long term for preventing heart disease, and that combination HRT is associated with a slightly increased risk for heart disease, stroke, venous thrombosis, and breast cancer. Both groups have an increased incidence of gallbladder disease. Combined therapy reduces the risks of colon cancer and osteoporotic fractures, but not enough to justify these increased risks.

Follow-up analysis of the WHI data tells us that the women who experience the heart disease and strokes are the older women in the study.

Conclusions from WHI that drive practice today:

- Combination HRT is associated with an increase in heart disease, stroke, venous clotting, breast cancer, and gallbladder disease. Unopposed estrogen use is not associated with the heart disease or breast cancer risks.
- Younger, perimenopausal women do not appear to have an increased risk for heart disease and stroke with short-term (up to 5 years) use of combination HRT. But older women do.
- Estrogen alone causes endometrial hyperplasia and increases risk of endometrial cancer. Combination estrogen-progestin in women with a uterus is not associated with this risk.
- Premature ovarian failure (menopause before age 40) can be safely treated with combination HRT until the woman is 50 years old; then, stop and discuss the risks.

The important concept: Do not give women > 50 years old combination HRT because it increases their risks for stroke, heart disease, breast cancer, venous clotting, and gallstones—and the reduction in fractures is inadequate to compensate for these increased risks. Perimenopausal use of estrogen replacement is discussed later in Office Gynecology on page 10-59.

NEUROLOGIC

Delirium

Delirium is a transient alteration in consciousness related to systemic factors. It is a common problem in the elderly. Patients with underlying dementia and/or stroke are at highest risk. Main features are:

- abnormal attention span (easily distracted),
- disorganized thinking (may have hallucinations), and
- altered consciousness (with increased or decreased mental activity) that fluctuates during the day and typically worsens at night.

Common precipitating causes of delirium include drugs, poor nutritional status, acute illness (e.g., infections, volume depletion). Know that physical restraints and bladder catheters can incite delirium as well. In the post-op period, uncontrolled pain is a major cause, especially in geriatric patients with hip fractures. Use of opioids to manage postoperative pain is not associated with increased rates of delirium.

1/3 of cases are caused by drugs. Be aware especially of meperidine, NSAIDs, any new antimicrobial, diphenhydramine, all cardiovascular drugs and antidepressants, antiemetics, baclofen, H_2 receptor blockers, sleep-inducers, and herbals (e.g., St. John's wort and valerian root). Acute discontinuation of alcohol, benzodiazepines (BDZs), SSRIs, and pain medications may cause withdrawal delirium.

Differentiate delirium from "sundowning": **Sundowning** is a disturbance in behavior that occurs predictably in the evening among some patients who live in chronic care environments. It is not associated with a precipitating illness and is not delirium. With sundowning, usually the care facility can tell you that the patient predictably deteriorates at night.

Know that in the elderly, delirium may be the only manifestation of illness. Any patient who becomes delirious should be thoroughly evaluated for a serious precipitating cause.

Evaluate the confused patient with an objective tool such as the MMSE or the CAM (see page 10-11). Physical exam should focus on identifying an underlying acute illness that may be associated with confusion (e.g., drug abuse, hepatic failure, uremia, head injuries, stroke, and seizures). Work up the central nervous system (imaging and LP) if no cause is found after a thorough search.

Treatment of delirium is supportive with focus on diagnosis and treatment of the underlying cause. Calendars and orienting signs, night lights, newspapers, a radio, glasses, and hearing aids help stabilize and prevent decompensation. It is also necessary to minimize daily stress.

Pharmacologic treatment of delirium in the elderly is tough because the meds themselves can worsen the confusion. Low-dose haloperidol is an option, but watch for prolongation of the QT interval—and do not use it

Quick Quiz

- What is apathetic hyperthyroidism?
- What are the main features of delirium? Precipitating factors?
- How is delirium different from "sundowning"?
- What is the recommended initial therapy for elderly patients with delirium? What are some options for drug therapy, and what are their associated risks?
- How is dementia different from delirium?
- What are the 3 most common causes of dementia in the U.S.?
- When do patients derive the greatest benefit from Alzheimer treatment?

in patients with Parkinson's. Alternative drugs include the atypical antipsychotics: risperidone, olanzapine (Zyprexa®), and quetiapine (Seroquel®). These drugs have fewer short-term side effects but have been associated with increased mortality with long-term use. Do not use BDZs in delirious patients because they make patients more confused and drowsy.

Use of a "sitter" and other nonpharmacologic interventions are always the best 1st choices. Remember to avoid physical restraint of geriatric patients at all costs because it precipitates delirium and causes falls.

Dementia

Patients with dementia have a progressive deterioration of cognition that is insidious and chronic—but without altered consciousness, as with delirium. The deterioration can be either very gradual or step-wise (related to the underlying cause). The cognitive impairment presents as:

- Difficulty learning and remembering new information
- Decreased problem-solving of both simple and complex tasks
- Decline in spatial organization → they get lost
- Trouble with impulse control → unusual behavior

Some decline in cognition occurs with normal aging, but in contrast to dementia, memory loss is mild and should not affect the patient's daily living or be especially noticeable by family.

Most patients in the U.S. with dementia are diagnosed with Alzheimer disease (80%), followed by either multi-infarct dementia or Lewy body dementia (a source of current debate). Dementia is a common development in patients with Parkinson disease as well. See Neurology, Book 5, for a more thorough discussion of dementia.

Depression can look like dementia, especially in the elderly. A couple of ways to tell the difference: Depressed patients often present complaining of memory loss, while demented patients are brought in by family or friends. Depressed patients have a depressed affect and slowing with completion of the MMSE or Mini-Cog, while demented patients have a more normal affect and try hard. Assessment tools can help identify the true cognitive defects of dementia. A score of < 24 points on the MMSE is consistent with dementia/delirium.

At this time, the position of the U.S. Preventive Services Task Force on screening for dementia is that there is insufficient evidence to recommend for or against it.

1st line treatment for Alzheimer's is the cholinesterase inhibitors (CIs): donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®). Best results with CIs are achieved in mild-to-moderate Alzheimer dementia, but other causes of dementia (e.g., multi-infarct and Lewy bodies) sometimes also improve. CIs do not help patients with Huntington disease, however. CIs can be combined with memantine (Namenda®), which is an N-methyl-d-aspartate receptor antagonist.

CIs provide a small benefit and help some patients carry out their activities of daily living (ADLs). CIs may be particularly useful in controlling behavioral problems in patients with dementia. There are conflicting data on their long-term effects. Not every patient receives benefit. The combination of cholinesterase inhibitor plus memantine appears to be better than CI alone.

CI side effects often involve the GI tract (nausea, vomiting, diarrhea, anorexia, and weight loss). Severe bradycardia due to AV block from excessive acetylcholine has been reported.

In March 2008, the ACP published dementia treatment guidelines. The evidence-based review found little benefit for any of the current cholinesterase inhibitors or memantine. The authors concluded that individual patient factors would likely determine need to initiate therapy because the data were not very compelling for initiating therapy in any patient. Know that the benefit from treating Alzheimer's is greatest early in the disease, and the cholinesterase inhibitors should be stopped in patients with severe dementia.

Vitamin E is no longer recommended as a supplement because it may increase the risk of heart disease and death. Ginkgo biloba extract and vitamins A and D have not been shown in clinical trials to improve cognition in elderly patients.

Lewy body dementia (**LBD**) is marked by progressive cognitive decline with concomitant hallucinations, sleep disturbances, and parkinsonian features. Treatment of LBD with neuroleptics may bring on a paradoxical psychosis and worsening of parkinsonism. The same may occur with use of dopaminergic agents, making behavioral therapies preferable to medications when possible.

Table 10-8: Antidepressants, Selective Receptor Blockers

Drug	T 1/2 (hrs)	Mechanism of Action/Blocks ...	Notes	Drug of Choice for ...	Caution (!) in patients ...
Fluoxetine (Prozac®, Serafem®)*	72	SSRI	May cause anxiety and insomnia		... with insomnia
Paroxetine (Paxil®, Pexeva®)*	20	SSRI	Most anticholinergic of the SSRIs Sedating in some		... in whom anticholinergics are to be avoided ... with insomnia
Sertraline (Zoloft®)*	25	SSRI	GI discomfort is common		... with insomnia ... with irritable bowel
Fluvoxamine (Luvox®)*	15	SSRI	Most sedating of the SSRIs	... pts with agitation ... pts with insomnia ... pts with obsessive-compulsive disorder	... with irritable bowel
Citalopram (Celexa®)*	35	SSRI	May cause anxiety and insomnia, N/V, headache, QT prolongation		... with long QT syndrome
Escitalopram (Lexapro®)	30	SSRI	S-enantiomer of citalopram; may cause QT prolongation		... with long QT syndrome
Nefazodone (Serzone®)	3***	SSRI and 5-HT2 and has anti-alpha adrenergic activity	Maintains sleep architecture Sexual dysfunction is unlikely	... pts with insomnia; ... to maintain sexual activity	... on benzodiazepines or antihistamines (interacts with cytochrome P-450 system)**
Venlafaxine (Effexor®)	4	SSRI and norepinephrine reuptake and some dopamine reuptake			... with insomnia ... with HTN—usually increases blood pressure, so not used in these patients
Duloxetine (Cymbalta®)	12	SSRI and norepinephrine reuptake and some dopamine reuptake	Also indicated for fibromyalgia	... pts with chronic pain syndromes	
Bupropion (Wellbutrin®)	15	Reuptake of dopamine and some norepinephrine	Sedation is unlikely Sexual dysfunction is unlikely		... with insomnia ... with HTN—may increase blood pressure
Mirtazapine (Remeron®)	20	Presynaptic alpha2 receptor (increases seritonin and norepi release) AND 5-HT2 AND 5-HT3	Agitation is unlikely Sexual dysfunction is unlikely Good for insomniacs	... pts with insomnia; ... to maintain sexual activity	Most anticholinergic of all these ... with HTN—may increase blood pressure

*All the SSRIs have a tendency to cause agitation, sedation, and sexual dysfunction. Pure SSRIs are not likely to increase blood pressure.
**May use loratadine (Claritin®) or lorazepam (Ativan®) with nefazodone.
***T 1/2 is higher than this in elderly, especially women.
Note 1: Buspirone is a 5-HT1A agonist that can be combined with an SSRI to decrease the dose or improve efficacy.
Note 2: Any SSRI may cause an increase of suicidal thought or actions in 1 of 50 age < 18 years.

QuickQuiz

- What are common symptoms of geriatric depression? What are common side effects of medications for depression?
- Name some medications typically associated with insomnia in the elderly.
- What is the role of benzodiazepines in treatment of insomnia?

Depression

Depression is the most common mental problem in the elderly. It is particularly likely to occur in those who live in institutionalized settings and/or have chronic diseases, especially just after a severe sickness or in states of chronic pain. Know that the depressed elderly (especially men) make up 1/4 of the successful suicide attempts in the U.S.

Look for dysphoria, psychomotor slowing, anorexia, weight loss, and multiple "aches and pains." Know that insomnia is associated with depression, especially in the elderly, although it is not known whether it is a symptom or a cause. Depression-associated delusions are more common in the elderly than in the general population. Pay special attention to the elderly man with depressed mood, hopelessness, chronic pain, and insomnia because his suicide risk is particularly high.

A host of substances and drugs can potentiate depression, including alcohol, BDZs, opiates, and barbiturates. Untreated thyroid disease, diabetes, and pain are organic causes. Always check that there is a recent assessment of thyroid function, prior to initiating antidepressant therapy.

Treatment is usually psychotherapy combined with antidepressants; electroconvulsive therapy (ECT) may be considered in severe cases. Exercise helps, too. Selective serotonin reuptake inhibitors (SSRIs) are the 1st line drugs because they have fewer side effects than other choices. The most common reason for stopping these agents is sexual dysfunction! (See Table 10-8.)

When using antidepressants in the elderly, always start with low doses (typically 1/2 the normal dose) and increase slowly with the goal of eventually reaching the normal therapeutic dose. See patients (or call them) within 2 weeks after initiating meds. Watch for the side effects of hyponatremia and tremor in elderly patients on SSRIs. It takes about 8 weeks to see improvement; 6–12 months is the usual duration of treatment. Know that treating a patient's depression can help their comorbidities improve as well.

Sleep Disturbance

Insomnia

Sleep disturbance is a common problem in elderly persons, and normal aging is associated with more frequent awakenings. These disturbances include difficulty falling asleep (> 30 minutes), frequent awakenings, waking too early, and feeling generally unrestored. When the disturbance also causes problems for the patient during the day (e.g., poor concentration, moodiness, sleepiness, fatigue), it is classified as "insomnia."

Know what is not insomnia:

- Some people can sleep well for only a few hours and have no problem functioning the next day. These patients simply have short-duration sleep.
- People who have chosen not to sleep at night (due to work or other reasons) and easily fall asleep during the day are classified as having "insufficient sleep" or "sleep deprivation," not insomnia.

Insomnia, especially in the elderly, is associated with worsening of hypertension, heart disease, lung disease, urinary incontinence, chronic pain, and depression.

History should focus on characterizing the sleep disturbance (sleep logs help) and identifying any untreated comorbidities and/or precipitants (e.g., naps, stress, newly stopped or started meds, alcohol, caffeine, nicotine).

Medications specifically associated with insomnia include corticosteroids, beta-blockers, beta-agonists, and stopping sedatives or pain meds.

Labs are recommended only to diagnose potential comorbidities (e.g., hyperthyroidism, restless legs). Sleep studies are unnecessary until a patient has failed to respond to conservative management.

Treatment should be directed at improving any poorly managed comorbidities, and advise the patient on good sleep hygiene:

- Set a schedule for sleep and stick to it.
- Get in the bed only when you're sleepy. When you're rested, get up.
- Minimize excess light and sound in the bedroom.
- Exercise during the day, at least 4 hours before bedtime.
- Stay away from caffeine, nicotine, alcohol, and excess fluids near bedtime.
- Eat dinner or an evening snack to prevent bedtime hunger.
- Do not fight sleep. If you can't sleep for > 20 minutes, get up and do something relaxing (reading or music). No bright lights or TV.

The most efficacious treatment in patients with uncomplicated insomnia is behavioral—not pharmacologic. Elderly patients are especially susceptible to bad outcomes from sleep drugs.

Benzodiazepines (BDZs) actually do help by decreasing the frequency of awakenings, reducing time to fall asleep, and increasing duration of sleep. But they have many negative side effects, including addiction, loss of memory, and accumulation of metabolites.

Non-benzodiazepine insomnia drugs, such as zolpidem (Ambien®), zaleplon (Sonata®), and eszopiclone (Lunesta®) have more selective effects than BDZs because they affect only a portion of the receptor subunits that BDZs affect. Because of this, non-BDZs tend to have more sedative than anxiolytic effects than BDZs. Additionally, they do not have as many side effects as BDZs. Their cost can be prohibitive.

Even so, both BDZs and non-BDZs can cause confusion, wandering, imbalance, and daytime grogginess in the elderly—hence both classes are avoided in geriatric patients.

Many sleep-aid drugs in both the BDZ and non-BDZ classes have received FDA-required label changes, indicating that the drugs can cause a hypnotic state that allows patients to attempt complex tasks while sleeping → bizarre behaviors (e.g., having sexual intercourse while not apparently awake, sleep eating, erratic driving, making incoherent phone calls). The FDA required reduced recommended doses for zolpidem products in 2013 because of persistent impairment the next morning.

The melatonin agonist, ramelteon (Rozerem®), does seem to improve sleep for some patients, and the drug is not associated with any known untoward effects. It is a good choice for the elderly, albeit with variable efficacy.

Stay away from older antidepressants (e.g., amitriptyline), diphenhydramine, haloperidol, and barbiturates in most patients (because of side effects), but especially in the elderly.

Restless Leg Syndrome

Restless leg syndrome (RLS) is a common sleep disorder in the elderly (prevalence = 20% in age > 80 years). The hallmark of RLS is leg discomfort +/– paresthesias at rest, relieved immediately with movement. Usually, pain is "deep seated" and localizes below the knees. Symptoms are worse in the evening and at night.

RLS can be primary or caused by other conditions: iron deficiency (even without anemia), dialysis, diabetic neuropathy, multiple sclerosis, Parkinson's, pregnancy, and others. Make sure that the patient's complaints aren't actually akathisia from medications (phenothiazines and SSRIs).

Diagnosis is made based on clinical history, a normal neuro exam, and absence of kidney disease. Always check a ferritin level to rule out iron deficiency even if the patient does not have anemia.

The following expert panel treatment recommendations are based on whether the RLS is intermittent, daily, or refractory.

- Intermittent: Try non-pharmacologic therapy first: iron-replacement therapy; mental-alerting activities (such as video games or crosswords); avoidance of caffeine, nicotine, and alcohol. Then, if needed, try one of the following:
  - Dopamine agonists generally are the drugs of choice: pramipexole, ropinirole.
  - Levodopa: Be careful—may cause augmentation (worsened symptoms or rebound).
  - Benzodiazepines (generally avoided).
  - Low-potency opioids (generally avoided).
- Daily: Try non-pharmacologic first, then dopamine agonists, gabapentin, and, lastly, low-potency opioids.
- Refractory to dopamine agonists: Try gabapentin, a different dopamine agonist, combination therapy, then tramadol and, lastly, high-potency opioids.

Dizziness

Dizziness is common in the elderly but is not a normal consequence of aging. When any patient complains of "dizziness," take a good history (more sensitive in making the diagnosis than PE, labs, or studies) to determine which of the following the patient is actually describing:

- Vertigo: "spinning," "whirling," or "moving" of either the patient or the environment that is worse with head movement and occurs in spells (days to weeks), then eventually resolves
- Presyncope: almost "fainting" or "blacking out" while either standing or seated (not supine), possibly associated with sweating, a sensation of warming, visual blurriness, and nausea
- Disequilibrium: imbalance with standing and walking, especially with turning
- Nonspecific dizziness: unable to characterize into one of the above categories

A complete discussion about the workup of vertigo is included in Neurology, Book 5. Multisensory deficits causing disequilibrium and benign positional vertigo are common. In geriatric patients, the cause is more often vestibular than in other patient groups.

The common causes of dizziness in the elderly usually can be discovered by history.

Presyncope: Dizziness that sounds like presyncope or "faintness" should be taken seriously and evaluated with a cardiovascular workup, especially if the patient has known heart disease, palpitations, or a history of true syncope.

Multisensory deficits: Think about multisensory deficits as a cause for disequilibrium in the patient with a mix of visual, hearing, orthopedic, and neuropathic impairments (sometimes also called "benign dysequilibrium of aging"). They complain of "feeling unsteady" and improve with a walker or when someone holds their arm. Treat this by maximizing support for each sensory impairment and providing assistance devices (e.g., canes, walkers).

Benign positional vertigo (BPV) presents as recurrent (lasts for weeks in spells), short-lived (< 1 minute) episodes of vertigo that predominantly occur when the patient changes position. The vertigo can be bad enough

Quick Quiz

- What dangerous side effects are sometimes seen with both benzodiazepine and non-benzodiazepine sleep agents?
- What is a common condition associated with restless leg syndrome?
- What cause of dizziness is associated with improvement when the patient holds onto a walker?
- Which maneuver helps identify benign positional vertigo?

to cause nausea and vomiting; but, otherwise, the patient has no other symptoms (e.g., hearing loss, headaches). Know that BPV occurs more often in geriatric patients who have giant cell arteritis. (See Rheumatology, Book 3.) So, take a good history in the dizzy elderly patient to determine whether symptoms of vasculitis or polymyalgia rheumatica are also present (e.g., weight loss, fevers, musculoskeletal pain).

In uncertain cases, BPV can be diagnosed by the Dix-Hallpike test. This maneuver involves turning the patient's head, then rapidly tilting the patient backwards for 30 seconds, then upright again, with subsequent observation for nystagmus. Repeat the maneuver with the head turned in the opposite direction. A positive test is visible nystagmus in either the recumbent or the upright position.

In these cases, the differential diagnosis includes central causes of vertigo such as cerebellar lesions (strokes or masses); so if the history is suggestive, do further workup with imaging and electronystagmography (water calorics).

Treatment of BPV can be accomplished through one of 2 office maneuvers, Epley and Semont, both equivalent in efficacy and designed to reposition the misplaced otoliths thought to be responsible for the vertigo. The maneuvers are extensions of the Dix-Hallpike test, where you lean the patient backwards and forwards with an associated neck tilt. Alternatively, exercises can be prescribed for home that aim to have the same result (but are less effective). No drugs are used to treat BPV.

HEARING

Decreased hearing is an age-related condition. About 1/3 of patients > 65 years of age have hearing loss. The most common cause is presbycusis, which is an age-related sensorineural hearing loss. It is bilateral, and loss of higher frequency sounds is more common. Be sure to check for cerumen impaction. See other causes of decreased hearing on page 10-49. Hearing aids can help these patients.

CARDIOVASCULAR

Walking more than 4 hours per week is associated with a dramatic decrease in cardiovascular-related hospitalizations in persons > 65 years of age.

Isolated systolic hypertension is a common finding in elderly patients. It increases the risk of myocardial infarction and stroke 2–4x. Several studies show these patients benefit from treatment, so long as the diastolic pressure does not fall too low (< 60 mmHg). Low diastolic pressures have been associated with increased cardiovascular events.

In the elderly, start with about 1/2 the standard dose of any one of the following: thiazides (chlorthalidone is now being favored over hydrochlorothiazide because of its superior efficacy in clinical studies), dihydropyridine calcium channel blockers (e.g., amlodipine), or ACE inhibitors/angiotensin II receptor blockers. Avoid beta-blockers for treatment of systolic hypertension in the elderly because they do not work as well as the other treatments and have been associated with increased mortality.

The 6-month mortality rate after an MI increases with age—from 4% around age 66 to 12% when older than 80 years. (Group = 1st MI, with thrombolytics, discharged from hospital.) Only about 75% of eligible patients receive aspirin on discharge from the hospital. Be sure to prescribe an antiplatelet drug to these patients!

CHF: The incidence of congestive heart failure (CHF) in the elderly is increasing dramatically and is now the number 1 cause of hospitalizations in this group. (Number 2 is pneumonia.)

Treat CHF itself primarily with diet, diuretics, beta-blockers (specifically metoprolol, carvedilol, or bisoprolol) and ACE inhibitors. Spironolactone can be a useful adjunct that can also lower mortality for systolic heart failure. Digoxin is indicated only for more severe heart failure and reduces hospitalizations, but not overall mortality. Isosorbide dinitrate and hydralazine has been shown to lower mortality in African-Americans with systolic heart failure. Use of NSAIDs is an important precipitant of CHF in older patients who already have risk factors for CHF.

Mortality benefit has been shown for ACE inhibitors, beta-blockers, and low-dose spironolactone. If you use spironolactone, follow K^+ closely. Spironolactone benefit has been shown in patients with class 3 or 4 heart failure.

PULMONARY

Geriatric Asthma

Elderly patients with asthma may have long-standing disease acquired in childhood/young adulthood, or they may have developed it as an aging adult. Around 8% of adults > age 65 are diagnosed with adult-onset asthma. Be aware that it is commonly misdiagnosed as

COPD because COPD is more likely to occur in this age group.

Risks for development of adult-onset asthma are the same as for younger patients: allergens and irritants (e.g., tobacco smoke, occupational vapors, air pollution).

Comorbidities are important, especially coronary heart disease, because treatment of asthma with beta-agonists can cause myocardial ischemia. Also, beta-blockers used as antihypertensive drugs can exacerbate airway obstruction, although this is primarily the case with older, nonselective beta-blockers.

Asthma in the older patient can present the same as in the younger patient, although the elderly tend to have fewer symptoms with the same amount of disease. Specifically, they complain less of dyspnea associated with obstruction and wheezing—likely due to their reduced activity, they fail to notice they are short of breath. Definitive diagnosis is made with spirometry, when the FEV_1 and FEV_1/FVC are reduced.

In the elderly, the traditional cutoff of 70% for a diagnosis of obstruction, as recommended by the GOLD group (see Asthma in Pulmonary Medicine, Book 2), is not used. This is due to the fact that this criterion is not as specific in this age group and overdiagnoses asthma! Instead, for diagnosis of asthma in the elderly, most experts use an FEV_1/FVC < 89% of the lower limit of normal for age. A response to bronchodilators is still expected, as per the GOLD criteria, for diagnosis: > 200 cc increase in FEV_1 post-bronchodilator and > 12% of predicted.

Separating COPD from asthma is important, especially in the elderly where rates of COPD are high. Know that reversible obstruction is consistent with asthma, and a low DLCO is consistent with emphysematous COPD.

Bronchoprovocation is used to diagnose asthma in patients with normal spirometry, the same way as it is used in younger people.

Management of geriatric asthma is the same as for younger patients, but theophylline is not recommended, even as an alternative drug, because of the significant potential for toxicity.

Geriatric Sleep Apnea

Think about sleep apnea as a potential cause of reduced cognition in geriatric patients. Know that apnea that results in poor sleep and excessive daytime somnolence carries a higher rate of morbidity in patients who are frail and already prone to falls. Diagnosis and management is the same as in younger patients.

UROLOGY

Urinary Incontinence

Overview

Normal micturition is dependent on an intact neurologic pathway from the brainstem to the bladder, which causes relaxation of the sphincter muscle's tonic contractile state just milliseconds before contraction of the detrusor (bladder muscle). Additionally, voluntary control of micturition requires communication between the cerebral cortex and the brainstem.

Urinary incontinence, although a common geriatric problem, is always considered a pathologic condition that is not a normal consequence of aging! Always consider the possibility that the patient has a serious underlying condition responsible for the leakage.

Normal, age-related changes to the urinary tract include decreased flow rate, decreased bladder capacity, and increased residual volume. As a function of these changes, it is normal for patients to get up once during the night to void.

Urinary incontinence may be thought of as either a "storage problem" ("detrusor" or bladder over- and under-contractility) or "outflow" problem (outlet obstruction or incompetence).

There are 4 general, symptom-based types of urinary incontinence:

1) **Urge** = leakage (a lot or a little) associated with the feeling of urgency
2) **Stress** = leakage associated with increased intra-abdominal pressure (e.g., coughing, sneezing)
3) **Mixed** = leakage associated with both an urgency and increased intra-abdominal pressure
4) **Incomplete bladder emptying** ("overflow") = leakage (a lot or a little) after voiding

Note that "overactive bladder" is not necessarily incontinence. It is a urologic condition defined by the urgent need to void frequently and during the middle of the night. Occasionally, the urgency may be associated with leakage, in which case it is called "urge incontinence."

Urge Incontinence

Urge incontinence (UI) is a common cause of geriatric incontinence. With urge incontinence, there is passage of either small or large amounts of urine, associated with a sense of urgency often set off by a precipitating stimulus: hearing running water, unlocking the door to the house, entering cold environments.

UI is related to overactive bladder. They are both caused by uncontrollable bladder contractions ("detrusor instability")—usually caused by CNS problems (termed "detrusor hyperreflexia"), but also sometimes a result of cystitis.

Quick Quiz

- What are the GOLD recommendations for diagnosis of asthma in the elderly?
- Is urinary incontinence considered a normal consequence of aging?
- What are the 4 types of incontinence?
- What is the best treatment for urge incontinence?
- What is the best initial treatment for stress urinary incontinence?
- What is a common cause for incomplete bladder emptying in males?
- What is the role of bladder catheterization in the treatment of geriatric incontinence?

Detrusor hyperreflexia is due to progressive loss of communication between the frontal lobes and the micturition center in the brainstem. As the bladder loses the modulating influence from the brain, it tends to spasm more often.

Treatment is best accomplished with behavioral therapy, called bladder training. When an urge to void becomes profound, the patient is instructed to attempt relaxation techniques that help the urge subside and allows short-term voiding delay. Once the urge is controlled, the patient can walk calmly to the restroom and urinate. The goal is to eventually delay voiding to every 4 hours with no interval leakage.

Bladder training is more effective than the more commonly prescribed therapy of antimuscarinic agents (oxybutynin, tolterodine, fesoterodine, trospium, solifenacin, darifenacin, hyoscyamine, and tricyclic antidepressants), all of which are equivalent in efficacy and relax the bladder muscle. They have other anticholinergic side effects (e.g., dry mouth, tachycardia, constipation). Even so, these antimuscarinic agents are helpful when used as an adjunct to bladder training—short term, as needed. Remember that anticholinergics can precipitate acute angle glaucoma! Also, do not use them for incontinence in patients who are taking cholinesterase inhibitors for dementia because the combination accelerates cognitive decline.

Pelvic muscle exercises (Kegel's) are also helpful for UI.

Stress Incontinence

Stress urinary incontinence (SUI) is second in frequency in geriatric women. With SUI, the urethra cannot maintain the pressure gradient required for urinary control when there is an increase in intra-abdominal pressure (cough, jumping, etc.). SUI is associated with multiple vaginal deliveries, pelvic surgery, postmenopausal hormonal changes (low estrogen → atrophic relaxation of the vaginal wall → lack of support for the urethra) but is sometimes seen in males post-prostatectomy. Stress incontinence is initially best treated with behavioral therapy, especially Kegel exercises (perineal muscle contractions); referral to a pelvic floor physical therapy specialist can be helpful in effective teaching of Kegel's. Note that some women with urinary incontinence have a mixture of SUI and urge incontinence. Surgery has high cure rates but with high risk of complications. Periurethral collagen injections are an option for those who cannot have (or do not want) surgery and who do not improve with exercises.

The history gives you the clues to determine whether incontinence is due to urge or stress incontinence—look for the stimuli that precipitate leakage in a patient with UI and look for leakage associated with increased intra-abdominal pressure with SUI.

Mixed Incontinence

Mixed incontinence, again, is a combination of urge and stress incontinence. The true etiology is unknown. Bladder training and Kegel's help these patients, too.

Incomplete Emptying

Incomplete bladder emptying is sometimes still called "overflow incontinence." It is caused by either an overactive bladder +/– an outlet obstruction or by an underactive bladder that has trouble contracting (e.g., diabetes, Parkinson's, MS, alcohol abuse).

Although rare in females, incomplete emptying in males is usually caused by prostatic hypertrophy. The outlet obstruction causes a distended bladder and high-volume, post-void retention. Anticholinergic drugs are the most common causes of drug-induced incomplete emptying. Psychogenic retention can also be a cause.

Most types of incomplete emptying do indeed cause urgency and may be seen as a type of urge incontinence.

Treatment includes alpha-blockers and/or 5-alpha reductase inhibitors for men with benign prostatic hypertrophy (BPH).

Review

- Bladder training and Kegel exercises: urge, stress, and mixed.
- Drugs for urge and mixed (anticholinergics with antimuscarinic effects): oxybutynin, tolterodine, trospium, solifenacin, darifenacin.
- Drugs for stress: None! Bladder training and Kegel only!
- Surgery: last resort for stress.
- Incomplete emptying: Treat underlying cause if possible; intermittent catheterization; "diaper-like" garments.

Asymptomatic bacteriuria, common in the elderly, is not a cause of incontinence. Also, incontinence is never an indication for a long-term bladder catheter.

Fecal Incontinence

Geriatric fecal incontinence is usually caused by fecal impaction and secondary overflow incontinence. The impaction is normally a result of lax muscles and neuronal degeneration. Typical presentation is an elderly person with complaints of diarrhea and abdominal discomfort and who has hard stool in the rectal vault on physical exam. Treatment is disimpaction and subsequent bulking agents.

Benign Prostatic Hyperplasia

The prevalence of benign prostatic hyperplasia (BPH) increases from about 10% at age 30 to > 80% at age 85; about 15% of these patients have impaired urination. We still do not understand what causes BPH and have yet to identify any specific risk factors—except age. BPH does not increase the chance of prostate cancer.

Symptoms of BPH are fairly specific for urinary retention: frequency, hesitancy, difficulty starting and stopping the stream, urgency, and nocturia. Certainly other diseases can cause these symptoms (e.g., bladder cancer, cystitis) and should be considered before making a diagnosis of BPH. Know that serum prostate-specific antigen (PSA) levels increase as the prostate increases in size, so PSA screening for prostate cancer is less specific in men with BPH (more false positives).

The 2 definitive tests that should be done:

1) a digital rectal exam to palpate the prostate and assess for irregularities and increased size, and
2) a urinalysis to assess for hematuria (with a culture if infection is suspected). BPH symptoms should not immediately trigger PSA testing.

Treatment

BPH is treated only if it significantly affects the patient adversely and/or if it is associated with outlet obstruction, causing hydronephrosis or acute kidney injury.

Treatment of symptomatic patients starts with behavioral therapy. Make sure patients know to reduce intake of caffeine and alcohol (diuretics), stay away from fluids before bed, and attempt to urinate twice to completely empty the bladder.

Medical therapy:

- Generally start with alpha-blockers (terazosin, doxazosin, tamsulosin, alfuzosin, silodosin) alone.
- A 5-alpha-reductase inhibitor (finasteride, dutasteride) is then added later, if needed.

Note: Of the alpha-blockers, prazosin is not used for BPH because it requires frequent doses and has more side effects.

Most common side effects of these meds are orthostasis and dizziness. Be careful with combining sildenafil or vardenafil with these drugs because the combination worsens hypotension.

The 5-alpha-reductase inhibitors, which reduce circulating testosterone, take at least 6 months to decrease prostate size and relieve symptoms. These drugs work better for large prostates and have a more durable effect. The major side effect is impairment of sexual function (decreased libido and delayed ejaculation). Know that these drugs decrease serum PSA, even in cancer patients, so recommendations are to multiply the measured PSA by 2–2.5, depending on how long the patient has been taking the drug.

Transurethral resection of the prostate (TURP) is now the treatment of last resort, used when drugs fail to work.

Erectile Dysfunction (Impotence)

Overview

The most common type of male sexual dysfunction is erectile dysfunction (ED), which is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse. It is not uncommon for men to experience brief episodes of ED. "Impotence" is the term reserved for ED that occurs in > 75% of sexual encounters.

The smooth muscle in the flaccid penis is in a state of tonus or contraction due to alpha stimulation by norepinephrine. cGMP is made, along with cAMP—made by the norepinephrine and vasoactive intestinal peptide (VIP) pathways. This cGMP causes the relaxation of the smooth muscle in the penis, which increases the inflow through the helicine artery into the erectile tissue. The swelling of this tissue causes compression of the outflow venules, resulting in a sustained erection.

ED can be caused by organic or psychological problems, or as a side effect of medications (25% of cases!). Most causes of ED are at least partially organic. The organic causes are neurogenic, vascular, hormonal, and normal aging.

Classic Presentations and Causes of ED

There are many causes of ED. These can be grouped as follows:

- **Organic causes**: Usually slow onset. Loss of nocturnal and morning erections.
  - **Neurogenic**: Usual cause is diabetes. Other causes are surgical procedures (especially prostate), MS, ALS, Parkinson's, and other causes of peripheral neuropathy. Cyclists who spend > 3 hours/week on an upright bicycle can experience ED due to pressure that the seat places on the pudendal nerves (reducing blood flow to cavernosal artery).
  - **Vascular**: Usual cause is diabetes and/or cardiovascular disease. Other causes are surgical procedures, inflammatory conditions, or pelvic fracture. In elderly men, ED is caused by vascular compromise in 50% (indicated by a low penile

Quick Quiz

- How does prostatic hyperplasia affect PSA levels?
- What is the initial treatment for BPH? What medications are commonly used for treatment?
- What is the most common cause of neurogenic ED?
- Which medications most commonly cause ED?
- If an exam presents a young male with ED who is on no medications, what is the most likely etiology?
- What is the mechanism of action for sildenafil?

brachial pressure index [PBPI]). ED due to vascular compromise indicates increased risk of present and future major vascular disease.

  - **Hormonal**: often accompanied by a loss of libido. Symptoms may include gradual onset of frontal headaches or visual disturbances (space-occupying tumor); hot flashes and decreased need for shaving (decreased androgens); fatigue + weight gain + dry skin + constipation (hypothyroidism).
  - Normal aging: Sexual potency does decrease with age.
- **Medications**: especially antidepressants (SSRIs), clonidine, spironolactone, beta-blockers, and thiazide diuretics. Many others also cause ED, but these are some of the most commonly prescribed meds in the geriatric population.
- **Psychogenic**: typically acute onset. This is the usual cause for ED in younger patients. They continue to have nocturnal and morning erections, but libido is lost. ED is directly correlated with depression. Unfortunately, SSRIs used for depression treatment are also associated with a very high incidence of sexual dysfunction (generally delayed ejaculation).

Treatment Options for ED

1st line treatment for ED [Know]:

Sildenafil citrate (Viagra®) inhibits phosphodiesterase type 5 (PDE5), an enzyme that inactivates cGMP. It works very well for many causes of ED, including psychogenic. Side effects are due to its vasodilatory properties—headaches, flushing, dyspepsia, bluish hue in the vision. Reports of hearing loss have also been documented.

Vardenafil (Levitra®, Staxyn®) is similar to sildenafil in mechanism, effectiveness, and side effects.

Tadalafil (Cialis®) has the same mechanism of action as sildenafil and vardenafil but with a longer half-life. Erectile function may be improved for up to 36 hours. This drug is approved for daily use. One specific side effect is back pain. Tadalafil has recently gained FDA approval as treatment for BPH symptoms when used on a daily basis, although the mechanism remains unclear.

Avanafil (Stendra™) is the newest agent (approved 2012) and is similar to the others.

PDE5 inhibitors are more likely to cause hypotension when taken with nonselective alpha-blockers (prazosin, doxazosin, and terazosin). Uroselective alpha-blockers (tamsulosin and alfuzosin) are less likely to cause hypotension. There is a risk of hearing loss with all of the PDE5 inhibitors. Contraindications are any concurrent nitrates. Relative contraindications are CHF, hypotension, unstable angina, HCM, and severe aortic stenosis.

Yohimbine is a naturally occurring alpha-blocker. It has minimal effect, but, because it is inexpensive and has minimal side effects, it is often tried on patients with a mostly psychogenic etiology. Better than placebo but much less effective than sildenafil.

Vacuum devices work well but are clumsy to use. They are indicated only when oral therapy is contraindicated or the patient prefers them to oral therapy.

2nd line treatment for ED:

Alprostadil (prostaglandin E1) injected into the corpora cavernosa of the penis works well. It is especially useful in patients with ED due to neurologic dysfunction.

3rd line treatment for ED:

Penile implants: Various types—hydraulic, semirigid, and flexible rods. Usually used only for those who have failed all other therapy. Complications are associated with the surgery. There is a risk of postsurgical infection. Scarring may cause erections to curve. Tissue erosion may occur. If there are no complications, they are effective and patient satisfaction rates are high.

ETHICS

OVERVIEW

Read the *ACP Ethics Manual*, 6th Edition (released 2012), available online at: http://www.annals.org/content/156/1_Part_2/73.full

PHYSICIAN'S DUTY AND PATIENT'S RIGHTS

The physician's duty to the patient is based on 4 principles that are the basis for all ethical physician-patient interaction:

1) Beneficence: the duty to act in the best interests and welfare of the patient and the health of society
2) Nonmaleficence: the duty to do no harm to the patient
3) Respect for the patient's autonomy: helping the patient make free, non-coerced choices
4) Justice: the duty to treat all patients (and by extension, society) equitably and fairly

Let's look at specifics.

The patient's right to accept or refuse health care is based on another 3 principles:

1) The philosophical concept of personal autonomy—a value held close to the heart in our culture
2) Personal liberty interest under the Constitution
3) Common law right of self-determination

Patients should be able to choose and follow their own ideas and plans for their life. Constraint of a person's free choices is permissible only when these choices infringe on another person's rights and welfare. Paternalism, the practice of overriding or ignoring preferences of patients in order to benefit them, used to be the standard of interaction between the physician and patient. Today, except for certain cases (mental illness and some emergencies), paternalism is considered ethically improper. Patients should be an active part of the decision-making process. Patients require informed consent, which is defined as the willing acceptance of medical intervention—after adequate disclosure by the physician—of the nature of the intervention and all of its risks and benefits.

Patients are entitled to disclosure of the following:

- The patient's current medical status with the probable course, whether or not medical intervention is used
- The medical interventions that may help and the risks associated with them
- The physician's opinion about other alternatives
- The physician's own recommendations based on best clinical judgment

Know that physicians are responsible for caring for patients with contagious infectious diseases. It is deemed unethical by ACP for internists to refuse care for patients with HIV/AIDS, hepatitis viruses, multidrug-resistant TB, and influenza because of a physician's own fear of becoming infected. It is assumed that the physician takes appropriate infection control precautions.

Know that physicians are responsible for providing honest information on disability claim forms and should not attempt to assist a patient in obtaining disability benefits erroneously.

Generally, physicians should avoid caring for close family members and friends.

Use of social media has added a new dimension to interactions with patients. The ACP warns that use of social media has the "potential to blur social and professional boundaries" and should be used with great caution.

It is absolutely unethical for physicians to have any sexual relationship with a current patient, regardless of who initiates the relationship. The ethics document from the Federation of State Medical Boards says that physicians cannot even have sexual relationships with the relatives of existing patients.

Even former patients can cause ethical problems. The ACP ethics document says that physicians should "consult with a colleague or other professional before becoming sexually involved with a former patient."

DISCONTINUING PATIENT RELATIONSHIPS

Physicians can sever relationships with patients so long as care is available by another physician (anywhere else), and the patient's health is not sacrificed. The physician must give the patient written notice of intent and must request approval from the patient for transfer of medical records to the accepting physician. If this process is not followed, legal action can be taken for physician "abandonment."

MEDICAL RECORDS

The physical chart belongs to the hospital or physician, but the information in the chart belongs to the patient. If requested, you must release the entire chart to the patient, and you cannot hold the chart hostage in exchange for payment of services. However, it is legal to charge a reasonable fee for copies.

ADVANCED DIRECTIVE

The **advanced directive** is the means patients have for stating which treatments they would accept or decline if they lost decision-making capacity. The advanced directive may also specify general goals for medical care and the patient's choice of a surrogate—a person with durable power of attorney for the patient's health care.

A **living will** is a more focused form of advanced directive, in which the patient, for example, refuses life support when in a terminal condition. A lawyer is not needed to make a living will.

The patient has a right to change his/her mind! "Joe" has a living will. If he comes into the emergency department and requires intubation to survive—and states that he has changed his mind and wants all possible treatments available—then you honor his current decision.

Know that fluids and nutrition are ethically regarded as the same as other forms of treatment, and patients can address the desire for discontinuation of fluids and nutrition in their advanced directives.

COMPETENCY OR DECISION-MAKING CAPACITY

The decision-making capacity refers to the ability to comprehend, evaluate, and choose among realistic options. Decision-making capacity is determined by the physician and at times may be difficult to determine. Competency refers to the legal determination of one's decision-making capacity. Most decisions on patient care are carried out without need for competency hearings.

There are many transitory or reversible conditions that can interfere with this capacity. Examples are anxiety,

Quick Quiz

- Name a scenario in which a physician can ethically have a sexual relationship with a patient.
- What is the difference between an advanced directive and a living will?
- 6 months ago a man with terminal cancer decided to invoke a living will that states he refuses all life support in case of cardiopulmonary arrest. Today, he presents to the emergency department in severe distress and says he wants everything done, including intubation. His family does not want anything done; you have the signed living will at the bedside. What should you do?

depression, drug-induced confusion, infection, and abnormal metabolic states. The waxing and waning associated with certain conditions, such as organic brain syndrome, is a manifestation of pathology, and the patient should be considered to have impaired capacity.

SURROGACY

A "surrogate" or "proxy" is a person who is authorized to make decisions on behalf of an incapacitated person. Traditionally, the next of kin has been considered the default surrogate. (In some states, there is a well-defined list of the priority for next of kin to assume surrogacy.) Another option is for the subject to give someone durable power of attorney. This means giving decision-making authorization to a person who supersedes family members. Remember: The "contract for health care" is between the physician and the patient, not the patient's family.

The surrogate's decisions must promote the patient's wishes and welfare. If the patient has expressed certain wishes on a topic regarding medical intervention in the past, the surrogate must use that knowledge in the decision-making process. This is known as substituted judgment. If the surrogate has no knowledge of the patient's wishes, then the surrogate should make decisions based on the patient's welfare. Welfare considerations include suffering, preservation of life, restoration of function, and quality of life; decisions should be based on what a reasonable person would want in similar circumstances.

The surrogate's authority ends when the patient dies (i.e., they are not able to give consent for autopsy). Organ donation decisions should be broached at the appropriate time with decision makers by organ procurement specialists who are separate from prospective donors' health care providers in order to avoid conflicts of interest or a perception of conflicts of interest. Health care providers of prospective recipients should not be providing care to prospective donors for similar reasons.

EMERGENCY SITUATIONS

For patients unable to express their preferences, the physician may perform life-sustaining emergency procedures under the presumption that the alternative would be death or severe disability. All states have statutes empowering health care professionals to hold certain patients with psychiatric conditions against their will for medical and/or psychiatric treatment, although the specific logistics vary from state to state.

QUALITY OF LIFE AND PAIN RELIEF IN PALLIATIVE CARE

The quality of life in terminally ill patients in pain is considerably improved by proper pain relief. Terminal patients in pain are in a special situation, and their requests for pain meds generally should be honored. The downside of pain medications is that they can cause confusion and a decreased ability to communicate. You have to strike a balance between maximum pain relief and minimal decrease in consciousness. The assistance of hospice workers in this situation can be very helpful.

PHYSICIAN ERROR

Physicians must disclose to the patient any errors in judgment and procedure when the information is deemed "material to the patient's well-being." In general, you always disclose errors---disclosure is not equivalent to admitting neglect.

PHYSICIAN-ASSISTED SUICIDE AND EUTHANASIA

Physician-assisted suicide (PAS) is when the physician supplies the means of death to a patient, such as a prescription for a lethal dose of medication along with instructions on its use for terminating one's own life.

Euthanasia is when the physician directly administers a lethal dose of a medication with the intention of causing death.

As of 2013, 3 states have legalized PAS (Oregon, Washington, and Vermont) and 1 state has a court case setting precedence for defense of the practice (Montana). Euthanasia is illegal in all 50 states.

The latest guidelines by the ACP and the AMA do not support any form of PAS or euthanasia.

Know that respecting a patient's choice to refuse life-sustaining treatment is different from either of these.

Good end-of-life care entails treatment based on many issues. For instance, the *ACP Ethics Manual* says that, when providing comfort to a dying patient, "… the physician may appropriately increase medication to relieve pain, even if this action inadvertently shortens life." This is known as the principle of "double effect."

CPR AND DNR

Cardiopulmonary resuscitation (CPR) is usually a standing order in a hospital; i.e., it is to be carried out, without specific order, on any patient who suffers cardiac or respiratory arrest. The only time CPR is not done is when there is an order stating such—a "do not resuscitate" (DNR) or "do not attempt resuscitation" (DNAR) or "no code" order. The decision about nonresuscitation has 3 considerations that must be assessed:

1) Whether or not CPR would be futile; i.e., that the resuscitation would be unlikely to succeed or, if it did, another cardiac or respiratory arrest would soon follow
2) The preferences of the patient
3) Expected quality of life of the patient if resuscitation succeeds

It is the responsibility of the physician to initiate code status discussions with the patient (or, if the patient is incompetent, with family members or a surrogate) who is terminally ill or has an incurable disease with an estimated 50% survival of less than 3 years. The attending physician should clearly write the "do not resuscitate" order on the order sheet in the patient's chart, if that is the final decision after discussion with the patient (and/or family, surrogate). The progress notes should detail the facts and opinions leading to that decision.

SUICIDE ATTEMPTS

Suicide attempts should always be treated despite the wishes of the patient. These patients are often "crying for help." They are also often in a pathological mental state that may be transitory or treatable. This situation is different from the patient who refuses life-sustaining treatment. The difference is that with refusal of care, the patients are not killing themselves—rather, they're refusing help that would keep them alive.

CULTURAL DIFFERENCES

A patient from another country/culture can present some ethical dilemmas. If family members of your elderly patient state a wish that their grandmother not be told about a terminal illness such as cancer, you can explain to your patient that she is very sick and ask whether she wishes to know her diagnosis. It is up to her to express whether she wishes to direct her own care or designate her family members to make decisions regarding her care. This can then be considered an authorized delegation of decision-making authority. If the patient says she wants to know everything and make her own decisions, you must side with the patient.

CONFIDENTIALITY AND PUBLIC WELFARE

The personal and medical information that a physician obtains from a patient is (ethically and legally) confidential. But! In general, if the condition or disease of a patient can endanger other persons, the physician is legally and ethically obligated to report the situation to the appropriate parties.

Many specifics are straightforward and are addressed with legal statutes. Common examples are sexually transmitted diseases and conditions that could affect the operator of a motor vehicle; e.g., seizures and severe cardiac arrhythmias. Others are more difficult. A patient with a serious, highly infectious disease (e.g., TB, meningococcemia) should not be allowed to infect others. These patients can be held against their will if their behavior is considered a threat to others. Some infectious diseases may necessitate informing the patient's employer (e.g., health care worker, food worker).

Adolescents are allowed to consent for some services without parental involvement in some states. Know the laws of your own state in this regard. Adolescent consent for contraception is protected under federal law by language in the federal budget that restricts individual states from passing teen contraceptive laws, if that state receives federal subsidies for health care. So, adolescent consent for birth control is acceptable in all states. Consent for abortion services, however, is state-dependent.

BRAIN DEATH

Physicians may stop treatment if a person is "brain dead" (loss of entire brain function, including brain stem). An EEG is not required for diagnosis. Organs can then be donated without patient's prior consent if the next of kin (or surrogate) gives permission, knowing that the patient would want that.

PHYSICIAN-PHYSICIAN vs. PUBLIC WELFARE OBLIGATIONS

The physician should not allow any incompetent or unethical conduct by other physicians. If you know of such conduct, the evidence should be presented to the appropriate authority. This may be the division chief or ethics committee of the hospital. Most state and many county medical societies now have confidential treatment of impaired physicians. Physicians who strongly suspect another physician is chemically impaired are obligated to urge the physician to seek treatment. If this impairment may affect medical competence, the obligation is to report the "credible evidence" to the local medical society. Note: A physician cannot act only on hearsay, but must have credible evidence before reporting it.

DRUG RESEARCH

It is unethical to use socioeconomic differences in choosing patients for a drug study, unless the socioeconomic status is considered a variable. For example, you cannot ethically test a drug only on those who can pay for it.

Quick Quiz

- You see a colleague drinking shots in a bar shortly before his 12-hour shift in the emergency department. Are you obligated to inform anyone?
- Know all of the scenarios in the ethics topic!

Conversely, you cannot ethically offer a free drug for research only to those in a lower socioeconomic status.

FINANCIAL CONFLICTS

The ACP ethics document is very clear that certain financial relationships are unethical:

- Physicians must disclose to patients if they intend to refer patients to a facility or research study in which the physician has a financial stake.
- A physician should not refer patients to a care facility where the physician holds a financial interest but is not employed.
- A physician may not pay another physician for referrals.
- A physician may not receive payment or gifts (even "small ones") from device manufacturers or pharmaceutical companies for recommending or using their products.
- Physicians should not sell products out of their offices, unless they are meeting an unmet need of the community (e.g., selling crutches or walkers in a small town). Physicians should not sell supplements or cosmetics out of their offices.
- Physicians should not use unsubstantiated or false statements in advertising nor should they omit necessary information.
- Physicians can and should act as expert witnesses to benefit society, but they cannot accept payment in exchange for biased testimony. Fees charged should be for "reasonable time and expenses."

SCENARIOS

Some scenarios:

1) A patient enters the hospital unconscious and near death with a terminal disease. What should the physician do if:
   - The patient has a properly executed living will that states no intubation, CPR, etc.
   - The patient has no living will, but family members say they strongly prefer the patient be allowed to die with dignity and without heroics.
   - The patient has a properly executed living will that states no intubation, CPR, etc., but family members (many of whom are lawyers) say they want all possible heroic measures to be done—and threaten dire consequences if their wishes are not followed!
2) A patient comes to the emergency department with an extensive acute MI, is mentally competent, and refuses to be admitted despite being fully informed of the possible consequences. What do you do?
3) A respirator-dependent patient requests in writing to be extubated. What do you do?
4) A female health care worker who is found to have hepatitis B antigen positivity requests that you not tell her supervisor at the hospital where she works.
5) A man is diagnosed with inoperable metastatic cancer. He states to his physician that he does not want his wife to know.
6) A newly married man just finds out that he has a serious autosomal dominant genetic disease; e.g., Huntington disease. He requests that the physician not tell his wife.
7) A man finds out he is HIV-positive and requests that you not tell his spouse.
8) A woman with suspected meningococcal meningitis refuses to be admitted and wants to go back to work.

Answers:

1) The physician should:
   - Follow instructions in the living will.
   - In this situation the physician needs more information; needs to know the wishes of the patient, not the family!
   - Follow instructions in the living will; the contract is between the physician and the patient. Besides, so far, all living wills have upheld in court.
2) You must show caring for the patient's situation, yet attempt to dissuade the patient from leaving. If the patient still leaves, it is prudent to have the patient sign out "AMA"—against medical advice (the patient is not legally required to do this). You cannot stop patients from leaving unless you think they are mentally incompetent or a danger to others (e.g., they want to drive home).
3) You need more information (mentally competent, fully informed, etc.). This is a problem with probable far-reaching consequences—not just for you, but for the patient's other doctors, the hospital, and the patient's family. The 1st step is to contact the hospital's ethics committee. You may also need assistance from the patient's other doctors, family, psychiatry, and social services.
4) This health care worker has a direct obligation not to cause harm to the patients with whom she interacts. If she refuses to inform the hospital infection control team, then you are obligated to do so.
5) Although the physician can strongly encourage the man of his wife's moral right to know the situation, communicating this to the spouse is ultimately the patient's obligation and not the physician's.
6) In this case, the physician should first strongly encourage the man to tell his wife. If that fails, the last resort is for the physician to tell the wife because of the risk of harm to future children.
7) In all HIV cases, the physician must make sure that anybody at risk (e.g., through sexual contact or IV drugs)

is notified. Whenever patients say they are going to do the notification, the physician must ensure it is done. Usually, this obligation is taken care of by the state health department.

8) This patient may be held against her will for the good of public welfare.

PREOPERATIVE CARDIAC EVALUATION

You must know how to preoperatively evaluate a patient in order to determine the risks of having a cardiac event in the perioperative period!

Several guidelines have been produced by different medical societies. As of this writing, the AHA/ACC Guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery is the most recent document, with a focused update in 2009 regarding the use of perioperative beta-blockers to minimize intraoperative cardiac risk.

These guidelines recommend 5 steps to be followed:

Step 1: Does the patient need emergency noncardiac surgery? If so, then the patient should proceed to surgery; perioperative surveillance and postoperative risk stratification and risk-factor management should proceed as best as possible.

If the answer is no, this is not emergent, proceed to Step 2.

Step 2: Does the patient have an active cardiac condition?

- Unstable coronary syndrome (unstable or severe angina or recent MI, defined as more than 7 days but ≤ 1 month)
- Decompensated heart failure
- Significant arrhythmias: 3rd degree AV block, Mobitz 2 AV block, symptomatic ventricular arrhythmias, supraventricular arrhythmias (includes atrial fib!) with uncontrolled ventricular rate (> 100 bpm at rest), symptomatic bradycardia, new ventricular tachycardia
- Severe valvular disease: any symptomatic aortic stenosis, asymptomatic aortic stenosis with gradient > 40 mmHg, symptomatic mitral stenosis

If so, then the patient should undergo evaluation and treatment before noncardiac surgery.

If these are not present, proceed to Step 3.

Step 3: Is the patient undergoing low-risk surgery? Here, the guideline gets murky. It is definite with defining very low risk as superficial, and the highest risk as major vascular procedures. It lists endovascular abdominal aortic aneurysm repair and carotid endarterectomy as intermediate risk. After listing these specifically, it goes on to state: "The physician must exercise judgment to correctly assess perioperative surgical risks and the need for further evaluation." Wow, thanks guideline … In general, though, any procedure that is "ambulatory" in nature and does not require "hospital admission" is usually considered low-risk. Other surgeries in this category include all breast surgeries, ophthalmologic procedures, and endoscopic procedures.

So, if you get to Step 3 and the surgery is low-risk, proceed with surgery; if not, go to Step 4.

Step 4: Does the patient have good functional capacity without symptoms? If this is true, proceed with moderate-to-high–risk surgery.

What is a simple, easy method to assess functional capacity? The guideline recommends using a MET level of ≥ 4. Now let's review that "MET" thing again. Remember that functional capacity can be expressed as metabolic equivalents (METs); 1 MET is the resting or basal oxygen consumption of a 70-kg, 40-year-old man in a resting state. Functional capacity is classified as excellent (> 10 METs), good (7–10 METs), moderate (4–7 METs), poor (< 4 METs), or unknown. Think of 4 METs as equivalent to carrying groceries up the stairs. Examples associated with < 4 METs include slow ballroom dancing, golfing with a cart, and walking at a speed of 2–3 mph. Activities that require > 4 METs include moderate cycling, climbing hills, skiing, singles tennis, and jogging. There are several scales (e.g., Duke Activity Status Index, Specific Activity Scale) out there, but, in general, this guide helps you.

So if the patient can run up a hill or mow the lawn without problems, then the patient likely can proceed with their planned surgery. If they cannot, then we go to Step 5.

Step 5: Here, we have the patient who has gotten to Step 5 because of either poor or unknown functional capacity, and we must use clinical risk factors to help us determine if we can proceed with surgery.

The 5 clinical risk factors to ask about:

1) History of ischemic heart disease (history of MI, + exercise stress test, current chest pain, nitrate use, ECG with pathologic Qs)
2) Heart failure history (prior or compensated)
3) Cerebrovascular disease history
4) Diabetes requiring insulin
5) Renal insufficiency (creatinine > 2 mg/dL)

If > 3 risk factors are present, the surgery-specific risk is important (Table 10-9). The guidelines say for "… intermediate-risk surgery, there are insufficient data to determine the best strategy (proceeding with planned surgery with tight heart rate control with beta-blockade or further cardiovascular testing if it will change management)."

Bottom line: Aortic, major vascular surgery or peripheral vascular surgery generally requires further cardiac evaluation. Low-risk procedures (endoscopic, superficial, cataracts, breast surgery, or any ambulatory surgery) do not. Intermediate … it's up to your judgment.

QuickQuiz

- Know the 5-step process used in determining if a patient requires a pre-op cardiac evaluation.
- What type of preoperative evaluation is done if a patient requires emergent noncardiac surgery?
- Which patients are started on beta-blockers before surgery?
- Know the preoperative screening labs and who gets them.

Scenarios you are likely to encounter:

- A low-risk patient who can proceed directly to surgery of any type without noninvasive testing
- A moderate-risk patient with good functional capacity who can go directly to a non-vascular surgery
- A major-risk patient who needs further workup as defined in the charts prior to going to surgery

Beta-blockers: Know that high-dose beta-blockers used perioperatively, given without a history of dose titration, in beta-blocker–naive patients do reduce primary cardiac events but carry an increased risk of mortality and stroke—hence, they are not recommended.

Who gets beta-blockers?

- Vascular surgery patients with positive preoperative stress tests.
- Continue these in patients already receiving them for angina, arrhythmias, or HTN.
- Beta-blockers should be titrated when used in order to avoid significant bradycardia or hypotension. Their use is not without risk.

PRE-OP SCREENING LABS

General guidelines follow, and are based on, an amalgam of various societies' recommendations!

Hematocrit:

- > 65 years of age for major surgery
- All surgeries that would/could result in major blood loss

Table 10-9: Risk of Procedure; AHA/ACC

Low Risk	Endoscopies, local biopsies, breast biopsies, vasectomy, cataract surgery
Intermediate Risk	Surgeries: carotid endarterectomy, intraperitoneal, intrathoracic, orthopedic, prostate, head and neck
Major Risk	Surgeries: aortic and major vascular, cardiothoracic, emergent major surgery, long procedures with large blood loss and/or fluid shifts

- Not for minor surgery!
- CBC is not recommended unless cheaper than hematocrit alone

Electrolytes: Not recommended unless history suggests reason to check.

Creatinine:

- > 50 years of age
- Major surgery
- Hypotension is likely
- Nephrotoxic drugs to be used

Glucose, liver function tests, PT/PTT, U/A: not recommended unless clinical signs/symptoms warrant.

ECG:

- Yes for all vascular procedures
- Nonvascular procedures:
  - Men > 45 years
  - Women > 55 years
  - Known cardiac disease
  - Clinical evaluation suggests possible cardiac disease
  - Diuretic use (electrolyte abnormality possible)
  - DM, hypertension, renal insufficiency
  - Major surgical procedure

CXR:

- > 50 years of age for major surgery
- Suspected cardiac or pulmonary disease

PFTs:

- Not recommended for healthy patients prior to any surgery
- Use for dyspnea that is unexplained

Stents and such—hold off on elective noncardiac surgery if:

- Within 4–6 weeks of bare-metal stent placement
- Within 12 months of drug-eluting stent if patient must stop thienopyridine/aspirin
- Within 4 weeks of balloon angioplasty

PERIOPERATIVE MEDICINE MANAGEMENT

Anticoagulant:

- Minor surgery---continue.
- Major surgery:
  - Stop IV heparin 6 hours before surgery.
  - Stop LMWH 12–24 hours before surgery.
  - Stop warfarin 3–5 days before surgery. (Use a heparin bridge for those who need it.)

Antiplatelet:

- Aspirin (ASA)---continue for minor surgery or in those with recent (6 months) MI, PCI, stroke; for major surgery stop 5–10 days before surgery.

- Clopidogrel—stop 3–7 days before surgery.
- NSAIDs and COX-2—stop 1–3 days before surgery.

Cardiovascular: Continue β-blockers, calcium channel blockers, nitrates, ACEIs, ARBs, and statins. Diuretics and cholestyramine are usually held.

Estrogen: Discontinue hormone replacement several weeks before surgery (or continue oral contraceptives and increase level of DVT prophylaxis).

Diabetes agents:

- Oral hypoglycemics—stop 12–72 hours before surgery depending upon half-life of drug and risk of hypoglycemia.
- Intermediate-acting insulin—give 1/2 to 2/3 of usual a.m. dose.
- Basal insulin—continue or reduce dose.

Psychiatric meds:

- MAOI—stop 10–14 days before surgery.
- SSRIs—consider withholding 2–3 weeks before neurosurgery.
- Antipsychotics—continue.
- Tricyclic antidepressants and lithium—continue, but some taper and discontinue several days before surgery.

Neurologic:

- Anticonvulsants—continue.
- Antiparkinsonian—continue, but some discontinue the night before surgery.
- Alzheimer drugs—discontinue.

PREVENTIVE MEDICINE

PATIENT EDUCATION

Know this entire topic. Consider all of Patient Education highlighted.

The most authoritative single source for preventive medicine in the United States is the U.S. Preventive Services Task Force ([USPSTF]; http://www.uspreventiveservicestaskforce.org/).

Because patient education improves outcomes, periodically review and counsel patients on the following:

- Tobacco
- Firearms
- Alcohol/Substance abuse
- Physical activity level
- Obesity

Check the elderly for functional status, gait abnormalities, and for osteoporosis risk factors.

Guide all patients about self-examination for skin disease, gum disease, STDs, and nutrition.

Recommend seat belts and good fluid intake.

Got all that?

Teaching women to perform a breast self-exam does not reduce their mortality from breast cancer, so most organizations are no longer recommending it and some are recommending against it.

Along similar lines, the USPSTF now recommends against testicular self-examination for early detection of testicular cancer because it is unlikely to change outcomes.

Firearm-related injury and death is a major public health problem. The physician's ethical role is to counsel patients about firearm safety and to become involved in community efforts to prevent firearm injuries. Some states have passed specific laws prohibiting physicians from inquiring about ownership of a firearm.

Smoking Cessation

Tobacco smoke is responsible for 90% of all lung cancer deaths and more than 10% of cardiovascular deaths.

The USPSTF 2009 recommendation suggests using a "5-**A**" framework:

- **A**sk about tobacco use.
- **A**dvise to quit through clear personalized messages.
- **A**ssess willingness to quit.
- **A**ssist to quit.
- **A**rrange follow-up and support.

Know that cessation of smoking can exacerbate ulcerative colitis.

1st line medications for smoking cessation:

- Bupropion SR
- Nicotine replacement products (gum, inhaler, lozenges, nasal spray, patch)
- Varenicline (Chantix®)

Counseling + meds: better than counseling alone.

Drug therapy for smoking cessation is generally safe. Nicotine replacement products do not increase cardiovascular risk, even for those who smoke while wearing the nicotine patch. Bupropion should be avoided in patients with seizure disorder.

Varenicline is a partial agonist of nicotinic acetylcholine receptors. Both bupropion and varenicline have been associated with serious neuropsychiatric side effects (behavior changes, suicidal ideation and behavior, and depressed mood). In 2008, the FDA issued a warning to closely monitor patients taking these drugs for mood or behavioral changes.

Note that cigar smoking increases the risk of coronary heart disease (relative risk = 1.27), COPD (1.45), and cancers of the mouth and throat (2.02).

QuickQuiz

- What patient education topics should you review and counsel patients about periodically?
- Memorize Table 10-10!

Other Disease Risks

The following increase risk of disease:

- High intake of red meat increases risk of colorectal cancer.
- Alcohol increases risk of colon, breast, esophageal, and oropharyngeal cancers.
- Obesity is associated with increased risk of colon, breast, endometrial, kidney, and esophageal cancers—and may increase risk for prostate, ovary and cervix, liver and gall bladder, and pancreatic cancers, myeloma, and lymphoma! (Is there anything left?)
- Bladder cancer is inversely associated with fluid intake. Incidence in the high-fluid intake group is half that of those in the low-fluid intake group.
- Agents that cause or increase the risk of cancer: HPV, HBV, HCV, HIV, EBV, and *H. pylori*.

The following decrease risk of disease:

- High intake of tomatoes decreases prostate cancer risk.
- Fiber reduces heart disease and diabetes. Not sure about cancer, though.
- Vitamin D may decrease colorectal and prostate cancer risk.

Note that supplemental vitamins and minerals do not decrease cancer risk in patients with adequate diets.

Certain drugs are used to decrease cancer risks in special patient populations:

- Tamoxifen and raloxifene decrease breast cancer.
- NSAIDs and aspirin decrease colon polyps and colon cancer.
- Dutasteride and finasteride decrease prostate cancer.
- Aspirin decreases risk of some colorectal cancers.

SCREENING EXAMS

Overview

Screening protocols: Table 10-10 provides a rough summary.

Every official entity detailing screening protocols has a different (but usually similar) suggested protocol for each disease. In the following, these abbreviations are used:

- ACP = American College of Physicians
- ACS = American Cancer Society
- NCI = National Cancer Institute
- USPSTF = U.S. Preventive Services Task Force

Table 10-10: Screening Exam Recommendations

Counseling about smoking	Each visit
Counseling, other	Initial visit and then periodically*
Blood pressure	Each visit; at least every 2 years
Cholesterol	Every 5 years is appropriate
Breast exams	Controversial*
Mammograms	Yearly after age 50*
Digital rectal exam	Yearly after age 50*
FOBT	Yearly after age 50 (not needed after colonoscopy)
Colonoscopy	See Gastroenterology, Book 1
Pap smear	Every 3 years*
PSA	Inconclusive*
*See text for more information	

Cardiovascular Disease

Blood Pressure and Cholesterol

Blood pressure (BP): every 2 years and every clinical encounter.

Cholesterol: Screen men 35–65 years old and women 45–65 years old every 5 years. If the patient is placed on lipid-lowering agents, then generally they are checked every 6 months to a year thereafter. If the screening total cholesterol is near the threshold, it should be repeated periodically. For treatment, see Endocrinology, Book 4.

The Endocrinology section also discusses the recommendations for lipid screening contained in the latest document from the National Cholesterol Education Panel (NCEP), entitled Adult Treatment Panel III (with the relevant update from 2004). NCEP is an advisory group formed out of the National Heart Lung and Blood Institute (NHLBI), which is a subset of NIH (as is NCI). The ATP III (and update) screening recommendations vary slightly from the ones listed above, but not by much.

The same situation is true for BP recommendations contained in the latest document from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7, 2003)—also an NHLBI advisory group. We discuss JNC 7 in Nephrology, Book 2. Again, slight differences.

Cardiovascular Disease in Women

In 2008, the American College of Cardiology wrote a guideline specifically looking at cardiology issues in all women. The main items to know:

- Hormone therapy should not be used as primary or secondary prevention of cardiac disease.

- Antioxidants should not be used as primary or secondary prevention of cardiac disease.
- Folic acid should not be used for prevention of cardiac disease.
- Aspirin in healthy women < 65 years of age is not recommended to prevent MI (but is recommended for ≥ 65 years to prevent stroke).

Estimating Cardiovascular Risk

For patients who do not currently have heart disease but have at least 2 risk factors for heart disease (per NCEP ATP III criteria—see Endocrinology, Book 4), know that 5-year, 10-year, or lifetime risk for heart disease can be estimated using one of the many established risk predictor models (e.g., Framingham Risk Assessment). The result gives you good insight into how aggressive you need to be about reducing their cardiovascular risk factors.

Diabetes

The American Diabetes Association (ADA) recommends annual screening with a venous fasting plasma glucose (not a fingerstick!) for people > 45 years of age if they have no risk factors. Start earlier if they have risk factors such as obesity and/or a family history. Hemoglobin A1C is also acceptable for screening.

Retest in 3 years if normal.

The American Association of Clinical Endocrinologists recommends starting screening at age 30 if any risk factors are present.

Abdominal Aortic Aneurysm

One-time screening for abdominal aortic aneurysms (AAAs) is recommended in men 65–75 years of age if they have a history of smoking (ACC/AHA and USPSTF) or in men > 60 if they had a sibling or parent with AAA (ACC/AHA). Repeat screening is not recommended. No organization recommends screening in women.

Breast Cancer

Breast cancer screening using breast self-exams, clinical breast exams, and mammography is now somewhat controversial. We discuss the topic in Oncology, Book 4.

Prostate Cancer

Prostate specific antigen (PSA) testing has contributed to the increased finding and treatment of early prostate cancer. Although no trials have been concluded indicating its effectiveness as a screening test, consumer demand has made it a commonly performed lab test.

The American Urological Association and ACS recommend PSA and digital rectal exam yearly for men > 50 years old.

The ACP recommends that annual PSA be discussed with men between the ages of 50 and 69 to determine if they want it based on benefits and harms. No PSA screening is recommended for men > 70 years or those with a life expectancy < 10–15 years. In general, discuss screening at age 40 with African-Americans and in patients with a family history of early prostate cancer. The digital rectal exam, previously combined with serum PSA screening, is no longer recommended by the ACP.

To add to the confusion, the 2012 USPSTF guidelines recommend against PSA screening altogether.

A large U.S. study showed no mortality benefit with PSA screening. Additionally, false-positive PSA tests (80%!) result in more testing and negative psychological effects, which have also been considered in these recommendations.

Colorectal Cancer

This is discussed in depth in Gastroenterology, Book 1.

Cervical Cancer

Pap smears have been proven effective, but the recommended intervals between these tests vary. Most recommend starting at age 21. After 3 negative results with annual exams, continue every 3 years until 65 years old. Women 30–65 years of age may opt for combined Pap/HPV testing every 5 years instead of Pap alone every 3 years.

If previous Pap smears have been negative and the patient does not have new sexual partners, patients > 65 years old do not need further smears. You do not need to get a Pap on women who have had hysterectomies for benign disease. See Oncology, Book 4, for workup of abnormal Pap smears.

HPV testing is recommended if the Pap smear cytology returns with atypical squamous cells of undetermined significance (ASCUS). Usually, the HPV test is collected with the Pap smear, but it is saved until cytology results are available. If ASCUS is discovered, then the lab is instructed to perform the HPV test (termed "reflex testing"). Women with ASCUS and the high-risk HPV types (e.g., 16, 18, 31) then go to colposcopy (instead of sending everyone with ASCUS to colposcopy; cuts down on unnecessary procedures). Other abnormalities on Pap smear almost always go to colposcopy.

Lung Cancer

About 85% of lung cancers are the result of smoking. The status of lung cancer screening is evolving based largely on the results of the National Lung Screening Trial (NLST). The NLST randomized over 50,000 current and former smokers age 55–74 to 3 annual low-dose CT scans (LDCT) vs. 3 annual chest x-rays. The study was halted early at 6.5 years due to a 20% reduction in lung cancer mortality in the group screened with LDCT.

QuickQuiz

- Should you do PSA screening in a 75-year-old man?
- When should Pap smears be initiated?

In July 2013, the USPSTF issued a draft recommendation in favor of low-dose CT scan screening (Grade B) of individuals who meet all of the following criteria:

- Men or women age 55–79
- Current smokers or have quit within the past 15 years
- ≥ 30 pack-years of smoking history

False-positive rates are high: In the National Lung Screening Trial, 24% of screening CTs were positive, and over 96% were false positives. Concerns about the new lung cancer screening proposal center around the potential of overdiagnosis, excess radiation exposure, and cost. However, the evidence would suggest that 1 lung cancer death is averted for every 450–500 scans done.

Tobacco avoidance and cessation continue to be important steps in decreasing the burden of disease. It is essential that all smokers are advised in this regard.

Vaccinations

Common adult vaccinations are discussed in Infectious Disease, Book 1.

MANAGED CARE ISSUES

ACCOUNTABLE CARE ORGANIZATION

Overview

The Accountable Care Organization (ACO) was introduced in 2009 as a potential new model of care for which the Centers for Medicare and Medicaid Studies (CMS) is encouraging demonstration projects. It is a health care delivery and reimbursement model that ties the reimbursement to the quality of health care delivered and the total cost of care.

Example: 4 regional hospitals combine their outpatient services to better serve the local population. Primary care physicians and specialists from each of the 4 hospitals participate. The costs of the services are bundled to meet predetermined budgets, which include incentives to meet specific performance improvement objectives.

ACO "Never Events"

These are events that occur (in the inpatient setting usually) that typically should not occur if the patient is receiving competent health care. These events, commonly called "never events," are not reimbursed by CMS:

- Foreign object retained after surgery
- Air embolism
- Blood incompatibility
- Pressure ulcer stages III and IV
- Falls and trauma (including fracture, burn, electric shock)
- Catheter-associated UTI or vascular-catheter infection
- Manifestations of poor glycemic control (DKA, hyperosmolar, hypoglycemia)
- Surgical site infection including mediastinitis following CABG
- Infection, DVT/PE following hip or knee replacement
- Death/Disability due to medication error, electric shock, burn, fall, use of restraints or bedrails, or contaminated drugs, incurred within a healthcare facility
- Incident due to wrong oxygen or other gas
- Impersonating a health care worker (physician or nurse!)
- Abduction of patient
- Sexual assault within or on facility grounds
- Surgery on wrong body part or patient
- Implantation of wrong egg
- Infant discharged to wrong person
- Death/Disability due to patient elopement
- Patient suicide or attempted suicide resulting in disability

POISONINGS

OVERVIEW

Deaths from drug overdose have been steadily rising over the past 2 decades, with a 102% increase from 1999 to 2010! In 2010, drug overdose was the leading cause of "injury death." In the age range of 25 to 64 years, deaths from overdose exceeded those caused by motor vehicle accidents! About 80% of fatal overdoses were unintentional, and prescription drugs accounted for the majority of deaths! Opioids were the most common drugs involved, often found in combination with benzodiazepines.

More information regarding drug overdoses in the U.S. can be found at the following site: http://www.cdc.gov/homeandrecreationalsafety/overdose/facts.html

First, we discuss an empiric approach to overdoses; then we focus on individual ingestions. Ingestions with HAGMA (high-anion gap metabolic acidosis) and increased osmolar gaps are covered exhaustively in Nephrology, Book 2. CO poisoning is discussed in Pulmonary Medicine, Book 2.

Table 10-11: Physical Exam in Toxic Ingestions

Physical Exam	Category	Examples
"Excited": agitation, restlessness, hypertension, tachycardia, hyperventilation, hyperthermia, mydriasis (usually)	Anticholinergics	• Antihistamines • Neuroleptics (chlorpromazine, quetiapine) • Tricyclic antidepressants • Atropine • Antispasmodics (hyoscyamine) • Plants: nightshade (belladonna) and jimson weed
	Sympathomimetics	• Ephedrine • Dextromethorphan (5–10x therapeutic dose) • Cocaine • Amphetamines • Methamphetamine • MDMA ("ecstasy") • 4-bromo-2,5-dimethoxyphenethylamine ("2CB") • 2,5-dimethoxy-4-(N)-propylthiophenethylamine ("blue mystic")
	Hallucinogens	• Lysergic acid diethylamide (LSD) • Mescaline (peyote) • Phencyclidine (PCP, "angel dust") • Psilocybin (found in certain mushrooms)
"Depressed": obtundation, hypotension, bradycardia, hypoventilation, hypothermia, miosis (usually)	Cholinergics	• Organophosphate and carbamate insecticides
	Sympatholytics	• Clonidine
	Opiates	• Oxycodone (frequently combined with acetaminophen; has extended-release formulations; ETH-Oxydose™, OxyContin®, OxyIR®, Roxicodone®, Percocet®) • Hydrocodone (frequently combined with acetaminophen; has extended-release formulations; Lorcet®, Lortab®, Vicodin®, Zydone®, Co-Gesic®, Hycet®, Margesic®)

OVERDOSE MANAGEMENT

General management of the obtunded or comatose patient is guided by history, vital signs, and physical exam. Assessment of airway is most important, with immediate intubation of the patient with unstable vital signs and/or inability to protect the airway. Next, assess rhythm with an ECG and continuous cardiac monitoring and assess blood oxygenation with pulse oximetry.

The following interventions are usually empirically performed, except as noted:

- IV D50 if blood glucose low.
- Thiamine 100 mg IM or IV.
- ABG +/– carboxyhemoglobin level, serum basic chemistry, and general toxicology screen. Be sure to calculate the serum anion and osmolar gaps. Measure salicylate level if AG is increased.
- Serum acetaminophen level.
- Serum CPK, if patient was immobilized for long periods.
- CXR and supplemental oxygen prn.
- Naloxone IV if you suspect opiate overdose, but be careful of dose (see Analgesics, next page).

Be able to characterize the patient's physical exam and determine whether the presentation is most consistent with "excitation" or "depression" and know which ingestions are associated with the presented scenarios (Table 10-11).

In clinical practice, many patients present with co-ingestions, and the physical exam can be a mixed bag of signs/symptoms.

Tip: mydriasis = dilated pupils (big word, big pupils); miosis = constricted pupils (small word, small pupils).

After the patient is stabilized, consider gastric lavage with a large bore orogastric tube; this may be effective even hours after ingestion if the drug was ASA, anticholinergics, or narcotics. (These drugs cause decreased gastric motility.) Lavage with only small amounts of tap water (100 cc) to prevent forcing the stomach contents into the duodenum. Follow with activated charcoal and a cathartic (sorbitol or Mg citrate). Know that activated charcoal is not effective when the overdose is with the metals lithium and iron. Continued dosing with oral charcoal is effective in decreasing the levels of a few drugs by gut dialysis (absorption via the enteric recirculation)—especially digoxin, phenobarbital, theophylline, tricyclics, and salicylates.

Note: There is a strong trend toward not lavaging patients with most overdoses. The thought is that lavage is, in most cases, ineffective; using activated charcoal with cathartics is at least as effective, if not more so.

Quick Quiz

- What are the procedures and tests that you should consider for general management of an obtunded patient?
- Activated charcoal is not used for what overdoses?

Shock is treated with central venous pressure (CVP) monitoring, IV fluids, +/− dopamine.

Alkalinization and acidification of the serum (and hence, the urine) are based on the principle that compounds in their ionized form are less tissue-permeable and more easily eliminated by the kidneys. Weakly acidic substances ionize in an alkaline environment while weakly alkaline substances ionize in an acidic environment. Alkalinization of the urine to a pH of > 7 increases excretion of ASA, tricyclics, and phenobarbital. Acidification of the urine with ammonium chloride increases excretion of amphetamine and phencyclidine (PCP). Mix 2.75 mEq/kg in 60 cc NS and give through the gastric tube. Clamp for 1 hour. Repeat q 6 hours until urine pH < 5.0.

Important: Hemodialysis may be necessary in patients with severe overdose or renal failure. It is effective in removing drugs with low molecular weights that are not lipid soluble, protein bound, or tissue bound—i.e., drugs with a small volume of distribution. These include lithium, chloral hydrate, salicylates, and alcohols (methanol and ethylene glycol). Dialysis is not effective in removing benzodiazepines, opiates, or tricyclics.

Also important: Charcoal hemoperfusion (blood pumped through a charcoal filter), in contrast to dialysis, removes drugs that are lipid soluble and protein bound! It can also remove some of the same drugs as dialysis. Also, like dialysis, it is most effective in removing drugs with a low volume of distribution (V). Charcoal hemoperfusion is especially good for digoxin, theophylline, and salicylate overdoses.

SPECIFIC TOXINS

Refer to Table 10-11. Also see Table 10-12 for a summary of common poisoning agents and their usual antidotes.

Analgesics

Opiates

Opioid prescriptions increased 700% from the years 1997 to 2007. Opioid overdoses have likewise dramatically increased. Of the 22,000 deaths from prescription drugs in 2010, 75% involved opioid analgesics!

Think opiate overdose (especially on an exam) when you see the following combination of signs/symptoms: obtundation, hypoventilation (decreased rate and tidal volume), decreased bowel sounds, and constricted pupils. Know that meperidine, propoxyphene, and tramadol are associated with seizures in intoxicated patients (especially those on dialysis!); and methadone can increase the QT interval, causing *torsades*.

Table 10-12: Toxins and Antidotes

Toxin	Antidote(s)
Acetaminophen	N-acetylcysteine
Digoxin	Ag-binding fragment
Opiates	Naloxone
Benzodiazepines	Flumazenil (some scenarios)
Nitrates	Methylene blue
Iron	Deferoxamine
Carbon monoxide	Oxygen
Ethylene glycol	Fomepizole
Methanol	Fomepizole
Organophosphates	Atropine, Pralidoxime (2-PAM)
Cyanide	Nitrates, Na-thiosulfate

Naloxone is usually given IV in doses of 2 mg, up to a maximum of 10 mg. The drug should be used to reverse hypoventilation induced by opiates—it should not be used in large doses as a diagnostic tool for opiate intoxication because of the risk of inducing withdrawal in the chronic user. The dose of naloxone should be titrated to result in normal ventilation (10–14 breaths/minute), not consciousness. Too great of a dose (enough to wake someone up completely) can cause rapid reversal and withdrawal. Too small of a dose can result in a need for intubation. Chronic users of opiates, and those patients who inhaled or ingested a large dose of the drug, may require an intravenous drip of naloxone because its half-life is very short. Generally, 2/3 of the dose that results in adequate ventilation is given per hour in a drip.

Know that acute lung injury is sometimes seen in opiate addicts who undergo rapid reversal of unconsciousness with naloxone + high-flow oxygen via facemask. Patients usually recover with supportive care.

Also recognize that naloxone is typically not the correct answer if a scenario presents a patient with dilated pupils.

Salicylates

Salicylates are metabolized in the liver by conjugation with glycine or glucuronide. These pathways are quickly saturated in a person who has overdosed, resulting in acidemia. The increased ASA level initially causes hyperventilation through a central effect. This has a protective effect since the ASA crosses the blood-brain barrier (i.e., is more tissue permeable) when the system is acidemic. Acidosis can worsen if

the HAGMA is compounded by lactic acidosis due to pulmonary edema. If the patient stops hyperventilating, it is probably due to respiratory muscle fatigue.

The classic presentation of the patient with an ASA overdose is tachypnea and a mixed acid-base disorder (HAGMA + respiratory alkalosis) and a history of having taken over-the-counter pain medicine. Depending on the dose, patients may additionally complain of tinnitus.

Treatment of salicylate overdose: decontamination with activated charcoal with cathartic and serum/urine alkalinization using sodium bicarbonate. Both hemodialysis and charcoal hemoperfusion have been used in severe cases (salicylate levels > 100 mg/dL). The charcoal hemoperfusion removes the salicylates better than hemodialysis but does not correct any fluid/electrolyte imbalance. (Patients are often hypokalemic.)

Acetaminophen

90% of this drug is metabolized in the liver, by glucuronidation or sulfation, to inactive metabolites. 5% is excreted unchanged through the kidneys. The last 5% is metabolized by way of the hepatic cytochrome P-450 system to active metabolites. One of the active metabolites is N-acetyl-p-benzoquinoneimine (NAPQI), which is highly hepatotoxic. Normally, the small amount of NAPQI is quickly detoxified by reacting with the sulfhydryl group of glutathione, forming nontoxic mercapturic acid. A large overdose results in depletion of the glutathione and subsequent increase in these metabolites. A severe overdose is often followed by mild N/V/D. It is only after 24–48 hours that liver toxicity ensues.

Many intentional overdose patients present with co-ingestion of multiple substances. Always suspect acetaminophen as part of the clinical picture of any overdose. It is standard to check acetaminophen levels regardless of the presentation—because untreated toxicity is potentially fatal.

Alcohol-acetaminophen syndrome: Chronic moderate-to-heavy use of alcohol has a 2-fold effect: The cytochrome P-450 system is cranked up (so that more NAPQI is produced), and the amount of glutathione is decreased (so less is available for detoxifying the NAPQI). Therefore, long-time users of moderate-to-heavy amounts of alcohol who take acetaminophen in normal or higher doses are at risk for severe hepatic toxicity or liver failure.

Treatment of acetaminophen overdose: Activated charcoal is beneficial, does not hinder use of N-acetylcysteine (NAC), and is usually used if patients present within 4 hours of ingestion. Although there is great variability in the hepatic response to the overdose, a 4-hour post-ingestion acetaminophen level of > 250 μg/mL indicates a high probability of hepatotoxicity—if untreated. NAC is an effective antidote that works by increasing the availability of hepatic glutathione.

NAC is effective when given within 8–16 hours after the acetaminophen overdose. Even when given late in the course to a patient with significant ingestion and toxicity, it reduces mortality and improves liver function. Treatment can be initiated with either an IV or oral protocol, which varies in their duration. IV is favored if patients are vomiting or present in liver failure.

Both protocols continue dosing until the measured acetaminophen level is undetectable or "clearly decreasing" with a minimum of dosing over 20 hours. (The specific definition of "clearly decreasing" is controversial.)

Anticholinergics

Do not forget the presentation of anticholinergic intoxication (discussed above and reiterated in Table 10-11). "Red as a beet; dry as a bone; hot as a hare; blind as a bat; mad as a hatter; full as a flask."

- Red: cutaneous vasodilation
- Dry: anhidrosis
- Hot: hyperthermia
- Blind: mydriasis
- Mad: hallucinations
- Full: urinary retention

The antidote is physostigmine.

Acid Alcohols

Isopropyl alcohol ("rubbing alcohol") is a common solvent and disinfectant. Like ethanol, it has CNS-depressant effects. It is 2nd to ethanol in the causes of alcohol overdose. The main metabolite is acetone, which causes a prolonged CNS effect. The acetone causes ketonuria but no anion gap acidosis, and the sweet odor of acetone is evident on the patient's breath. CNS depression is the major effect, although there may also be cardiac depression. Abdominal pain and vomiting are usually present. An osmolar gap of > 35 mOsm is typically seen with toxicity. Treatment: Give supportive care, including lavage if < 2 hours has passed since ingestion. Make early use of hemo/peritoneal dialysis in severe cases.

Methanol (wood alcohol) toxicity is usually due to contaminated moonshine. It is only mildly inebriating, and many signs of toxicity are delayed > 24 hours—especially visual impairment, from blurring to blindness. The toxic metabolites are formaldehyde and formic acid. Serum analysis shows an increased anion and osmolar gap. Treat with fomepizole, folic acid, and immediate dialysis. Give folic acid to increase metabolism of the formic acid.

Ethylene glycol (antifreeze): Alcohol dehydrogenase breaks down ethylene glycol to its very toxic metabolites, especially oxalate. Presence of oxalate is indicated by calcium oxalate crystals in the urine and hypocalcemia (oxalate chelates calcium). Suspect if a patient appears intoxicated but without an alcohol smell, and with

Quick Quiz

- What is the common acid-base disorder typically found when a patient presents with ASA overdose?
- What drugs are used to treat acetaminophen overdose?
- Methanol causes what neurologic deficit?
- Does ethylene glycol cause an increased osmolar gap, anion gap, or both?
- What ECG finding correlates most closely with the degree of intoxication with a tricyclic antidepressant?
- For tricyclic overdose, what should you do to the urine?

a HAGMA and increased osmolar gap. Treat with fomepizole, bicarbonate for the acidosis, calcium prn, and immediate dialysis.

Prescription Drugs

Theophylline: This drug more often presents as inadvertent toxicity rather than intentional overdose. Toxicity often occurs in the context of the patient having been prescribed another drug (or herbal preparation) that increases theophylline levels. Suspect toxicity when you see a clinical history of obstructive lung disease and tremulousness, tachycardia/ventricular arrhythmias, vomiting, +/– seizures with a theophylline level > 20 mcg/mL. This toxicity can look like cocaine or methamphetamine use. Be aware of it in patients with asthma who also use these illicit drugs! Know the drugs that commonly interact with theophylline and increase levels: CYP3A4 inhibitors, certain macrolides, quinolones, and zileuton.

Treat with supportive care (paying attention to hypokalemia because it predisposes to ventricular arrhythmia) and multiple doses of activated charcoal with cathartic. If vomiting is too severe to allow for charcoal, give ondansetron +/– ranitidine. Treat seizures with diazepam. Treat supraventricular tachycardias (SVT) with adenosine. Stable ventricular arrhythmias usually respond to amiodarone; treat hypotension with alpha agonists (phenylephrine or norepinephrine). Oddly, beta-blockers can reverse hypotension, if the alpha agonists don't work, but beta-blockers should be given only under the guidance of a medical toxicologist. Call poison control to get such advice. Dialysis is recommended in patients with seizures or ventricular arrhythmias.

Lithium: Mental status changes are the most common manifestation of overdose—affecting > 90%. Other CNS changes include seizures and symptoms due to encephalopathy (poor memory, incoherence, disorientation). Patients may also get parkinsonian symptoms and movement disorders. Nausea, vomiting, and diarrhea are also common. A lithium level is obtained for purposes of documenting definitive overdose, but symptoms do not correlate with levels.

Don't forget about the complications from chronic lithium use: renal tubular acidosis, nephrogenic diabetes insipidus, and sicca symptoms.

Treatment: Activated charcoal is not effective. Gastric lavage is recommended in this setting. Restore fluid and electrolyte balance, and use hemodialysis in severe lithium overdose cases. Consider severe intoxication when there are any symptoms characteristic of lithium poisoning, when the lithium levels are > 3.5 to 4 mEq/L, or when the serum level does not decrease appropriately.

Tricyclic antidepressants: These drugs are lipophilic and are protein-bound, so they have a very large volume of distribution and cannot be removed by dialysis. Clinical presentation of toxicity includes: sedation or confusion and arrhythmias.

Treatment includes gastric decontamination with activated charcoal with cathartic, if presentation is within 2 hours of ingestion. Give supportive care and monitor for cardiotoxic side effects. Tricyclics cause tachycardia and PR, QT, and QRS prolongation. The QRS prolongation is the ECG change that correlates most closely with the degree of intoxication! Ventricular tachycardia and fibrillation are also common. The cardiac problems often respond to maintaining an alkalemic state—either by hyperventilation if the patient is intubated or with IV bicarbonate. Keep serum pH 7.5 to 7.55 using sodium bicarbonate ("alkalinizing the urine"). Give lidocaine (1st choice) or phenytoin as needed for arrhythmias. Use benzodiazepines for seizures.

Digoxin: This drug is not commonly prescribed, but toxicity is not uncommon because the drug has a very narrow therapeutic index. Levels do not correlate with toxicity, so you have to pay close attention to signs and symptoms. Clinical presentation of toxicity includes anorexia, N/V, belly pain, confusion, weakness, changes in color vision, scotoma, and bradycardia with hypotension. The presentation can appear as if the patient is being overtreated with an antihypertensive drug—this is important because patients who take digoxin often also take antihypertensives. Labs may show potassium disturbances (hypo- in acute toxicity; hyper- in chronic toxicity) and acute kidney injury, which is often the cause of the increase in the serum level.

Know the commonly used drugs that can increase digoxin levels when coadministered: diltiazem, verapamil, amiodarone. Because digoxin is cleared by the kidney, decreases in GFR increase the serum level.

Treatment includes continuous cardiac monitoring. PVCs are common. Other conduction abnormalities include AV block with junctional escapes and serious ventricular arrhythmias. The ECG should be evaluated periodically because digoxin can flatten or invert T

waves, shorten the QT interval, and depress lateral ST segments (findings often referred to as "dig effect").

Treat with activated charcoal if presented within 2 hours of ingestion. Treat patients who have serious ventricular arrhythmias (tachycardia, fibrillation, complete heart block, Mobitz 2, and symptomatic bradycardia), serum K > 5 mEq/L, and renal failure or mental status changes with Fab fragments (a digoxin antibody). Be aware that presenting hyperkalemia rapidly reverses with Fab antibodies, so do not be overly aggressive in treating hyperkalemia.

Much controversy exists about whether to give calcium to patients with hyperkalemia from digoxin toxicity (to stabilize cardiac membranes). Conventional teaching is to withhold the calcium (and this is what we have written in Nephrology, Book 2), but several case reports and retrospective studies show that calcium does not harm these patients. The current standard, however, is not to give calcium if you are giving Fab antibodies because the hyperkalemia is rapidly corrected, and arrhythmias are unusual.

Benzodiazepines: Overdose with oral benzodiazepines alone rarely causes severe toxicity, but it is a common drug seen in coingestion, especially with alcohol or opioids. More common scenarios of benzodiazepine toxicity occur in the setting of operative anesthesia. Patients with benzodiazepine toxicity have CNS depression with otherwise normal vitals and exam ("coma with normal vitals"). Treatment is usually supportive. Activated charcoal is not recommended. Use of the antidote flumazenil is controversial because it may precipitate withdrawal seizures in patients who are tolerant to benzodiazepines.

Illicit Drugs

Cocaine: Cardiotoxicity can occur no matter what the route of use. This drug causes rhythm disturbances (including V fib/tach), ischemia (irrespective of whether the patient has preexisting atherosclerotic disease), myocarditis, and systolic dysfunction. Suspect use in a young patient presenting with MI. Seizures and stroke are also common with cocaine; consider it in patients with 1st time seizure. Know that beta-blockers are not used in this group to treat angina or verified myocardial ischemia due to concerns of unopposed alpha-receptor stimulation. Instead, nitro, calcium channel blockers, and BDZs are 1st line treatments.

Methamphetamine is a powerful CNS stimulant that acutely increases the release of epinephrine, norepinephrine, serotonin, and dopamine. Consider methamphetamine toxicity in the sweaty, severely agitated or psychotic patient with tachycardia and hypertension. Severe tooth decay occurs in chronic users. Acute treatment of the severely agitated patient is with IV benzodiazepines first and then antipsychotics, such as haloperidol, if needed. IM doses are given if unable to give IV. Watch for rhabdomyolysis in these patients by monitoring electrolytes, BUN, Cr, CPK, serum lactate, liver enzymes, and clotting times.

Phencyclidine (PCP) can cause acute psychotic agitation, seizures, dystonia (including laryngospasm), and hypertensive crisis. Severe dystonia can cause rhabdomyolysis. Treat with a calm environment and IV BDZs as needed, with supportive care for complications such as rhabdomyolysis.

Heroin is an opiate. Be careful with the use of naloxone in chronic users because of the risk of precipitating withdrawal if you overshoot in dosage. Heroin intoxication is sometimes difficult to differentiate from alcohol intoxication because both substances are CNS depressants, but alcohol usually does not constrict the pupils or decrease the bowel sounds.

MDMA (3,4-methylenedioxymethamphetamine; a.k.a. "Ecstasy") is commonly used by young people in the setting of parties or raves. The ingestion of MDMA results in feelings of euphoria, loss of inhibitions, cozy feelings of intimacy, and increased sexual arousal due to an increased release of serotonin. The drug is commonly perceived as being very mild with minimal risk and physical effects; but in actuality, ecstasy possesses properties that resemble a combination of amphetamines and peyote (stimulant + hallucinogen). The drug is taken in tablet form, and overdoses can result in death.

Side effects of MDMA include bruxism (jaw grinding), anxiety, sweating, hypertension, and tachycardia. Dangerous complications include severe hyponatremia, malignant hypertension, stroke, cardiac ischemia, arrhythmias, aortic dissection, and serotonin syndrome. Hyperthermia and rhabdomyolysis are possibilities, especially in patients who dance all night and use ecstasy.

Activated charcoal is given if the patient presents within 1 hour of ingestion. In intoxicated states, most symptoms respond to benzodiazepines (hypertension, tachycardiac, agitation). Haloperidol can potentially exacerbate hyperthermia. Arrhythmias respond to calcium channel blockers. Beta-blockers are not recommended because of the possibility of unopposed alpha-adrenergic stimulation. Hyponatremia usually responds to water restriction; hyponatremic seizures should be treated with hypertonic saline.

LSD: Lysergic acid diethylamide is referred to as "acid" and causes hallucinations. Fatalities and morbidity during use are unusual—generally attributable to bad decisions being made while intoxicated.

Miscellaneous

Carbon monoxide: Carbon monoxide quickly binds with hemoglobin—with an affinity of ~ 250x greater than O_2. This carboxyhemoglobin (COHb) decreases arterial oxygen content, which leads to tissue hypoxia.

QuickQuiz

- A 30-year-old man presents with acute MI. What illicit drug should be ruled out as the cause?
- Know carbon monoxide poisoning!
- What are the 3 drugs used to treat cyanide poisoning?

Symptoms are progressive and range from headache and lightheadedness to lethargy to unconsciousness to coma to death.

Be especially suspicious if the patient has been working around cars, gas/oil heating units, or generators. Typical real-life scenarios:

- Car exhaust: garage music band using a running car to warm up the garage on a cold winter day—with the door closed.
- Exhaust from gasoline-powered generators: Especially suspect after electricity has been lost, such as after a flood, hurricane, or ice storm.
- Poor combustion in heating unit: Suspect when a patient calls from home in winter (especially near start of the cold season) and says the family is suffering from headache and lightheadedness. The patient may sound slow to respond. Or, the patient calls in the winter and complains of headache and lightheadedness, which improves when he goes outside.

What to do? The answer to any scenario in which the patient calls you with suspect symptoms, especially with the above environmental factors, is to tell the patient to leave and get the family out of the house immediately; then, you send an EMS unit there.

CO poisoning is responsible for most deaths in patients with smoke inhalation, so do not forget to check COHb levels when managing smoke inhalation.

The brain and heart are especially sensitive to CO. Poisoning often causes long-term to permanent CNS impairment with cognitive deficiencies (i.e., memory and learning) and personality and movement disorders.

Fetal hemoglobin has especially high affinity for CO, so treat pregnant patients aggressively.

If you suspect carbon monoxide poisoning, get a carboxyhemoglobin level. A hand-held breath analyzer can quickly rule out CO poisoning, but ethanol causes false positives:

- Mild-to-moderate CO toxicity occurs at 15–30%.
- Moderate-to-severe toxicity occurs if > 30%.
- > 50% is often fatal.

"Cherry red" coloration is rare.

Treat CO poisoning with 100% O_2—this decreases the half-life of COHb from about 5 hours to 1 hour. Hyperbaric O_2 further decreases the half-life to 30 minutes, but its main benefit is that it decreases the CO-induced ischemic reperfusion injury to the brain.

Hyperbaric oxygen is generally given for moderate-to-severe CO poisoning. Indications for hyperbaric oxygen (give within 6 hours):

- CoHb > 25% and > 20% in pregnant women
- Loss of consciousness, or any focal neuro deficit
- Acidosis pH < 7.1
- End-organ damage, especially acidosis

Smoke inhalation: Respiratory impairment results from the noxious chemicals in the lungs or laryngeal/airway edema. Suspect laryngeal involvement if face or airways are burned (e.g., singed nasal hairs). Do not forget about the association between CO poisoning and smoke inhalation.

Cyanide poisoning clues: Patient's breath has an almond odor, and lab draw shows bright red venous blood. Cyanide immediately binds to the ferric molecule in the mitochondrial cytochrome oxidase complexes, thereby blocking cellular aerobic metabolism. These patients very quickly develop headache, tachycardia, and tachypnea. This may quickly progress to coma and various cardiac arrhythmias. Think about cyanide poisoning in patients who have been in a fire or who have received sodium nitroprusside or amygdalin (chemical derived from apricot and peach pits that is used often in herbal compounds). Laboratory evaluation routinely shows significant lactic acidosis. Diagnosis is clinical, after excluding other causes of lactic acidosis and carbon monoxide poisoning. Assays exist to find the chemical in the blood, but these are reference tests that take a long time to return.

Treatment for cyanide poisoning is the 3-step cyanide antidote package. Goal is to induce methemoglobinemia because cyanide preferentially binds methemoglobin and produces a less toxic reaction.

- **Step 1:** Hold amyl nitrite under the patient's nose for 30 seconds.
- **Step 2:** Administer 3% sodium nitrite IV. The nitrites convert hemoglobin to methemoglobin (the ferric form of hemoglobin), which more effectively competes with the cytochrome oxidases for the cyanide. Amyl nitrite inhalation causes a 3–5% methemoglobinemia while the sodium nitrite causes 20% methemoglobinemia.
- **Step 3:** Administer sodium thiosulfate IV, which acts as a substrate for the enzyme rhodanese. This enzyme converts the cyanide released from hemoglobin to inactive thiocyanate, which is excreted renally.

Significant toxicity can result in a parkinsonian-type syndrome because cyanide is toxic to the basal ganglia.

Inorganic lead: There are 3 scenarios to test for lead exposure, depending on when the exposure occurred:

1) For ongoing exposure, check whole blood lead level.
2) After exposure has occurred, RBC protoporphyrin and zinc protoporphyrin levels remain elevated for several months.
3) For evaluating the effect of exposure from years before, the best test is to measure urine lead 24 hours after giving 1 gm of EDTA.

Organic lead is lipid-soluble and rapidly excreted, and previous exposure is not detectable!

Insecticide: Organophosphate and carbamate poisonings present identically. Symptoms include increased salivation, miosis (small pupils), N/V/D, and abdominal cramps. Affected patients also complain of chest tightness and generalized weakness. Organophosphates are more toxic than carbamates; they bind irreversibly to acetylcholinesterase, whereas the carbamate binding is reversible. This is reflected by a decrease in the level of RBC (not plasma!) acetylcholinesterase for several months after organophosphate poisoning, while it returns to normal within hours after carbamate poisoning.

Treatment for insecticide poisoning: The route of the poison into the body is dermal absorption (especially organophosphates), so decontaminate by removing clothes and showering with soap. For moderate-to-severe symptoms, give atropine (1–2 mg IV, repeat q 5 min prn). Additionally, for organophosphates only (not carbamate), give 2-protopam (2-PAM) IV.

DRUG WITHDRAWAL

So far, the discussion has focused on intoxication. You should also know the following presentations of specific drug withdrawal.

Heroin is the major opiate associated with physiologic withdrawal—it also has the most addictive potential. Symptoms usually start within 6 hours to a day after the last dose of drug—or can present immediately in the setting of opiate antagonists (e.g., naloxone, buprenorphine). Early symptoms include agitation, rhinorrhea, tearing, muscle aches, nausea, vomiting, abdominal pain, and diarrhea. Definitely think about this entity in the tearful patient who is yawning—those two activities typically do not go together.

Exam shows dilated pupils, yawning, hyperactive bowel sounds, and piloerection (from which the term "quitting cold turkey" is derived!). Tachycardia and hypertension are seen in patients in severe distress (but often are not present in most patients).

Methadone is given to patients who are chronically addicted to opiates and present in acute withdrawal. If the patient desires to stop opiate use entirely because of addiction and refuses methadone, symptoms can be ameliorated with clonidine and diazepam. Promethazine is given for vomiting, and loperamide helps the diarrhea.

Benzodiazepine (BDZ) withdrawal can be fatal. It presents with anxiety and tremulousness, melancholy, and sometimes psychosis/seizures. Time of withdrawal from last dose depends on whether the drug used has a short or long half-life (up to 3 weeks for diazepam). Ideally, these drugs would be tapered over a prolonged period when a patient is discontinuing chronic use. Withdrawal is treated with long-acting benzodiazepines.

Ethanol: Patients severely addicted to ethanol start having withdrawals within about 6 hours from the last drink. (This can happen even though the patient still has a measurable blood alcohol level. If it's lower than the patient is accustomed to having, then they can withdraw.) Symptoms get more severe as time passes. After about 12 hours, patients usually have an isolated generalized seizure. The next phase is hallucinosis, where the patient's sensorium is intact and BP/pulse are normal; but they see, hear, and feel nonexistent phenomena. The last withdrawal syndrome is delirium tremens (DTs). DTs are marked by autonomic instability and delirium. Untreated, they last about 5 days. Complications include volume depletion, hypokalemia, hypomagnesemia, and hypophosphatemia. For DTs, give good supportive care, replace thiamine with glucose, and give long-acting BDZs. Replace electrolytes prn. Watch out for refeeding hypophosphatemia (discussed in Nephrology, Book 2).

For patients who can be frequently observed, give repeat BDZ doses when symptoms recur. The Clinical Institute Withdrawal Assessment (CIWA) protocol is commonly used to direct BDZ dosing, and has been shown to result in lower total BDZ doses than unstructured clinician assessment. In situations where observation is not as feasible, fixed dosing schedules are used. Do not use haloperidol for the delirium because it can precipitate seizures. Chlordiazepoxide can be given orally to patients not in DTs, if they desire to quit drinking, to prevent alcohol withdrawal.

OPHTHALMOLOGY

OVERVIEW

Aqueous humor is produced by the ciliary body, flows through the pupil into the anterior chamber, and then goes through the trabecular network and into the Schlemm canal. The greater the resistance to this flow in the trabecular network and the Schlemm canal, the greater is the intraocular pressure. Normal pressure is < 21 mmHg (Figure 10-6).

Quick Quiz

- How do you check for ongoing inorganic lead exposure? What about exposure 2 years ago? What if 10 years ago?
- What is the treatment for organophosphate poisoning?
- What is the difference between open-angle and angle-closure glaucoma? Which is a medical emergency?
- What is the treatment for open-angle glaucoma? Angle-closure glaucoma?

GLAUCOMA

Overview

Glaucoma is an insidious disease in which a prolonged, elevated intraocular pressure causes progressive visual field loss due to optic nerve damage. There are 4 broad classifications: primary open-angle (POAG), closed-angle, congenital, and secondary. Know the specifics about POAG and angle-closure glaucoma.

Primary Open-Angle Glaucoma

Primary open-angle glaucoma (POAG) is the most common type. It is called "open-angle" because the orb has elevated pressure with no closure of the inlet of the trabecular network. These patients suffer unnoticed gradual loss of peripheral vision (tunnel vision) that can progress to legal blindness before it is detected.

Risk factors include advanced age, family history, African-American race (5x increased risk compared to other races), and increased intraocular pressure.

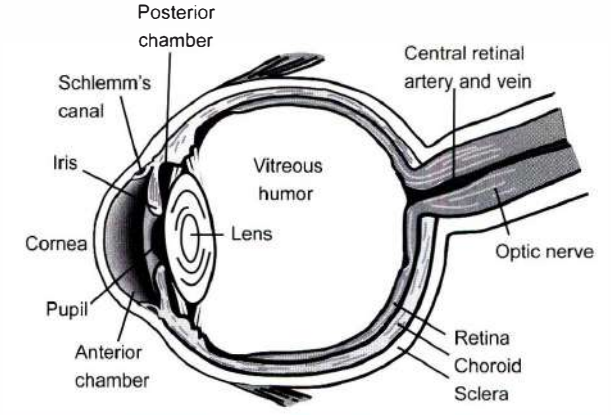


Figure 10-6: Structures of the Eye

Be suspicious and refer for ophthalmologic evaluation those patients with risk factors and/or those who have "cupping" on funduscopic exam. ("Cupping" = cup occupying > 50% of the optic disc; normal cup occupies < 50%.)

Screening of POAG: The American Academy of Ophthalmology (AAO) recommends a comprehensive eye exam by an ophthalmologist or skilled optometrist after the age of 40. After the initial screening exam, repeat screening is usually recommended every 3–5 years in patients without risk factors and every 1–2 years for those with one or more risk factors (borderline intraocular pressure, cupping, African-American race, and family history). Patients with DM should be seen yearly. The AAO also recommends that African-Americans have periodic exams between the ages of 20 and 39 as well. For all individuals older than 60, a complete exam should be done every 1–2 years. The USPSTF found insufficient evidence to recommend for or against screening adults for glaucoma.

Treatment of POAG is with medications or laser surgery. The following meds are used:

- **Prostaglandins** (topical) are 1st line drugs because of the once-daily dosing and the few systemic side effects, especially compared to the topical beta-blockers. These are expensive!
- **Beta-blockers** (topical) dramatically decrease intraocular pressure—probably by decreasing production of aqueous humor. It is thought aqueous humor production is mediated by tonic sympathetic (beta) stimulation.
  - Nonselective (timolol, carteolol, levobunolol, metipranolol)—may cause lethargy, bradycardia, and exacerbations of COPD
  - $Beta_1$-selective (betaxolol)

Angle-Closure Glaucoma

Primary angle-closure (closed angle, narrow angle) glaucoma, the most severe form of narrow-angle glaucoma, is an ocular emergency—know it well. Risk factors include age > 40 years, female, hyperopia (farsightedness), Asian race, and family history.

In contrast to primary open-angle glaucoma, elevated intraocular pressure in angle-closure glaucoma is caused by mechanical obstruction of aqueous outflow through the trabecular network, due to an anomalous iris configuration or iris neovascularization. The resulting rapid increase in intraocular pressure causes redness, severe eye pain, nausea, and halos around lights. It can also be associated with headache and present similar to migraine. Low-light conditions that precipitate pupillary dilatation (e.g., night time or in the movie theater) are associated with onset.

Physical exam shows decreased vision, increased intraocular pressure (often > 30 mmHg), a narrow anterior chamber (difficult to assess), corneal edema, conjunctival hyperemia, and a fixed, mid-dilated pupil.

Ideal treatment includes immediate ophthalmologic referral for a laser iridotomy. If an ophthalmologist cannot see the patient immediately and the patient has decline in vision, institute immediate treatment:

- place patient supine, then
- give timolol 1 drop, wait 1 minute, then
- give apraclonidine 1drop, then
- give pilocarpine 1 drop, then
- give prednisone 1 drop, then
- give acetazolamide.

Instructions with over-the-counter medications often include admonitions to "avoid use in patients with glaucoma" (decongestants). These warnings apply only

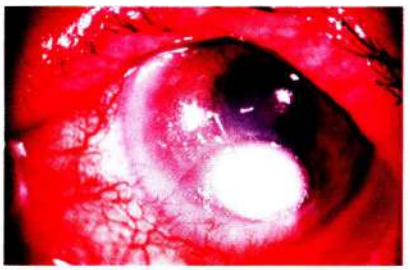


Image 10-1: Corneal ulcer. Usually caused by improper use of contact lenses. It is especially seen with the extended-wear contact lenses.

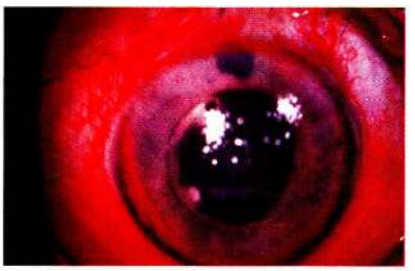


Image 10-2: Proliferative diabetic retinopathy. Rubeosis. Blood vessels grow onto the iris. This may cause intractable glaucoma. Also caused by central retinal vein thrombosis.

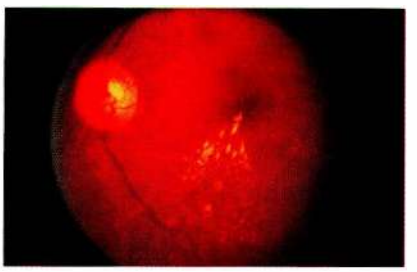


Image 10-3: Hard exudate as seen in non-diabetic retinopathy. This is caused by leakage of protein and lipids from capillaries. Treatment is photocoagulation of the leaking capillaries.

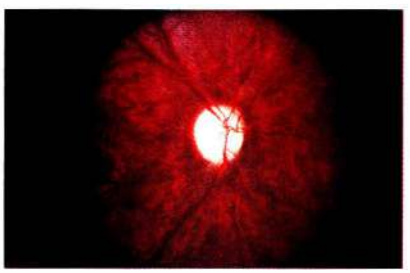


Image 10-4: Optic atrophy has various causes, including proliferative diabetic retinopathy and central retinal artery occlusion. In older patients, also consider ischemic optic neuropathy.

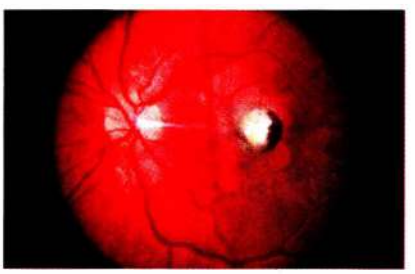


Image 10-5: Toxoplasmosis.

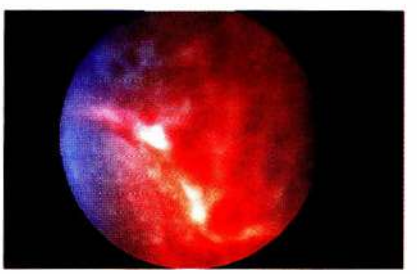


Image 10-6: Proliferative diabetic retinopathy. Vitreous hemorrhage.

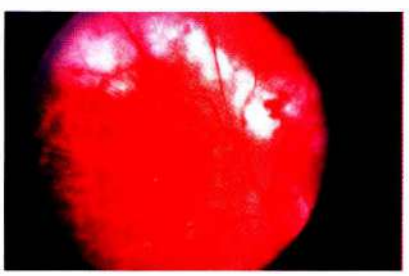


Image 10-7: CMV retinitis. Especially seen in people with AIDS.

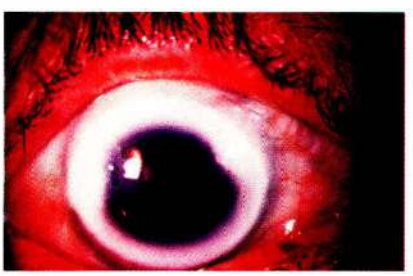


Image 10-8: Arcus senilis. Common in older patients. In patients < 40 yrs, it may be a sign of a lipid disorder.

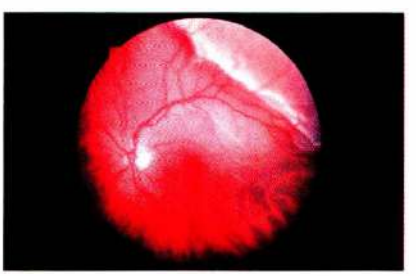


Image 10-9: Retinal detachment. This usually occurs in very myopic people. It often occurs after a vitreous hemorrhage.

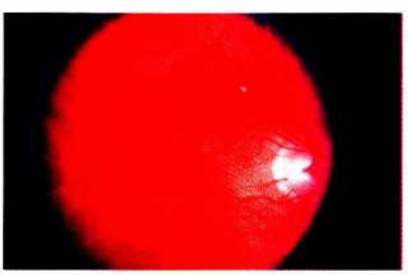


Image 10-10: Branch retinal vein occlusion (BRVO). Main cause is hypertension but also seen with diabetes and with hyperviscosity syndromes. Think of this as exaggerated AV nicking with the artery pinching off the vein.

Image 10-11: Heterochromia, ocular melanosis. This is a normal finding in darkly pigmented persons. Rarely caused by Fuch's iridocyclitis.

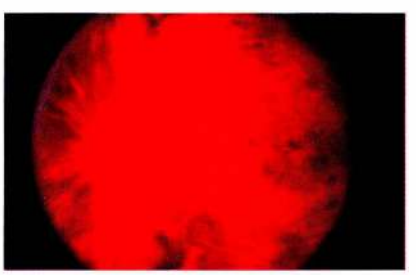


Image 10-12: Central retinal vein occlusion (CRVO). Same causes as BRVO.

Quick Quiz

- Describe the findings with retinal detachment.
- What is the treatment for retinal detachment?
- How do retinal artery occlusion and retinal vein thrombosis differ?

to patients with angle-closure glaucoma not already treated with iridotomy.

THE RETINA

Retinal Detachment

Retinal detachment may occur spontaneously. It often presents as flashes or streaks of light (photopsias), showers of black dots (hemorrhage), or a "shade coming down" or "waving curtain" in a portion of the visual field. Visual acuity may be normal initially. Myopia (nearsightedness) is the biggest risk factor. (Closed-angle glaucoma risk is farsightedness, or hyperopia.)

Presumptive diagnosis is based mainly on history, but occasionally a portion of the retina appears elevated or folded on ophthalmoscopic exam.

Treatment: This condition requires an emergent referral because untreated partial detachment can progress over hours to total retinal detachment with permanent blindness. Small retinal detachments are treated with laser surgery to tack down the area. Larger detachments require scleral buckling (a band around the sclera to restore contact of retina with the wall of the eye), trans-scleral drainage of fluid, vitrectomy (removal of vitreous), or injection of gas or other fluid into the eye (to tamponade the retina).

Retinal Vascular Occlusion

Retinal Artery Occlusion

Occlusion of the central retinal artery—usually embolic-—causes sudden, painless, unilateral blindness. This is a true ocular emergency in which every minute counts. Retinal edema (sparing the relatively thin fovea) creates pallor and the appearance of a "cherry red spot" in the macula.

Treatment is directed toward dislodging the embolus and includes ocular massage and/or paracentesis of the anterior chamber (to lower pressure). While waiting for the ophthalmologist, have the patient get into the Trendelenburg position and breathe into a paper sack. You may massage the affected globe with your index fingers (5 sec pressure, 5 sec no pressure, repeat). Unfortunately, all these temporary measures are rarely effective. Patients subsequently require a thorough systemic evaluation for embolic and carotid disease.

Retinal Vein Thrombosis

Retinal vein thrombosis (RVT) causes sudden, painless, near-total loss of vision. Causes include hypertension, polycythemia vera, and Waldenström macroglobulinemia. Retinal edema is accompanied by hemorrhage—not a cherry red spot.

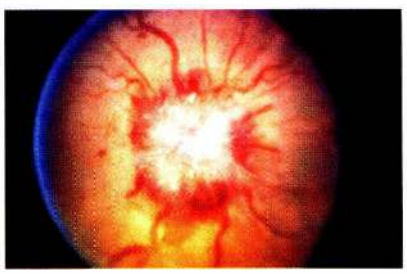


Image 10-13: Papilledema. Seen with increased intracranial pressure. Think of tumor and pseudotumor cerebri. Mimics optic neuritis/ papillitis, except papilledema is bilateral.

Image 10-14: Allergic conjunctivitis. Usually seasonal.

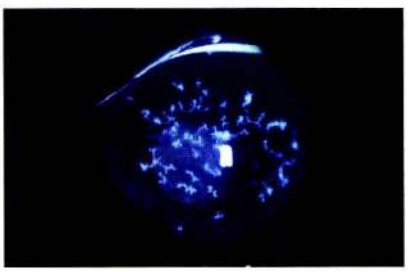


Image 10-15: Herpes keratitis of the cornea. Frequently recurs.

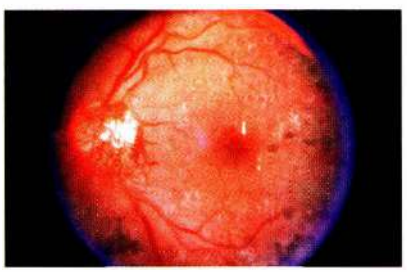


Image 10-16: Proliferative diabetic retinopathy with disc neoplasia.

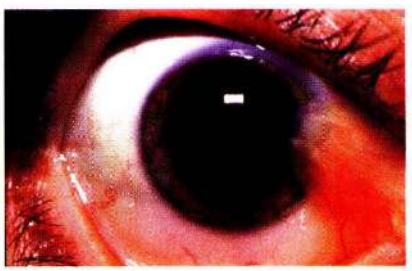


Image 10-17: Pterygium. Associated with exposure to ultraviolet light and dry wind. Seen in farmers, professional golfers, etc.

Image 10-18: Synechiae. This is a possible sequela of iritis (iridocyclitis). 90% of iritis is idiopathic, but it is seen in inflammatory diseases such as viral infections and connective tissue diseases.

Diagnosis is made with an ophthalmoscopic exam showing a "blood and thunder" fundus with multiple hemorrhages.

Patients with RVT usually are just observed; however if they have macular edema or neo-vascularization, refer immediately to an ophthalmologist.

Macular Degeneration

Age-related macular degeneration is the leading cause of irreversible acquired legal blindness in developed countries. The macular area of the retina consists of the fovea and the surrounding area. The fovea is responsible for fine (20/20) visual acuity. Although the macula comprises only 2% of the visual field, 25% of the cone photoreceptors are here, and it correlates with 50% of the primary visual area of the brain.

There are 2 types of age-related macular degeneration:

- **Atrophic** (or "dry"). This is the most common type. It causes a gradual loss of central acuity down to 20/400 (peripheral vision is spared).
- **Neovascular** (or "wet"). This type is somewhat amenable to treatment with laser photocoagulation, photodynamic therapy, and/or intra-vitreal ranibizumab or bevacizumab.

Risk factors for both types include smoking and low levels of zinc and antioxidants in the diet. However, most trials have not shown any reduced risk with vitamin supplementation or antioxidants. One recent trial, however, did show reduced risk with vitamin B supplements. This is being investigated further.

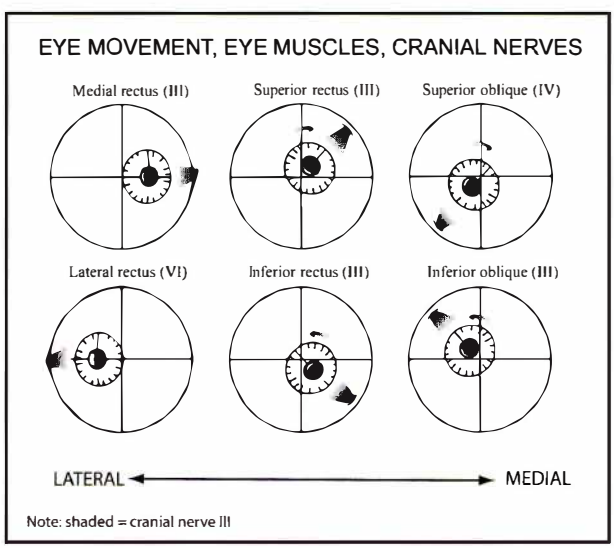


Figure 10-7: Cranial Nerves Associated with Eye Movements

OPTIC NERVE

Optic Neuritis

Optic neuritis (ON) is an inflammation of the optic nerve and is a frequent presentation of multiple sclerosis (MS).

ON presents with ocular pain, especially with eye movement. On exam, the optic disc is usually normal initially ("the doctor sees nothing, the patient sees nothing") and only later develops pallor. Refer the patient to an ophthalmologist. IV glucocorticoids improve vision more quickly, but these are controversial because patients not given steroids ultimately regain vision as well. Typically, an MRI is done, looking for evidence of MS.

Ischemic Optic Neuropathy

Ischemic optic neuropathy is the feared complication of giant-cell (temporal) arteritis. Other signs and symptoms are those of polymyalgia rheumatica: malaise, fever, weight loss, muscle aches, jaw claudication, elevated ESR (erythrocyte sedimentation rate). Corticosteroids are started as presumptive treatment even before the diagnostic temporal artery biopsy is done.

VITREOUS HUMOR

Vitreous degeneration occurs in all elderly persons. They tend to get bothersome floaters, brief unilateral flashing lights (from the vitreous traction on the retina), and vitreous detachment (with a sudden shower of floaters and flashing lights). Vitreous detachment is not dangerous unless it damages the retina.

Vitreous hemorrhage is a cause of sudden, painless loss of vision. It is caused by either a vitreous detachment tearing a retinal vessel or as a result of breakage of the fragile blood vessels in diabetics with neovascularization (proliferative diabetic retinopathy).

Any patient with vitreous detachment should be referred to an ophthalmologist, who looks for current retinal detachment and also defects that, when repaired, may forestall future retinal detachment. The eye with vitreous hemorrhage must be examined by ultrasound to check for retinal detachment.

CATARACTS

The crystalline lens of the eye is a clear biconvex structure behind the iris and supported by the zonules. The lens is initially pliable and reactive to accommodation. As the lens ages, it gets less pliable and may get less clear. Any lens opacity is called a cataract. Cataracts cause a very gradual, painless, progressive loss of vision. Treatment is cataract surgery with replacement of the lens.

Quick Quiz

- What is the leading cause of acquired legal blindness in the U.S.?
- Optic neuritis may signal the development of what neurologic disorder?
- What is vitreous hemorrhage?
- Know the eye movements associated with the 3rd, 4th, and 6th cranial nerves, and the symptoms of their associated dysfunctions.

CRANIAL NERVE DYSFUNCTION

Suspect cranial nerve (CN) involvement in the patient who presents with sudden onset of painless double vision (Figure 10-7):

6th CN (abducens; CN VI) supplies the lateral rectus. Paralysis: cannot move the eye laterally.

4th CN (trochlear, CN IV) paralysis: Eye is deviated upward and the head tilted toward the uninvolved side (Bielschowsky sign).

3rd CN (oculomotor, CN III). Motor: 2 branches, superior and inferior. The superior branch supplies the superior rectus and the levator palpebrae superioris (eyelid muscle). The inferior branch innervates the inferior rectus, inferior oblique, and the medial rectus. There is also a parasympathetic component of CN III, which is yet another branch. It results in tonic constriction of the pupil. Complete paralysis of CN III results in an eye that is deviated "down and out" (due to unopposed activity of the superior oblique [CN IV] and lateral rectus [CN VI]), a ptotic eyelid, and a dilated pupil. If the eye is not dilated, the patient probably has diabetic vascular disease affecting only the somatic branches.

EYE INJURY

Trauma

Check acuity; inspect anterior chamber for layered blood (hyphema), corneal laceration, subconjunctival hemorrhage, puncture wound, or pupil distortion; use ophthalmoscopy to confirm clear view of retina and no other signs of hemorrhage. If there is pain, instill fluorescein to check for corneal abrasion and evert, inspect, and swab the upper lid, looking for a foreign body. Any abnormal finding, except perhaps a small corneal abrasion, requires consultation. Never patch corneal abrasions in contact lens wearers.

Alkali Injury

Alkali injury is a special form of trauma where treatment delay of minutes can devastate the eye. Alkali rapidly penetrates the cornea and enters the anterior chamber, where it wreaks havoc.

Treatment is immediate, consisting of profuse irrigation, with lid eversion to remove any alkali-containing particles. Check pH of tears to confirm that it is normal before discontinuing irrigation. Vessels may be blanched by alkali solution in severe injury, paradoxically creating the appearance of a "white and quiet" eye.

RED EYE

Assessment

The most common cause of a red eye is conjunctivitis. Conjunctivitis may be bacterial, viral (most common cause), chemical, or allergic. A red eye also may indicate more urgent conditions. Workup should include evaluation of certain key differentiating features—acuity, pain, and photophobia (light sensitivity). Other features to assess are preauricular adenopathy, amount and type of discharge, and the location and amount of redness.

Significant findings:

1) Decreased visual acuity may indicate a serious problem requiring prompt consultation. Check for an afferent pupillary defect (seen more often in serious eye conditions).
2) Photophobia is a key feature of iridocyclitis (and other more serious conditions), which should be evaluated promptly (within 24 hours) for possible intensive topical steroid treatment.
3) Type of redness:
   - Bright red confluent blood is seen with subconjunctival hemorrhage.
   - Ciliary flush (red near corneal limbus only in a sun ray-like pattern) suggests iridocyclitis, keratitis, or angle closure glaucoma and warrants referral to an ophthalmologist.
   - Diffuse conjunctival hyperemia is nonspecific.
4) Pain is not common in typical infectious causes of red eye. In patients who have photophobia, foreign body sensation, and/or vision complaints, consider the more serious conditions of anterior uveitis, keratitis, or acute closed-angle glaucoma.
5) Preauricular adenopathy (may be tender) is highly suggestive of adenoviral conjunctivitis.
6) Discharge, if purulent, suggests bacterial etiology. Clear exudate more likely suggests viral. White, stringy exudate may be allergic, especially if associated with pruritus. If there is no pruritus, it is more likely dry eye (keratoconjunctivitis sicca, see next page).

Anterior Uveitis

This is autoimmune inflammation of the anterior eye structures. It occurs as a solitary problem but is also seen with many diseases (e.g., spondyloarthropathies, sarcoidosis, lupus, and vasculitides).

You can make a presumptive diagnosis with symptoms of ocular pain, photophobia, and a ciliary flush with a normal cornea and normal intraocular pressure. Slit

lamp exam reveals inflammatory cells floating in the aqueous humor or deposited on the corneal epithelium. This presentation requires emergent referral!

Treatment: steroids (to reduce inflammation and scarring) and cycloplegics (to prevent synechiae).

Keratoconjunctivitis Sicca (Keratitis)

This is most common in the elderly and in middle-aged women. It may be an early sign of systemic inflammatory disease, including Graves disease, rheumatoid arthritis, and sarcoidosis. Treat most cases with artificial tears (electrolyte solutions, methylcellulose, or other formulations).

Viral Conjunctivitis

Viruses are, by far, the most common cause of red eye. Patients have diffuse conjunctival hyperemia and profuse watery discharge (often with other signs/symptoms of a viral infection). No specific treatment, just practice strict hygiene. Adenovirus is one of the most common etiologies, especially in the summer around swimming pools. It should resolve in 5–7 days.

Bacterial Conjunctivitis

Bacterial conjunctivitis may be caused by staph, strep, *H. influenzae*, *Pseudomonas*, *Moraxella*, or *Neisseria*. Most cases of bacterial conjunctivitis resolve in 5 days even without treatment; but we do treat and follow closely because the patient can develop vision loss.

Red eye with profuse purulent discharge is the typical presentation.

Treat uncomplicated cases with topical erythromycin, sulfa, or polymyxin/trimethoprim (drops or ointment; drops are preferred for adults because vision is blurry for ~ 20 minutes after insertion of ointments). Remember: Some patients have sulfa allergy, so worsening conjunctivitis after sulfa treatment may be due to allergy. Reserve quinolones for the more serious cases.

If complicated, obtain cultures, initiate treatment with gatifloxacin or moxifloxacin, and refer to an ophthalmologist. Aminoglycosides are not used much anymore because they irritate the cornea and cause inflammation after a few days.

Neisseria conjunctivitis (can be gonococcal or meningococcal) is a "hyperacute" (severe conjunctival discharge and redness) conjunctivitis that requires early recognition and aggressive topical treatment to prevent progression to corneal perforation. Systemic therapy is also indicated.

Patients who use extended-wear contact lenses have an impaired ability to fight conjunctivitis and are at high risk for developing vision-threatening complications. Always consider an ophthalmology referral at presentation if the patient wears contact lenses. *Pseudomonas* conjunctivitis can progress to corneal perforation overnight in these patients. Any contact lens wearer with conjunctivitis should immediately discontinue use of the lenses. Start these patients on topical gatifloxacin to cover *Pseudomonas* and gram-positives, and refer to an ophthalmologist.

Acanthamoeba is a known cause of infection with contact lens wearers, especially if the patient uses tap water for lens cleaning. Usually, it progresses rapidly to keratitis.

Infectious Keratitis

Think about **bacterial keratitis** in patients who wear contact lenses and who present with a painful eye that is difficult to keep open. Non-lens wearers can also get bacterial keratitis, especially if immunocompromised. Organisms usually responsible: staph, *Pseudomonas*, and pneumococcus.

On exam, the eye is red with a mucoid discharge and a visible white spot (corneal opacity) that is easily seen with a penlight. Fluorescein staining shows the area as well.

Treatment includes emergent referral to an ophthalmologist.

Viral keratitis can be caused by reactivation of latent herpes simplex. It may present similarly to bacterial conjunctivitis (discussed above). Fluorescein staining shows a characteristic dendritic branching pattern. Risk factors for reactivation include laser eye treatments and a compromised immune system. Diagnosis is purely clinical because most patients have antibodies to HSV, and viral culture takes days. Treatment is with oral or topical antivirals (but not both). Know that topical steroids can seriously exacerbate the infection, so do not prescribe any topical steroids for an eye unless you are certain that the underlying diagnosis is not herpes keratitis. Some patients have problems with recurrent disease (similar to fever blisters from HSV); these patients can be managed with chronic oral antivirals.

Again: Remember *Acanthamoeba* in contact lens wearers who use tap water for lens cleaning!

OTHER EYE INFECTIONS

Endophthalmitis

Endophthalmitis (infection inside the eye) can have an ocular (traumatic) or systemic (blood stream seeding) source—and can be bacterial or fungal. The most common presentation is bacterial infection after cataract surgery (with intraocular lens [IOL] replacement), and the organism is usually a coagulase-negative *Staphylococcus*. Remember: If trauma to the orbit is involved, suspect *Bacillus cereus*!

Patients present with decreased visual acuity, hazy cornea, pain, and hypopyon (layering of white cells visible in the anterior chamber).

QuickQuiz

- What virus is usually responsible for conjunctivitis?
- A contact lens wearer presents with severe keratitis and says she uses tap water frequently for lens care. What organism should you consider?

Treatment: Refer immediately. The ophthalmologist does vitrectomy and cultures the vitreous fluid; then intraocular antibiotics are injected (vancomycin + ceftazidime or amikacin). Systemic antibiotics are added in severe cases, although utility is controversial. It is important to choose antibiotics that cross the blood-brain barrier; otherwise, the drugs do not reach the vitreous fluid. A cataract IOL does not have to be removed, unless the infecting organism is a fungus.

Candida endophthalmitis is seen more commonly because of the widespread use of prolonged intravenous access and cases of fungemia. *Candida* can reach the eye via trauma or bloodstream infection. Bacterial and fungal endophthalmitis present similarly, which is the reason why cultures are of paramount importance in postsurgical patients. Risk factors for candidemia include long-term venous access, neutropenic immunocompromise, long-term broad-spectrum antibiotics, and corticosteroid treatment. Know that injection drug users who dilute drugs (usually heroin) in contaminated lemon juice are at increased risk. Treatment includes removal of the IOL and systemic azole antifungal treatment (not ampho B because it does not achieve high levels in the eye).

Periorbital and Orbital Cellulitis

Periorbital cellulitis usually is a rapidly progressive cellulitis of the periorbital area, which may become orbital if not treated. Patients present with warmth, redness, and swelling around the eye. The key physical exam finding is normal extraocular muscle movement, without associated diplopia or pain.

If the patient has disconjugate gaze, diplopia, or pain with eye movement, it is probably the result of infection that has moved into the orbital space. This warrants a periorbital CT or MRI, and IV antibiotics with MRSA and strep coverage, such as vancomycin and ceftriaxone.

Chalazion

Chalazion is caused by obstruction of one of the tarsal (meibomian) glands forming a small nodule found in the tarsus under the eyelid. Treat with warm compresses. Chalazion is not a problem unless secondary infection occurs. Such infections often require ophthalmologic surgery.

Stye

Stye is an abscess at the base of an eyelid. Treat it with warm compresses and a topical ophthalmologic antibiotic. Occasionally, it requires drainage.

EYE EMERGENCIES — REVIEW

Briefly, here is how to approach ophthalmologic emergencies.

Treat emergently and immediately refer:

- alkali burn,
- trauma,
- orbital cellulitis,
- central retinal artery occlusion,
- angle-closure glaucoma, and
- optic nerve infarction in giant-cell arteritis.

Refer immediately without on-site treatment:

- penetrating ocular injury,
- endophthalmitis,
- retinal detachment, and
- keratitis/keratoconjunctivitis.

Refer to be seen within 1–2 days:

- retinal vein thrombosis,
- optic neuritis, and
- vitreous detachment/hemorrhage.

HEARING LOSS

CONDUCTIVE HEARING LOSS

Hearing loss is conductive, sensorineural, or both. Conductive hearing loss occurs because something blocks sound from entering the inner ear (e.g., otitis media, eustachian tube blockage, otosclerosis, invasive external otitis, TM perforation, and ceruminosis—or any other impaction of the external canal).

Otosclerosis is an autosomal dominant trait with poor penetrance. It is much more common in Caucasians than in African-Americans. 10% of Caucasians develop otosclerosis; 1% become symptomatic.

SENSORINEURAL HEARING LOSS

Sensorineural hearing loss is caused by either cochlear damage or nerve damage (CN VIII). It may be caused by viral infections, ototoxic drugs, meningitis, cochlear otosclerosis, Ménière disease, acoustic neuromas, or aging (presbycusis).

Presbycusis is characterized by bilateral symmetrical sensorineural hearing loss in the frequencies > 2,000 Hz. 1/3 of persons older than 65 years have some form.

Ménière disease is an uncommon condition that stems from excess production or decreased drainage of endolymphatic fluid. Affected patients have recurrent, severe

attacks of vertigo that persist for several hours and often are associated with vomiting and prostration. Patients have tinnitus, fullness in the ear, and, in more severe cases, progressive hearing loss (which is frequently one-sided) until deaf, at which time symptoms stop!

Diagnosis is made with the combination of typical clinical symptoms and demonstration of sensorineural hearing loss on audiometry.

Treatment of acute episodes is benzodiazepines and antiemetics (not meclizine!). Chronic treatment includes avoidance of caffeine and salt, with the addition of diuretics if symptoms continue. Surgery can play a role, but usually comes at the expense of hearing loss. (Alan Shepard, the first American astronaut, suffered from Ménière disease and was grounded from space flight for 5 years. He eventually made it to the moon after a corrective surgery.)

Acoustic neuromas (vestibular schwannomas) are benign, very slow-growing tumors of the 8th cranial nerve. Patients usually present with tinnitus, unilateral hearing loss, and gait imbalance. MRI is the diagnostic test of choice. Treatment is radiosurgery or surgical resection.

ACUTE HEARING LOSS

Acute sensorineural hearing loss should be evaluated and treated immediately. If the patient cannot be seen immediately, put them on prednisone (40–80 mg/day) and evaluate as soon as possible. There is suggestion that earlier steroids may allow for a larger percentage to have hearing return to them.

RINNE AND WEBER TESTS

Know how to perform the Rinne and Weber tests to differentiate between conductive and sensorineural hearing loss.

Rinne test (Figure 10-8 and Table 10-13) is based on the observation that air-conducted sound is normally louder than bone conducted. The base of the vibrating 256 Hz (best) tuning fork is placed over the mastoid, and the sound of this bone-conducted hearing is compared to the air-conducted sound the patient hears when the tuning fork is placed next to the ear on the same side.

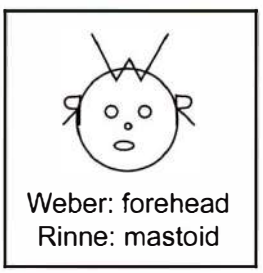


Figure 10-8

- With no hearing loss, the air-conducted sound is loudest.
- With conductive hearing loss, the bone conduction is louder.
- With sensorineural hearing loss, both air and bone conduction are decreased, but the air conduction is perceived as being louder.

Weber test consists of placing the base of a 256 or 512 Hz tuning fork on the middle of the forehead. The patient tells you whether the sound lateralizes to one side or stays in the middle.

- If the sound is perceived as being in the middle, the patient either has normal hearing or the hearing loss is symmetrical.
- If the sound lateralizes, there is either a conductive hearing loss in the ipsilateral ear or sensorineural loss in the opposite ear.

You can simulate the Weber test by humming and sticking your finger in one ear (causing a conductive hearing loss). If your hearing is normal, the sound lateralizes to the plugged-up ear.

OFFICE PSYCHIATRY

PSYCHOSOCIAL DISORDERS

Eating Disorders

Anorexia Nervosa

Anorexia nervosa syndrome usually begins postpuberty and in early adulthood. It almost always occurs in middle-to-upper–class Caucasian women. Anorexia may have a genetic component (concordance in monozygotic twins and increased risk in 1st degree relatives). Currently, data do not support any increased incidence of sexual abuse in anorexics.

Diagnosis is clinical. Typically, diagnosis consists of a combination of the following:

- Weight loss has resulted in a weight at least 15% under ideal.
- Patients have a preoccupation with food and have an intense fear of becoming fat.

Table 10-13: Diagnosing Conductive vs. Sensorineural Hearing Loss with the Rinne and Weber Tests

Type of Hearing Loss (examples)	Rinne Position A = Air (i.e., fork held next to ear) Position B = Bone (i.e., base on mastoid)	Weber Tuning fork base held at middle of forehead
None	Sound A > B	Sound does not lateralize
Sensorineural loss (in left ear)	Left ear: Both A & B decreased equally so still: sound A > B	Lateralizes to the right ear
Conductive loss (in left ear)	Left ear: B > A	Lateralizes to the left ear

Quick Quiz

- What is the best way to diagnose an acoustic neuroma?
- A Rinne test is done. The patient can hear the tuning fork more loudly when it is on the bone. What does this mean?
- A Weber test is done on the same patient. He can hear sounds more loudly on the left side. What does this mean?
- A young woman is brought in by her husband for weight loss and lack of menses for 6 months. What diagnosis should you consider?
- How does anorexia nervosa differ from bulimia?

- There are disturbances in the way body weight and size are experienced. These patients have a distorted self-image and, despite often extreme weight loss, they not only deny thinness but complain of feeling fat. This is a "soft" criterion because many young individuals have a similar self-perception, although without the weight loss.
- Women have had absence of 3 or more consecutive menstrual cycles.

In advanced cases, patients become emaciated, bradycardic, and hypotensive. Lab studies show anemia, hypokalemia, and hypoalbuminemia. These patients are at risk for sudden death from ventricular tachyarrhythmias, especially when refeeding.

Treatment: It is important to establish a supportive advisor role with the patient. Patients are very resistant to psychotherapy, and outpatient supportive care often works just as well as inpatient therapy. Explain the dangers of starvation, such as sudden death, and set realistic, short-term goals for weight gain. Acknowledge the patient's perception and continually reinforce that you do not let them get fat as they gain weight. Treatment is long-term with frequent failures and setbacks. Antidepressants may exacerbate severe anorexia because some are dietary depressants. Cyproheptadine, an appetite stimulant, may help a little.

Outcome is very poor in 20–30%. Anorexics are more likely to abuse drugs and have comorbid anxiety, obsessive-compulsive, and/or personality disorders.

Bulimia

Bulimia is the term used for binge eating of large amounts of food, followed by purging—either with vomiting or with laxatives. It may be a variant of anorexia nervosa, and many bulimia patients have a history of anorexia in their past. Bulimia patients are typically 20–30 years old (older than anorexia patients). These patients are usually not < 85% of ideal weight.

Diagnosis of bulimia is clinical. Typical symptoms of bulimia include:

- Recurrent episodes of binge eating—at least 2 per week for at least 3 months
- Sense of lack of control over eating behavior
- Overly concerned with body weight and shape
- Regular use of self-induced vomiting, laxatives, dieting, fasting, and vigorous exercise to prevent weight gain

Physical exam may show erosive skin lesions on the fingers where the teeth cause injury during attempts to induce vomiting. Dental erosions and an increase in the size of the salivary gland are also seen. The most common lab abnormalities are hypokalemia and metabolic alkalosis from vomiting and laxative use. Think about bulimia in young patients presenting with a Mallory-Weis tear or severe GERD.

Treatment is again supportive, with the focus on slowly decreasing the amount of food eaten and decreasing the frequency of binge-eating episodes. Treatment, as with anorexia, is long-term, with frequent failures and setbacks. Antidepressants may help.

Anxiety Disorders

Anxiety disorders are classified in 2 ways:

1) Generalized anxiety disorder, which is chronic and low-grade
2) Panic disorder, with brief and dramatic panic attacks

Generalized anxiety disorder: DSM-IV diagnostic criteria include anxiety/worry about several activities or events—that is more than what is reasonable for the events—for ≥ 6 months. Generalized anxiety disorder is associated with substance abuse and other psychiatric diagnoses: obsessive-compulsive disorder, depression, panic disorder, and social phobias. Somatic complaints are common (fatigue, memory problems, tension, and inability to sleep).

Treat with behavioral therapy. Know that several brief encouraging follow-up visits to a primary care physician has the same effect as prescribing benzodiazepines. Patients who require more than behavioral therapy can be treated with SSRIs as the 1st line of therapy. Benzodiazepines (BDZs) can be considered if SSRIs are ineffective. Abuse of BDZs is very low in this patient population. Buspirone is useful as a BDZ substitute. Chronic treatment is usually required.

Panic disorder is diagnosed when 4 attacks have occurred within 1 month, or 1 or more attacks are followed by 1 month of intense fear of another attack. These patients often have phobic avoidances of places or situations associated with attacks. Secondary major depression is a common complication.

Treatment of panic disorder is usually with SSRIs and anxiolytics, such as benzodiazepines or buspirone HCl. The optimal treatment is an SSRI, with only short-term use of benzodiazepine. Psychotherapy may have some benefit. Longer-acting benzodiazepines (e.g., clonazepam) are preferred over alprazolam, due to alprazolam's potential for abuse and higher toxicity in overdose.

Bipolar Disorder

Bipolar disorder is characterized as a major depression with at least 1 episode of mania or hypomania. Bipolar disorder is further categorized based on severity as type I (presence of psychosis, frequent need for emergency department visits and hospitalizations, poor overall functioning) or type II (milder level of dysfunction). Most manic patients are euphoric and have inflated self-esteem, decreased need for sleep, and pressured speech. Hyper-sexuality and hyper-religiosity are common, as is overspending. Some patients are just irritable, possibly also paranoid—this is termed dysphoric mania. Psychotic symptoms are common during manic episodes.

While manic episodes can be quite dramatic, most disability associated with bipolar disorder stems from depression. Bipolar patients have high rates of suicide, anxiety disorders, and substance abuse.

Treatment of bipolar disorder is usually accomplished with mood stabilizing medications such as antipsychotics (quetiapine, olanzapine), lithium, and seizure medications (divalproex sodium, lamotrigine, carbamazepine), either alone, or in combination. Antidepressant medications are generally not helpful in patients with bipolar disorder. Antidepressants also carry the risk of "switching" the patient into a manic phase of illness.

The atypical antipsychotics (e.g., olanzapine) do not appear to cause tardive dyskinesia associated with older antipsychotics such as haloperidol. The atypical drugs are associated with weight gain, diabetes, and hyperlipidemia. Know that many of the antiepileptic drugs are associated with increased risk of suicide. Also know that thiazide diuretics, ACE inhibitors, and NSAIDs increase the lithium level. Refractory bipolar disorder is often treated with electroconvulsive therapy.

Depression

Depression is discussed briefly under Geriatrics (see page 10-19). Of course, this does not mean it occurs only in the elderly, but the general population has the same treatment options as the elderly.

For mild-to-moderate depression the current guidelines recommend psychotherapy and/or medications for an initial 12-week period. If psychotherapy is tried alone and there is no response, then definitely begin medications. After you start meds, the guidelines say to monitor the patient every 1–2 weeks by phone or office visit for the initial 8 weeks. Expect a 56% response rate at 2 weeks, 81% at 4 weeks, and 90% at 6 weeks. If there is no response at 8–12 weeks on maximum doses of the chosen medication, switch to a different drug or augment with bupropion or buspirone. Thyroid augmentation is controversial and not included in current guidelines. Treat for 6–9 months for initial therapy, with a 2–4 week taper after improvement. Ongoing treatment with antidepressant medications is also very acceptable in patients with recurrent depression.

Medication Complications

Neuroleptic malignant syndrome (NMS) is an idiosyncratic response to potent neuroleptics, resulting in autonomic dysfunction, extrapyramidal symptoms, and high fever. The fever may reach 106° F. The neuroleptics most commonly involved are haloperidol, piperazine, phenothiazines, and thiothixene. NMS is thought to be due to a depletion of dopamine. It persists for up to 10 days after the drug is stopped. Treatment is to stop the causative drug and cool down the patient. Give oral dopamine agonists also to counteract the depletion. Bromocriptine is the drug of choice, but you may also use amantadine and dantrolene.

Serotonin syndrome (SS): One of the functions of serotonin in the brain is to modulate body temperature. Serotonin drugs can cause derangement in thermoregulation—a condition termed "serotonin syndrome." Think about it in patients who are on at least 1 serotonin drug, but it more often occurs in patients on 2 or more serotonergic agents. Onset is generally within 6 hours of starting the new or additional drug. Serotonin syndrome can have the presentation of SSRI overdose.

Clinical presentation is anxiety, disorientation, sweating, tachycardia, hypertension, vomiting, and diarrhea. Hyperthermia can be marked. Exam may show rigidity, hyperreflexia, and tremors. This condition looks like neuroleptic malignant syndrome, toxicity from anticholinergics, or overdose of sympathomimetics. Serotonin syndrome is a clinical diagnosis. No lab test confirms it. Nonspecific findings such as rhabdomyolysis and metabolic acidosis may be seen.

Treat by discontinuing the serotonergic drug and giving supportive care, including cardiac monitoring. BDZs are helpful for the anxiety and tachycardia. The syndrome usually resolves in 24 hours. The hyperthermia often results from muscle rigidity; so, very hyperthermic patients typically require intubation and paralysis. Cyproheptadine is a serotonin antagonist that is given in severe cases.

Differentiating NMS and SS based on symptoms is difficult because they present similarly with autonomic changes, hyperthermia, and mental changes. It is important to know that blood tests easily distinguish between them. NMS has increased CK, LDH, AST (SGOT), and WBCs along with a low serum iron. Normal labs are often seen with serotonin syndrome.

Quick Quiz

- Describe a patient with neuroleptic malignant syndrome.
- Define the Philadelphia chromosome.

SSRI discontinuation syndrome: It is very important to slowly titrate patients off SSRIs. It is generally done over several months, but some patients require much longer. If done too quickly, patients can develop lightheadedness, vertigo, shock-like paresthesias, visual symptoms, anxiety, insomnia, and gastrointestinal symptoms (N/V/D). Diagnosis is usually easy with the history of recent SSRI dosage decrease. Treatment is to boost the drug a little and, once stable, restart the tapering at a slower pace.

GENETICS

Histocompatibility antigens are the antigens involved in graft rejection. These are the markers that identify "self" vs. "non-self" for the body's immune surveillance system. Many of the histocompatibility genes are closely grouped on chromosome 6, and this area is called the major histocompatibility complex (MHC). The human MHC is termed HLA.

General review of transcription and translation: The DNA has coding sequences called exons, separated by very small noncoding sequences called introns. The full gene (introns + exons) is transcribed by DNA dependent RNA polymerase into RNA. The introns are then spliced out of the RNA before it leaves the nucleus, thereby forming the messenger RNA (mRNA). The mRNA is then translated into protein: Each 3-base sequence comprises a codon, which determines the amino acid that attaches when it is translated.

Point mutations are a change to a single base, and can result in either a missense or a nonsense mutation. Missense mutation is when a point mutation causes a different amino acid to be produced, as in SS (valine is substituted for glutamic acid). Nonsense mutation produces a stop codon, which stops the translation.

Insertion and deletion mutations: These cause a "frame shift," which causes an abnormal protein from that point to the end.

Splicing mutations result from a point mutation at the area defining the junction between the intron and the exon. This results in dysfunctional proteins. Beta thalassemias often are caused by splicing mutations.

Clues for autosomal dominant disease:

- Vertical transmission (involving several generations).
- Risk to each child of affected individual is 50%.
- Male-male transmission is observed.
- Normal parents do not transmit the trait (unless a new mutation occurs).

Clues for X-linked inheritance:

- Inheritance of trait is father to daughter—all daughters of affected males are carriers; no sons of the father are affected.
- If mother is a "carrier," she has a 50% risk of transmitting the gene to her sons, and each son with a resulting abnormal X chromosome would therefore be affected. A "carrier" mother also has a 50% risk of transmitting the gene to her daughters who, in turn, become unaffected carriers.

Acquired chromosomal abnormalities: A viral gene that can transform DNA is called a viral oncogene. The human chromosomes also contain genes that are associated with malignancy, called cellular oncogenes or proto-oncogenes. These proto-oncogenes probably have something to do with embryonal development and are otherwise silent, but, with certain chromosomal rearrangement, they become active. In both Philadelphia chromosome and Burkitt's, the proto-oncogene becomes active by an acquired reciprocal translocation.

The Philadelphia (Ph1) chromosome t(9;22) was the 1st chromosomal abnormality found to be associated with malignancy (first found in CML). The switch causes the "*c-ABL*" proto-oncogene to be moved from chromosome 9 to 22.

Burkitt lymphoma and its leukemic analog, ALL (FAB type 3), have a reciprocal translocation that switches the proto-oncogene "*c-MYC*" on chromosome 8 to chromosome 14, 22, or 2: i.e., t(8;14), t(8;22), or t(8:2). Chromosome 14 has the heavy chain locus. The lambda light chain locus is on chromosome 22, and the kappa light chain locus is on chromosome 2.

Many leukemia and lymphoma patients have a chromosomal abnormality. Solid tumors rarely have abnormal chromosomes.

WOMEN'S HEALTH

OFFICE OBSTETRICS

The following is a compilation of everything written on pregnancy in these Core Curriculum books—plus more. This compilation makes it easier to review pregnancy as a specific topic. Because this is a very important topic, consider the entire section highlighted!

Drugs in Pregnancy

Drug safety in pregnancy is categorized as follows:

A = Well-controlled human studies have failed to show risk of a drug to the fetus. Very few drugs meet this category. Examples include levothyroxine, magnesium sulfate, and prenatal vitamins (of course!).

B = Animal reproduction studies have not demonstrated a risk to the fetus, and there are no adequate trials in pregnant women. Examples include acetaminophen, ranitidine, metformin, insulins, enoxaparin, and many antibiotics.

C = Some adverse effect in animal studies but there are no controlled studies in women. Use only if potential benefit outweighs potential risk to fetus. Examples include unfractionated heparin, oseltamivir, and many antidepressants (fluoxetine, citalopram, bupropion).

D = Positive evidence of human fetal risk, but may be acceptable despite the risk (e.g., life-threatening illness). Examples include aspirin and NSAIDs, most seizure medications (phenytoin, carbamazepine, phenobarbital, valproate), ACE inhibitors, thiazides, diazepam, lithium, paroxetine, tetracycline, and aminoglycosides.

X = causes fetal abnormalities. Do not use. Examples include isotretinoin, warfarin, thalidomide, DES, simvastatin and OCPs.

Keep in mind that pregnant women are generally excluded from most trials of medications, so information is often unavailable regarding the safety of a particular agent. A 2001 study noted that there is insufficient information on 90% of drugs that were approved by the FDA over the prior 20 years. Bottom line: You must carefully weigh the risks and benefits of all medications during pregnancy from the standpoint of both the fetus and the mother.

Also know Table 10-14: Most Asked-About Drugs in Pregnancy.

Table 10-14: Most Asked-About Drugs in Pregnancy

Do Not Use	Okay to Use
ACE inhibitors, ARBs, nitroprusside	Clonidine, labetalol, calcium channel blockers in trials, digoxin, verapamil, procainamide
Ciprofloxacin, doxycycline, tetracycline, podophyllin, metronidazole in 1st trimester	Sulfasalazine, beta-lactams, erythromycin, azithromycin, amphotericin B
Most aminoglycosides	Gentamicin
I^{131}, methimazole	PTU
Most antihistamines	Chlorpheniramine
Warfarin	Heparin

Gastroenterology

Endoscopic Workup

Esophagogastroduodenoscopy (EGD) is the option of choice for workup of many GI diseases during pregnancy in order to limit or preclude the use of radiation.

Endoscopic ultrasonography (EUS) is normally used in evaluating pancreatic diseases. It is also used in biliary duct disease when an ERCP would normally be used but is contraindicated (e.g., gallstone pancreatitis and pregnancy).

GE Reflux Disease

LES pressure is decreased by progesterone (pregnancy increases GE reflux) as well as chocolate, smoking, and some medications, especially those with anticholinergic properties. Ranitidine, famotidine, and lansoprazole are category B for refractory symptoms. Avoid bismuth subsalicylate due to the salicylate exposure.

Crohn Disease Meds

FDA risk category B (no evidence of risk in humans):

- Metronidazole (although because of lack of data, it is contraindicated in 1st trimester)
- Prednisone
- Sulfasalazine
- Mesalamine

Constipation

The altered progesterone and estrogen levels are the probable cause of constipation in pregnancy.

Pancreatitis

Cullen sign is also seen with intra-peritoneal bleeding (especially ruptured ectopic pregnancy), and Turner sign is seen with other causes of retroperitoneal bleeding.

Liver Disease

Unlike hepatitis A, hepatitis E carries a very high risk for fulminant hepatitis in the 3rd trimester of pregnancy—with a 20% fatality rate.

1st trimester: Hyperemesis gravidarum can cause N/V, volume depletion, and mild increase in AST and ALT.

2nd trimester: best time for surgery for severely symptomatic gallstone patients.

3rd trimester:

- Remember that hepatitis E can cause fulminant hepatitis in the 3rd trimester of pregnancy—with a 20% fatality rate. The scenario presented may be a pregnant woman traveling to Southeast Asia who contracts hepatitis E (fecal-oral transmission like hepatitis A).

Quick Quiz

- Know Table 10-14!
- Are ACE inhibitors safe in pregnancy?
- During what trimester is metronidazole contraindicated?
- A pregnant woman has a DVT. What commonly used anticoagulant is contraindicated?
- Is an S_3 gallop normal in pregnant women?
- Is electrical cardioversion possible during pregnancy?
- What do you have to rule out in a pregnant patient who presents with new-onset atrial fibrillation and pulmonary edema?

- Fatty liver of pregnancy is a very serious condition in which there is microvesicular fat deposition in the liver (as in Reye syndrome), with only modest elevation of AST/ALT/Bili. It occurs in the 3rd trimester and is associated with encephalopathy, hypoglycemia (again like Reye syndrome), preeclampsia, pancreatitis, DIC, and renal failure. Early delivery is required.
- Intrahepatic cholestasis of pregnancy causes itching and increased alk phos, bili, AST, and ALT.

Pulmonary Medicine

Asthma Treatment

Budesonide is preferred in pregnancy, but all ICS may be used.

Tuberculosis Treatment

Do not use PZA in pregnancy because it causes birth defects. Streptomycin is also avoided.

Pulmonary Embolism and DVT Treatment

The risk of venous thromboembolism is elevated during pregnancy and postpartum. Pregnancy is generally considered an absolute contraindication for warfarin. Warfarin is a small molecule that crosses the placenta and is a known teratogen. Unfractionated heparin is large and does not cross the placental barrier, but poses challenges such as parenteral dosing and need for frequent monitoring. Low-molecular-weight heparins (LMWH) can be self-administered and require little or no monitoring. Enoxaparin is generally considered to be safe for both the mother and fetus in pregnancy (category B). The 2012 American College of Chest Physicians guidelines recommends the use of LMWH during all phases of pregnancy for prevention and treatment of venous thromboembolism in women with VTE or at elevated risk (e.g., anti-phospholipid antibody syndrome).

Cardiology

Normal Findings in Pregnant Women

S_3: An S_3 is normal and commonly heard in children and in persons with high cardiac output, such as pregnant women. S_3 is virtually always abnormal in nonpregnant patients > 40 years old.

Most pregnant women experience some pedal edema. Flow murmurs (and S_3 gallops) are also common, and the jugular venous pressure increases.

Abnormal Cardiac Issues in Pregnancy

Absolute contraindications to pregnancy include pulmonary arterial hypertension and Eisenmenger syndrome. In secundum ASD, aortic stenosis, and dilated cardiomyopathy, the patient must be closely watched. In aortic stenosis and dilated cardiomyopathy, patients are normally kept at bedrest. Secundum ASD patients are usually not at risk for cardiac decompensation, unless they develop atrial fibrillation. Cyanotic heart disease is the worst risk.

Atrial fibrillation: Like secundum ASD above, the initial presentation of mitral stenosis (MS) in a pregnant patient may be new-onset atrial fibrillation and pulmonary edema. The increased blood volume in pregnancy can cause a precipitous exacerbation of MS—so consider treating all pregnant MS patients with digoxin. Electrical cardioversion is not contraindicated in pregnancy.

Remember: In a pregnant patient presenting with new-onset atrial fibrillation and pulmonary edema, you need to rule out both mitral stenosis and secundum ASD.

Aortic dissection: 3rd trimester of pregnancy, systemic hypertension, cystic medial necrosis, bicuspid aortic valve, and coarctation of the aorta are predisposing factors.

Valve surgery: Porcine valves (vs. mechanical valves) are often given to women of childbearing age to preclude the use of anticoagulants during pregnancy.

There is recent controversy about use of LMWH vs. warfarin for anticoagulation with prosthetic valves during pregnancy. Most now recommend discussion with the woman about the risks and benefits to her and the unborn child of using warfarin (less risk of thrombosis for her; increased risk of defects for the infant) vs. LMWH (increased risk of thrombosis for the mother; decreased risk of defects for the infant). Long-term use of heparin in pregnancy is associated with osteoporosis, and many recommend increased RDAs for calcium.

Maternal rubella infection during pregnancy is a common cause of patent ductus arteriosus (PDA), supravalvular aortic stenosis, branch pulmonic stenosis ("peripheral PS"), and other congenital cardiac defects.

Infectious Disease

Bacterial Infections

UTIs: *Streptococcus agalactiae* and *E. coli*. Treat with ampicillin, cephalexin, or nitrofurantoin. Ciprofloxacin is not given to pregnant women due to concerns of joint problems developing in the fetus.

Listeria monocytogenes infections occur most in those with decreased cellular immunity syndromes like AIDS, lymphoma, and leukemia, but they also are seen in neonates, the elderly, and pregnant women. The most common presentation is in the 3rd trimester and presents as a flu-like illness and is picked up by blood culture. Also suspect this in a pregnant woman with a UTI and negative urine culture.

Streptococcus agalactiae (group B) is also a cause of postpartum endometritis and bacteremia. So suspect this in any woman who develops a postpartum fever!

Approximately 5% of pregnant women have *Chlamydia trachomatis* in their genital tracts; antibiotic ointment in infants' eyes at birth does not prevent this conjunctivitis. (This ointment is given only for gonococcal conjunctivitis.)

Gonorrhea is more likely to disseminate in pregnant women. The newborn is at risk for gonococcal conjunctivitis.

Asymptomatic bacteriuria should be treated in pregnant women (1/3 go on to pyelonephritis!), neutropenic patients, and transplant patients.

Parasitic Diseases

Toxoplasma gondii is serious in the immunocompetent only if acquired during pregnancy, when it can cause congenital toxoplasmosis (resulting in intellectual disability and chorioretinitis). The fetus is more likely to have a congenital infection if the disease is acquired later in pregnancy (15% if 1st trimester; 70% if 3rd trimester). Previous infection with toxoplasmosis before pregnancy is generally not a concern in pregnancy.

Viral Infections

Viruses with the greatest teratogenic potential are CMV, varicella zoster, herpes simplex, and rubella. This is especially true if acquired in the 1st trimester.

CMV is ubiquitous and the most common cause of congenital viral infection. 1–2% of all newborns have the infection *in utero*, but only a few have any abnormalities. These abnormalities, which range from mild neurologic problems to microcephaly, usually occur in mothers with a primary CMV infection.

Rubella is German measles (ssRNA virus). If it is acquired by a pregnant patient in the 1st trimester, there is an 80% chance that the baby has congenital defects—usually severe. Defects include cataracts, heart problems, intellectual disability, and fetal death. It is diagnosed in the mother by the hemagglutination-inhibition test. If this test is negative in a newly exposed pregnant patient, repeat it in 3 weeks (after incubation period) before making any decisions. If it is then positive, a therapeutic abortion should be considered. You can diagnose rubella prenatally by finding rubella IgM antibody in fetal blood. Immune globulin does not prevent the infection, but it may give some fetal protection in the patient who declines therapeutic abortion.

Varicella-zoster infection has a slight risk of causing congenital defects. The pregnant woman with chicken pox has a 10% chance of developing severe pneumonia.

HIV: There is a mother-to-fetus transmission risk of 30%. This is reduced to < 1% with 3-drug antiretroviral therapy (ART). So ensure that all pregnant women with HIV receive ART.

Fungal Infections

High dose (400–800 mg/day) fluconazole is now contraindicated in pregnancy (category D) because of associated abnormalities of the cranium, face, bones, and heart. Single, low-dose fluconazole (150 mg) to treat yeast infection remains category C.

Nephrology

During pregnancy, there is increased calcium absorption and excretion because the 1,25-$(OH)_2$-D is > 2x normal. Even so, frequency of renal stones is the same as in the nonpregnant patient. The urinary tract of the pregnant patient is dilated and, if stones do develop, most pass easily!

There are 4 categories of HTN in pregnancy:

1) Chronic HTN: preexisting HTN or HTN before 20th week of gestation
2) Preeclampsia: HTN + proteinuria after 20th week of gestation in woman with no history of HTN
3) Preeclampsia that complicates chronic hypertension: worsening HTN + proteinuria after 20th week of gestation in a woman with history of controlled, chronic HTN
4) Gestational HTN: occurs after 20th week and has no proteinuria

Per the JNC 7 report, the stages of HTN do not apply in pregnancy. HTN in pregnancy is defined as mild if BP is 140–159/90–109 and severe if BP ≥ 160/110.

Eclampsia is defined as grand mal seizures in a woman with preeclampsia or gestational HTN.

Preeclampsia (or pregnancy-induced hypertension) more commonly occurs in primigravidas, usually in the 3rd trimester, and resolves after delivery. It is defined as SBP > 140 or DBP > 90 and proteinuria > 300 mg in 24 hours in a pregnant woman > 20-weeks gestation. The elevated blood pressure must be sustained with at least 2 readings at least 6 hours apart.

Quick Quiz

- Should asymptomatic bacteriuria in a pregnant woman be treated?
- What is the problem with rubella being acquired in the 1st trimester?
- What is the maternal-to-fetal transmission rate of HIV without ART? With ART?
- How do you make the diagnosis of preeclampsia?
- What are the symptoms that may occur with preeclampsia?

Preeclampsia may be symptomatic or asymptomatic (both have HTN and proteinuria). Symptoms of preeclampsia can be mild (headache, vision changes) or severe (seizures, low platelets, stroke or intracerebral hemorrhage, pulmonary edema, hepatic and/or renal failure, and placental abruption). **HELLP syndrome** is preeclampsia with elevated liver enzymes, low platelets, and microangiopathic hemolytic anemia.

Treat hypertension in pregnancy (regardless of category) to prevent stroke. Treatment of the BP does not affect the outcome of preeclampsia (weird … but true). Know that pregnant women with hypertension are at risk for adverse fetal outcomes if blood pressure is driven too low. This is one patient group in whom we actually have higher BP goals, not lower! Each 10 mmHg reduction in SBP is associated with a reduction in fetal birthweight.

For women with preeclampsia, recommendations are to start treatment if:

1) symptoms are present, or
2) in asymptomatic women when SBP ≥ 150 or DBP ≥ 95 (although these specific numbers are controversial), with a target BP goal of < 130–150/80–100 mmHg.

Bedrest is still recommended for asymptomatic or mild preeclampsia (especially if before 34-weeks gestation), although there are no clinical trials to suggest it affects outcome. For severe, symptomatic preeclampsia, definitive treatment is delivery. Ultimately, care providers walk a fine line between delivering a baby too early to relieve preeclampsia and allowing for longer gestational development.

Women with controlled, chronic HTN (BP < 120/80) are taken off BP meds, with frequent BP and symptom monitoring. Meds are reinstituted for same BP as mentioned above for preeclampsia (SBP ≥ 150 or DBP ≥ 95), with target of < 130–150/80–100 mmHg.

Any pregnancy complicated by malignant HTN or severe, symptomatic preeclampsia is treated with parenteral antihypertensives—labetalol is the preferred drug. Hydralazine and CCBs are also sometimes used, but there are less data for these drugs. Know that the following antihypertensives are contraindicated: ACEIs/ARBs/renin inhibitors (teratogenic) and nitroprusside (cyanide poisoning in the baby).

Oral agents used to treat chronic, asymptomatic preeclampsia, gestational hypertension, and chronic hypertension in pregnancy include labetalol (other beta-blockers have less desirable effects, so labetalol is preferred), methyldopa, extended-release nifedipine, and thiazide diuretics (but watch for signs/symptoms of volume contraction).

Be aware that eclampsia can definitely occur postpartum, although rarely. A woman who presents hypertensive with generalized seizures within 12 weeks after delivery should be considered eclamptic.

SLE with lupus nephritis: If the disease has been in remission, there is a 90% chance of a successful pregnancy. If it flares up during pregnancy, however, 25% of fetuses die, usually from the lupus anticoagulant antibody causing thrombotic events.

Pregnancy and **chronic renal failure**: If the creatinine is < 2 and the patient with chronic kidney disease is not hypertensive, there is not an increased risk of abortion or malformation, and there is no increase in the rate of progression of the renal disease. There is an increased risk of pregnancy-induced hypertension.

As renal failure progresses, chance of pregnancy decreases. Dialysis patients rarely become pregnant. In stable renal transplant patients, the outcome of pregnancy is usually great!

Endocrinology

The Serum Osmostat

Pregnant women increase their circulating blood volume by almost 50%! This is accomplished by resetting the osmotic set point causing ADH to be released at a lower osmolality.

Prolactin Levels

Estrogen directly inhibits dopamine outflow, so elevated PRL levels also can be seen in pregnancy and in patients taking estrogen.

Pituitary Adenoma

About 1/3 of pituitary macroadenomas, some of which cause increased prolactin levels, enlarge during pregnancy. If the tumor enlarges enough to cause symptoms, bromocriptine can be restarted (or surgery, if vision is threatened). Bromocriptine is almost assuredly safe in pregnancy, and cabergoline is probably also safe (less experience). But neither drug is FDA-approved for this use.

Thyroid Disease

One can usually safely give I^{131} treatment to hyperthyroid patients, but it is not safe to give it to either pregnant patients or patients with severe hyperthyroidism.

In pregnancy, surgery may be indicated to treat Graves disease—in patients with an associated cold nodule or relapse after radiation, and in some young patients with a large goiter.

Always treat pregnant hypothyroid patients and follow their TSH levels during pregnancy—because their requirements increase. (The dose needs to be increased to 50% more than the prepregnancy dose.) Failure to treat maternal hypothyroidism during pregnancy can adversely affect the baby.

Pregnancy in Patients with Polycystic Ovaries

Treatment of PCOS first includes education about weight loss and then is dependent on the degree of hyperandrogenism and whether pregnancy is desired:

- No hirsutism and no desire for pregnancy: Prescribe medroxyprogesterone every 1–3 months to induce withdrawal bleeding and to protect the endometrium from hyperplasia.
- Hirsute and no desire for pregnancy: Prescribe combined estrogen-progesterone oral contraceptives; hirsute symptoms also can be ameliorated with depilatories/shaving. An insulin sensitizer, such as metformin or a thiazolidinedione, may also confer a very modest additional benefit on hirsutism.
- Hirsute and desires pregnancy: Induce ovulation with clomiphene with or without metformin.

Pregnancy also increases insulin resistance due to placental hormones.

Diabetes in Pregnancy

With pregnancy, strict diabetic control even before conception is important. Maintain FPG < 100 mg/dL and A1c < 7%. Before conception, control of blood glucose reduces fetal malformation, and, during pregnancy, it reduces miscarriages, fetal anomalies/death, and newborn problems. Tight glycemic control decreases the risk of macrosomia (birth weight ≥ 9–10 lb) and shoulder dystocia in the newborn.

During pregnancy, insulin requirements increase based on gestational age of the fetus. This increased requirement is gone immediately after delivery, so anticipate a reduction in insulin dosage of at least 50% postpartum and observe the patient carefully the day after delivery. Metformin and insulins are the drugs of choice for managing DM in pregnancy. [Know:] These medications commonly employed in diabetic management are contraindicated in pregnancy:

- Statins and ACEIs/ARBs should be discontinued before pregnancy.
- Many oral hypoglycemics are category C.

Hematology / Oncology

Fe deficiency is commonly seen in pregnant women who have had no prenatal care.

Breast cancer rates increase with early menarche, late menopause, and late 1st pregnancy.

Neurology

Migraine

Do not use triptans in pregnancy, because of the risk of inducing ischemia.

Pseudotumor Cerebri

Pseudotumor cerebri usually occurs in premenopausal obese women (90%) and may occur during pregnancy.

Seizures During Pregnancy

The background risk for birth defects is 2–3%. The goal of treatment during pregnancy is to control the seizures—uncontrolled seizures can cause placental abruption and early labor and premature delivery. When the risk of teratogenicity is compared to the problems that seizures cause during pregnancy, the risk of uncontrolled seizures is greater!

Maintain a pregnant woman on monotherapy and at the lowest dose of medication possible; risk of malformations increases as each drug is added.

There is no "safe" antiepileptic drug (AED), but valproate is more likely to cause neural tube defects than other commonly used anti-epileptics.

The teratogenic risk of AEDs is decreased by folic acid, and all women of childbearing age on antiepileptic drugs should take high-dose folate daily—some recommend 4 mg/day for these high-risk patients.

Physicians generally give prophylactic vitamin K during the last month of pregnancy in patients on AEDs. This is based on reports indicating increased bleeding in patients on AEDs. Most recent guidelines (AAN AES 2009) say there is not enough evidence to recommend for or against use of prophylactic vitamin K.

Carpal Tunnel

Know that pregnancy can cause an acute presentation of carpal tunnel syndrome (CTS) that typically improves after delivery. Splints are the best treatment for this patient group.

Rheumatology

Methotrexate use: Definite contraindications include preexisting renal or liver disease (e.g., HBV, HCV, alcohol abuse) and pregnancy.

Leflunomide use: contraindicated in pregnancy.

QuickQuiz

- A pregnant woman has Graves disease. What can you do to treat her?
- What is a common mineral deficiency in pregnant women who have not had prenatal care?
- True or false? DUB usually does not require any workup.

SLE and Pregnancy

SSA (Ro)/SSB (La) antibodies are associated with neonatal lupus and congenital heart block. General internists need to know about this risk when counseling women with lupus about pregnancy.

Lupus patients have a higher incidence of failed pregnancies. Risk of pregnancy complications (flare or fetal problems) is much greater if disease is active (especially renal manifestations) or if the mother has anti-dsDNA or antiphospholipid antibodies (APS). Pregnant women with APS and a history of recurrent miscarriages can be treated with heparins (low molecular weight or unfractionated) plus low-dose aspirin—to decrease incidence of miscarriage. Heart block starting in the 3rd trimester can be seen in babies of mothers with SLE who have SSA (Ro)/SSB (La) antibodies.

If an SLE patient wishes to become pregnant and has had a recent lupus flare, continue the glucocorticoids. Measure baseline complements, anti-dsDNA, SSA/SSB, and a 24-hour urine protein before or very early in the pregnancy. Flares during pregnancy are managed with corticosteroids. Refer pregnant women with systemic lupus to a high-risk obstetrician (and pediatric cardiologist, if appropriate).

Avascular Necrosis of the Hip

Causes include pregnancy, steroid use, sickle cell disease, HIV/AIDS, alcoholism, trauma, Gaucher disease, and hypercoagulable states.

Dermatology

Treatment of Acne

Acne is more pronounced in pregnancy due to increases in progesterone. Treatment is focused on safer topical agents (erythromycin, clindamycin, and azelaic acid) and avoidance of other agents which are known to be harmful (isotretinoin, tazarotene, tetracycline, minocycline).

Topical benzoyl peroxide is category C.

Allergy and Immunology

Persistent nasal congestion may accompany pregnancy (rhinitis of pregnancy). It is generally treated with non-pharmacologic measures. Intranasal steroids have not been shown to be effective.

OFFICE GYNECOLOGY

Office gynecology has been partially covered in previous sections. Especially review gynecologic infections in Infectious Disease, Book 1. Pap smear, ovarian cancer, and breast cancer are covered in Oncology, Book 4. Osteoporosis is discussed earlier in this section. Amenorrhea is discussed in Endocrinology, Book 4.

Postmenopausal Bleeding

A woman should undergo endometrial assessment (biopsy or transvaginal ultrasound) if she has postmenopausal bleeding:

- In the absence of HRT therapy
- After she has been on combined HRT continuously for 1 year without bleeding
- At an unexpected time during cyclic replacement

Treatment Recommendations for Menopausal Symptoms

Vasomotor instability (hot flashes): short-term estrogen therapy (if no history of breast cancer or cardiovascular disease). Multiple other agents have proven efficacy including SSRIs, SNRIs, and gabapentin.

Urogenital atrophy: vaginal estrogen for moderate-to-severe symptoms; moisturizers and lubricants for mild symptoms.

Dysfunctional Uterine Bleeding (DUB)

DUB refers to excessive bleeding due to persistent anovulation in a reproductive-age woman with ovaries capable of producing estrogen. The patient's periods may be too frequent, too long, or with too heavy of a flow. DUB is a diagnosis of exclusion. There are many causes, including hypothyroidism, liver disease, renal disease, coagulopathies, pregnancy complications, anatomic lesions, and drugs, among others.

Treatment for young women with DUB usually consists of oral estrogen/progestin preparations. Oral contraceptives containing 35–50 µg of ethinyl estradiol are often used. 4 tablets a day are given initially; this increases bleeding for 1–2 days and generally stops the bleeding in 3–4 days. The patient is then given 2 pills per day for 20 more days. Withdrawal bleeding then occurs within 2–5 days after ending treatment. This hormonal therapy is given for 2–3 more cycles, using 1 pill per day, and then stopped.

Premenstrual Syndrome (PMS)

PMS is a group of symptoms, which most often start during the late luteal phase and are gone within 1–2 days of the onset of menses. The biochemistry of this dysfunction has not been established.

No single treatment has been proven effective, but the cause may be multifactorial, so there are many avenues of treatment to explore with each patient. You can achieve ovulatory suppression with oral contraceptives. These patients may also respond well to the newer mini-pill, which contains only progestin. Other similar options include Depo-Provera® and Norplant®. Oral natural progesterone has been used with varying success.

Various dietary changes help some patients, such as avoiding caffeine, salt, sugar, alcohol, and/or chocolate. Vitamin supplements, such as vitamin B_6 and vitamin E, have also been effective for some. Magnesium 360 mg (as magnesium pyrrolidone carboxylic acid) orally tid, given from day 15 of menstrual cycle to the 1st day of menses, may also help. Note that no one of the above treatments is effective for everyone.

SSRIs are 1st line therapy for women with moderate-to-severe symptoms. Drugs such as fluoxetine, sertraline, paroxetine, and citalopram can be efficacious in up to 2/3 of patients.

FOR FURTHER READING

[Guidelines in blue]

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Neurology

COMA

OVERVIEW

Lethargy, confusion, stupor, obtundation, and coma are terms that apply to diminished levels of consciousness. Consciousness depends on the degree of a person's alertness and attention. Both the reticular activating system (RAS) and the cerebral cortex must be working effectively in order to sustain normal consciousness.

Thus, coma can be caused by either a decrease in the activity of the reticular activating system (RAS) or a process that involves the cerebral cortex of both hemispheres. The RAS resides within the brainstem, so injury to the brainstem, such as a hemorrhage in the pons or midbrain, can cause coma. Certain drugs (prescribed, OTC, and illicit) also affect the RAS directly.

Metabolic disorders are the most common cause of coma, followed by intoxications and anoxic brain damage.

Plum and Posner classify the causes of coma in the following ways:

- Supratentorial
- Infratentorial
- Metabolic
- Diffuse
- Multifactorial

WORKUP OF COMA

Neurologic Exam Findings

Overview

A thorough history and neurological exam are required to establish the diagnosis and the possible cause of coma. This includes a review of underlying medical and mental health illnesses, medications, ingestions, and intoxications. The Glasgow Coma Scale was constructed to assess responsiveness of patients with cerebral trauma. The components of the neurological examination must include observations about respiration (and respiratory patterns), pupillary responses, and motor responses (or a lack thereof). However, the use of this scale in the evaluation of other etiologies of acute coma provides little insight into the localization of the anatomical dysfunction. The prognostic value in non-traumatic coma depends significantly on the etiology. Vital signs including temperature, pulse, respiratory rate, and blood pressure can provide clues to the diagnosis.

Motor Responses

Motor responses, such as decerebrate and decorticate posturing, can help to localize the site of injury:

- **Decerebrate posturing** is a type of rigidity that occurs when the tonic labyrinthine reflex that resists gravitational force acts without modulation of the higher brain, causing extension of all extremities.
  - It indicates an effective severing of the brain from the spinal cord at the level of the midbrain, specifically below the level of the red nucleus. This posturing can be seen during uncal (transtentorial; see next page) or tonsillar (cerebellum) brain herniation.
  - It is also seen in a variety of conditions such as midbrain compression by a mass, cerebellar or other posterior fossa lesions, and severe metabolic insults. It may occasionally be seen in cerebral white matter disease and basal ganglia lesions.
  - Decerebrate posturing is not seen much because it occurs in less common situations and is rapidly followed by death.
- **Decorticate posturing** is a type of rigidity that is characterized by flexion of upper limbs with extension of lower limbs. It is caused by lesions at a more rostral level of injury to both corticospinal and rubrospinal tracts resulting from damage to brain areas that can include the cerebral white matter, internal capsule, and thalamus. These are upper motor neuron lesions. Causes may include anoxic or traumatic brain injury, stroke, intracranial hemorrhage, brain tumors, and encephalopathy.

In uncal herniation, patients may progress from decorticate to decerebrate posturing.

Respirations

Cheyne-Stokes respiration describes a particular pattern of breathing in which the patient has periods of hyperventilation alternating with apnea. This pattern occurs in bilateral cerebral disease, impending herniation, and brainstem lesions; it can also be due to metabolic causes.

Apneustic breathing is characterized by a series of slow, deep inspirations, each one held for 30 seconds or longer, after which the air is expelled by elastic recoil of the lungs, followed by an apneic pause. The rate of apneustic breathing is commonly around 1.5 breaths per minute. It is due to a lesion of the lower pons.

Ataxic breathing is very irregular and typically indicates a lesion of the medulla.

Central neurogenic hyperventilation: Lesions of the lower midbrain-upper pontine tegmentum cause central neurogenic hyperventilation, which produces an increase in the rate and depth of respiration resulting in advanced respiratory alkalosis.

Pupils

Remember that in the comatose patient, any asymmetry between the sizes of the pupils must be considered pathologic (Table 11-1). Light reactivity also needs to be carefully assessed.

Table 11-1: Pupil Size in Coma

Size	Description	Cause	Examples
	One dilated unreactive pupil	Parasympathetic nerve problem	Oculomotor nerve compression from uncal herniation, rupture of an internal carotid artery aneurysm
	One pinpoint pupil (miosis)	Sympathetic nerve problem (Horner)	Lateral medullary syndrome, hypothalamus injury
	Two midpoint nonreactive pupils	Parasympathetic and sympathetic nerve destruction	Midbrain disruption (can affect one or both pupils), anoxia, hypothermia, anticholinergics, severe barbiturate overdose
	Two dilated unreactive pupils		Anoxia, hypothermia, anticholinergics, severe barbiturate overdose
	Two pinpoint reactive pupils		Opiates, pontine destruction

Oculovestibular Testing

Oculocephalic (doll's eyes) and ice-water caloric testing (eyes look toward the cold) test the same vestibular-brainstem-ocular muscle pathway. The complete absence of eye movement in response to oculovestibular testing indicates either severe disruption of brainstem tegmental systems (midbrain or pons) or a profound overdose of sedative, anesthetic, or anticonvulsant drugs.

Doll's eyes:

- Definition: When the head is turned, the eyes keep "looking" in the initial direction (eyes do not follow the movement of the head). Doll's eyes in a comatose person indicates that the brainstem is intact. Absent doll's eyes is a poor prognostic sign. Generally, doll's eyes are preserved in early metabolic coma. The exceptions are metabolic comas due to barbiturates and phenytoin.
- Testing for doll's eyes, which requires moving the head, should be done only after C-spine injury has been ruled out.

Reduction or absence of spontaneous blinking and loss of corneal reflexes are signs of deepening coma.

Scans and Lab Work for Coma

Quickly obtain a CT or MRI of the brain in order to narrow the differential, especially when the cause is unclear.

Check CBC, electrolytes, BUN, creatinine, glucose, ABG, urinalysis, and a toxicology screen for illicit drugs.

Other tests, such as an EEG, are helpful in identifying nonconvulsive status epilepticus, especially when there is a prior history of seizures. In one series of comatose patients in whom the cause was unknown, 8% were found by EEG to be in nonconvulsive status epilepticus.

Finally, you may need to do cerebrospinal fluid examination (including the usual bacterial and viral tests) if you suspect meningitis or encephalitis.

Evaluation of Findings

Supratentorial coma is due to an injury of the hemisphere(s).

There are 2 mechanisms:

1) Lateral (uncal) herniation: An expanding mass lesion (tumor, stroke, hemorrhage) forces the uncus through the middle opening in the tentorium. This puts pressure on the brainstem and, therefore, the RAS. Because of the course of the 3rd cranial nerve, the herniating uncus compresses this nerve, causing an enlarged pupil ipsilateral to the supratentorial lesion.

2) Central herniation: Injury to the thalamus (such as hemorrhage) results in diminished consciousness very early in its course. Later, the pupils are in mid-position and become fixed. As the herniation continues, the course begins to merge with that of uncal herniation. In other words, central and uncal herniation syndromes can be differentiated early on, but, later, their courses merge.

Note, however, that on CT scan of the brain, it is horizontal shift of the pineal body that correlates with consciousness level rather than transtentorial herniation:

Pineal Shift on CT	Consciousness Level
0–3 mm	Alert
3–4 mm	Drowsy
6–8 mm	Stupor
8–13 mm	Coma

Infratentorial coma is due to an injury that causes destruction or compression of the brainstem. Signs of infratentorial herniation include bilateral reactive pinpoint pupils (due to pontine involvement) and respiratory abnormalities, including cluster breathing, apneusis (deep gasping), and ataxic breathing. There are 3 possible causes:

1) Basilar artery occlusion with pontine infarction
2) Cerebellar infarction or hemorrhage
3) Posterior fossa neoplasms

Expansion of the contents of the posterior fossa forces the contents of this compartment in 1 of 2 directions: up (upward herniation) or down (downward herniation).

Quick Quiz

- What is the significance of doll's eyes?
- What pupil finding is associated with uncal herniation?
- What is the presentation of locked-in syndrome?
- What is the definition of persistent vegetative state?
- What is akinetic mutism vs. catatonia?

Upward herniation pushes the posterior fossa contents up under the tentorium, compressing the brainstem. Downward herniation forces the cerebellar tonsils down through the foramen magnum, compressing the medulla.

Metabolic coma has many causes, including ischemia, hypoxia, hypoglycemia, thiamine deficiency (Wernicke's encephalopathy), organ disease (lung, liver, kidney), and drugs. Early in metabolic encephalopathy, patients have changes in respiratory pattern and mentation. The pupils are typically reactive until the terminal stages. Exceptions include anticholinergic toxicity, which causes fixed dilated pupils, and severe barbiturate intoxication. In addition, both hypothermia and anoxia/ischemia can cause fixed pupils of varying size. Anoxic-fixed pupillary dilatation lasting more than a few minutes implies severe and usually irreversible brain damage.

CONDITIONS THAT MIMIC COMA

LOCKED-IN SYNDROME

The locked-in syndrome is rare and most often caused by a lesion of the ventral pons as a result of basilar artery occlusion. The lesion typically spares the somatosensory pathways and the ascending RAS responsible for arousal and wakefulness, as well as midbrain structures that allow the eyelids to be raised. Thus, the lesion interrupts the corticobulbar and corticospinal pathways, depriving the patient of speech and the capacity to respond except by vertical gaze and blinking. Persons with locked-in syndrome are awake and aware of the surrounding environment but may have only the ability to control eye movements. Typically, they can communicate only by using eye blinks and vertical eye movements. (The efferent abducens nerve fibers controlling horizontal eye movements are commonly destroyed.) Because the cerebral cortex is spared, an EEG is normal. Some patients can recover some function, so treatment should be multi-disciplinary and should include physical and speech therapy, pulmonary rehab, and help with swallowing.

VEGETATIVE STATE

Vegetative state results from severe bilateral cerebral dysfunction, often following a period of coma. Vegetative state is often caused by anoxic brain damage (e.g., after MI) and may be the terminal phase of progressive cortical degenerative processes such as Alzheimer and Creutzfeldt-Jakob diseases.

These patients typically have normal sleep-wake cycles but no discernible cognitive function. Respiration can quicken in response to stimulation, and you may see certain automatisms such as swallowing, bruxism, grimacing, grunting, and moaning. There is loss of sphincter control. EEG abnormalities include low-amplitude delta-frequency background activity, burst suppression, widespread alpha and theta activity, an alpha coma pattern, and sleep spindles. Stimulating the patient causes minimal if any change in background EEG activity.

Neuropathology shows cortical laminar necrosis, which is often extensive, with a relative or complete sparing of brainstem structures (including the RAS).

Comatose patients who enter into vegetative states may recover or progress to death—normally within 2 weeks. Vegetative state that persists more than 3 months is called persistent vegetative state. Patients who do not recover after 3 months are unlikely to recover. Generally within 5 years, demise occurs from pneumonia, urosepsis, or sudden death.

AKINETIC MUTISM

Patients with akinetic mutism are profoundly apathetic, although they register most of what is happening around them. They may speak normally and relate events from the recent and distant past. This state is caused by bilateral lesions generally of the anterior parts of the frontal lobes, leaving intact the motor and sensory pathways.

CATATONIA

Catatonia is a state of stupor and of neurogenic motor immobility associated with psychiatric states such as schizophrenia, depression, PTSD, and drug abuse. Patients with catatonia are unresponsive, although they preserve oculocephalic responses (doll's eyes). Some patients display a waxy flexibility of passive limb movement and hold seemingly uncomfortable limb postures for long periods (catalepsy). Peculiar motor mannerisms or repetitive motions, seen in a number of these patients, can give the impression of seizures. There are no signs of structural brain disease. The EEG is typically normal, although it shows diffuse slowing with malignant catatonia.

BRAIN DEATH

The central features of brain death are an irreversible absence of all cerebral functions and absence of all brainstem functions, including spontaneous respiration. This regularly results from catastrophic brain damage (e.g., trauma, cardiac arrest, cerebral hemorrhage), but you need to exclude reversible causes such as drug overdose.

Signs indicating the absence of cerebral function are the presence of deep coma along with the lack of spontaneous movement and motor and vocal responses to all visual, auditory, and cutaneous stimulation.

Diagnostic criteria for brain death:

1) Diagnosis of brain death requires knowledge of the preceding catastrophic event (clinical or imaging) responsible for the current status.
2) All possible metabolic confounders should be excluded (e.g., electrolytes abnormalities).
3) Toxins should be excluded.
4) Core temperature should be > 97° F.
5) SBP should be > 100 mmHg (pressors allowed).
6) Absence of brainstem function on exam, as indicated by following:
   - Loss of spontaneous eye movements
   - Mid-position of the eyes
   - Lack of oculocephalic (doll's eyes) and oculovestibular (caloric) responses
   - Presence of dilated or mid-position fixed pupils (not smaller than 3 mm)
   - Paralysis of bulbar musculature (no facial movement or gag, cough, corneal, or sucking reflexes)
   - Absence of motor and autonomic responses to noxious stimuli
   - Absence of spontaneous respiratory movements

After fulfilling all the above criteria an apnea test should be carried out.

Apnea test: Pre-oxygenate the patient with 100% O_2; pCO_2 should be normal. Then, disconnect the ventilator for 10 minutes and observe for respiration. A positive test occurs when there is no respiration even with a pCO_2 > 60 mmHg or > 20 mmHg from baseline. Repeat this test 6 hours later.

Diagnosis of brain death can be made only by fulfilling the above clinical criteria.

Tests that can support a diagnosis of brain death (but are not mandatory except in children) include:

- Evaluation of brain blood flow
  - Angiography
  - Transcranial Doppler
  - MRA/CT angiography
  - SPECT
- Electrophysiological tests
  - EEG
  - Evoked potentials

HEADACHE

OVERVIEW

The history and examination are crucial in diagnosing the type and etiology of headache, including the quality of pain (dull, sharp, throbbing, and constant), location, duration, exacerbating or ameliorating factors, and associated symptoms. Also important are the mode of onset of pain and variation over time. First, determine if the headache is primary or secondary.

According to the International Classification of Headache Disorders 3rd edition (2013) published by the International Headache Society, headaches can be classified as primary or secondary. For a detailed description, see: http://www.ihs-classification.org/_downloads/mixed/International-Headache-Classification-III-ICHD-III-2013-Beta.pdf

Primary headaches:

- Migraine
- Tension-type headache
- Cluster headache and other trigeminal autonomic cephalgias
- Other primary headaches
- Primary headaches tend to be chronic, recurrent, and without signs of neurologic disease.

Secondary headaches:

- Headache due to head and/or neck trauma, cranial hypertension, brain tumors
- Headache due to cranial or cervical vascular disorders (e.g., carotid dissection, giant cell arteritis)
- Temporal arteritis
- Headache due to nonvascular intracranial disorders (tumors, etc.)
- Headache due to a substance or its withdrawal (EtOH, caffeine)
- Headache due to infection (meningitis, encephalitis)
- Headache due to disorders of homeostasis (HTN, hyperviscosity)
- Headache of facial pain (cranium, neck, eyes, sinuses, teeth)
- Headache due to psychiatric disorders

MIGRAINE

Presentation

[Know.] Migraines are a common, largely familial disorder characterized by periodic, often unilateral, pulsatile (throbbing) headaches that begin in childhood, adolescence, or early adult life and diminish in frequency as patients get older. Migraines are more common in females. 90% of patients who present to emergency departments with recurrent headaches have migraines. These headaches are typically unilateral (~ 60%) but not consistently on the same side (unlike vascular headache secondary to arteriovenous malformation). They last several hours, typically 4–72 hours.

QuickQuiz

- How is brain death diagnosed? Is an EEG required?
- What is an apnea test, and when should it be repeated?
- Name some triggers of migraine headaches.
- What is the main difference between a complicated migraine and a migraine with aura?
- Which migraine patients should not receive a triptan drug?

They are considered episodic if < 15 episodes per month and chronic if > 15 episodes per month for 3 months. Less than 5% of episodic sufferers progress to chronic sufferers per annum.

Triggers include emotional stress, certain foods (e.g., chocolate, aged cheese, and other foods that are rich in tyramine), alcohol (particularly red wine or port), menstruation, exposure to glare or other strong sensory stimuli (including perfumes), and rapid changes in barometric pressure. In women, they often occur in the premenstrual period and can be worsened by oral contraceptives. Migraines are frequently associated with nausea, vomiting, sensitivity to smell, photophobia, and phonophobia. Movement of the head exacerbates the pain, while sleep and darkness may help lessen the pain.

Migraine with aura (previously called classic migraine) makes up 25% of all migraine headaches. It is preceded by an aura—most commonly visual symptoms, such as sparkling lights (scintillating scotomata) or jagged zigzag lines (fortification spectra) that move slowly across the visual fields for several minutes—and may leave scotomatous defects. Migraine auras last for 5–60 minutes and not longer!

Migraine without aura (previously called common migraine), occurs without an aura and is ~ 5x more common than migraine with aura.

Complicated migraine (rare) is associated with focal neurologic symptoms, including numbness and tingling of the lips, face, and hand (on one or both sides), arm or leg weakness, slight confusion, and/or dizziness. In any given patient, only a few of these phenomena are present, and they tend to be stereotyped with each attack. If symptoms spread from one part of the body to another or evolve over time, they do so relatively slowly, over several minutes (not seconds, as in seizures). Such symptoms last 5–15 minutes on average and are followed by unilateral headache. The neurologic deficits can be prolonged but are rarely permanent.

Basilar migraine affects the brainstem. Patients are typically young women or children with a family history of migraine.

Patients with basilar migraines may experience:

- visual phenomena that occupy both visual fields (temporary cortical blindness may occur),
- vertigo,
- dysarthria,
- staggering,
- incoordination of the limbs,
- diplopia ("seeing double"), and
- tingling. (Tingling may occur in both hands and feet and sometimes around both sides of the mouth.)

These symptoms last 10–30 minutes and are usually followed by an occipital headache. In exceptional cases, coma or transient quadriplegia may develop.

Acephalic migraine (migraine without headache) can present with abnormal transient neurologic dysfunction such as visual symptoms, focal sensory deficits, transient aphasia, or hemiparesis. This type frequently occurs with advancing age in patients who previously experienced migraines with or without aura.

Status migrainosus is characterized by multiple or virtually continuous headaches with persistent scalp tenderness, over 72 hours or longer.

Acute Treatment of Migraine

Acute treatment refers to any treatment that is given within the 1st hour of the headache. Acetaminophen, aspirin, and NSAIDs are effective in some patients, especially if the migraine is mild and infrequent. Next is the "triptans":

- Sumatriptan (Imitrex®)
- Zolmitriptan (Zomig®)
- Rizatriptan (Maxalt®)
- Naratriptan (Amerge®)
- Almotriptan (Axert®)
- Eletriptan (Relpax®)
- Frovatriptan (Frova®)

No head-to-head trials yet exist comparing the triptans; therefore, which to choose is based on a few features of the drugs:

- Rizatriptan works fastest. But know that concomitant use of propranolol requires that you adjust the rizatriptan dose downward (propranolol increases the levels).
- Sumatriptan has 3 methods of delivery (injection, intranasal, and oral).
- Combination tablet of sumatriptan + naproxen works synergistically and better than taking either agent as monotherapy.

Because of risk of inducing ischemia, do not use triptans for any of the following conditions:

- Complicated or basilar migraines
- Coronary heart disease (CHD) or Prinzmetal angina
- History of stroke
- Uncontrolled blood pressure
- Pregnancy

Also, do not combine triptans with monoamine oxidase inhibitors or use within 24 hours of ergot drugs.

Instead of the triptans, IV prochlorperazine or metoclopramide also is effective for termination of migraine in patients who present to the emergency department with vomiting. Diphenhydramine, 25 mg IV, helps prevent the unusual dystonic reaction.

Dihydroergotamine (DHE) can be effective in some patients, but it also must be avoided in patients with CHD, HTN, history of peripheral arterial disease, and liver or kidney disease. You can try narcotics, but their use should be restricted to 2 days per week. Oral or IV corticosteroids can be used to terminate status migrainosus.

Increased use of any medication, including triptans and NSAIDs, to treat frequent headaches can incite a rebound called "medication overuse headaches." Patients should be instructed not to take analgesics more than 10 days per month. If they need meds this often, then prescribe prophylactic treatment.

Prophylactic Treatment of Migraine

Migraine seems to be associated with an increased risk of ischemic stroke, especially in certain groups of women who have recurrent headaches with aura.

The American Heart Association/American Stroke Association 2014 Guidelines for the Prevention of Stroke in Women recommend prophylaxis for women with frequent migraines with aura if younger than 55 years and especially if they are taking oral contraceptives (OCPs). This guideline also recommends aggressive smoking cessation efforts in women with migraine with aura.

Generally avoid OCPs in women who have migraine with aura (increased risk of stroke). For other patients, the frequency of headache determines whether prophylaxis is needed; normally, the threshold is > 2–3 headaches per month. There is usually a lag of 2–4 weeks between the start of prophylaxis and its effect.

The major categories of migraine prophylaxis agents:

- Beta-blockers: Propranolol and timolol are FDA-approved for migraine, but atenolol, metoprolol, and nadolol are also used; not recommended in patients > 60 years and/or smokers.
- Tricyclic antidepressants: amitriptyline; side effects = oversedation, dry mouth, palpitations, orthostasis, blurry vision, weight gain, constipation, and short-term memory impairment or confusion—especially in the elderly, or those with baseline cognitive impairment.
- Tetracyclic antidepressants, also known as noradrenergic and specific serotonergic antidepressants (NaSSA) (e.g., mirtazapine), and mixed serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine, duloxetine).
- Anticonvulsants (valproate, topiramate), which are sometimes used off-label. Topiramate can cause kidney stones and thus is contraindicated in patients with kidney stones.
- Calcium channel blockers (verapamil, nimodipine) may develop tolerance.
- ACE inhibitors and ARBs (lisinopril and candesartan).
- NSAIDs.
- SSRIs: There are not enough data for SSRIs; they may even cause headaches.
- Botulinum toxin injection (Botox®) was approved by the FDA in 2010 for refractory chronic migraine (i.e., migraine occurring 15 or more days per month with headaches lasting 4 hours per day or longer). Thirty-one injections are delivered into 7 specific head and neck sites. The treatment usually needs to be repeated every 12 weeks, on average.

Definitely use prophylactic agents to treat complicated and basilar migraines. Relaxation techniques also may be helpful for patients to prevent headaches.

CLUSTER HEADACHE

Cluster headache is a distinct syndrome that frequently responds to treatment with oxygen. The term "cluster" is derived from the periodicity of the headaches: They can occur up to several times/day for a few weeks before remitting. Cluster headache becomes chronic in 10% of patients. Occasionally, this headache is referred to as the "suicide headache," because the associated pain is so intense that some patients have committed suicide when they were unable to get relief from a cluster episode.

Cluster headaches are more common in men (5:1). They tend to occur in the 20–50 year age group. 70% of patients find that alcohol triggers their headache.

The daily attacks may occur at the same hour each day (in 50% of patients). The pain is unilateral, severe (described as an "ice-pick" or "hot poker"), and peri- or retro-orbital. It peaks quickly in 5–10 minutes and resolves in an hour or two.

Another characteristic feature is nightly recurrence, about 1 to 2 hours after the onset of sleep or several times during the night. The cluster headache has been called the "alarm clock headache" because it recurs regularly each night for 6 to 12 weeks, followed thereafter by complete freedom for many months or even years.

Associated vasomotor phenomena include ipsilateral blocked nostril, rhinorrhea, lacrimation, miosis, and flush and edema of the cheek that last about 45 minutes.

Cluster patients tend to be restless during attacks, as opposed to most migraine sufferers who prefer a dark, quiet room and stillness.

Treatment: The best acute treatment is oxygen. Inhalation of oxygen at 6 L/min x 15 minutes is commonly rapidly abortive, acting to inhibit neuronal activation in the

Quick Quiz

- Which migraine prophylactic drug causes kidney stones?
- Are cluster headaches more common in men or women?
- What are the clinical features of cluster headache?
- How do you treat cluster headache?
- What agent is 1st line to prevent cluster headaches?
- What is the most common variety of headache?

trigeminocervical complex. However, this is not always practical or available. Subcutaneous and intranasal triptans are effective and can be combined with oxygen; but remember, the triptans should not be used in patients with a history of or strong risk factors for CHD and stroke. For patients who don't get better with O_2 and can't take triptans, octreotide and intranasal lidocaine are options.

Once a patient experiences the 1st of what will become a cluster episode, prophylactic treatment can be instituted. Verapamil is the drug of choice (outpatient oral titration up to 480 mg), but monitor the patient's pulse and ECG for bradycardia and heart block when titrating higher than 240 mg. Other drugs sometimes used include lithium, methylsergide, prednisone, and topiramate. The corticosteroids are used as acute drugs while waiting for verapamil to work. Taper off the meds once the cluster is over.

TENSION HEADACHE

Tension headache, the most common variety of headache, is characterized by pain that is chronic, bilateral, constant, non-throbbing, "squeezing," and devoid of migrainous or cluster features. It can be intermittent or chronic. Unlike most other headaches, it can be present throughout the day for long periods of time. The onset is slow with gradual increment in intensity typically at the end of the day. Sleep is normally undisturbed, but headache returns upon awakening. It is more common in women. A third of patients with chronic tension headaches have symptoms of depression.

Treatment: Aspirin, acetaminophen, or NSAIDs can be used for acute attacks.

Preventive medication should be considered when attacks occur more than 2 days per week—this should help prevent medication overuse, which can predispose to chronic headache. Limiting treatment to 9 days per month (2 doses of meds/day) helps prevent this complication. Effective prophylactic drugs include amitriptyline and other tricyclics, tetracyclics (e.g., serotonin receptor blockers [mirtazapine, venlafaxine—see migraine prophylaxis on page 11-6]), and gabapentin. Not SSRIs. Relaxation, biofeedback, and behavioral therapy are helpful in dealing with the tension that brings about the headaches.

BENIGN SEXUAL HEADACHE

Also called "coital headache," benign sexual headache occurs more often in men than women (4:1). The headache occurs either as a tension-type headache as sexual excitement increases or as a severe, throbbing headache at the time of orgasm. These headaches can persist for several minutes or hours; they are benign. If the headache does not resolve after 2 hours or is accompanied by neck stiffness, vomiting, and/or neuro deficits, rule out an underlying AV malformation with or without subarachnoid hemorrhage. Evaluate with urgent neuroimaging. Treatment with NSAIDs before sexual activity may prevent the headache.

POST-TRAUMATIC HEADACHE

Post-traumatic or post-concussion headache can occur even after a minor head injury. It can be vascular, like migraine; however, some have proposed that the headache is due to abnormal neurotransmission within the brain. Accompanying symptoms include dizziness, fatigue, insomnia, nervousness, irritability, and inability to concentrate. Symptomatic treatment is usually effective, and the headache often spontaneously remits. Patient reassurance is important.

GIANT CELL ARTERITIS

Giant cell (temporal) arteritis usually occurs in patients > 55 years old. History is typically a recent onset of headache. Jaw claudication, fatigue, weight loss, and low-grade fever may be associated symptoms. Up to 50% of patients have a history of polymyalgia rheumatica. Do not miss this diagnosis! If untreated, ischemic optic neuropathy can cause irreversible vision loss. Diplopia occurs in 10–15% of patients. Physical exam may show temporal artery tenderness. The erythrocyte sedimentation rate is commonly very elevated, but C-reactive protein is a more sensitive marker of inflammation. Do a temporal artery biopsy if the diagnosis is suspected. Yield of bilateral artery biopsy (~ 2 inches of tissue) in expert centers is about 85%. For the Boards, if ESR and CRP are normal, it is not GCA. More in Rheumatology, Book 3.

IDIOPATHIC INTRACRANIAL HYPERTENSION / PSEUDOTUMOR CEREBRI

Idiopathic intracranial hypertension ([IIH]; also called pseudotumor cerebri) is a set of signs and symptoms—headaches, papilledema, and loss of vision—caused by increased intracranial pressure. It ordinarily occurs in obese, premenopausal women (90%) and can occur during pregnancy. It rarely occurs in children or in men.

Obesity is strongly correlated (90–95% of patients) and causal; with the increasing obesity of the U.S. population, the incidence of IIH is also increasing.

Drugs that are associated with IIH include vitamin A (especially in the form of isotretinoin, used for the treatment of severe acne), tetracycline, and corticosteroids; but the condition may also be precipitated by steroid withdrawal.

Severe, irreversible vision loss is the major morbidity. It occurs in > 6% of patients and is twice as common in men as in women.

The cardinal symptom of IIH is a morning headache described as dull or as a feeling of pressure (90%) made worse by coughing or straining. There is almost always (90–100%) a peripheral visual field loss accompanied by blind spots that may be noticeable only with formal visual field testing. Pulse-synchronous tinnitus (60%) may be present.

Other, less-frequent complaints are blurred vision, dizziness, minimal horizontal diplopia (38%) from 6th nerve paresis, transient visual obscurations that often coincide with the peak intensity of the headache, or mild numbness of the face on one side.

On exam, papilledema is a hallmark finding. 6th nerve palsy may be obvious either unilaterally or bilaterally. CT/MRI is typically normal, with absence of deformity, displacement, or obstruction of the ventricular system—but may show "slit-like" ventricles. The CSF pressure is elevated, usually in the range of 250–450 mm H_2O. (Normal CSF pressure is generally < 200 mm H_2O.)

Treatment of IIH includes a low-sodium weight-reducing diet, symptomatic treatment for headaches, carbonic anhydrase inhibitors (acetazolamide), and prevention of vision loss.

Repeat lumbar punctures, with drainage of sufficient fluid to maintain CSF pressure < 200 mm H_2O, may be helpful in ~ 25%.

Prednisone works acutely but is not recommended for chronic cases of IIH because of side effects, not the least of which is increasing intracranial pressure. Unilateral optic nerve sheath fenestration may preserve vision in the acute setting.

In patients whose headaches are unresponsive to medications and weight reduction, lumbar-peritoneal shunt may have considerable success.

THALAMIC PAIN SYNDROME

This syndrome causes refractory unilateral pain, which can affect the trunk, as well as the arm and leg. Thalamic pain syndrome can occur weeks to years after a thalamic infarct (with hemisensory loss).

DELIRIUM

Delirium is an acute, and often transient, onset of altered mental status, typically within hours to days. It is most commonly seen in hospitalized elderly patients in the ICU. The diagnosis is based on the clinical hallmarks of decreased attention span and varying states of confusion. Treatment is aimed at identifying any underlying cause and supportive care. Delirium is also discussed in General Internal Medicine, Book 5, Geriatrics.

DEMENTIA

DEFINITION

Dementia is defined as a chronic cognitive decline with or without behavioral impairment that:

- Is progressive
- Interferes with normal daily functioning
- Is not due to delirium or an underlying psychiatric disorder

Note how this definition contrasts with encephalopathy, which causes altered states of consciousness—from delirium to stupor.

WORKUP

Evaluating Domains of Function

According to multiple guidelines by the Institute of Aging and the Alzheimer's Association, dementia is diagnosed only after completion of the following 3 tasks, which evaluate specific "domains" of function (discussed next):

1) The health care professional performs a thorough H&P that includes obtaining history from the patient and an additional informant (because history from a potentially demented patient is not always reliable).
2) Neuropsychiatric testing (to exclude underlying psychiatric diagnoses).
3) Objective cognitive assessment using a validated tool (e.g., the Montreal Cognitive Assessment, the Folstein Mini-Mental State Exam).

Diagnosis of Dementia

Dementia is diagnosed when abnormalities exist in 2 or more of the following 5 domains, and when the abnormalities also are progressive and interfere with daily functioning:

1) **Memory** = acquiring and/or remembering new information: Do they ask repetitive questions, lose items, or get lost?
2) **Executive function** = reasoning and performing complex tasks: Do they understand appropriate danger? Can they perform their ADLs, such as grocery shopping?

QuickQuiz

- Name some risk factors that are associated with IIH.
- What is the clinical presentation of IIH?
- What is delirium?
- What is the current definition of "dementia"?
- Which 5 domains may be impaired in patients with dementia?
- What is the definition of "mild cognitive impairment"?
- What percentage of patients with MCI progress to dementia annually?
- What is the clinical triad in normal pressure hydrocephalus?

3) **Perception** = assessing visuospatial orientation: Do they recognize faces and objects? Can they dress themselves?
4) **Language** = comprehension and speaking appropriate language: Do they have problems recalling common words without hesitations?
5) **Behavior** = behaving normally and appropriately: Is there undue agitation, apathy, loss of empathy, compulsive behavior?

Psychosis that is refractory to treatment is a common feature of advanced dementia.

Mild Cognitive Impairment

When only 1 or more of the domains is in decline, but the impairment does not significantly impact daily functioning, the diagnosis is "mild cognitive impairment" (MCI).

MCI can be either amnestic or non-amnestic. Amnestic MCI is most common. Not all patients with MCI deteriorate into dementia. MCI progresses to dementia at a rate of about 5–10% per year. Such progression is more likely in patients with a family history of Alzheimer disease. Patients with amnestic MCI have memory impairment that does not significantly impact daily living, and general cognition is intact. Of those who do deteriorate to Alzheimer disease, more often they are the patients with amnestic MCI.

Patients with non-amnestic MCI have impairment in 1 or more of the other domains (executive function, perception, words, or behavior), but daily living is not impacted.

Reversible Causes

In evaluating dementia, exclude the following treatable causes of impaired cognition:

- Medications
- Vitamin B_{12} deficiency (may have associated polyneuropathy/myelopathy)
- Heavy metal poisoning (arsenic, mercury, and lead)
- Hypothyroidism
- Diabetes
- Chronic subdural hematomas (consider especially in alcoholics, in patients on anticoagulants, and in elderly patients with a history of falls)
- Normal pressure hydrocephalus
- Tumors, especially involving the frontal lobes
- Infection and inflammation:
  - AIDS
  - Neurosyphilis
  - Neurosarcoidosis
  - Chronic meningitis
  - Lupus cerebritis
  - Vasculitis

CAUSES OF DEMENTIA

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus (NPH) is a potentially treatable cause of dementia. It is characterized radiologically by enlargement of the ventricles without obstruction of the aqueduct (i.e., a "communicating hydrocephalus") and no cerebral atrophy. Significant central atrophy (with or without cortical atrophy) may result in hydrocephalus "ex vacuo."

NPH often occurs after head trauma, meningitis, or subarachnoid hemorrhage—and a history of 1 of these premorbid conditions appears to be the best predictor of a beneficial response to shunting (see below). One thought about how this develops is that there is obstruction of the outflow of cerebrospinal fluid at the level of the arachnoid granulations. However, the intracranial pressure is normal, there is no papilledema, and the person has no headache.

NPH causes the classic triad of:

1) a gradually worsening dementia,
2) gait ataxia/apraxia (a "magnetic" gait, with the feet apparently glued to the floor), and
3) urinary incontinence.

Often, the gait problems and incontinence precede the dementia. Patients may present with frequent falls due to gait instability.

Differentiate NPH from ventricular dilatation caused by diffuse white matter changes (Binswanger disease, see page 11-11), which is more common in patients with hypertension or diabetes mellitus. Note that it may present with the same clinical triad as NPH.

Treatment: In most cases of NPH, the CSF opening pressure is above 155 mm H_2O, and the cell count is normal. The treatment is ventriculoperitoneal or ventriculoatrial shunt. Certain tests may help to identify patients who are most likely to respond to shunting. These include clinical response to lumbar puncture (LP), isotope cysternography, and dynamic MRI, which measures the direction of CSF flow (but none of these tests is universally reliable). The most consistent improvement is attained in patients with an identified cause such as subarachnoid hemorrhage, chronic meningitis, or head trauma.

Alzheimer Disease

AD Diagnosis

Alzheimer disease (AD) is the most common cause of dementia after age 60. 1st degree relatives have a 4x normal increased risk of developing it.

According to 2011 guidelines, AD is diagnosed when the illness is insidious, progressive, and marked by impairments in 2 or more domains (memory, executive functioning, perception, words, and behavior), such that there is significant impairment in normal daily functioning. As with MCI (page 11-9), the amnestic presentation of AD is the most common. Patients with Alzheimer's have a normal LP.

Initial signs of AD commonly reflect hippocampal dysfunction, with poor immediate recall and short-term memory. Impairment of naming may also be an early sign. As the disease progresses, impairments emerge in visuospatial and executive domains, reflecting dysfunction in the parietal and frontal lobes, respectively. Changes in environment (such as vacations or hospital stays) may be disorienting, and the patient may become lost on walks or while driving.

Note the contrast in the presentation of AD with the presentation of Lewy body and frontotemporal dementias and sporadic Creutzfeldt-Jakob disease, which are seen in younger patients and have a more rapid and volatile course (more in the next section).

Also in contrast, multi-infarct dementia presents with stepwise deterioration that is often accompanied by motor or sensory impairment related to the areas of stroke.

Do not use any of the following for diagnosis of AD: MRI scans that show disproportionate atrophy, PET scans demonstrating amyloid deposition or decreased tracer uptake, and CSF tau measurements. These biomarkers are not specific enough yet, and abnormalities sometimes are seen in patients with normal cognition or MCI only.

Additionally, do not diagnose AD as a cause of dementia if the patient:

- has a history of significant cerebrovascular disease,
- has clinical features of Lewy body or frontotemporal dementia,
- has evidence of another psychiatric or neurologic illness, or
- takes a medication that can cause cognitive impairment.

These must be ruled out as causes of the dementia symptoms. In an elderly patient presenting with dementia without a movement disorder, the main diagnoses to consider are Alzheimer disease, vascular dementia, and mixed dementia (with both neurodegenerative and vascular components).

AD Treatment

The 1st line treatment for Alzheimer's is cholinesterase inhibitors (CIs):

- Donepezil (Aricept®)
- Rivastigmine (Exelon®)
- Galantamine (Razadyne®)

Note: Tacrine (Cognex®) causes liver toxicity and is no longer used.

Additive drug treatment includes the N-methyl-d-aspartate receptor antagonist memantine (Namenda®).

The combination of CI + memantine appears to be better than CI alone, especially for advanced AD.

The CIs produce a small improvement in cognition and, sometimes, in neuropsychiatric instability. Data are conflicting on their long-term effects. Not every patient receives benefit. Note that these drugs are for dementia only and should not be used to treat minor cognitive impairment (MCI). Best results with CIs are achieved in mild-to-moderate Alzheimer disease, but other types of dementia (e.g., multi-infarct and Lewy body dementia) sometimes also improve.

Dose escalations for each of these medications must be carried out over 4–6 weeks to minimize side effects. The main side effects are anorexia, nausea, and occasionally diarrhea or bradycardia (cholinergic symptoms). Rivastigmine is available as a patch that has fewer GI side effects and is useful in demented patients who will not swallow medications.

The neuropsychiatric instability of late-stage AD is common and difficult to treat. Mild-to-moderate depression in the early stages may respond to SSRIs, trazodone, or CIs, but definitely avoid tricyclic antidepressants because of the anticholinergic symptoms, particularly short-term memory impairment and confusion. Atypical antipsychotics (olanzapine, quetiapine, risperidone, clozapine) have been used to treat the agitation, insomnia, delusions, aggression, and wandering, but in 2011, the FDA published an advisory that these drugs are associated with increased mortality in the elderly with dementia (any cause). They should be used only in the most extreme cases of psychosis.

- How is AD diagnosed?
- How are CSF tau measurements used in the diagnosis of AD?
- What drug is used with a CI for the treatment of advanced AD?
- What is a potential complication from the use of atypical antipsychotics in elderly patients with dementia?
- Compare and contrast the features of normal pressure hydrocephalus, Alzheimer disease, and vascular dementia.
- How does the clinical presentation of frontotemporal dementia differ from that of Alzheimer disease?
- Is CJD insidious or rapid?

Vascular Dementia

Overview

Dementia associated with cerebrovascular disease can be divided into 2 general categories: multi-infarct dementia and diffuse white matter disease (Binswanger disease).

Multi-infarct Dementia

Multi-infarct dementia is the term used for the chronic cognitive deficits that can occur in patients who have had several strokes. The strokes may be large or small but usually involve several different brain regions. The occurrence of dementia depends partly on the total volume of damaged cortex but is also more common with left hemisphere lesions.

Multi-infarct dementias generally have prominent motor, reflex, visual, and gait abnormalities, but they typically do not involve difficulty in naming of objects, as associated with Alzheimer disease. Another difference is the clinical course of symptoms. Multi-infarct dementia has an abrupt onset with stepwise deterioration of mental function, with more prominent fluctuations of cognition. By contrast, Alzheimer's has a slow, steady progression.

Diffuse White Matter Disease

Chronic hypertension is the most common cause of dementia due to lacunar infarcts and diffuse white matter changes that are visible on MRI. The changes result from chronic ischemia mediated by occlusive disease of small, penetrating cerebral arteries and arterioles. Diabetes is also a common cause of this condition.

Early symptoms include mild confusion and impairments in memory, perception, and executive functions. Marked difficulties in judgment and orientation develop later, along with dependence on others for activities of daily living. Neuropsychiatric symptoms (apathy, anxiety, psychosis, euphoria, depression, aggression) also develop as the deep white matter changes and infarcts accumulate. Pyramidal and cerebellar signs may be seen. With advanced disease, urinary incontinence and dysarthria with or without other pseudobulbar features (e.g., dysphagia, emotional lability) are frequent.

Frontotemporal Dementia

Frontotemporal dementia ([FTD]; previously Pick disease) is quite similar in presentation and course to Alzheimer disease, but it is characterized by a more rapid and significant change in personality and behavior, often with disinhibition, language deficits, or both. The onset is in the 5th to 6th decades (relatively young, compared to Alzheimer's), and the incidence in males exceeds females.

Common behavioral features include apathy, disinhibition, weight gain, food fetishes, compulsions, and emotional distance or loss of empathy.

Cognitive testing typically reveals spared memory but impaired planning, judgment, or language. Patients often show an absence of insight into their condition.

The naming of FTD subtypes is evolving based on their primary manifestations; e.g., behavioral variant vs. progressive nonfluent vs. semantic. Patients with FTD have more focal atrophy of the frontal and temporal lobes on CT or MRI scan, compared with the diffuse atrophy of Alzheimer's. However, histology is the only sure way to differentiate the two, typically at autopsy.

Currently, there are no primary pharmacologic treatments for the frontotemporal dementias. Trazodone has been shown to result in some behavioral improvement, mainly in irritability, agitation, depressive symptoms, and eating disturbances.

Creutzfeldt-Jakob Disease

Creutzfeldt-Jakob disease (CJD) is one of the very rare (1 per million people) prion diseases. It's mainly an infectious illness. Based on observations of causes, CJD is divided into sporadic (sCJD, most common, 95%), familial (about 5%), iatrogenic (iCJD), and variant (vCJD). Usually, sCJD presents around ages 55–65, and we have no idea what causes it. When you see CJD in younger patients, think either iCJD or vCJD. vCJD is believed (but not definitively proven) to be caused by the prion that causes "mad cow disease" (bovine spongiform encephalopathy) in cattle. It appears that the prion jumped species and now infects humans. iCJD is caused by receipt of infected human tissues, hormones (growth hormone, gonadotropins, dural grafts, corneal or liver transplants), or exposure to contaminated surgical instruments. Familial CJD has genetic associations.

Regardless of cause, CJD develops as a rapidly progressive dementia (weeks as opposed to years) with characteristic startle myoclonus (response to loud noises

or startle). The early stages of the neurologic disease are characterized by changes in behavior, emotional response, and intellectual function, often followed by ataxia and visual distortions, confusion, hallucinations, delusions, and agitation. Dementia and muteness quickly follow the early symptoms. Younger patients with vCJD tend to have dementia with predominantly psychotic features. The disease involves the cerebral cortex, basal ganglia, and spinal cord.

The diagnostic gold standard is brain biopsy. Supportive studies include:

- T1/T2 MRI with diffusion weighted images and FLAIR sequences (helps also to differentiate sCJD from vCJD)
- EEG (characteristic pattern of "periodic sharp waves complexes" on a diffusely slowed background)
- 14-3-3 protein in an otherwise bland CSF (Only the National Prion Disease Pathological Surveillance Lab does this test, at Case Western, and sensitivity/specificity is < 80%.)

Creutzfeldt-Jakob disease is fatal in < 1 year in > 90%.

Parkinson Disease Dementia (PDD)

Parkinson disease (PD) is caused by a loss of dopaminergic neurons in the substantia nigra. (See the later discussion under Movement Disorders on page 11-44.)

Dementia in PD (PDD) is common, eventually affecting as many as 80% of patients. Its frequency increases with aging and, in contrast to Alzheimer disease, primarily affects executive functions and attention in its earlier stages, with relative sparing of language, memory, and calculations until later in the disease course. When dementia precedes or develops within 1 year after the onset of motor dysfunction, it is referred to as dementia with Lewy bodies (DLB). Neuropathology shows Lewy bodies mixed with amyloid plaques and neurofibrillary tangles characteristic of Alzheimer disease (Image 11-1). Lewy bodies are spherical eosinophilic inclusions within the neuron (Image 11-2).

The Lewy body elements seem to correlate most with the degree of dementia, so Parkinson disease dementia is frequently called DLB. DLB sometimes occurs without preceding Parkinson disease—but is otherwise the identical disease.

The core clinical features of PDD/DLB (besides dementia) are spontaneous motor features of parkinsonism; recurrent, vivid visual hallucinations; and prominent fluctuations of attention and cognition. Other supportive clinical features include hallucinations in other modalities (e.g., tactile, olfactory, or auditory), delusions, REM sleep behavior disorder (dream enactment), unexplained falls or loss of consciousness, and depression.

Both the dementia and psychosis may be at least partially responsive to acetylcholinesterase inhibitors and memantine. Patients with DLB have poor responses to the older antipsychotic drugs that block the D_2 dopamine receptor, including haloperidol and chlorpromazine—and even to some of the newer "atypical" neuroleptics. They have a dramatic and severe worsening of symptoms with extreme sedation, increased confusion, and postural instability with falls. However, clozapine, which spares the D_2 dopamine receptor, can be helpful, with inconsistent benefit from quetiapine. As mentioned in the section on Alzheimer's, antipsychotic drugs are under an FDA safety advisory because they are associated with an increased risk of death when used in elderly patients with dementia, and especially so in those with DLB. All antipsychotics other than clozapine and quetiapine should be avoided in DLB.

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) has its onset typically in the 6th decade, with clinical features such as difficulty in balance, abrupt falls, visual and ocular disturbances, slurred speech, dysphagia, and personality change, with prominent apathy. Difficulty in voluntary vertical movement of the eyes, consistently downward initially but sometimes upward, and later paresis of voluntary saccades in all directions are characteristic. Patients can also have apraxia of eyelid opening (resembling blepharospasm) and eyelid closing. Cognitive slowing and dementia are prominent features. Buzzwords for PSP: dementia with gaze palsy and falls.

Huntington Disease

Huntington disease (HD) causes both a dementia and a movement disorder. (More movement disorders are discussed starting on page 11-44.) The gene responsible for HD is the *HTT* gene on chromosome 4p, which codes for a mutant huntingtin protein that is probably toxic. (Note: The protein is spelled with an **i**, while the disease is spelled with an **o**.) It is inherited in an autosomal dominant fashion with complete penetrance. Problems typically begin in persons in their late 30s.

HD causes dementia, chorea, and psychiatric disturbances, including personality changes, depression, and psychosis. Memory is relatively spared. Chorea is usually the heralding symptom. The emotional disturbances and changes in personality may be so severe as to cause psychosis with persecutory delusions or hallucinations.

Disease is progressive with death (typically from pneumonia) within 30 years after symptoms begin. Diagnosis is made in the setting of positive family history, clinical features, and genetic testing demonstrating the *HTT* gene.

Atrophy of the caudate nuclei on CT or MRI ("boxcar" ventricles) is characteristic and correlates with deterioration in cognition. No curative medication exists, and the disease is invariably fatal. Tetrabenazine has been approved and is effective in controlling mild chorea. Side effects are significant and include depression, sedation, and bradykinesia. Other symptoms can

QuickQuiz

- How do you diagnose Creutzfeldt-Jakob disease?
- Compare and contrast DLB and PSP with Parkinson disease.
- What is the problem with using antipsychotic drugs to treat patients with Parkinson dementia?
- What are the clinical features of Huntington disease?
- Name some features that distinguish depression from dementia.
- Name the maneuvers frequently employed to treat BPV.

be ameliorated with antipsychotics (neuroleptics), benzodiazepines (e.g., clonazepam), and antidepressants.

Genetic counseling is available for family members but is performed only ~ 15% of the time. There are no guidelines that specifically recommend screening because of the gravity of the diagnosis, if the test is positive.

AIDS

AIDS is the most common cause of dementia in younger patients. Dementia affects half of all AIDS patients not on antiretroviral therapy (ART). The manifestations can be mild (minor cognitive-motor disorder) to severe (HIV-associated dementia). Impairment is related to the degree and duration of immunosuppression. Controlling the virus in a patient who has had AIDS for a prolonged period, with a low CD4 count, often does not reverse dementia.

HIV-associated dementia (HAD) is characterized by cognitive impairment, movement disorders, and depression. It starts with small comprehension problems and anhedonia, accompanied by tremor and gait abnormalities. Over time, patients develop slower movements with substantial cognitive impairment. Exclude opportunistic infections of the CNS as part of the workup.

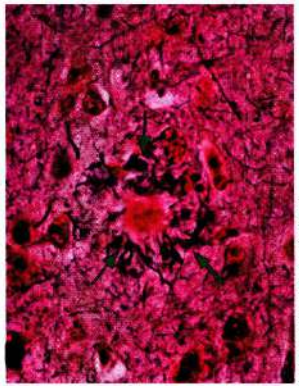

Image 11-1: Senile plaques with amyloid core

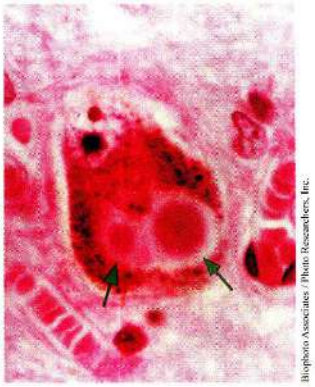

Image 11-2: Parkinson disease with Lewy bodies

Treatment includes treating the HIV with ART, focusing specifically on designing a regimen of medications that enter the CNS at higher levels (although this has not been shown to cause neurologic improvement). Associated depression should also be treated. More on treatment of AIDS in Infectious Disease, Book 1. Also, see more on HIV-associated dementia (HAD) on page 11-19.

Depression

Some patients with major depression present with significant cognitive dysfunction, known as depressive "pseudo-dementia." One differentiating feature is that frontal lobe release signs (e.g., grasp, suck, rooting, and palmomental reflexes) are common in patients with dementia, particularly if moderate or advanced, but they are not seen in isolated depression. In addition, immediate recall is commonly poor in depression, due to attentional dysfunction, but good in dementia.

Depression can be reactive or endogenous. Symptoms are the same for both. In endogenous depression, patients, as expected, may have an abnormal response to the dexamethasone suppression test in which the cortisol is initially suppressed, but the duration of suppression is shortened (normal is > 24 hours).

DIZZINESS

SIGNS AND SYMPTOMS

When the term "dizziness" is used by a patient, it is necessary to differentiate among the following:

- Vertigo = a sense of spinning or swaying.
- Lightheadedness = presyncope ("I feel like I'm going to pass out").
- Imbalance = unsteadiness.
- Vague = not one of the 3 above. It may be hard for the affected person to describe.

When we discuss dizziness here, we are considering only vertigo.

CAUSES OF VERTIGO

Benign Positional Vertigo

Benign positional vertigo (BPV) describes recurrent, brief episodes of vertigo caused by the motion of changing head position. It is thought to be due to loose otoconia in the semicircular canal. Otoconia are crystals that reside in the saccule and utricle. When they escape this region, they can set up eddy currents in the endolymph, causing symptoms of vertigo. BPV can also be caused by head trauma, labyrinthitis, or aging.

Most BPV resolves spontaneously over a couple of weeks or can be treated successfully with various repositioning maneuvers that move the otoconia to a position of the inner ear that is less likely to induce vertigo. These are the Epley and Semont maneuvers

and their variations. In some patients, episodes recur periodically from several days to many months—rarely for years.

Meclizine doesn't cure BPV, but it is sometimes used to control nausea. BPV and non-vertigo causes of "dizziness" are discussed in General Internal Medicine, Book 5.

Vestibular Neuritis

Vestibular neuritis (vestibular neuronitis, acute peripheral vestibulopathy) causes a sudden onset of non-positional vertigo that is self-limited but may last weeks to months and occasionally can recur. This disorder occurs mainly in young to middle-aged adults, without preference for either sex.

Vestibular neuritis is caused by an inflammatory process affecting the vestibular portion of the 8th cranial nerve and can be associated with viral infections. Pure vestibular neuritis does not affect hearing. If hearing is affected, it means it is no longer solely the nerve being affected but also the labyrinthine canals—and this is called vestibular labyrinthitis.

Usually the onset of vertigo is fairly abrupt, although some patients describe a prodromal period of several hours or days in which they felt off balance. Persistence of the symptoms for a day or more differentiates the disorder from Ménière disease. The vertigo is severe as a rule and is associated with nausea and vomiting, tinnitus is commonly absent, and hearing is not affected—unlike Ménière disease (see below). The severe vertigo and associated symptoms subside in a matter of several days, but lesser degrees of these symptoms, made worse by rapid movements of the head, may persist for several weeks or months.

Corticosteroids probably help recovery. More studies are needed to confirm this effect. If steroids are not used, treatment is symptomatic only. During the acute stage, antihistamine drugs (e.g., promethazine, clonazepam, and scopolamine) may be helpful in reducing the symptoms.

Aminoglycoside Toxicity

Aminoglycoside toxicity can cause some initial sensorineural hearing loss and, later, intermittent mild vertigo.

Ménière Disease

Ménière disease is characterized by recurrent attacks of vertigo associated with intermittent tinnitus that begins between 20 and 40 years of age. The characteristic triad is episodic vertigo (often associated with nausea and vomiting) and tinnitus, with development of low-frequency hearing loss after recurrent episodes. It frequently begins unilaterally but can become bilateral in 20–30% of patients.

The main pathologic changes consist of an increase in the volume of endolymph and distention of the endolymphatic system (endolymphatic hydrops), partly related to salt intake.

Diagnosis is clinical. Audiometry can help determine if hearing loss has occurred. If hearing loss is present at diagnosis, exclude neurosyphilis as a cause by checking a serum VDRL or RPR.

Antihistamines, antiemetics, and sedatives are used in acute episodes. Chronic treatment includes eradicating caffeine and reducing the intake of salt, alcohol, nicotine, and monosodium glutamate. Thiazide diuretics are used when spells continue after dietary modification. 95% of patients get their disease under control and function normally. For medically recalcitrant Ménière disease, endolymphatic sac surgery, surgical labyrinthectomy, and vestibular nerve sections remain therapeutic options.

Vertebrobasilar TIAs

Vertebrobasilar TIAs (transient ischemic attacks) may cause intermittent, recurrent vertigo. This posterior circulation TIA is usually easy to diagnose because it also causes other symptoms of vertebrobasilar insufficiency, such as bilateral vision loss, diplopia, dysarthria, ataxia, and bilateral extremity motor or sensory dysfunction. And, the patient regularly has risk factors for stroke.

Workup of the posterior circulation requires special imaging. [Know:] The standard workup of looking at only the anterior circulation does not catch stenoses in the posterior circulation. Currently, the recommended testing for imaging of the posterior circulation is CT or MR angiography. Know that duplex Doppler ultrasound is not recommended for these vessels because of a lack of sensitivity.

NYSTAGMUS

Nystagmus is an involuntary oscillation of the eyes. The movements may be pendular (like a pendulum) or jerk. Jerk nystagmus has 2 components: slow and fast. The eyes "drift" (= slow component), and try to quickly recover (= fast component). The fast direction defines the direction of the nystagmus. Nystagmus is sometimes (but not always) associated with vertigo.

Jerk nystagmus is most common in vestibular disorders, but does not indicate whether the lesion is within the central nervous system, or if it involves the cranial nerve itself. Upbeating jerk nystagmus usually indicates a lesion in the pons but can be seen in lesions of the medulla or cerebellum. Downbeating jerk nystagmus indicates a lesion at the cervicomedullary junction.

Gazing in particular directions precipitates the abnormal eye movements in certain types of nystagmus. For instance, drugs (e.g., antiepileptic medications) may

Quick Quiz

- What are the clinical features of Ménière disease?
- Which TIAs cause vertigo?
- What brain lesion is suggested by upbeating jerk nystagmus? Downbeating?
- What are some differences between generalized and focal seizures?
- What test should you order if you suspect recurrent pseudoseizures (PNES)?

cause horizontal and vertical gaze-evoked nystagmus (occurring when the person looks right, left, or up)—in other words, it is present "in all directions." Isolated vertical gaze-evoked nystagmus typically indicates disease in the posterior fossa.

TINNITUS

Know these causes of tinnitus:

- Pulse synchronous tinnitus with IIH
- Intermittent tinnitus with Ménière's
- Aspirin overdose
- High noise levels
- Hearing loss

The tinnitus that occurs with hearing loss is thought to be a compensatory reaction to the hearing loss itself. Note that no tinnitus occurs with vestibular neuritis.

SEIZURES

OVERVIEW

Convulsion is an intense paroxysm of involuntary repetitive muscular contractions, and it does not always have to be present during seizures. **Seizure** is preferable as a generic term because it includes all paroxysmal electrical discharges of the brain that cause loss of consciousness; alteration of perception or impairment of psychic function; convulsive movements; disturbance of sensation; or some combination thereof. **Epilepsy** is defined as a condition of recurrent, unprovoked seizures. The condition of prolonged or repetitive convulsive seizures is termed **status epilepticus** and can be life-threatening.

It is crucial to determine whether the seizures are primary (idiopathic) or secondary.

GENERALIZED vs. FOCAL

Seizures arise from the cerebral cortex.

The 2010 International League Against Epilepsy (ILAE) International Classification of Epileptic Seizures now categorizes seizure disorders into generalized and focal (previously partial):

- Focal (or partial) seizures involve 1 side of the brain. These are noted for motor activity on 1 side of the body (usually) and no impairment of consciousness.
- Generalized seizures involve both hemispheres of the brain and result in diminished consciousness. Any motor activity generally involves both sides of the body (but not necessarily).

Further (international) classification of epileptic seizures:

- Focal (partial) seizures
  - Simple partial; consciousness maintained
  - Complex partial; consciousness is impaired
  - Partial with secondary generalization
- Generalized seizures
  - Nonconvulsive: absence seizure (typical and atypical based on 3-second spike on EEG)
  - Convulsive
    - Myoclonic seizure
    - Clonic seizure
    - Tonic seizure
    - Tonic-clonic seizure
    - Atonic seizure

Focal seizures are more commonly due to focal brain lesions while primary generalized seizures are more commonly genetic (although there are many exceptions to this rule of thumb).

PSYCHOGENIC NONEPILEPTIC SEIZURES (PNES)

PNES (pseudoseizures) are not due to abnormal brain activity but are psychogenic. Features that suggest PNES include: forced eye closure during event, pelvic thrusting, vocalization, absence of a post ictal state.

Order video EEG monitoring if PNES is suspected. Note, however, that 20% of patients with PNES also have epilepsy.

SEIZURE AURA

An aura is a perceptual disturbance that may precede a focal seizure. Auras do not occur with primary generalized seizures. Note that auras do occur with migraine, but all discussion here is in reference only to seizures.

Auras have various manifestations affecting the senses. They can be somatosensory perceptions such as pain, numbness, or tingling or related to other senses. They

can be mostly motor, ranging from tremors or shaking to gross motor movement. They can also be:

- Visual with lights, patterns, seeing objects
- Auditory with voices, noises, tones, and other sounds
- Olfactory, typically with a burnt rubber smell
- Gustatory with the perception of strange tastes

[Know:] Auras, in the context of seizures, have been used as a warning manifestation of seizure and have allowed the patient to take precautions. These auras are thought to be produced by early seizure activity.

A focal seizure can evolve into a focal seizure with diminished consciousness, and either of these can evolve secondarily into a generalized seizure. In any of these situations, the preceding seizure is also called an aura by some.

COMMON SEIZURE TYPES

The discussion here addresses 4 main types of seizures:

1) **Generalized tonic-clonic** seizures are also known as a grand mal in older epilepsy literature. These involve both hemispheres, with resulting bilateral motor involvement. Consciousness is impaired with a pronounced postictal period. These seizures can be generalized from the start, or they can be focal seizures with secondary generalization.
2) **Absence** seizures are a type of generalized seizure that used to be called petit mal. These are nonconvulsive, generalized seizures with no aura and no postictal symptoms. The attacks occur without warning and consist of a sudden interruption of consciousness during which the patient stares and briefly stops talking or ceases to respond. They can be induced by hyperventilating. Absences have a characteristic 3-per-second spike and

Table 11-2: Notable Advantages and Disadvantages of Antiepileptic Drugs (AEDs)

Drug	Used to Treat	Notable Advantages/Disadvantages
Phenytoin	Focal (1) Generalized tonic-clonic (alternative)	Good: long half-life so dose 1–2x/d Bad: gum hyperplasia, hirsutism, coarsening of features, lymphadenopathy, osteomalacia; toxicity may present at near-normal concentrations; teratogenic; complex pharmacokinetics; significant interactions, liver inducer
Carbamazepine	Focal (1) Generalized tonic-clonic (alternative)	Good: Toxicity is uncommon. Bad: hyponatremia, leukopenia, thrombocytopenia, aplastic anemia, hepatotoxicity, teratogenic, liver inducer
Valproic acid	Generalized tonic-clonic (1) Absence (alternative) Focal (alternative, esp. if it generalizes)	Good: wide spectrum, good efficacy, IV form available Bad: GI side effects (less with Depakote® formulation); may rarely cause bone marrow suppression and hepatotoxicity/liver failure; teratogenic (neural tube defects)
Ethosuximide	Absence (1) only	Bad: may cause bone marrow suppression (rare)
Lamotrigine	Focal (adjunctive use)	Good: wide spectrum, good efficacy, well tolerated in elderly patients Bad: may cause severe rash and Stevens-Johnson syndrome with rapid titration
Gabapentin	Focal (adjunctive use)	Good: the only one with no significant drug interactions; renal clearance so it is useful in those with liver disease Bad: ataxia, amnesia, limited efficacy
Clonazepam	Absence (short-term adjunctive use only)	Bad: loses efficacy
Phenobarbital	Focal (last choice)	Bad: sedation in adults, hyperactivity in children, among other cognitive changes; teratogenic
Topiramate	Focal (monotherapy or adjunctive) General (monotherapy or adjunctive)	Good: weight loss, headache prophylasis if present Bad: kidney stones and increased glaucoma, weight loss
Levetiracetam	Focal and generalized (monotherapy)	Good: well tolerated in elderly patients; safe in Asian patients with HLA-B 1502 at increased risk for Stevens-Johnson syndrome Bad: depression, fatigue, irritability, and increased infections

Note: (1) = primary drug Note: Any of the above AEDs can cause ataxia, dizziness, and somnolence.

- Name some environmental triggers for seizures in susceptible people.
- What is the treatment of status epilepticus?
- Which drug is used to treat absence seizures?

wave pattern on EEG. 2/3 of affected children outgrow absence seizures.

3) **Focal** (a.k.a. simple partial) seizures originate in a small area of the cortex. Consciousness is preserved. The symptoms of a focal seizure depend on the region of cortex from which the event is generated. For instance, a focal seizure arising in the occipital lobe (visual cortex) may be manifested by complex visual hallucinations; e.g., spinning colorful spheres. Jacksonian seizures are focal seizures that involve the motor strip. There can be transient, postictal paralysis of affected limbs.
4) **Focal seizures with diminished consciousness** (a.k.a. complex partial seizures) have many causes. A common type is the temporal lobe seizure. In this, the preceding aura may be a hallucination or perceptual illusion. There is a period of altered behavior and consciousness, for which the patient is later found to be amnesic. The motor components of the temporal lobe seizure take the form of automatisms (e.g., lip-smacking, chewing or swallowing movements, salivation, fumbling of the hands, or shuffling of the feet).

Status epilepticus is defined as a seizure lasting > 30 minutes or a series of 2 or more seizures without regaining consciousness in between. It is considered a medical emergency. A cause can be determined about 2/3 of the time. Usual causes in adults include stroke, alcohol or other drugs, stopping or changing seizure medications, hypoxia, CNS infection, metabolic causes, tumor, and trauma.

Triggers for seizures in susceptible people include alcohol, cocaine, intense emotions, strobe lighting, loud music, stress, menstruation, and lack of sleep.

SEIZURE MANAGEMENT

History

When obtaining the history, check for alcohol or drug use, head injury, sleep deprivation, diabetes, and thyroid or parathyroid surgery.

Scans and Lab

Lab tests should include glucose, sodium, calcium, magnesium, LFTs, and BUN. If there are any meningeal symptoms, do a lumbar puncture and include a VDRL on the CSF studies. Order either an MRI with gadolinium or a CT with contrast after the 1st seizure to exclude a structural abnormality; MRI is almost always the best neuroimaging test. Neuroimaging is normal in classic childhood absence seizures and certain genetic epilepsy syndromes. An EEG showing epileptiform spikes (+/– following a slow wave) confirms the diagnosis of seizure and may localize the origin of the seizures. A normal EEG never excludes the diagnosis of epilepsy.

After an initial seizure, the risk of recurrence is increased when there is an abnormal EEG, history of a prior neurologic injury, family history of seizures, the 1st seizure is a focal seizure, and/or when the MRI reveals an abnormality. In approximately 70% of all patients with epilepsy, the seizures are controlled completely or almost completely by medications; in an additional 20–25%, the attacks are significantly reduced in number and severity.

Acute Treatment of Seizures

Acute treatment of seizures: Intravenous benzodiazepines (diazepam, lorazepam, midazolam) are the drugs of choice. Phenytoin also is effective, but it takes longer to infuse. Alcohol withdrawal seizures are customarily treated acutely with IV benzodiazepines or phenytoin (again, benzodiazepines 1st).

Typical treatment of status epilepticus in the adult: Give thiamine and then D_{50} 50 mL if the rapid glucose test is low; then benzodiazepine (lorazepam preferred x 2 doses) followed by a loading dose of phenytoin or equivalent fosphenytoin. Fosphenytoin lacks the injection site necrosis and cardiac rhythm complications of intravenous phenytoin infusion but is much more expensive and may result in lower initial brain phenytoin levels, based on the time required for conversion from fosphenytoin to phenytoin. Nevertheless, it is popular in the emergency department.

If the patient is still seizing, give a 3rd dose of lorazepam, maximize the phenytoin dose, and then proceed to a barbiturate (phenobarbital or pentobarbital). ICU settings are generally needed if seizures are not controlled by the first 2 doses of lorazepam and a dose of phenytoin.

Chronic Treatment of Seizures

Antiepileptic drugs (AEDs) are the mainstay of treatment, with monotherapy the preferred goal (Table 11-2). AEDs in epilepsy are generally started after 2 or more unprovoked seizures. (Some say after 1 focal unprovoked seizure if EEG is abnormal or head injury history.) The risk of seizure recurrence after 2 seizures is ~ 60% and is ~ 35% after a single seizure. The choice of antiepileptic drug depends primarily on the seizure type, with additional considerations including cost, side-effect profile, and patient preference for a dosage schedule. Commonly, drugs are not started until a patient has suffered at least 2 seizures.

Focal seizures: Almost all available AEDs are effective in the treatment of focal seizures. The notable exception is ethosuximide, an agent that is used to treat only absence seizures. With few exceptions, the AEDs are considered equally effective. The main differences are that the older

AEDs are generally cheaper; however, the newer ones are generally better tolerated and have fewer side effects.

Generalized seizures: The list of effective agents for generalized seizures is shorter, and includes:

- Valproate
- Lamotrigine
- Topiramate
- Levetiracetam
- Felbamate
- Rufinamide
- Zonisamide

When can you stop the medication? This must be individualized. Risk factors include a seizure within the last 2 years, epileptiform spikes on the EEG, abnormal MRI, and a late age of onset of the seizures. Patients who are seizure-free for 2–4 years and have their AEDS gradually withdrawn have a ~ 40% risk of recurrent seizures within 2 years.

Know also that certain AEDs reduce the efficacy of oral contraceptive pills:

- Phenytoin
- Phenobarbital
- Carbamazepine
- Felbamate
- Topiramate
- Oxcarbazepine

Women taking these AEDs should use a method of birth control other than oral contraceptives.

Note: Oral contraceptives that contain estrogen can decrease the drug concentration of the AED lamotrigine, and, thus, doses may need to be increased empirically. Conversely, lamotrigine can decrease serum concentrations of progestins (mini pill). Thus, women on progestin-only contraceptives are at risk of getting pregnant and should switch to alternate methods of contraception.

Many of the drugs mentioned above are also teratogens; hence, the importance of knowing their effect on pregnancy. The teratogens include: phenytoin, phenobarbital, carbamazepine, topiramate, and valproic acid. (See Treatment of Seizures During Pregnancy, next.)

Options for intractable epilepsy include resective surgery (best for temporal lobe epilepsy), vagus nerve stimulation (doesn't work as well as surgery), and the ketogenic diet (works well in children).

Driving restrictions vary from state to state and continue to evolve. The Epilepsy Foundation has updated information for your state: www.epilepsyfoundation.org.

Treatment of Seizures During Pregnancy

[Know!]

The background risk for birth defects is 2–3%. The goal of treatment during pregnancy is to control the seizures—uncontrolled seizures can cause placental abruption and early labor and premature delivery. When the risk of teratogenicity is compared to the problems that seizures cause during pregnancy, the risks of uncontrolled seizures is greater!

Maintain a pregnant woman on monotherapy at the lowest dose of medication possible; risk of malformations increases as each drug is added.

There is no "safe" AED, but valproate is more likely to cause neural tube defects than other commonly used antiepileptics. The teratogenic risk of AEDs is decreased by folic acid, and thus, all women of childbearing age on antiepileptic drugs should take 1–2 mg of folate daily.

Physicians generally give prophylactic vitamin K during the last month of pregnancy in patients on AEDs, based on reports indicating increased bleeding in patients on AEDs. However, most recent guidelines say there is not enough evidence to recommend for or against use of prophylactic vitamin K.

INFECTIONS

BACTERIAL CNS INFECTIONS

Acute Meningitis

Diagnose with analysis of the cerebrospinal fluid (CSF). If there are focal neurologic signs or papilledema, do a CT before the lumbar puncture (LP). CSF latex agglutination tests are no longer recommended in the initial evaluation of meningitis; they test for *H. influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitides*, *E. coli*, and *Streptococcus agalactiae*. With suspected meningitis, start antibiotics immediately after the LP and blood cultures; do not wait for any LP results. Also, if doing the LP is going to be delayed more than 30–60 minutes, go ahead and give antibiotics immediately (before the LP)! Further discussion and treatments are featured in Infectious Disease, Book 1.

Neurosyphilis also is discussed in Infectious Disease, Book 1.

Brain Abscess

The classic triad of symptoms is headache, fever, and focal neurological deficit(s). Most abscesses arise from intracranial extension of cranial infections (sinuses, teeth) or after skull fracture or neurosurgical procedures. Much less often, they are due to bacteremic seeding. In adults, the most common organisms are staph and strep species (e.g., *S. epidermidis* after a penetrating head injury), but don't forget about *Nocardia*. In the immunocompromised, consider toxoplasmosis.

Quick Quiz

- Which AEDs decrease the effectiveness of oral contraceptives?
- Which AED serum concentration is reduced by estrogens?
- Which AED reduces the serum concentration of progestins?
- What is the classic triad of symptoms observed in patients with a brain abscess?
- How does treatment of a varicella infection differ from the treatment of herpes simplex?
- What is the diagnostic test for West Nile virus encephalitis?

VIRAL CNS INFECTIONS

CSF in Viral Encephalitis

With viral encephalitis, CSF has increased lymphocytes, normal to slightly increased protein, and normal glucose. EEG is almost always abnormal with diffuse slowing or focal temporal changes. The MRI is more sensitive than CT and may show hemorrhagic changes.

Herpes Simplex Encephalitis

Herpes simplex encephalitis is the most common type of non-epidemic viral encephalitis. In adults, it is usually due to a reactivation of the HSV-1 virus, although 25% are due to primary HSV-1 infection. HSV-2 is sexually transmitted and can cause aseptic meningitis during primary infection. HSV-2 less commonly causes encephalitis but can cause polyradiculitis and myelitis.

Varicella zoster virus (VZV) can also cause encephalitis, especially in the immunocompromised; and, it is associated with vesicular lesions that can be confused for herpes simplex. It's important to think about VZV because the dose of acyclovir required to treat is higher.

Treat herpes encephalitis with IV acyclovir and assume it is caused by VZV until you can exclude. (So, use higher initial doses of acyclovir.) Much more on herpes is covered in Infectious Disease, Book 1.

Mosquito-Borne Arboviruses

If mosquitoes are around, think about arboviruses, especially eastern/western equine and St. Louis encephalitis viruses. West Nile virus tends to cause encephalitis only in the older patients with comorbidities and in the immunocompromised. (It causes "West Nile fever" in younger and healthy patients.) If a patient has clinical picture of encephalitis and has flaccid paralysis, think of West Nile encephalitis.

Diagnosis of Viral Encephalitis

Polymerase chain reaction (PCR) DNA amplification of the herpes viruses now allows for an easy, rapid, and accurate diagnosis of herpes simplex and zoster.

Acute and convalescent serum titers are drawn to diagnose most arboviruses. West Nile diagnosis requires finding antibody in spinal fluid. Viral culture of spinal fluid is useful to identify most other causes of simple viral meningitis/encephalitis.

Viral Myelitis

Myelitis is infection of the spinal cord—a classic viral cause is poliomyelitis! Typically this presents as "transverse myelitis," meaning it affects a transverse segment of the cord. Common causes today are other enteroviruses (coxsackie and enterovirus) and flaviviruses, such as West Nile. Other forms of myelitis (less segmental) can be caused by herpes simplex, varicella zoster, and Epstein-Barr.

Slow Viruses and Prions

Slow viruses:

- Subacute sclerosing panencephalitis (SSPE) is caused by the measles virus; most cases occur around age 10, many years after the initial infection.
- Progressive multifocal leukoencephalopathy (PML): See below and also under Demyelinating Diseases on page 11-42.

Prion: Creutzfeldt-Jakob disease (CJD) (See page 11-11.)

HIV

Infection with HIV can result in dysfunction of any part of the nervous system. Patients get subacute encephalitis, peripheral neuropathies including mononeuritis multiplex, vacuolar myelopathy, and aseptic meningitis.

HIV-associated cognitive impairment is common. It ranges from asymptomatic to mild to what is called HIV-associated dementia (HAD). In adults, it takes the form of a slowly or subacutely progressive dementia with loss of retentive memory, inattentiveness, language disorder, and apathy.

Know that the differential diagnoses include progressive multifocal leukoencephalopathy, toxoplasmosis, and lymphomas.

Since the use of ART began, the incidence (new cases per year) of HAD in the U.S. has dropped by half. Patients are getting a different type of dementia post-ART; this dementia is associated more with deficits in complex reasoning and less with global impairment. In addition, even though the incidence is dropping, HAD is occurring in patients with higher CD4 counts, even in patients who have had long-term viral suppression on antiretroviral agents.

Poliomyelitis is more likely to occur in AIDS patients. Differentiation between AZT myopathy and poliomyelitis may require a muscle biopsy.

Peripheral AIDS neuropathy has 3 forms:

1) In chronic inflammatory demyelinating polyneuropathy (CIDP), there is progressive weakness of the legs and loss of deep tendon reflexes. There is a high protein level and a high cell count in the patient's CSF. Treatments are corticosteroids, IVIG, and plasmapheresis—all equally effective.
2) Distal symmetric polyneuropathy is common in AIDS patients (1/3 get it). Symptoms are paresthesias of the feet and distal weakness in the legs. Treatment commonly includes tricyclic antidepressants or gabapentin.
3) A painful mononeuritis multiplex thought to be due to focal vasculitis also occurs.

Progressive multifocal leukoencephalopathy (PML) affects white matter only. It is typically seen in patients with T-cell immune defects (HIV/AIDS, chronic steroids, monoclonal antibodies) and chronic neoplastic diseases. In addition, we are now seeing cases of PML in patients taking a number of immunosuppressants for treatment of rheumatologic, hematologic, and inflammatory bowel diseases (rituximab, fludarabine, mycophenolate, chronic corticosteroids), and with a newer drug to treat multiple sclerosis, natalizumab.

PML is caused by the human JC polyomavirus, resulting in a progressive demyelination of the CNS white matter.

Symptoms are varied and usually start with abnormal mentation (personality changes and intellectual impairment) and then slurred speech. Initial symptoms can be followed by hemiparesis progressing to quadriparesis, visual field defects, cortical blindness, aphasia, ataxia, dysarthria, dementia, confusional states, and/or coma. Some patients have a predominantly cerebellar syndrome.

Diagnose with brain biopsy. Finding JC virus in the CSF by PCR is supportive, although this occurs less often in patients with PML being treated with ART.

Vacuolar myelopathy (see Infectious Myelopathies on page 11-32) causes progressive weakness, incontinence, hyperreflexia, and ataxia. There is vacuolation and deterioration of the dorsal and lateral spinal columns. It is uncommon. This myelopathy must be differentiated from B_{12} deficiency and from spinal cord compression due to some other cause, such as lymphoma.

PARASITIC CNS INFECTIONS

Toxoplasmosis

AIDS-related brain lesions: If you see multiple ring-enhancing lesions, think toxoplasmosis. (CNS lymphoma, TB, and bacterial infections are less likely.)

Because toxo is a reactivation infection, patients typically have IgG (but not IgM) antibody to *T. gondii*. But many people have toxo antibodies, so a positive toxo IgG is only supportive and not diagnostic. Also know that an absent toxo IgG does not exclude toxoplasmosis as the cause of a brain lesion in an AIDS patient.

Treat with sulfadiazine, pyrimethamine, and leucovorin. Add dexamethasone if there is midline shift or rapid deterioration.

Do a brain biopsy if there is no improvement after empiric treatment, if there is a mass effect, or if there is only 1 lesion. Some empirically treat single lesions if the CD4 count is < 100 and the patient hasn't been on toxo prophylaxis. Relapses occur often.

Neurocysticercosis

Neurocysticercosis is the most common worldwide parasitic CNS infection. It is caused by ingesting food or water contaminated with *Taenia solium* (a tapeworm). It forms cysts in the brain, which initially cause no symptoms. But when the cyst walls break down several years later, it causes cerebral edema, commonly with seizures as the 1st symptom. In some patients, a large subarachnoid or intraventricular cyst may obstruct the flow of CSF. In a more malignant form of the disease, the cysticerci are located in the basilar subarachnoid space, where they induce an intense inflammatory reaction leading to hydrocephalus, vasculitis, and stroke as well as cranial nerve palsies.

MRI is the preferred imaging modality—when worms are viable, MRI shows multiple, non-enhancing hypodense lesions. As the worms die, they are surrounded by edema and flair. When dead, they calcify and shrink. Support the diagnosis with *T. solium* antibody testing on serum.

Treatment of CNS infection is controversial because of both the lack of randomized studies and the propensity of dying worms to cause symptoms. Most experts now treat with high-dose praziquantel or albendazole +/– corticosteroids. AEDs are given to patients at high risk for seizures. More about this infection in Infectious Disease, Book 1.

FUNGAL CNS INFECTIONS

Cryptococcal Meningitis

Especially consider cryptococcal meningitis when working up a progressive headache, cognitive impairment, and/or meningeal signs in patients with AIDS or on chronic corticosteroids.

CSF pressure is usually very elevated. Standard CSF studies can be entirely normal, so always check the cryptococcal antigen titer in the blood and CSF (in HIV patients, sensitivity/specificity is > 95%). In HIV-negative patients, the CSF antigen is still 93–98% sensitive.

Treat with amphotericin B deoxycholate or liposomal ampho B and flucytosine x 2 weeks, then change to oral fluconazole x 8 more weeks (minimum). Lower doses

Quick Quiz

- Aside from patients with AIDS, PML can occur in which patients? What are the symptoms of PML?
- What is the treatment for CNS toxoplasmosis?
- What is the clinical presentation of neurocysticercosis?
- Characterize the CSF of a patient with cryptococcal meningitis.
- How useful is the CSF/serum cryptococcal antigen (sensitivity/specificity) in diagnosing meningitis?
- Which viral infection recently has been associated with subsequent stroke?

of oral fluconazole are used for secondary prophylaxis in immunocompromised patients. Manage elevated intracranial pressures with daily taps to keep CSF pressure < 200 mm H_2O, or patients can lose their vision. Shunts are appropriate if daily taps are needed. Do not use mannitol, acetazolamide, or corticosteroids.

More about this infection in Infectious Disease, Book 1.

STROKE and TIA

OVERVIEW

Stroke, after heart disease and cancer, is the 3rd most common cause of death in the U.S. The term **stroke** is applied to a sudden focal neurologic syndrome caused by cerebrovascular disease. **Cerebrovascular disease** refers to an abnormality of the brain caused by pathology of blood vessels such as:

- **Occlusion** by embolus or thrombus
- Vessel **rupture**
- Altered **permeability** of the vessel wall
- Increased **viscosity** or other change in the quality of the blood flowing through the cerebral vessels

The primary vascular disorder may be atherosclerosis, hypertensive arteriosclerotic change, arteritis, aneurysmal dilatation, or a developmental malformation. The secondary parenchymal changes in the brain resulting from the vascular lesion could be ischemia, with or without infarction, and hemorrhage.

Know that varicella zoster infection has been identified as a risk factor for ischemic and hemorrhagic strokes and TIA (increases risk by 30%), especially if the presentation is herpes zoster ophthalmicus.

TIA

Brain ischemia **without infarction** has been recently defined by the American Stroke Association as a transient ischemic attack (**TIA**). **Ischemic stroke** has been defined as **infarction** and may result in temporary or permanent cognitive, motor, and/or sensory deficits.

Note that the latest guideline on TIA from the American Stroke Association has **removed** all references to **duration** of symptoms. The definition was changed because true infarction sometimes occurs even when symptoms last < 24 hours, making the previous definition of TIA occasionally incorrect.

COMPLICATIONS OF TIA

TIA signals:

- Impending CVA
  - 10% have ischemic stroke within 3 months.
  - 50% do so within 48 hours.
- Impending cardiac event
  - 3% have cardiac events within 90 days.
  - AMI risk is increased.
  - Mortality in AMI after TIA is increased.

Risk stratification of TIA, $ABCD^2$ score:

- **A**ge: ≥ 60 = 1 point, < 60 = 0
- **B**P: ≥ 140/90 = 1, < 140/90 = 0
- **C**linical: weakness = 2, isolated speech = 1, other = 0
- **D**uration: ≥ 60 min = 2, 10–59 min = 1, < 10 min = 0
- **D**iabetes: present = 1, absent = 0

Score	2-day Risk of Stroke
0–1	0%
2–3	1.3%
4–5	4%
6–7	8%

2009 AHA/ASA guideline recommends hospitalization within 72 hours of event if:

- $ABCD^2$ score ≥ 3
- $ABCD^2$ score 0–2 and unable to complete workup within 48 hours
- $ABCD^2$ score 0–2 and other evidence that events were caused by ischemia

Patients with TIA should have imaging within 24 hours or ASAP after their symptoms to determine if any infarction is present. Also order CT or MR angiography of intracranial and neck vessels, echo, and blood work: chemistries, BS, lipids, CBC. Order an ECG to rule out atrial fibrillation (AF). See more under Evaluation of Ischemic Stroke on page 11-25.

CLASSIFICATION OF STROKES

Strokes are classified as ischemic or hemorrhagic. Ischemic strokes can be thrombotic or embolic.

Ischemic strokes (87% of all strokes):

- 20% are due to large artery atherosclerosis.
- 20% are due to cardiac emboli.
- 25% are due to lacunar/small vessel infarcts.
- 5% are due to vascular disorders (e.g., vasculitis or dissection).
- 35% are cryptogenic.

Hemorrhagic strokes are mainly caused by:

- Intracerebral hemorrhage (ICH)
- Subarachnoid hemorrhage (SAH)

PRIMARY PREVENTION OF STROKE

The American Heart Association (AHA) and the American Stroke Association (ASA) published the 2010 guidelines for primary prevention of stroke, which include:

- Treatment of blood pressure and lipids (per guidelines)
- Smoking cessation
- Diet and exercise
- Treatment of atrial fibrillation with anticoagulation based on national guidelines (See more on AF in Cardiology, Book 3) using any of the following:
  - Aspirin
  - Warfarin
  - Aspirin + clopidogrel (in patients unable to tolerate warfarin)
  - Dabigatran, rivaroxaban, or apixaban (alternatives to warfarin)
- Carotid endarterectomy if > 70% stenosis in selected patients, if operative morbidity and mortality is < 3%
- Prophylaxis for migraine (previously discussed on page 11-6)
- Evaluation and treatment of obstructive sleep apnea
- Screening for aneurysms with CTA or MRA for the following:
  - Patients who have 2 or more 1st degree relatives with SAH/aneurysm (But screening is not recommended in patients who have only 1 affected 1st degree relative.)
  - Patients who have autosomal dominant polycystic kidney disease (ADPKD) and 1 or more relatives with ADPKD + SAH/ aneurysm

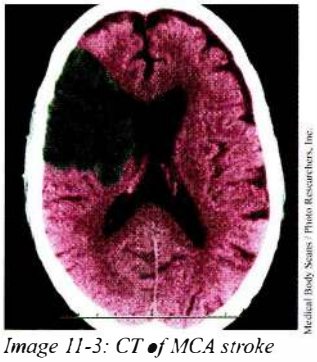

Image 11-3: CT of MCA stroke

IMAGING OF STROKES

In 2009, the American Heart Association published recommendations for how best to image patients with possible stroke, based on an extensive literature review and specialty consensus publications. The recommendations focus on the best use of CT and MRI. A main reason to do neuroimaging is to determine whether a patient is eligible for tissue plasminogen activator (t-PA), but there are other uses:

- Exclude intracerebral (ICH) or subarachnoid hemorrhage (SAH)
- Detect ischemia
- Exclude other illnesses that present as stroke
- Image the vessels
- Assess possible viability of infarcted tissue

Imaging with CT: A non-enhanced CT (NECT) scan can be performed as a basic form of stroke imaging (Image 11-3). The NECT can be enhanced by adding either of the following:

- Angiography (CTA)
- Dynamic perfusion studies (CTP)

When adding angiography, evaluation of source images (SI) helps to interpret the study (CTA-SI).

Imaging with MRI: MRI can also be enhanced using additional imaging sequences:

- Diffusion weighted imaging (DWI)
- Perfusion (MRP)
- Angiography (MRA)
- Gradient-recalled echo (GRE)
- Fluid-attenuated inversion recovery (FLAIR)

The CT and MRI enhancements help to better accomplish the purposes of imaging. Usually most, if not all, of these sequences are performed whenever you order an MRI of the brain. In the best circumstances, a CT scan with enhancements takes the same amount of time as an MRI with enhancements. For example, it takes 10 minutes to do either NECT with CTA/CTA-SI and dynamic CTP or MRI with FLAIR, GRE, MRP, and intracranial MRA! The major problem today is that not all hospitals provide access to the MRI scanner for triage situations. In many emergency departments, only CT is available.

Now that you know the abbreviations and acronyms, we'll go over which imaging to use in particular situations:

- Intracerebral hemorrhage (ICH): MRI-GRE is equivalent to NECT for finding blood. We used to believe that CT was better, but many studies now show that it is not. MRI is also better for detecting hemorrhagic transformation of ischemic stroke.
- Subarachnoid hemorrhage (SAH): Use NECT. There are some data showing MRI with FLAIR is as sensitive as NECT. No matter which test you choose, a lumbar puncture is still mandatory if the CT or MRI is negative.

QuickQuiz

- In addition to exercise, smoking cessation, and control of diet, blood pressure, and lipids, what other interventions should be offered to certain patient groups in order to prevent stroke?
- What imaging study would you do for a patient with a suspected SAH?
- Which imaging study is best to evaluate the anterior carotid and posterior circulations in patients with TIA or stroke?
- How does a patient with an ACA stroke typically present?
- How does a patient with an MCA stroke typically present?

- Ischemia: MRI-DWI is best. CTA-SI is comparable, but it is not as good for imaging of the posterior fossa/brain stem and for discovering small infarcts. MRI is also better than NECT to detect an occluded vessel.

Because of the above, unless your patient has signs and symptoms of SAH, MRI + DWI and MRI + GRE sequences (at minimum) are the best imaging for possible ischemic stroke, because they both exclude ICH and identify areas of infarction—provided you can get the test without delay. Remember that time from symptom onset > 4.5 hours precludes use of t-PA (< 3 hours best). If you cannot get an MRI in a reasonable time frame, then get a CT with CTA-SI.

CTA or MRA is recommended to evaluate the intra- and extracranial vasculature of patients with TIA or stroke symptoms. Both imaging modalities are significantly more sensitive and specific than carotid Doppler ultrasound for diagnosing extracranial vascular stenosis. Carotid ultrasound also tends to overdiagnose lesions and leads to unnecessary surgery in some patients. CTA is better than MRI at identifying intracranial aneurysms.

If performing CTA or MRA doesn't extend the time period from symptom onset out past 4.5 hours maximum (< 3 hours best), either is recommended as part of the initial evaluation of stroke because, sometimes, clotted vessels can be treated with urgent intraarterial therapy or stents. Patients with a large clotted vessel—often the middle cerebral artery (MCA), so-called "hard thrombus"—do not respond as well to t-PA as to direct intervention.

Although assessing viable brain tissue after infarction is one of the main purposes for imaging a stroke patient, we are still in the beginning stages of learning how to incorporate the data into treatment plans. Dynamic CTP and MRP are the leading imaging techniques.

ISCHEMIC STROKES

Thrombotic vs. Embolic Strokes

Thrombotic strokes: Atherosclerotic occlusion is most common in the internal carotid, middle cerebral, vertebral, and basilar arteries.

The initial neurologic symptoms often occur in a slow, stepwise progression (termed "stroke in evolution"). Often patients have a history of TIAs in the same distribution as the presenting symptoms of their stroke. If the patient has not had TIAs, a clear differentiation between thrombotic and embolic may be difficult. Other, rarer causes of thrombotic occlusion are lupus anticoagulant, polycythemia, meningovascular syphilis, dissecting aortic aneurysm, and thrombocytosis.

Embolic strokes: Neuro deficit is commonly worst at onset. Embolic strokes typically are not preceded by a TIA. Emboli from the heart usually go to the middle > posterior > anterior cerebral arteries. Emboli can also be multiple.

Anterior Circulation

Anterior Cerebral Artery (ACA) Strokes

When the ACA is affected distal to the anterior communicating artery, the weakness and sensory loss affect primarily the contralateral leg.

Urinary incontinence and gait abnormalities may also be present. If the corpus callosum is affected, patients may develop "tactile agnosia," which is an inability to recognize objects by touch.

Occlusion of the stem of the ACA proximal to the anterior communicating artery is generally well tolerated because collateral flow is provided by the other ACA. When both arteries arise from one stem, there is resulting paraplegia, incontinence, lack of motivation (termed "abulia"), and frontal lobe personality changes.

Buzz phrase: The patient with the ACA stroke typically presents with leg weakness that is opposite to the side of the stroke.

Middle Cerebral Artery (MCA) Strokes

Most MCA stem occlusions are from emboli. MCA strokes result in contralateral weakness ("hemiplegia"), which is denser if the internal capsule is involved; sensory loss ("hemianesthesia"); and a homonymous hemianopsia. If the dominant hemisphere is involved (the left side in most people, even left-handed individuals), these patients experience aphasia. A lesion that affects the lower part of the left frontal lobe (Broca's area) causes expressive (a.k.a. Broca) aphasia. These patients understand language, but they have trouble forming words and sentences, so their speech is nonfluent and effortful. A lesion at the boundary of the temporal and parietal lobes causes a "fluent" or "sensory" aphasia, called Wernicke aphasia. These patients can't comprehend written or spoken language and have

errors in their spontaneous speech, often speaking in invented words, termed "neologisms." An extensive infarction may produce "global aphasia," which is both expressive and sensory. If the nondominant hemisphere is involved, patients may experience changes in spatial perception and may develop hemineglect syndrome.

With parietal lesions of either hemisphere, "cortical" sensory signs are often present: contralateral loss of 2-point discrimination, failure to perceive tactile stimuli on the opposite side of the involved hemisphere when stimuli are presented to both sides simultaneously (termed "sensory inattention"), tactile agnosia, and an inability to recognize letters drawn on their palm (termed "agraphesthesia").

If the lesion involves the frontal lobe, patients may have a gaze preference or gaze deviation—they look toward the side of the lesion for 1–2 days after the stroke.

Buzz phrases: The patient with the MCA stroke typically presents with arm/leg weakness that is opposite to the side of the stroke and a language deficit if the dominant hemisphere is involved.

Posterior Circulation

Posterior Cerebral Artery (PCA) Stroke

PCA strokes typically cause contralateral homonymous hemianopsia—usually a superior quadrantanopsia with temporal lobe lesions, an inferior quadrantanopsia with parietal lobe lesions, or a homonymous hemianopsia with medial occipital lesions. There may be mild contralateral sensory loss, inability to name colors (termed "color anomia"), failure to see to-and-fro movements, inability to count objects, inability to fixate on points in peripheral visual fields (termed "ocular apraxia"), inability to see more than 1 object at a time if the dominant occipital lobe is involved (termed "simultanagnosia"), visual hallucinations and/or memory loss.

If the patient has color anomia, the posterior aspect of the corpus callosum (splenium) may have been affected.

If disruption of blood flow occurs bilaterally, the memory loss is severe and persistent.

Bilateral cortical blindness can result from simultaneous or successive posterior cerebral artery occlusion but may also be due to anoxia related to surgery, especially cardiac surgery. Occasionally, patients with cortical blindness deny their visual defect (Anton syndrome).

Buzz phrase: The patient with PCA stroke typically presents with visual field defects + color anomia + paresthesias without any motor findings.

Single Hemisphere Strokes

Single hemisphere strokes typically do not affect paraspinal muscles or muscles of the pharynx, jaw, and forehead. If these muscles are affected, think bilateral hemispheric involvement or brainstem stroke (below). Remember: Upper motor neuron lesions of cranial nerve 7 do not affect eye closure or forehead wrinkling, which helps you to distinguish clinically between a central lesion and Bell's palsy (peripheral 7th nerve involvement).

Vertebral / Basilar Artery Occlusion

Vertebral and/or basilar artery occlusion is the usual cause of brainstem strokes. That the problem involves the posterior circulation delivering blood to brainstem (posterior fossa) structures is suggested by the following:

- Bilateral extremity motor and sensory dysfunction (quadriplegia in severe cases)
- "Crossed" sensory findings (e.g., right face, left arm)
- Horner syndrome
- Cerebellar signs
- Stupor and coma
- Cranial nerve dysfunction commonly not affected by single hemisphere strokes (diplopia, pharyngeal weakness, jaw weakness, and deafness)
- Crossed hemiplegias (e.g., ipsilateral cranial nerve deficit and contralateral arm or leg weakness)

[Know.] A vertebral stroke may cause **lateral medullary syndrome** (also called Wallenberg syndrome), which has a mixed bag of symptoms:

- Ipsilateral cerebellar signs and symptoms (due to involvement of the inferior cerebellar peduncle and cerebellum)
- Nausea, vomiting, nystagmus (vestibular nuclei)
- Ipsilateral Horner syndrome (due to involvement of the descending sympathetic fibers)
- Ipsilateral palate and vocal cord weakness (involvement of the nucleus ambiguus)
- "Crossed" sensory loss (ipsilateral face and contra-lateral body, due to involvement of the trigeminal nucleus and tract and spinothalamic tract, respectively)

Buzz phrases: The patient with the posterior circulation stroke typically presents with:

- Vertigo and diplopia if due to vertebrobasilar artery; sometimes with antecedent TIA symptoms
- Lateral medullary syndrome (defined above)
- Vertigo + nystagmus + nausea + ataxia (if cerebellar)

(There are other brainstem infarction syndromes, but we won't discuss them here.)

QuickQuiz

- How does a patient with a PCA stroke typically present?
- How do you distinguish a central vs. peripheral 7th cranial nerve palsy on physical exam?
- What is the clinical presentation of lateral medullary syndrome? What type of stroke causes it?

Lacunar Infarcts

Small artery disease, typically due to chronic hypertension or diabetes, can lead to small vessel occlusion with resultant necrosis of small areas of the brain. Over time, resorption of these necrotic regions causes small infarcts or "lacunae" to develop.

Although most are silent, hallmarks of symptomatic lacunar infarcts are:

- Pure hemiplegia (with no sensory dysfunction)
- Pure hemisensory stroke (with no motor dysfunction)
- Sensory motor stroke
- Ataxic hemiparesis (ataxia ipsilateral to hemiparesis)
- Clumsy hand-dysarthria syndrome

Multiple bilateral frontal lobe lacunae can result in pseudobulbar palsy—emotional lability with uninhibited crying or laughter and evidence of upper motor neuron signs such as brisk jaw jerk, hyperreflexia, and Babinski sign.

Evaluation of Ischemic Stroke

The patient with a neurologic deficit should be assessed like any other emergency, using the **ABC**s first: stabilize **a**irway, **b**reathing, and **c**irculation.

If the patient is stable, take a good history. The most important element is the time of symptom onset because that determines eligibility for an IV thrombolytic. If the patient awoke with deficits, then the last time he/she remembers having normal function is the time of symptom onset. Remember that complicated migraines, postictal states, and subdural hemorrhages can resemble a stroke; so ask about headaches, seizure activity, and falls.

Physical exam focuses on possible sources and alternative diagnoses. Look for evidence of seizures (tongue biting), trauma, myocardial ischemia, carotid and vertebral artery bruits, heart murmurs, and arrhythmias.

The National Institutes of Health Stroke Scale (NIHSS) score is a standardized instrument incorporated as part of a physical exam at most stroke centers. We've reproduced the general concepts of the scale in Table 11-3, but you really should study and use the full scale.

The NIHSS helps to quantify neurologic deficits, communicate with neurologists, possibly identify the occluded vessel, make an early prognosis, and identify a patient's suitability for thrombolytics. Patients get points for their inability to complete the various parts of the assessment.

Table 11-3: NIH Stroke Scale

Assessment	Instructions
Consciousness: Level	Choose a response: alert, arousable by minor stimuli, requires repeated or painful stimuli, unresponsive or reflexes only, or areflexic.
Consciousness: Questions	Ask month and age. No partial credit. Aphasic and stuporous patients score 2. Intubated patients score 1.
Consciousness: Commands	Ask patient to open and close eyes, then to grip and release non-paretic hand.
Gaze	Test horizontal eye movements.
Vision	Test visual fields by confrontation with finger counting.
Facial palsy	Ask patient to show teeth or raise eyebrows and close eyes.
Motor: Arm and Leg	Test for pronator drift.
Ataxia	Perform finger-nose-finger and heel-shin tests.
Sensation	Assess for sensation or grimace to pinprick or withdrawal from noxious stimulus.
Language	Describe what is happening in a picture, name items printed on paper, and read a sentence.
Speech	Read words from a list.
Extinction and Inattention	Assess previous tests to determine if patient orients only to one side.
For the full scale with scoring, go to www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf	

AHA/ASA 2013 Guideline for the Early Management of Acute Ischemic Stroke recommends the following immediate diagnostic tests at presentation:

- NECT or MRI of the brain (discussed on page 11-22) is done to rule out hemorrhage. If negative for hemorrhage and the subsequent lumbar puncture is negative, then an MRA can be done to evaluate vessels—but this should not delay any necessary reperfusion therapy.
- Blood glucose
- Oxygen saturation measurement
- Serum electrolytes and renal function tests
- CBC with platelets
- PT, PTT, INR
- 12-lead ECG ± telemetry monitoring for arrhythmias
- Optional tests in selected patients:
  - Thrombin time and/or ecarin clotting time (ECT) if on direct thrombin inhibitors.
  - Hepatic function test.
  - Toxicology and alcohol screen.
  - Pregnancy test.
  - Again, a lumbar puncture with CSF assessment should be done if SAH is a concern and NECT (or MRI with FLAIR) does not show blood.
  - EEG (if you suspect patient has seizures).
  - CXR if lung disease is a concern.
  - ABG if hypoxic.

Acute Treatment of Ischemic Stroke

Critical Times

Always refer via 911 to a Primary Stroke Center (PSC) or a Comprehensive Stroke Center (CSC).

The AHA/ASA 2013 guideline recommends these goals:

- Door to physician should be ≤ 10 minutes.
- Door to stroke team should be ≤ 15 minutes.
- Door to CT initiation should be ≤ 25 minutes.
- Door to CT interpretation should be ≤ 45 minutes.
- Door to drug (≥ 80% compliance) ≤ 60 minutes.
- Door to stroke unit admission should be ≤ 3 hours.

If the stroke occurred < 4.5 hours ago and the NIH stroke scale rating is > 4, t-PA has been shown to be effective in decreasing severity or reversing neurological deficits, provided that the patient fits inclusion criteria (2013 stroke treatment guidelines from the American Stroke Association).

t-PA Criteria for < 3 Hours

Less than 3 hours t-PA inclusion criteria:

- Diagnosis of ischemic stroke causing measurable neurologic deficit
- Onset of symptoms < 3 hours before beginning treatment
- Age ≥18 years

Less than 3 hours t-PA exclusion criteria:

- Minor or rapidly improving stroke symptoms
- Significant head trauma or prior stroke in last 3 months
- Symptoms suggest SAH
- History of prior intracranial hemorrhage
- Intracranial tumors or arteriovenous malformation (AVM) or aneurysm
- Arterial puncture at noncompressible site
- Infarct in last 7 days
- Recent intracranial or intraspinal surgery
- SBP > 185 mmHg or DBP > 110 mmHg
- Active internal bleeding
- Platelets < 100,000/mm^3
- Anticoagulation with INR > 1.7 or PT > 15 seconds
- Used direct thrombin inhibitors with abnormal INR/aPTT/PT/ECT/TT/Xa activity assay (e.g., hirudin and derivatives [the -rudins], argatroban, melagatran, dabigatran)
- Blood glucose < 50 or > 400 mg/dL
- CT with multilobar infarction (hypodensity > 1/3 cerebral hemisphere)

Relative exclusions:

- Seizure with postictal deficits
- Major surgery or serious trauma in prior 14 days
- GI or GU hemorrhage within last 21 days
- AMI within 3 months

Additional t-PA criteria for 3–4.5 hours

Inclusion criteria (3–4.5 hours):

- Diagnosis of ischemic stroke causing measurable neuro deficit
- Onset of symptoms within 3–4.5 hours before beginning treatment

Relative exclusion criteria (3–4.5 hours):

- Age > 80
- Severe stroke (NIHSS > 25)
- On anticoagulation regardless of INR
- History of both DM and prior ischemic stroke

Endovascular Interventions

Intra-arterial fibrinolysis is beneficial for carefully selected patients with major ischemic strokes < 6 hours caused by occlusions of the MCA who are not candidates for IV fibrinolytics.

Intra-arterial fibrinolysis or mechanical thrombectomy is reasonable in patients who have contraindications to use of IV fibrinolytics.

Intra-arterial fibrinolysis or mechanical thrombectomy is reasonable as rescue therapy in patients with large occlusions who have not responded to IV fibrinolytics.

Quick Quiz

- What tests are recommended in the initial evaluation of ischemic stroke?
- If imaging for SAH is negative and suspicion is high, what is the next diagnostic test and what does it look for?
- What is the timeframe for prescription of t-PA in patients with ischemic stroke?
- Which patients with a stroke between 3 and 4.5 hours are excluded from t-PA?
- What are the recommendations for lowering of blood pressure in patients with ischemic stroke who do not receive t-PA?
- Why should you keep a patient with an ischemic stroke in the posterior fossa under close observation?
- What are the recommended antiplatelet regimens post-ischemic stroke?
- What are the most common causes of an intracerebral hemorrhage?

Note: No aspirin or anticoagulation (e.g., for DVT prophylaxis) within 24 hours of t-PA.

Intravenous streptokinase is not recommended for acute ischemic strokes.

Other Aspects of Acute Ischemic Stroke Care

Management that emphasizes supportive care and treatment of complications:

- Give airway support to stroke patients with reduced consciousness or airway compromise; oxygen prn.
- Use cardiac monitoring for the first 24 hours after a stroke to assess for arrhythmias.
- Treat hypertension cautiously, so as not to extend infarct size. If the patient meets criteria for t-PA except for BP, go ahead and treat to reduce BP to ≤ 185/110, then give t-PA. If not giving t-PA, withhold meds for BP < 220/120 and allow the patient to gradually drop their pressure on their own. If BP > 220/120, then treat with the goal of reducing the BP ~ 15% in the first 24 hours. Recommended meds from guidelines include IV labetalol, nitroprusside, and nicardipine infusion.
- Restart antihypertensives for patients with long-standing hypertension after 24 hours (if not treated already for BP > 220/120).
- Maintain normoglycemia 140–180 mg/dL.
- Look for and treat sources of fever. Give antipyretics to reduce fever.

In patients ineligible for treatment with t-PA, and who are not taking anticoagulation for any other underlying disease, give 325 mg aspirin once, followed by daily aspirin 150–325 mg/day while hospitalized. Optimal dose is not yet clear. The risk of hemorrhagic transformation of an infarct is not high enough to offset the benefits of aspirin therapy, so treat all eligible patients, even if a small hematoma is present within the infarcted area. There is no benefit to treating ischemic strokes with heparin or LMWH, unless the patient meets criteria for anticoagulation with heparin use otherwise (e.g., atrial fibrillation or a cardiac thrombus).

If the stroke occurs in the posterior fossa, admit the patient for close observation. Expansion of the contents of the posterior fossa can cause either upward or downward herniation; these patients then decompensate quickly and without warning.

Chronic Treatment of Ischemic Stroke

Reduce the patient's risk factors for stroke by treating hypertension, diabetes, and lipids according to national guidelines, and add either aspirin 50–325 mg/day + extended-release dipyridamole or clopidogrel.

The combination of ASA + ER-dipyridamole is better than either agent alone. Use clopidogrel in patients with aspirin allergy. Know that aspirin + clopidogrel does not offer additional benefit and does increase risk of bleeding.

Headache is a common side effect of dipyridamole and sometimes causes patients to self-discontinue the drug. Normally the headaches can be treated symptomatically with acetaminophen. Do not use ticlopidine—it's expensive, performs no better than the agents above, and can cause significant neutropenia.

Anticoagulate patients who have atrial fibrillation if the patient meets guidelines. (See more on AF in Cardiology, Book 3.) Refer for carotid endarterectomy if the patient has > 70% occlusion and an expected lifespan of > 5 years and the anticipated operative morbidity and mortality is < 6%.

INTRACEREBRAL HEMORRHAGE

Overview

Hemorrhagic stroke is generally due to rupture of small arteries, especially when the small artery branches off at a 90-degree angle from the parent vessel and the blood pressure is very high. The 2 most common causes are hypertension and amyloid angiopathy. Warfarin use is a risk factor, especially when the INR is > 3.

Some patients have preexisting evidence of intermittent, small bleeds on MRI of the brain. It is possible that these MRI-visible "microbleeds" are indicators of which patients are prone to future intracerebral hemorrhage. Because the bleeding arises from small arteries, the symptoms of microbleeds typically evolve gradually but continuously.

Signs and Symptoms

Hemorrhagic stroke occurs in the following 4 areas of the brain (from most common site to least common):

1) Putamen and adjacent internal capsule (50%): If the hematoma involves the internal capsule, there is contralateral hemiparesis and usually sensory loss and hemianopsia. This type of hemorrhage may be difficult to distinguish from a middle cerebral artery infarct (one of the reasons to do the enhanced NECT or MRI looking for blood at presentation). For central white matter of the temporal, parietal, or frontal lobes, symptoms are based on the lobe affected.
2) Thalamus: contralateral hemianesthesia without "cortical" sensory signs. Some motor signs may be present if the adjacent internal capsule is involved.
3) Pons: coma, pinpoint pupils, and quadriplegia. There may be decerebrate posturing bilaterally.
4) Cerebellum: acute dizziness, ataxia, and vomiting with no change in mentation and no loss of consciousness.

Amyloid angiopathy is a common cause of hemorrhagic stroke after the 5th decade of life. The hemorrhage tends to be lobar and subcortical (Image 11-4) and can be multiple. It rarely involves the deep structures (as does a hypertensive bleed). Hemorrhages may recur within months or years. Dementia occurs in 30%. Other clinical features include acute reactive hypertension, vomiting, headache, and nuchal rigidity.

Remember: There are other causes of intracranial hemorrhage, including bleeding diatheses, trauma, and bleeding into a tumor mass. Know that cocaine use can cause vascular malformations and aneurysms, which can lead to major bleeding during episodes of severe drug-induced hypertension. So, all active cocaine users with a cerebral bleed should have an angiography (conventional, CT or MRA) to evaluate for AVM and aneurysms.

Treatment of Intracerebral Hemorrhage

Treatment includes the basic supportive care given to ischemic stroke patients. (See page 11-27.)

Any anticoagulant effects should be immediately reversed with both vitamin K and replacement of clotting factors, no matter the reasons for anticoagulation. Give protamine sulfate for any hemorrhage associated with unfractionated heparin. Also, stop any antiplatelet agents.

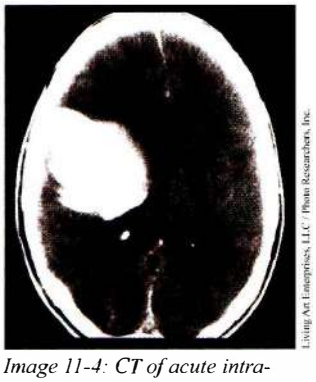

Image 11-4: CT of acute intracerebral hematoma

Control of intracranial pressure (ICP) is important, and mannitol is usually used.

Current guidelines to manage blood pressure recommend continuous IV antihypertensives (e.g., labetalol, esmolol, nicardipine, and enalapril) if systolic blood pressure (SBP) > 220 mmHg or mean arterial pressure (MAP) is > 150 mmHg. For those with SBP 180–220 (MAP 130–150) and increased ICP, consider intermittent or continuous antihypertensives, keeping the perfusion pressure 31–80 mmHg. Rapid reduction of BP is contraindicated because it can lead to vascular compromise and worsening of neurologic deficits.

Depending on the site of bleed, some clots should be surgically removed. Consider clot removal for cerebellar hematomas > 3 cm. Also consider surgery for lobar clots > 30 mL within 1 cm of the surface. In patients with minor deficits or deeply comatose patients, surgery is generally not done. Neurosurgeons are customarily consulted.

SUBARACHNOID HEMORRHAGE

Overview

Subarachnoid hemorrhage (SAH) usually results from bleeding from an intracranial aneurysm. Aneurysms are most common at the bifurcation of vessels in the circle of Willis or its major branches. The age when this most likely occurs is between 40 and 60, and it occurs in women more often than in men.

The majority occur in the anterior circulation: 40% of aneurysms affect the internal carotid artery, 35% involve the anterior cerebral artery, and 20% the middle cerebral artery.

Subarachnoid hemorrhage can also occur after a parenchymal bleed, when there is rupture into the ventricular system. Non-aneurysmal causes of SAH are rare but include AV malformations, sickle cell disease, bleeding diatheses, pituitary apoplexy, trauma, cocaine abuse, and intracranial arterial dissection. Among persons with saccular aneurysms, there is an increased incidence of congenital polycystic kidneys, fibromuscular dysplasia of the extracranial arteries, moyamoya disease, arteriovenous malformations of the brain, and coarctation of the aorta.

Ruptures commonly occur when the patient is active rather than at rest. More than 1/3 of patients report a history of "sentinel bleed" symptoms days or weeks earlier.

The characteristic symptoms of SAH are the acute "thunderclap" or "worst headache of my life" sensation in combination with neck stiffness. Common associated symptoms include loss of consciousness, nausea/vomiting, and photophobia. Systemic manifestations of SAH may include ECG changes of large, peaked T waves, hyponatremia, and diabetes insipidus.

The most important determinant of outcome is the neurological condition of the patient upon arrival at the hospital. If comatose, the prognosis is poor.

Quick Quiz

- What further evaluation is indicated in cocaine users who present with a cerebral bleed even if hypertensive?
- What are the recommendations for treatment of blood pressure in a patient with an intracerebral hemorrhage?
- What is the most common cause of SAH?
- What causes mycotic aneurysms?
- Which patient groups are prone to subdural hematomas?

Diagnosis of SAH

Non-enhanced CT (NECT) is the best test to identify blood in the subarachnoid space. If this is negative and the NECT does not show a mass, then do a lumbar puncture. The CT misses progressively more subarachnoid bleeds as time passes from initial rupture—picking up only about 50% of bleeds after 5 days. In a SAH, CSF is bloody with xanthochromic supernatant (pink or yellow tint); however, even clear CSF does not preclude the diagnosis because it may take hours after onset of the bleed before you find red cells at the level of the spine where you draw the CSF sample.

If a bleed is still suspected in the setting of a normal NECT and LP, then angiography is the procedure of choice. CTA and MRA are alternatives to invasive angiography, and their sensitivity and specificity are close to the standard angiogram. CTA is now very often included as an enhancement to the basic triage NECT for patients with stroke symptoms. The NECT in Image 11-5 shows a massive subarachnoid hemorrhage in which all the white in the brain tissue is due to blood in the subarachnoid space.

Complications of SAH

After a sentinel bleed, rebleeding is common. The risk is highest in the first 24 hours, but the risk remains high for at least 1 month.

Vasospasm may occur in up to 70% of patients and begins 3–5 days after the hemorrhage. It reaches a peak at 5–14 days and resolves in 2–4 weeks.

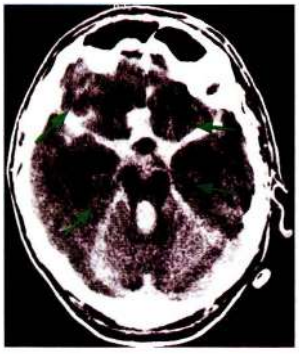

Image 11-5: Massive subarachnoid hemorrhage

The 3rd major complication is communicating hydrocephalus, which occurs in 15–20% of patients after SAH. The likelihood of hydrocephalus depends on the volume of intraventricular and subarachnoid blood.

Seizures occur in 5–10%; 2/3 begin within the 1st month after the hemorrhage, while the remaining occur within the 1st year.

Treatment of SAH

If the patient is on an anticoagulant or antiplatelet agent, stop the drug before performing any interventions. Surgical clipping and endovascular coil insertion into the bleeding vessel are the major interventions used to prevent the aneurysm from bleeding again. Remaining treatment focuses on preventing the complications, such as calcium channel blockers to prevent vasospasm. Control of ICP and blood pressure is important as well, although recommendations are less clear-cut than with intracranial hemorrhages.

Know that 1st degree relatives of patients who experienced a SAH have a 2–5x increased risk of a SAH. 2010 guidelines on the primary prevention of stroke do recommend aneurysmal screening, as discussed previously under Primary Prevention of Stroke on page 11-22.

Note on other aneurysms: Mycotic aneurysms are caused by septic emboli, most often from infected heart valves. They are commonly small and occur in the distal vasculature. This is in contrast to saccular aneurysms that occur more proximally, at the branch points of the arteries (at the point where the middle cerebral artery branches off of the internal carotid artery).

SUBDURAL HEMATOMA

Subdural hematoma (SDH) is not always due to direct trauma; deceleration forces can also cause it. Consider SDH in patients with a history of falls, blows to the head, and vehicle accidents. Subdural bleeds are usually of venous origin.

SDH can be acute or chronic, and each manifests differently. In acute SDH, 1/2 of the patients immediately become comatose, but the other 1/2 remain lucid for a period of hours to days, after which cognition becomes gradually and progressively impaired until coma develops.

Symptoms may also be fluctuating. Other signs of increased ICP are often present; e.g., headache, nausea/vomiting, neck stiffness, and gait abnormalities.

In chronic SDH, the trauma is often forgotten. Over a period of weeks, patients may develop headache, lightheadedness, slowness in thinking, apathy, drowsiness, unsteady gait, and occasionally seizure. Initially, they may be diagnosed as having a vascular lesion, brain tumor, drug intoxication, a depressive illness, or Alzheimer disease.

NECT is used in triage of these patients, but MRI with FLAIR is the most sensitive test. NECT in Image 11-6 shows a subdural hematoma with a skull deformity.

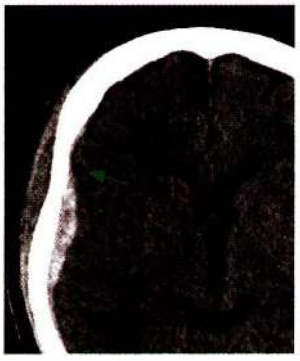

Image 11-6: Subdural hematoma

Treatment for SDH is typically surgical—except for very small bleeds without any neurologic symptoms, which are observed closely.

EPIDURAL HEMATOMA

Epidural hematomas, because of their arterial origin, evolve more rapidly than subdural hematomas. These are typically caused by temporal trauma that damages the middle meningeal artery—in association with temporal bone fractures. Symptoms of increased ICP are typically rapid after the head trauma, but a short period of lucidity may occur, followed by rapid obtundation.

As with SDH, diagnosis can be accomplished with NECT, but MRI with FLAIR is most sensitive.

Treatment consists of early evacuation of the hematoma via a craniotomy. If untreated, herniation occurs, with mortality varying from 15–40%.

TRANSIENT GLOBAL AMNESIA

Transient global amnesia (TGA) is characterized by abrupt onset of global anterograde amnesia, with a variable impairment of retrograde memory not associated with any other major neurologic signs or symptoms. Except for amnesia during and around the event, patients recover completely in 2/3 of cases within 2–12 hours and in almost all cases within 24 hours. TGA is considered benign, and the condition recurs infrequently.

Patients are commonly between 50 and 80 years of age and suddenly develop an inability to make new memories. They act disoriented, asking multiple questions repeatedly. The amnesia can even extend back to years, although more commonly just days to weeks. Some patients have accompanying nausea and dizziness. TIA can present similarly and should be considered.

Precipitating events are seen in many cases and include strenuous exercise, intense emotion, sexual intercourse, mild head trauma, pain, temperature extremes (e.g., swimming in cold water), cervical manipulation, coughing spells and other Valsalva-like activities, and medical procedures that require anesthesia (e.g., colonoscopy). The etiology is unknown, although migraine may be a predisposing factor.

NECT and brain MRI with DWI are typically normal. PET and SPECT studies have shown hypoperfusion and hypometabolism in the hippocampi and associated mesial temporal lobe structures during the attack, with resolution following the attack. The attacks self-resolve. No treatment is necessary.

CNS METASTASES

CNS metastases typically cause a slow onset of symptoms (headaches, focal neuro deficits, impaired cognition, seizures, and/or stroke symptoms), although they can be abrupt if there is hemorrhage into a tumor.

Know the following main mets to the brain (Table 11-4):

Parenchymal brain metastases occur most commonly with lung, renal, and breast cancer, as well as with melanoma and lymphoma.

Dural metastases occur with breast and prostate cancer.

Epidural metastases at the level of the spinal cord cause back pain, usually worse when lying down. New onset of bladder or bowel dysfunction (incontinence, urgency) is very important and should alert you to consider spinal epidural metastases, especially in the setting of new back pain. In a patient with a history of cancer—especially prostate, breast, and lung cancer—and with cord compression symptoms (cauda equina), metastases must be ruled out!

Meningeal malignancy is most frequent in lymphomas, carcinoma of the breast, and melanoma. It is less commonly seen in cancers of the lung and the gastrointestinal tract, childhood leukemia, and systemic lymphoma. MRI with contrast is the best imaging study.

Treatment of CNS metastases depends on how many metastases are present, the cancer prognosis, and the functional status of the patient. An approachable, single metastasis in a functional patient is treated with surgery and radiation. Small lesions (< 3 cm) and/or surgically inaccessible lesions can be treated with stereotactic radiosurgery. Less functional patients with numerous lesions are usually treated with whole brain radiation and chemotherapy +/– corticosteroids.

Table 11-4: Main Mets to the Brain

	Breast	Lung	Prostate	Melanoma	Lymphoma	Renal
Parenchymal	+	+		+	+	+
Dural	+		+			
Epidural	+	+	+			
Meningeal	+			+	+	

QuickQuiz

- Describe the differences between subdural and epidural hematomas.
- A patient with history of prostate cancer and new onset of urinary incontinence should make you consider what diagnosis?
- What is Wernicke encephalopathy? How is it treated?
- How does the presentation of the typical Wernicke patient differ from that of the typical Korsakoff patient?
- What are the symptoms of lithium toxicity?
- What effect does a hyponatremic state have on lithium resorption by the kidney?

METABOLIC AND TOXIC DISORDERS

WERNICKE'S / KORSAKOFF'S

Wernicke encephalopathy and Korsakoff syndrome are considered different presentations of the same disease process. Wernicke's is milder and reversible while Korsakoff's is more severe and only partially reversible. The cause is thiamine (B_1) deficiency.

Wernicke encephalopathy is most often associated with alcoholism, but it can be seen in cases of protein-energy malnutrition (extreme catabolic states, kwashiorkor, marasmus), malabsorption, and specific loss of thiamine during dialysis.

It is characterized by global confusion with inattention, apathy, disorientation, and memory loss that worsens over days to weeks.

Abnormal eye movements are typical and include horizontal nystagmus and a disordered conjugate gaze that progresses to ophthalmoplegia (bilateral lateral rectus weakness, either in isolation or together with palsies of other extraocular muscles). The pupils may become sluggishly reactive to light. The person may have trouble standing or walking due to truncal ataxia.

Diagnosis is clinical. If the early signs of the disease are not recognized and treated, a progressive depression of consciousness occurs with stupor, coma, and death in a matter of a week or two.

Know the typical Wernicke's presentation: confused + walks drunk + trouble moving eyes.

Korsakoff syndrome is a chronic amnestic syndrome associated with alcoholism, malnutrition, and vitamin B_1 deficiency often coincident with Wernicke's and may emerge as the symptoms of Wernicke's are treated. The amnesia that occurs with Korsakoff's can be both retrograde and anterograde. Attention and mentation appear normal. Patients often confabulate because of the memory problems. The stories are frequently happy-go-lucky fantasies, so-called "gleeful confabulation."

The typical Korsakoff's presentation: an underweight, poorly nourished, but very attentive alcoholic who tells fantastical stories that couldn't possibly be true and then has no memory of the discussion.

Other neurologic manifestations of the Wernicke/Korsakoff syndromes are peripheral neuropathy, retrobulbar optic neuropathy, impaired olfactory discrimination, and postural hypotension.

Treatment: Immediate treatment with thiamine resolves the problem of Wernicke's and prevents Korsakoff syndrome. Once Korsakoff syndrome develops, thiamine has only partial effect. In fact, the majority of patients who emerge from Wernicke's have irreversible symptoms of Korsakoff's.

Treatment for Wernicke encephalopathy is thiamine, at a minimum dose of 500 mg (in saline) by infusion 3x/day for 2–3 days, followed by 500 mg thiamine IV or IM daily for another 5 days. Thereafter, oral thiamine supplementation should be continued, typically at a dose of 100 mg/day. Deficiency in other vitamins and minerals, especially niacin and magnesium, should also be corrected. Wernicke's typically improves within hours of thiamine replacement.

In Nephrology, Book 2, we discuss how IV glucose given to a chronic alcoholic causes a decrease in the already depleted stores of phosphate and can cause hypophosphatemia. A similar sequence can occur with the thiamine stores—IV glucose can precipitate Wernicke encephalopathy in alcoholics.

Remember: Give IV thiamine before IV glucose in any patient with a possible metabolic cause of coma.

LITHIUM TOXICITY

Lithium levels in the upper therapeutic range frequently cause tremor and asterixis. Remember: Hyponatremia causes increased lithium resorption from the kidney. Above a level of 1.5–2 mEq/L, the patient develops confusion, delirium, dizziness, nystagmus, ataxia, stammering, diffuse myoclonus, nephrogenic diabetes insipidus, vertical nystagmus, and opsoclonus. Toxic lithium levels cause seizures and coma; treat with hemodialysis.

The symptoms of toxicity may resemble Creutzfeldt-Jakob disease.

Note: Opsoclonus is rapid, involuntary, multivectorial (horizontal and vertical), unpredictable, conjugate eye movements.

ANTICHOLINERGIC TOXICITY

Classically, symptoms are:

- red as a beet (cutaneous vasodilation),
- dry as a bone (anhidrosis),
- mad as a hatter (hallucinations),
- blind as a bat (mydriasis),
- full as a flask (urinary retention), and
- hot as a hare (hyperthermia).

See General Internal Medicine, Book 5, for more detail on these and other toxicities and treatments.

DISEASES OF MUSCLE AND NERVE

MYELOPATHIES

Myelopathies are diseases of the spinal cord. Typical manifestations are gait ataxia, spasticity, and hyperreflexia. Bowel and bladder incontinence arise as disease worsens. There are many subcategories.

Metabolic Myelopathy

Subacute Combined Degeneration of Spinal Cord

Subacute combined degeneration of the spinal cord due to B_{12} deficiency is the prototype for metabolic myelopathy. Severe B_{12} deficiency causes segmental loss of myelin, especially in the dorsal and lateral columns. Clinical presentation is gradual weakness associated with paresthesias and loss of proprioception with development of ataxia. Severe cases end in extensive bilateral lower extremity weakness, spasticity, and urinary incontinence +/– cognitive impairment. These cognitive changes include confusion, apathy, delusions, paranoia, and mental deterioration.

Tip: Think of B_{12} deficiency in a patient with brisk knee jerks (due to pyramidal tract dysfunction) and absent ankle jerks (due to peripheral neuropathy).

Know that the neurologic changes can occur without any associated macrocytosis or anemia! The CSF is typically normal and EMG shows slowing of sensory conduction.

Diagnose by measuring serum B_{12}, methylmalonic acid (MMA), and homocysteine (HC) levels. MMA and HC are more sensitive tests that are included to make a diagnosis in patients who have low-normal or normal B_{12} levels. In states of B_{12} deficiency, both MMA and HC are increased. Know that copper deficiency in patients with malabsorption or post gastric bypass can present like subacute combined degeneration of the cord due to B_{12} deficiency.

Infectious Myelopathies

AIDS

Advanced AIDS patients can get vacuolar myelopathy with vacuolation and deterioration of the dorsal and lateral spinal columns that presents as ascending paresis with a sensory component (loss of vibration and proprioception) and urinary incontinence. Clinical presentation is very similar to subacute combined degeneration of the cord. It commonly accompanies HIV-associated dementia but occasionally occurs alone. Many other things can do this in a patient with virtually no immune system, but be sure to exclude a cord lesion with MRI.

Epidural Abscess

Spinal epidural abscess is a medical emergency that requires rapid diagnosis and treatment of the bacterial infection. The abscess can develop from bacteremic seeding from any source or contiguous infection after spine surgery, but rarely from lumbar puncture. Risk factors include immunodeficiency states (e.g., diabetes, HIV/AIDS), alcoholism, and any conditions or behaviors associated with transient bacteremia (e.g., injection drug use and boils). The abscess may start as a spinal osteomyelitis and progress to an abscess, causing cord compression. *S. aureus* is the most common etiology of epidural abscess.

Remember: The main symptom of epidural abscess is back pain. Suspect epidural abscess in anyone who has been bacteremic from any cause and presents with back pain and fever. For example, rule out epidural abscess in the postpartum patient who had an epidural during delivery—the cause is almost always some type of nosocomial *Staphylococcus* species.

Initial symptoms include a few days to 2 weeks of fever and backache with localized tenderness, radicular pain, and neurologic deficits. Not all patients have all of the symptoms, and the diagnosis can be easily missed.

Abscess is best diagnosed with immediate contrasted MRI with FLAIR (contrasted CT is a less sensitive alternative), TB skin test, and blood cultures. Perform myelography if the abscess is not clearly seen by MRI (or CT, if that is the only option).

Treatment: immediate decompression with laminectomy and drainage followed by appropriate antibiotics, except in cases of TB where treatment is entirely medical (using 4-drug antituberculous antimicrobials).

Tuberculosis

Pott disease is tuberculous osteomyelitis of the spine and is sometimes associated with cord compression. Usually, this form of TB is due to reactivation disease (rarely is it primary tuberculosis). Less than 40% of affected patients have constitutional symptoms (fever, night sweats, and weight loss). They also have back pain and possible neurologic deficits and/or radicular symptoms.

Diagnosis requires a high index of suspicion and is confirmed by biopsies for pathology and culture. A positive TB skin test or serum interferon-gamma release assay (IGRA) supports the diagnosis. Treatment is with standard 4-drug TB therapy. (See Pulmonary Medicine, Book 2, for specific details.)

- Describe the findings in subacute combined degeneration due to B_{12} deficiency.
- What other mineral deficiency can present like the subacute combined degeneration due to vitamin B_{12}?
- What are risk factors for an epidural abscess? What is the most common cause?
- What causes Pott disease?
- Describe the clinical presentations of neurosyphilis.
- What is the clinical presentation of transverse myelitis?
- What is Devic disease? Which auto-antibody is the culprit?
- What are the symptoms of cervical myelopathy?

Syphilis

Neurosyphilis is a potential complication if syphilis is untreated and as an earlier presentation in patients with HIV/AIDS. Both secondary and tertiary syphilis can affect the cord. The secondary manifestation of meningovascular syphilis can present as stroke or as infarction of the spinal cord (rare). Tertiary syphilis presents as cognitive impairment, tabes dorsalis, and/or aortitis.

The cognitive impairment can be remembered by the mnemonic **PARESIS**: **p**ersonality, **a**ffect, **r**eflexes, **e**yes (Argyll-Robertson pupil), **s**ensorium, **i**ntellect, **s**peech. The Argyll-Robertson pupil is constricted and reacts to accommodation but does not react to light.

Tabes dorsalis is syphilitic involvement of the posterior columns that causes deficits in proprioception, manifesting as ataxia and paresthesias. Tabes dorsalis is diagnosed using the following:

- Screening tests for syphilis (RPR or VDRL)
- *T. pallidum*-specific testing (MHA-TP)
- +/– Lumbar puncture and biopsies with routine path and cultures

Read more about diagnosis and treatment of syphilis (including neurosyphilis) in Infectious Disease, Book 1.

Inflammatory Myelopathy

Transverse Myelitis (TM)

TM is a rare problem causing inflammation of both sides of 1 or 2 segments of the cord (usually thoracic). The exact cause is uncertain, but it appears to be an autoimmune reaction. Onset typically follows a viral infection, but it is also associated with multiple sclerosis and several autoimmune disorders (lupus, mixed connective tissue disease, Sjögren's, scleroderma, and rheumatoid arthritis). There are cases of it occurring even more rarely after some vaccinations.

Clinical presentation is most often acute and progressive over a few days, with early paresthesias, bilateral leg weakness, and numbness with a sensory deficit below the level of the lesion. Sphincteric disturbances and backache are also common. A slight asymmetry of the symptoms and signs, a sensory level over the trunk, or a Babinski sign differentiate it from a rapidly progressive polyneuropathy such as Guillain-Barré syndrome.

MRI with contrast shows the inflammation of the cord. CSF analysis shows increased protein, lymphocytosis, and normal glucose.

Neuromyelitis optica ([NMO], a.k.a. Devic disease): This variant of myelitis manifests primarily by attacking the optic nerves and spinal cord. The presence of serum NMO-IgG antibodies, also known as anti-aquaporin antibodies, is associated with increased risk of recurrent myelitis. NMO antibodies also have a sensitivity of 73% and specificity of 91% for the diagnosis of Devic disease. Lesions on brain MRI are also predictive of progression to MS in idiopathic cases of transverse myelitis.

A 2011 AAN guideline recommends empiric steroids and even plasmapheresis if there is no response to steroids, although the level of evidence for these is weak.

Compression-Induced Myelopathies

Cervical Spondylosis with Myelopathy

Cervical spondylosis is age-related wear and tear on the cervical spine. It begins with changes in the intervertebral discs, which occur gradually and accumulate with age. Neck pain is common. If the disc herniates, it will compress a nerve root, causing a radiculopathy at that level. Note: Radiculopathy manifests by numbness, paresthesias, weakness, and hyporeflexia in the corresponding region that is supplied by the compressed nerve root. The area affected is referred to as dermatome (sensory) or myotome (muscle groups).

When the spondylosis becomes more severe, it may result in compression of the spinal cord itself (myelopathy), causing spasticity, hyperreflexia, and gait abnormalities. Gait abnormalities may be attributed incorrectly to increasing age of the patient. A quick test is to check reflexes; in patients > 65 years of age, a brisk ankle reflex could be the sole clue to cervical myelopathy.

If a rheumatoid arthritis patient presents with a post-op focal neuro deficit, suspect C1–C2 spinal cord trauma induced by intubation. This is likely if the patient has chronic asymptomatic C1–C2 subluxation. Anesthesiologists are generally well aware of this susceptibility, and order C-spine flexion/extension views preoperatively to assess for any signs of cervical subluxation. Of course, other mechanisms can cause similar injury in these patients.

Thoracic Myelopathy

Thoracic sensory levels: T4/T5 at nipple line and Tl 0 at umbilicus. Thoracic spondylosis is distinctly unusual.

In thoracic myelopathies, think tumor, vertebral compression fracture, or transverse myelitis—not compression from spine osteoarthritis.

Lumbosacral Myelopathy

The cord ends at L1–2. Lumbosacral disease affects the cauda equina and nerve roots, and may cause L4, L5, or S1 radiculopathy with the following presentations:

Affected dermatomes:

- L4 = medial aspect of leg
- L5 = anterolateral aspect of leg and dorsum of foot, including great toe (L5 = Large toe)
- S1 = lateral side of foot by the small toe (S1 = Side of foot near Small toe)

Affected myotomes:

- L5 = weakness of the great toe extensor and ankle dorsiflexion. (Patients have trouble standing on the heel and present with foot drop.)
- S1 = weakness of ankle plantar flexion. (Patients have trouble standing on the toes.) Ankle reflex is absent.

Lumbar spinal stenosis is a congenital narrowing of the spinal canal in the area of T10–L1, the conus medullaris. Patients are more susceptible to impingement of the cauda equina secondary to disc disease, ligamentous degeneration, and arthritis.

Lumbar spinal stenosis may result in neurogenic claudication, characterized by a deep, progressive ache in the legs, sometimes associated with lower extremity numbness, paresthesias, or weakness, which is precipitated by standing or walking for a few minutes. These symptoms are aggravated by upright posture, which extends the spine, and relieved by sitting or squatting (flexing hips/spine).

Buzz phrases that help diagnose spinal stenosis include "gets better when bending over the shopping cart" or "improves when walking uphill." These activities curve the vertebral bodies and open space in the canal.

Differential diagnosis for spinal stenosis includes vascular claudication, which also causes symptoms when walking or exercising leg muscles but not when standing upright (Table 11-5).

A presumptive diagnosis of spinal stenosis is made clinically. Neuroimaging (usually MRI) before treatment is not necessary for patients < 50 years old with no neurological deficits. In this group of patients, MRI is done only if there is worsening of symptoms during the 1st month of treatment or no improvement by the end of this 1st month. In patients > 50 years old and in those with neurological deficits, imaging is often done immediately to confirm the diagnosis before determining treatment.

Treatment is conservative: physical therapy and analgesics. Surgery is a last resort for patients who have debilitating pain not relieved with conservative measures. Surgery is indicated urgently, however, in patients with progressive neurologic deficits or incontinence.

Miscellaneous Myelopathies

Syringomyelia

Syringomyelia is a progressive myelopathy caused by cavitation of the central spinal cord, typically in the cervical region but may extend into the thoracic region. It can be idiopathic, developmental, or acquired. About 2/3 of cases are associated with Arnold-Chiari malformation—a congenital malformation in which there is a downward shift of the cerebellar tonsils and medulla through the foramen magnum into the cervical area of the spine, sometimes with syrinx (cyst) formation.

Syringomyelia causes a painless weakness and wasting of the hands and arms (brachial amyotrophy) and segmental sensory loss of dissociated type (i.e., loss of thermal and painful sensation with sparing of tactile, joint position, and vibratory sense). Symptoms of syringomyelia typically occur as a "suspended" or "cape-like" sensory deficit across the shoulders and proximal upper limbs.

The loss of pain and temperature, with initially preserved light touch and vibration sensation, indicates involvement of the crossing spinothalamic fibers in the central part of the cord. When the anterior horn cells are affected, with lateral expansion of the syrinx, weakness and atrophy of the upper limbs occur, starting in the hands and moving proximally to include the arms and then shoulder muscles. Occipital and nuchal headaches are also very common.

Diagnose syringomyelia with MRI.

Anterior Horn Cell Disorders

Anterior horn cell problems cause motor deficits only. **Amyotrophic lateral sclerosis** ([ALS], a.k.a. Lou Gehrig disease) is the most common cause of anterior horn cell disorder. The hallmark of ALS is marked, simultaneous upper and lower motor neuron signs. Men are affected more often than women.

Table 11-5: Spinal Stenosis vs. Vascular Claudication

	Change in Symptoms: Walking	Standing	Sitting
Lumbar Spinal Stenosis	Worse	Worse	Better
Vascular Claudication	Worse	Better	Better

QuickQuiz

- What is lumbar spinal stenosis? What are the classic exacerbating and relieving body positions and movements?
- From the patient's history, what clues help you differentiate lumbar spinal stenosis from vascular claudication?
- What is the clinical presentation of syringomyelia?
- What is the clinical presentation of ALS?
- What conditions can cause UMN and LMN signs in the same patient?

A patient with ALS presents with some variation of:

- diffuse hyperreflexia and spasticity (upper motor neuron), along with
- fasciculations, weakness, and atrophy (lower motor neuron).

Consider ALS in the patient with lower extremity weakness (possibly even falls), difficulty with fine motor skills, and fasciculations and/or atrophy on exam. Patients report severe muscle cramping. Cognitive dysfunction is not a feature.

ALS is relentlessly progressive, involving upper and lower extremities, truncal and bulbar musculature, and is terminal typically within 3–5 years after diagnosis. Management of these patients includes determining how to proceed with respiratory and nutritional support as the disease progresses. Riluzole is commonly used, but extends life by only about 3 months.

Polio used to be the most common cause of anterior horn cell disorder; now post-polio syndrome must also be considered. Post-polio syndrome causes areflexia and progressive weakness without upper motor neuron signs. "Spinal muscular atrophy" is a set of hereditary disorders of the anterior horn lower motor neurons. A polio-like presentation today is more likely to be due to West Nile virus encephalitis.

Conditions that cause upper motor neuron (UMN) and lower motor neuron (LMN) findings in the same patient include:

- ALS (motor)
- B_{12} deficiency with subacute combined degeneration of the cord (motor + sensory)
- Cervical myelopathy (motor + sensory)
- Syringomyelia (LMN = arms, UMN = legs, motor + sensory)
- Friedreich ataxia (ataxia + motor + sensory)
- Syphilis (motor + sensory)
- Hyperthyroidism (motor + sensory)

NEUROPATHIES

Overview

Neuropathies can be divided into several categories based on which nerves are affected.

If the process involves only 1 nerve, it is called **mononeuropathy**. Mononeuropathies are generally due to entrapment (as with carpal tunnel syndrome); other causes include focal ischemia and trauma.

If 2 or more nerves are affected in a limited distribution, the term **mononeuritis multiplex** is used. Mononeuritis multiplex results from systemic disorders like diabetes or vasculitis.

Neuropathies that symmetrically and diffusely involve the peripheral nerves are called peripheral neuropathies (or polyneuropathy). Peripheral neuropathies involve distal segments more than proximal. There are many causes of peripheral neuropathy (see below).

Involvement of multiple nerves within a plexus is referred to as plexopathy.

The workup for any neuropathy includes glucose, HbA1c level, free T_4 and TSH levels, vitamin B_{12}, ESR, creatinine, CBC, and a chest x-ray. Electromyography and nerve conduction studies (EMG/NCS) are done regardless of whether the symptoms are mono- or polyneuropathy. EMG/NCS help to identify any disease of muscle and nerve conduction. Serum protein electrophoresis, immunoglobulin electrophoresis, and quantitative immunoglobulin assays are also done if the patient is > 40 years of age, particularly if the EMG/NCS suggest a demyelinating neuropathy.

Inflammatory and hereditary neuropathies are the most frequently missed causes of polyneuropathy. So, consider inflammatory causes and include a careful family history in your evaluation of peripheral neuropathies!

Mononeuropathies

Focal / Compressive

Focal mononeuropathies are caused by localized peripheral nerve damage, usually from a compression injury (although ischemia can also cause damage, especially in autoimmune diseases associated with vasculitis). Single nerve involvement can be caused by leprosy, sarcoid, and herpes zoster (in addition to the dermatomal rash).

The main sites of compression or entrapment are the ulnar nerve at the elbow, the median nerve at the wrist, and the peroneal nerve at the knee (discussed below). Because radiculopathies and mononeuritis multiplex can have presentations similar or identical to focal/compressive neuropathies, they must also be considered in the workup of patients presenting with focal neuropathic symptoms.

Radial neuropathy (acute wrist drop) is mostly from nerve compression but is occasionally seen as a result of diabetic neuropathy (page 11-39) and may also occur

with lead toxicity. It has been called "Saturday night palsy" in inebriated patients because it occurs after bouts of unconsciousness whereby the nerve becomes compressed in the radial groove of the humerus. This typically resolves slowly over several weeks or months—provided the patient doesn't continually reinjure the nerve! Physical therapy is the best treatment, using wrist splints.

Lower brachial plexus injury (from surgery/tumor/trauma) causes a claw-hand deformity, similar to that which may be seen with severe ulnar neuropathy.

Carpal tunnel syndrome (CTS) is median nerve entrapment at the wrist, typically from repetitive stress, causing sensory loss, paresthesias, and weakness involving the first 3 or 4 digits of the hand, but patients can have pain anywhere in the arm or shoulder! Thenar muscle atrophy may occur. Median nerve entrapment at the wrist almost invariably causes nocturnal awakening due to hand pain or paresthesias (Image 11-7). Prevalence of hypothyroidism is 1–10% in patients with CTS, so most experts recommend screening with TSH. Don't forget about the association of CTS with acromegaly, as well.

Initial treatment of carpal tunnel syndrome is neutral alignment wrist splints and modifying the repetitive stress. If this is ineffective, steroid injection may help. Next step is median nerve release. Certain exercises (yoga and some specific physical therapy exercises such as "nerve gliding") seem to help. Ultrasound helps some.

[Know:] Pregnancy can cause an acute presentation of CTS that typically improves after delivery. Splints are the best treatment for this patient group.

Ulnar neuropathy causes sensory loss and paresthesias in the little finger and ulnar aspect of the ring finger, as well as weakness of finger abductors and adductors. It is usually due to compression of the nerve at the elbow (cubital tunnel syndrome) but also may result from a lesion at the wrist. Rarely, trauma to the heel of the hand can result in an ulnar injury. Elbow pads and splints help. Surgery is also an option for refractory cases.

Sciatic nerve compression causes pain and paresthesias that travel down the back or side of the leg into the foot or ankle. It can, like S1 radiculopathy, cause difficulty standing on toes. Unlike S1 radiculopathy, it does not cause a decreased ankle jerk when compared to the opposite ankle (Table 11-6).

Image 11-7: Thumb muscle wasting due to carpal tunnel syndrome

Peroneal nerve compression typically occurs at the proximal head of the fibula, causing foot drop. Remember that L5 radiculopathy also causes foot drop.

To distinguish between peroneal nerve compression and L5 radiculopathy: Patients with peroneal nerve compression cannot evert the foot well but can still invert it, while L5 radiculopathy prevents or hinders both eversion and inversion (Table 11-7). Also, it is useful to test proximal L5 innervated muscles such as the hamstrings and thigh abductors, which will not be affected with peroneal nerve compression.

[Know:] Charcot-Marie-Tooth disease (page 11-38) can cause symptoms similar to peroneal nerve compression.

Mononeuritis Multiplex

Note that mononeuritis multiplex can present identically to the focal/compressive neuropathies above. Rather than being caused by nerve compression, mononeuritis multiplex is caused by a systemic disease. Vasculitis and vascular occlusion of the vasa nervorum (vessels that supply the nerves) are the main causes.

Consider any of the following as a possible cause of mononeuropathy +/– multiplex:

- Rheumatoid arthritis
- DM
- Connective tissue diseases
- Vasculitis
- Polyarteritis
- Lyme disease (Think of this in a hiker with new-onset foot drop.)
- Neuralgic amyotrophy

Neuralgic amyotrophy (other names: Parsonage-Turner syndrome, brachial plexus neuropathy, acute brachial radiculitis) is temporary inflammation of the brachial plexus that may follow a vaccination or viral illness. Initially, it causes extreme pain in the shoulder with radiation to the arm, neck, and back. Within hours to days after the onset of pain, the shoulder muscles and proximal arm musculature become weak. Bilateral involvement may occur. Diagnosis is clinical, supported by EMG/NCS. It improves in 1–3 years with conservative management.

CNS Lyme disease is discussed in Infectious Disease, Book 1.

Bell's Palsy

Bell's palsy is caused by dysfunction of the external 7th cranial nerve. It is regarded as idiopathic, but herpes simplex (or its associated immune response) is the cause of most cases (definitively supported by finding evidence of the virus by PCR in the affected nerve roots).

Quick Quiz

- Where are the main points of compression for ulnar, median, and peroneal nerves?
- Nocturnal awakening with hand pain is frequently due to what diagnosis? Which nerve?
- Mononeuritis multiplex is associated with which diseases?
- What infection should you consider in a hiker from Connecticut who presents with new onset of foot drop?
- Name 3 disease processes that can cause facial palsy.
- What is the clinical presentation of Bell's palsy?
- Diabetes is associated with which neuropathies?

Varicella zoster is also a cause and is the probable diagnosis when a clinical scenario includes vesicles involving the tympanic membrane and external auditory canal (Ramsay Hunt syndrome).

2 important systemic diseases can also cause a facial palsy that presents identically:

1) Lyme disease
2) Acute HIV

Some experts call these palsies "Bell's," but others prefer to identify them as a systemic manifestation of Lyme or HIV.

Other causes of facial palsy: neurosarcoidosis, Guillain-Barré syndrome, and parotid tumors.

Bell's palsy affects an entire half of the face, including the forehead. It causes ipsilateral facial muscle paralysis and occasionally results in no taste sensation on the anterior 2/3 of tongue, loss of lacrimation, and hyperacusis. Pregeniculate lesions are associated with the loss of taste, salivation, and lacrimation, while more distal lesions spare these functions.

Table 11-6: S1 Radiculopathy vs. Sciatica

	Able to Tiptoe?	Decreased Ankle Jerk?
S1 Radiculopathy	No	Yes
Sciatica	No	No

Table 11-7: L5 Radiculopathy vs. Peroneal Nerve Injury

	Foot Drop?	Able to Invert Foot?	Able to Evert Foot?
L5 Radiculopathy	Yes	No	No
Peroneal Nerve Injury	Yes	Yes	No

To help differentiate Bell's palsy from other nerve damage, know that cortical lesions spare the muscles of the forehead and upper eyelid, whereas Bell's palsy affects them.

Diagnosis is clinical. Imaging of the head is reserved for patients who don't improve within 6 months or who continue to progress with facial weakness after 3 weeks.

Know that if the palsy is preceded by a period of facial twitching, the risk of tumor is higher. These patients should have urgent imaging.

Patients who begin to improve within 3 weeks will commonly recover completely. If complete ipsilateral paralysis occurs, full recovery is less likely.

A week of prednisone shortens the course and improves function if started within 7 days of clinical onset. Studies assessing combined antiviral drugs (acyclovir or valacyclovir) + prednisone show conflicting results. Some experts give both; others do not, unless obvious signs of herpes are present (i.e., vesicles). Eyelid surgery is reserved for patients with severe palsy, or where there is corneal anesthesia or xerophthalmia not amenable to eye lubricants.

Diabetic Mononeuropathies

[Know:] Diabetes is associated with several cranial neuropathies. Neuropathies affecting cranial nerves 3, 4, and 6 present with eye pain, drooping eyelids, and double vision; those affecting cranial nerve 7 present with Bell's. Radial, ulnar, and peroneal isolated neuropathies are also more common in diabetics.

Note that diabetic involvement of the 3rd cranial nerve typically presents with double vision and weak eye movements without any changes in the pupils. Exam questions might have the patient presenting with diplopia and (pick one) chronic sensory dysfunction, wrist drop, or foot drop.

Remember: A diabetic 3rd cranial neuropathy spares the pupil. If a patient has a 3rd cranial neuropathy with pupillary dilatation, think compression of the 3rd cranial nerve by an aneurysm of the posterior communicating artery. This warrants an urgent MRI and MRA!

Diabetic lumbosacral plexopathy (amyotrophy) presents with leg pain (82%) followed by proximal weakness of the leg. It initially tends to be unilateral (88%) but eventually involves both legs. Autonomic dysfunction occurs in 50%; weight loss > 10 lbs occurs in about 80% of patients. Sensory symptoms and signs can also occur. The condition develops over months and so does partial or complete recovery. No specific treatment exists, though steroids and cyclophosphamide have been tried.

Polyneuropathies

Demyelinating vs. Axonal Polyneuropathies

Demyelinating polyneuropathies affect motor fibers and present primarily as weakness.

Axonal polyneuropathies are usually a sensorimotor combination, with sensory abnormalities appearing first (paresthesias progressing to numbness), then motor weakness appearing later.

Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is the most common autoimmune, inflammatory polyneuropathy. We now understand that GBS is a syndrome with demyelinating (most common) and axonal variants.

In the vast majority of cases, a mild gastrointestinal or respiratory infection precedes the polyneuropathy. GBS was reported after influenza vaccination in the late 1970s and 1990s and after the meningococcal conjugate vaccine in 2005. Causality has not been established for either vaccine, and the subject is highly controversial. There is no requirement with these vaccines to warn patients about possible GBS, but patients with a history of GBS are cautioned to avoid vaccination for the 1st year after their illness.

Classic demyelinating GBS (termed acute inflammatory demyelinating polyradiculoneuropathy [AIDP]; 90% of U.S. cases) presents as an ascending paralysis of muscles, including respiratory muscles, with areflexia. In practice, patients may have some mild sensory abnormalities and paresthesias initially, but GBS is typically portrayed as a pure motor illness with absent reflexes. Disturbances in autonomic function and urinary retention may also be seen.

The Miller Fisher axonal variant ([MFV]; 5% of cases) is a type of GBS that includes only areflexia, ataxia, and ophthalmoplegia; e.g., patients unable to move their eyes or walk upright.

Two other rare axonal variants comprise the remaining 5% of cases.

Paraparetic (partial paralysis), ataxic, and purely motor or purely sensory forms of the illness have also been observed.

In patients with any type of GBS, the CSF has a normal cell count and a high protein ("albuminocytologic dissociation"); suspect another diagnosis if the CSF has more than 10 WBC/mm^3. EMG/NCS helps to characterize the variant (axonal or demyelinating).

Anti-GQ1b IgG is a unique serum protein measurable in over 80% of MFV cases of GBS, and it assists with diagnosis of this variant.

The acute axonal variants are commonly associated with preceding *Campylobacter jejuni* infections and also with development of many antibodies against the gangliosides found in peripheral nerves (especially anti-GQ1b).

Close respiratory monitoring and care are important. Measurement of vital capacity (VC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP) are used for the bedside estimation of diaphragmatic strength and respiratory function. The trend of these measurements is a guide to the likelihood of respiratory failure. Use the 20–30–40 rule to determine need for ventilator support. VC < 20 mL/kg, MIP less negative than –30 cm H_2O, and MEP < 40 cm H_2O.

Plasmapheresis and IV immunoglobulin therapy (IVIG) are equally effective. Use 1 or the other if patients present within 4 weeks of initial symptoms.

Do not use steroids because they are not effective.

Complete recovery is the norm for about 80%; however, 10% of patients have a very prolonged course with or without significant residual weakness. Approximately 5% of patients do not survive the illness.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

CIDP begins insidiously and evolves slowly, either in a steadily progressive or stepwise manner, attaining its maximum severity after several months. In about 15% of cases, CIDP begins like a mild or moderate variant of GBS, but it slowly worsens or has a chronic relapsing course.

Chronic symmetric sensorimotor loss, EMG findings of demyelination, and elevated CSF protein define the illness.

CIDP cases are usually not traceable to an inciting event such as an infection. (Still, it's useful to think of CIDP as "Guillain-Barré that won't go away.") Consider CIDP in the patient with a demyelinating polyneuropathy (by EMG/NCS) that extends beyond 8 weeks in duration.

LP and EMG results are identical to GBS (high protein, no pleocytosis, and demyelinating polyneuropathy). Exclude systemic disorders, specifically HIV, hepatitis viruses, Lyme, thyroid disease, diabetes, myeloma, sarcoid, and connective tissue disorders such as lupus.

Unlike in Guillain-Barré, glucocorticoids hasten recovery and prevent relapse in CIDP. Plasmapheresis or IVIG are also standard treatments. (Pick 1 of the 3.) Several other immunomodulators have been used chronically.

Charcot-Marie-Tooth (CMT)

CMT disease is a hereditary motor and sensory neuropathy and is by far (90%) the most common inherited peripheral polyneuropathy. There are 7 "types" composed of > 30 separate disorders under the general heading of CMT, all caused by mutations in myelin genes that are inherited variably (autosomal dominant, autosomal recessive, or X-linked).

CMT diseases are demyelinating and are differentiated based on genetic markers. All have both motor and

QuickQuiz

- What CSF findings are characteristic of Guillain-Barré syndrome?
- How does the treatment of CIDP differ from the treatment of Guillain-Barré syndrome?
- Name the drug used to treat diabetes that also can induce B_{12} deficiency and cause a severe peripheral neuropathy.
- What are the clinical presentations of myasthenia gravis?

sensory impairment and commonly present within the first 2 decades of life. The neuropathy is symmetrical and progresses slowly. The really rare ones tend to cluster in families. Diagnosis is very simple with genetic testing. EMG/NCS is rarely needed. Treatment is supportive.

Diabetic Peripheral Neuropathy (DPN)

Diabetes mellitus is the most common cause of polyneuropathy in general clinical practice. DPN is an axonal neuropathy that mainly causes sensory changes, including pain, paresthesias, and numbness.

Muscle weakness is generally mild. Some have loss of reflexes. In long-standing cases, trophic changes are noted. Some patients have predominant loss of joint position and vibration sensations.

Control of blood sugars is the most important therapy. Effective treatments for pain include the FDA-approved DPN drugs duloxetine (Cymbalta®) and pregabalin (Lyrica®)—both are equally effective. Other drugs that are used include tricyclic antidepressants, carbamazepine, gabapentin, lamotrigine, tramadol, and venlafaxine. Topical treatment with capsaicin cream and lidocaine also help.

Be aware that in 30% of patients, metformin treatment of diabetes mellitus can result in malabsorption of vitamin B_{12} with subsequent peripheral neuropathy resembling DPN. This is a potentially debilitating side effect of metformin.

Alcoholic Peripheral Neuropathy

Alcohol is directly toxic to both nerves and muscles and causes many kinds of neuropathies (peripheral, autonomic, compressive). The polyneuropathy is typically axonal but is made worse if demyelination is superimposed (caused by nutritional deficiencies).

Symptoms of alcoholic axonal neuropathy start with pain and numbness in the feet in a stocking distribution. Over time, patients lose reflexes, proprioception, and strength.

Patients slowly recover with multivitamin therapy and abstinence from alcohol.

Remember: Acute thiamine deficiency presents as Wernicke's, a polyneuropathy (weakness of extraocular muscles and ataxia) associated with delirium.

Other Causes of Axonal Neuropathies

Know other somewhat common causes of axonal polyneuropathy including:

- Toxins, such as heavy metals (lead, arsenic)
- Chemotherapy drugs (vincristine)
- Isoniazid
- B_6 (pyridoxine) overdose from nutritional supplements
- Organophosphates
- Systemic illnesses (myeloma, porphyrias, thyroid disease, hepatitis viruses, amyloidosis, and HIV/AIDS)

Time of Onset

Differentiating among the polyneuropathies is aided by the time of onset:

- **Short** time of onset (days) is nearly always due to inflammatory, immunologic, toxic, or vascular etiology. Think porphyria, Guillain-Barré, and a few of the toxic polyneuropathies.
- **Long** onset (over several years) is seen with the hereditary disorders, such as Charcot-Marie-Tooth or CIDP.
- **Subacute** onset (several weeks to 2 years) occurs in the majority:
  - Toxicity (Lead and glue-sniffing cause mainly motor effects, while INH and vincristine cause sensorimotor effects.)
  - Nutritional deficiencies (especially B_1, B_6, and B_{12})
  - Paraneoplastic (See Lambert-Eaton page 11-40.)
  - Rheumatologic disorders

NEUROMUSCULAR JUNCTION

MYASTHENIA GRAVIS

Myasthenia gravis (MG) is an autoimmune disorder. Most patients have autoantibodies to either the postsynaptic acetylcholine receptor or muscle-specific tyrosine kinase receptor (MuSK)! An even smaller group of MG patients has neither anti-acetylcholine receptor nor anti-MuSK antibodies (termed "seronegative MG").

MG is associated with thymomas (~ 15% of patients) and thymic hyperplasia (~ 60%), although it is not understood exactly how the thymus is related to antibody formation. Do a chest CT in patients with MG.

There are 2 forms of MG:

1) **Generalized MG** presents as episodic weakness with repetitive movements (weakness—not tiredness, not soreness). Symptoms are worse at the end of the day. Common presenting complaints include weakness while brushing hair, putting away dishes or climbing stairs, and diplopia after a long day. Weakening with repetitive muscle stimulation during the physical exam

(muscle fatigability) suggests the diagnosis. Ptosis is common. Muscles of facial expression, mastication, swallowing, and speech are affected in 80% of patients at some time in the illness. Muscle atrophy is rare, and tendon reflexes are normal.

2) **Ocular MG** presents as weakness localized to the eyes (lids and extraocular muscles).

Practice pearls: Demonstrating fatigable ptosis (i.e., worsening of ptosis on 30 seconds of sustained upgaze) is a good way to differentiate myasthenic ptosis from other forms of ptosis. Of course, the pupil size will be normal, unlike in Horner syndrome. In addition, the pattern of extraocular muscle weakness often does not fit the distribution of a single oculomotor nerve, and may change from one examination to the next.

Diagnosis of myasthenia gravis is best confirmed by measuring antibodies against acetylcholine receptor (AChR-Abs) and against muscle-specific tyrosine kinase ([MuSK-Abs]; a receptor-associated protein). AChR-Abs are present in 85–90% of patients with generalized disease but only in ~ 60% of those with isolated ocular disease. Often, MuSK-Abs are present in patients who are negative for AChR-Abs (~ 50%). Antibody levels are not necessarily prognostic, but they do rise and fall with immunotherapy.

The edrophonium (Tensilon®) test is usually not performed because results are not as reliable as antibody measurements.

The ice pack test can be used for patients with ptosis as part of their symptoms. Ice in a glove is applied to the closed eyelid for 2 minutes, which results in less ptosis. Sensitivity of this test is ~ 80%.

Routine electrodiagnostic studies, including repetitive nerve stimulation studies and single-fiber EMG, are useful in supporting the diagnosis.

Do thyroid function studies because **30%** of patients with myasthenia gravis have chronic autoimmune thyroiditis. Look out for symptoms that suggest lupus or rheumatoid arthritis, since there is considerable overlap. Image the chest with CT or MRI in all confirmed diagnoses to rule out thymoma.

Note: Deep tendon reflexes are preserved in MG as opposed to Lambert-Eaton syndrome.

Treatments used for myasthenia gravis:

- Anticholinesterase agents (e.g., pyridostigmine [Mestinon®])
- Immunomodulators in patients uncontrolled on pyridostigmine (e.g., steroids, cyclosporine, mycophenolate)
- IVIG or plasmapheresis (for myasthenic crisis only because duration of action is very short)
- Thymectomy (takes years to see effects, but definitely perform in patients with thymoma)

Myasthenic crisis is a rapid deterioration of myasthenia that can cause respiratory failure and quadriplegia. A respiratory infection or certain medications can precipitate crises. Besides respiratory support, patients respond to plasmapheresis and IVIG.

Know the few drugs that can precipitate myasthenic crisis in patients with either known or undiagnosed MG:

- Aminoglycosides
- β-blockers
- Procainamide
- α-interferon
- Magnesium sulfate
- Penicillamine
- Quinidine

LAMBERT-EATON SYNDROME

Lambert-Eaton myasthenic syndrome is a paraneoplastic syndrome. About 60% of cases are seen in small cell lung cancer; other associated cancers include prostate, breast, stomach, rectum, and lymphomas. It is also seen rarely in autoimmune diseases. It is itself an autoimmune disease in which antibodies are produced that are specific for calcium channels in presynaptic peripheral nerve terminals, causing decreased release of acetylcholine from the nerve terminals.

Know the following about symptoms:

- Typical symptoms are gradually progressive proximal muscle weakness, aching thighs, dry mouth (autonomic dysfunction), and hyporeflexia, especially in the lower extremities.
- It looks like myasthenia gravis, except it rarely involves the ocular muscles and repetitive exercise may improve the weakness for the first few contractions.

Note: Deep tendon reflexes are depressed in LE as opposed to MG where they are preserved!

Diagnose Lambert-Eaton by measuring voltage-gated calcium channel antibodies (anti-VGCC). Anti-VGCC antibodies are not 100% specific; they are sometimes found in patients who do not have Lambert-Eaton. Therefore, measure them only in patients who have a high pretest probability of true disease. EMG can help distinguish between Lambert-Eaton and myasthenia—with decremental response (weakening) to rapid stimulation in myasthenia and incremental response (strengthening) to rapid stimulation in Lambert-Eaton syndrome.

Look for malignancy in anybody diagnosed with Lambert-Eaton—especially small cell lung cancer.

Treatment includes addressing any underlying malignancy along with drugs that increase the amount of acetylcholine in the synapse (guanidine, 3,4-diaminopyridine, and pyridostigmine). Refractory cases can be treated with IVIG or prednisone.

Quick Quiz

- How is MG diagnosed?
- What other tests should be done in patients with myasthenia gravis?
- What cancers are associated with Lambert-Eaton syndrome?
- What happens to deep tendon reflexes in MG and Lambert-Eaton syndrome?
- Where is the muscle weakness that occurs with inclusion body myositis?
- Progressive limb girdle weakness in an adult patient who has a family history of the same is indicative of what diagnosis?

MYOPATHIES

NOTE

Myopathy simply means muscle disease. Myopathies are typically classified under neuromuscular diseases (hence their discussion here). Symptoms can be muscle weakness, stiffness, cramps, and spasms.

INFLAMMATORY MYOPATHIES

Inflammatory myopathies are caused by chronic muscle inflammation. Usual causes are:

- Dermatomyositis
- Polymyositis
- Inclusion body myositis

Both dermatomyositis and polymyositis commonly cause:

- Elevated CK
- Proximal muscle weakness

Both respond to corticosteroids.

Inclusion body myositis is a less common type of myositis in which patients present with:

- A slowly progressive, painless muscle weakness with involvement of proximal (initially) then distal muscles
- Elevated CK
- Oculomotor muscle sparing

Inclusion body myositis does not respond to corticosteroids. Muscle biopsy in inclusion body myositis shows vacuolar inclusions.

More on dermato- and polymyositis in Rheumatology, Book 3.

ENDOCRINE MYOPATHIES

Proximal muscle weakness of varying degrees may be seen in patients with hyperthyroidism, acromegaly, severe vitamin D deficiency, and conditions of steroid excess.

Hypothyroid patients have generalized muscle weakness, myalgias, slowness of contraction and relaxation, and may have increased CK. Muscle cramping is prominent in hypoparathyroidism.

METABOLIC MYOPATHIES

Consider a metabolic cause of muscle dysfunction in patients with muscle fatigue, pain, cramping, and, in more severe cases, contractures and myoglobinuria. These symptoms are precipitated by exercise in patients with disorders of carbohydrate metabolism and by fasting in those with disorders of lipid metabolism. The major categories are:

- Disorders of carbohydrate metabolism (e.g., myophosphorylase and phosphofructokinase deficiency)
- Disorders of lipid metabolism (e.g., carnitine deficiency)
- Disorders of mitochondrial function (Mitochondrial myopathies are distinguished by the presence of ragged red fibers on light microscopy of a muscle biopsy.)

MUSCULAR DYSTROPHIES

Duchenne muscular dystrophy is an X-linked disorder that causes progressive muscle weakness, starting at about 2 years of age, and progressing to death as a young adult. The weakness is more proximal than distal. Look for an elevated CK.

Myotonic dystrophy consists of 2 types of inherited, adult-onset, neuromuscular disorders that have multisystem effects. Myotonic dystrophy type 1 is caused by mutations in the *DMPK* gene, while type 2 results from mutations in the *CNBP* gene. The genetic abnormalities result in weakened skeletal muscle, myotonia (prolonged contraction on muscle percussion), cardiac conduction defects, cataracts, hypogonadism, and insulin resistance. Patients characteristically have frontal balding and a "hatchet" face appearance as a result of jaw and temporal muscle wasting. Typically, patients complain of skeletal muscle weakness (often limb girdle) and have positive family history. Consider this disease in a patient who presents as an adult with symptoms of muscle dystrophy. These patients should be referred to a neurologist who can make the diagnosis using genetic tests. Treatment is supportive only.

AIDS-RELATED MYOPATHY

AIDS-related myopathy is uncommon and typically thought to be due to zidovudine (ZDV, AZT), but some investigators attribute this to the direct effects of the virus (controversial). Patients present with a generalized (proximal > distal) weakness and an elevated CK. Treatment: Stop the AZT.

NEUROMA

Morton neuroma (or Morton metatarsalgia) is a fairly common disease of the foot in which the patient has metatarsal pain. Generally, it is diagnosed with MRI or ultrasound, which shows a small intrametatarsal ovoid mass. Differential diagnosis includes a metatarsal stress fracture. Treatment is surgical excision.

DEMYELINATING DISEASES

MULTIPLE SCLEROSIS

Overview

[Know all the following!] Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that usually begins between the ages of 20 and 30. Women are affected more often than men (about 2:1). The incidence is higher in northern latitudes, possibly because of reduced sun exposure. It has recently been recognized that vitamin D may have an important role as a modifiable environmental risk factor. It is a chronic condition with episodes of focal disorders of the optic nerves, spinal cord, and brain, which remit and recur over a period of many years.

The disease process is thought to be autoimmune, although no specific antibodies have been found and the disease may not always respond to immunomodulators. Infections as an etiology haven't been excluded from theory. One theory is that there is an initial infectious insult and an autoimmune reaction acts as a secondary trigger. Another is that MS is a result of T-cell sensitization to myelin. A familial aggregation of MS has also been reported.

The neurological symptoms depend on the region of brain that is affected.

There are 3 types of MS:

1) Relapsing-remitting (RLRM)
2) Secondary progressive
3) Primary progressive

The relapsing-remitting type (initially normal but later on with residual deficit between spells) can slowly transform into the progressive type (which may be slowly progressive from onset). Indeed, although 85% of cases are initially RLRM, after several years, most have transformed to the progressive type.

Patients with a 1st episode and with 2 or more lesions on brain MRI have a 90% risk of developing MS in 10 years—as opposed to a 28% risk if no lesions are found on brain MRI.

Clinical Manifestations of MS

Paroxysmal symptoms make up the usual course of early disease (except in chronic progressive cases). Weakness or numbness in 1 or more limbs is the initial symptom in about 1/2 of the patients. Tingling of the extremities and tight band-like sensations around the trunk or limbs are commonly associated symptoms.

Although strict criteria are used to diagnose MS (see "Diagnosis of MS" on next page), place MS in the differential anytime you encounter the following characteristic syndromes (especially if recurrent!).

Optic neuritis (ON) is the most common presentation of MS eye disease and the 1st manifestation in about 25% of patients. It occurs at some time in 50% of all MS patients. It presents as a rapid loss of vision in one or both eyes, often accompanied by slight pain, especially on eye movement. The vision loss is usually central, but a variety of field defects may be seen. With unilateral involvement, the Marcus Gunn pupil (a.k.a. relative afferent pupillary defect) is typically seen. (Light shined into the eye with optic neuritis produces slower and incomplete constriction of both pupils than light shined into the healthy eye. On the swinging flashlight test, when light is presented to the normal eye, both pupils constrict briskly; but when the flashlight is swung to the affected eye, both pupils paradoxically dilate.) There is swelling of the optic disk, but with progression, the disk becomes pale. More than 90% of these cases recover completely.

Internuclear ophthalmoplegia (INO) is another abnormal finding often seen in MS cases. INO is caused by a lesion in the "medial longitudinal fasciculus," and, although it presents as difficulty in moving the eyes horizontally, convergence is normal. (Remember that normal convergence means the patient can turn each eye inward slightly as he follows your finger to his nose, so that he continues to see a single object.) There is adduction paresis ipsilateral to the lesion, with the deficit ranging from complete medial rectus paralysis to slight slowing of an adducting saccade. Gaze-evoked horizontal jerk nystagmus is present in the abducting eye contralateral to the eye with adduction weakness. (Remember: Adduction means "toward the midline" and abduction means "away from the midline.") When you hear of a relatively young patient being diagnosed with "internuclear ophthalmoplegia," think multiple sclerosis. In older patients, however, it is more commonly due to cerebrovascular disease. The presence of bilateral internuclear ophthalmoplegia in a young adult is virtually diagnostic of MS.

Acute myelitis causes a rapidly evolving (several hours or days) symmetrical or asymmetrical paraparesis or paraplegia; ascending paresthesia; loss of deep

QuickQuiz

- What are 2 ocular presentations of MS?
- What findings in CSF are helpful for the diagnosis of MS?

sensibility in the feet; a sensory level on the trunk; sphincteric dysfunction; and bilateral Babinski sign (upturning big toe with firm stroking of sole of foot).

Other symptoms of MS may include generalized fatigue, nebulous sensory abnormalities (pain, paresthesias, itching, feeling of coldness or swelling, numbness [especially of the face]), vertigo/diplopia, lower-extremity motor weakness/paralysis, ataxic gait, and bowel/bladder dysfunction. Flexion of the neck may induce a tingling, electric-like feeling down the shoulders and back known as the Lhermitte sign.

Young women with bilateral trigeminal neuralgia and/or bilateral INO have MS until proven otherwise!

Dementia is not a typical feature of MS, especially in the earlier stages, but substantial cognitive impairment may occur in some patients with advanced chronic progressive disease. If your patient presents with dementia and gait abnormalities, a more likely diagnosis is Parkinson disease, progressive supranuclear palsy, or normal pressure hydrocephalus.

All symptoms of MS tend to worsen in the heat, called "Uhthoff phenomenon." This is because heat increases conduction block in demyelinated pathways.

Diagnosis of MS

The diagnosis of MS is no longer based only on the history and neurologic exam. The traditional (Posner) criteria incorporated signs and symptoms indicating 2 CNS lesions separated in time and space and not caused by other CNS disease. CSF findings were also used. The fact that MS lesions disseminate over "time and space" has been, and still is, an essential component of making the diagnosis. MS develops slowly over time with new lesions occurring in different parts of the brain, thereby causing different neurological signs and symptoms. Newer criteria include CNS imaging.

MRI has become an essential tool in the workup of MS. T1 gadolinium MRI shows the characteristic enhancement or "plaques" of patchy myelin loss (white matter disease) with 90% sensitivity. T2 weighted MRI shows MS lesions as hyperintense areas (Image 11-8). Many non-MS lesions can show up as hyperintense, so the specific location where these lesions are found has diagnostic weight. "Dawson's fingers" refers to MS lesions around the veins that radiate out from the ventricles.

The current McDonald criteria consider more heavily the MRI findings and have less consideration of the CSF findings than the previous (Posner) criteria. These newer criteria permit acute lesions found on MRI to be considered for the diagnosis; that is, use them to define new lesions disseminating over time and space:

- Time:
  - T2 MRI showing a new hyperintense lesion more than 30 days after the initial event or
  - T1 gadolinium showing enhancement more than 3 months after the initial event
- Space (requires 3 of the following):
  - At least 1 T1 gadolinium-enhancing lesion or 9 T2 hyperintense lesions
  - At least 1 infratentorial lesion
  - At least 1 juxtacortical lesion
  - At least 3 periventricular lesions

In addition, consider MRI of the cord, especially if brain imaging doesn't reveal plaques and the patient's presentation is very suspicious for MS. The diagnostic criteria equate certain cord lesions to certain brain lesions. MRI is also essential to rule out conditions that could mimic MS. White matter disease due to ischemia (elderly) and vasculitis both have a very different pattern of distribution from that seen with MS.

CSF analysis is particularly useful during acute exacerbations. IgG immunoglobulins to myelin can be found in the cerebrospinal fluid. (When these globulins are examined using electrophoresis, a few "bands" appear; thus the term oligoclonal bands.) 90% of MS patients have increased IgG index and oligoclonal IgG bands in the CSF. CSF protein and cell count is generally normal—on occasion, a small CSF lymphocytosis may be present, but should be no more than 50 cells/mm^3.

Evoked action potentials (visual, brainstem auditory, and somatosensory evoked potentials) can help to establish the diagnosis of MS by identifying a clinically silent 2nd lesion.

So, again, the workup for MS now includes an MRI, a lumbar puncture, and evoked potentials. Ultimately, the diagnosis is made using a combination of clinical history, physical exam, laboratory, and imaging data.

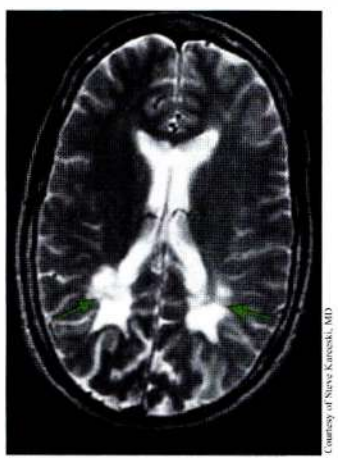

Image 11-8: Multiple sclerosis MRI

Treatment of MS

There is no cure for MS. Treatment has now become very specialized by neurologists. As a result, general internists are expected to know that the treatment of acute exacerbations is **high-dose corticosteroids** (as opposed to the myriad treatment options for both intermittent and progressive disease). Glucocorticoids may shorten the duration of exacerbations but do not alter the natural history of MS. IV methylprednisolone, 1 g/day for 3–7 days, followed by a rapid prednisone taper, is often offered. However, a recent (2012) systematic review (Cochrane Database) showed no difference in clinical, radiological, or pharmacological outcomes when comparing oral vs. IV steroids for MS relapses. Parenteral corticosteroids are the treatment for optic neuritis.

Other drugs used to treat chronic MS are **immunomodulators** (beta interferons and monoclonal antibodies), glatiramer acetate (Copaxone®, a synthetic amino acid polymer), and **antineoplastic drugs**.

New drugs include fingolimod. Be aware of the association of progressive multifocal leukoencephalopathy ([PML]; discussed next) with the drug natalizumab, which is used to treat MS. For interferons, monitor CBC and LFTS every 6 months. Interferon causes flu-like symptoms, fatigue, and depression.

Interferon and glatiramer reduce relapses by 30%, while natalizumab reduces relapses by ~ 60%. You will not be expected to know detailed information about the pharmacological treatment of MS.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

PML (affects white matter only) is a progressive demyelination seen in patients with severe T-cell immunodeficiencies, especially HIV/AIDS patients with CD4 counts < 200 cells/mm^3; it is caused by the JC virus. PML is also seen in patients treated with chronic steroids or monoclonal antibodies.

An example of the monoclonal antibodies is natalizumab, used in the treatment of MS and moderate-to-severe Crohn disease. Natalizumab is an antibody to the VLA-4 antigen expressed on activated T cells and monocytes. Most cases of PML of this type have occurred with the combination of natalizumab and other immunomodulators.

The classic presentation for PML is a rapid cognitive impairment associated with motor deficits, aphasias, ataxia, and visual field defects. (Manifestations are variable depending on what parts of the brain/cord are affected.) Dementia and focal cortical dysfunction such as hemiparesis, visual deficits, aphasia, dysarthria, and sensory impairment are prominent. The course is subacute and progressive, often leading to death in 3–6 months.

Diagnose with brain biopsy. Finding JC virus by PCR in spinal fluid is supportive, although sensitivity of the PCR analysis decreases as the immune system is reconstituted on ART. ART has improved mortality in patients with PML, but many patients have persistent neurologic deficits because the nerves are unable to re-myelinate. Antiviral drugs are ineffective.

CENTRAL PONTINE MYELINOLYSIS

Central pontine myelinolysis (a.k.a. osmotic demyelination syndrome) occurs in patients with severe hyponatremia that is corrected too quickly with hypertonic saline. There is a progressively higher risk that is directly correlated with how long the patient had been hyponatremic before correction is started, how low the sodium concentration was, and how rapid the infusion of hypertonic saline is.

These patients may present with quadriparesis, mutism, pseudobulbar palsy, chewing and swallowing dysfunction, and/or locked-in syndrome. Paralysis is initially flaccid, but spasticity develops within a few days. See Hyponatremia in Nephrology, Book 2, for more discussion.

MOVEMENT DISORDERS

PARKINSONISM

[Know this topic well.] Parkinsonism (secondary Parkinson's, Parkinson syndrome) is a neurological syndrome with the characteristic set of 4 motor features (the **4 Rs**).

Signs and symptoms of parkinsonism have 4 major characteristics:

1) **R**esting tremor
2) **R**igidity and flexed posture
3) **R**etarded movement (bradykinesia and hypokinesia)
4) Loss of postural **R**eflexes

Resting tremors at a rate of 4–5 Hz (cycles per second) occur in the distal extremities. Tremor is usually the 1st symptom noticed. Sometimes the tremor is present with use, with dramatic worsening at rest.

Patients with parkinsonism have diffuse increased muscle tone, which, combined with the tremor, causes the "cogwheeling" seen with passive range of motion of the limbs. The flexed posture may include the entire body. The spine, elbows, hips, and knees ultimately may become flexed. The classic hand position is flexed MCP joints with straight IP joints.

Hypokinesia/bradykinesia is the primary feature. With hypokinesia, the patient has decreased amplitude of voluntary movements—especially with repetitive tasks. This may manifest as micrographia (progressive reduction in amplitude of writing). Bradykinesia is difficulty initiating movement, slowness of movement, and

Quick Quiz

- What is the treatment for an acute exacerbation of MS?
- What disease is associated with the use of natalizumab?
- What is the cause of central pontine myelinolysis? What clinical findings are seen in this condition?
- What are the 4 motor features of parkinsonism?
- Name some common drugs used to treat Parkinson disease.

decrease or loss of spontaneous movement (masked facies, tendency to sit motionless, decreased blinking).

Loss of postural reflexes contributes to the "festinating gait" and eventually causes falls and then the inability to stand or walk without assistance. Festinating gait is when the patient walks progressively faster to remain under the forward center of gravity caused by truncal flexion.

There are many causes of parkinsonism. These range from Parkinson disease to drugs, toxins, metabolic disease, infections, repeated head trauma, and cerebrovascular disease.

The most common cause of parkinsonism is Parkinson disease ([PD]; discussed next).

Many drugs can cause secondary parkinsonism. The usual culprits are:

- Dopamine-depleting drugs (e.g., reserpine)
- Dopamine antagonists such as phenothiazines or butyrophenones
- Antiemetics such as metoclopramide

Drug-induced parkinsonism is typically much more symmetric than PD.

Common toxins: carbon monoxide, manganese, and organic solvents. Repeated head trauma can also cause parkinsonism (punch drunk syndrome). Parkinsonism also occurs in some forms of Huntington disease (rigid form), frontotemporal dementia, and spinocerebellar ataxia.

PARKINSON DISEASE

Diagnosis

[Know!] Parkinson disease (PD) is a clinical diagnosis. Diagnosis is especially important and often missed in the early stages.

The core features of Parkinson disease are the tetrad of:

1) hypo- and bradykinesia,
2) resting tremor,
3) postural instability, and
4) rigidity.

These are manifested as an expressionless face, poverty and slowness of voluntary movement, "resting" tremor, stooped posture, axial instability, rigidity, and festinating gait. For unknown reasons, symptoms always start on one side of the body and spread to the other side after a few years.

Rule out causes of secondary Parkinson's. Rule out other neurodegenerative disorders such as progressive supranuclear palsy ([PSP]; see page 11-46).

The pathologic findings are loss of pigmented cells in the substantia nigra and other pigmented nuclei (locus ceruleus, raphe, and dorsal motor nucleus of the vagus). Many of the remaining cells contain eosinophilic cytoplasmic inclusions, surrounded by a faint halo, called Lewy bodies.

The motor features of Parkinson disease are caused by a dropout of dopamine-producing cells in the substantia nigra of the midbrain. In a normally functioning brain, the nigrostriatal neurons produce dopamine. This dopamine is released in the basal ganglia, where it has a complex effect on the motor system, facilitating voluntary movement. When there is a decrease in dopamine from deterioration of the substantia nigra, the motor symptoms of PD emerge. 80% of patients with PD will eventually develop a dementia of the Lewy body type.

Treatment

Overview

As with MS, treatment for PD is very specialized. Focus on diagnosis, major treatments, and side effects of treatment. Staying active and exercising are important goals that keep patients independent as long as possible.

Drugs that stimulate the dopamine system are the mainstay of therapy to treat symptoms:

- Levodopa + carbidopa, with or without the catechol-O-methyl-transferase (COMT) inhibitor entacapone (Comtan®) or tolcapone (Tasmar®)
- Non-ergot direct dopamine receptor agonists:
  - Ropinirole (Requip®)
  - Pramipexole (Mirapex®)
  - Rotigotine (Neupro® skin patch)
- Amantadine
- Anticholinergics
- Monoamine-oxidase (MAO)-B inhibitors:
  - Selegiline
  - Rasagiline

NEUROLOGY

Treatment of Mild PD

Anticholinergics such as amantadine, benztropine (Cogentin®), and trihexyphenidyl are used to treat mild symptoms, especially tremor.

Anticholinergics can cause altered mental status, including psychosis, especially in patients > 70 years old and in individuals with cognitive impairment.

Tricyclics, which have some anticholinergic properties, may be considered in select patients for initial therapy—as long as cognition is intact.

Treatment of Mild-to-Moderate PD

Dopamine receptor agonists (ropinirole and pramipexole) can be useful as monotherapy for mild-to-moderate PD, but 60% of patients will require adjunctive L-dopa after 4 years.

Know that these dopa agonists, ropinirole and pramipexole, are associated with impulse control disorders, such as hypersexuality, compulsive shopping, and pathological gambling.

The **MAO-B inhibitor** selegiline delays the need for L-dopa in patients with mild PD by approximately 9 months. There is now some evidence that rasagiline may also slow decompensation in early Parkinson disease. To date, however, no treatment for PD has been proven to be "neuroprotective."

Know that combining selegiline with tricyclics or SSRIs can potentially cause the **serotonin syndrome**. This problem is caused by excessive serotonergic activation of both CNS and peripheral receptors. Signs and symptoms include cognitive impairment ranging from confusions to hallucinations to coma; autonomic effects such as hyperthermia, tachycardia, shivering, and sweating; and somatic effects such as hyperreflexia and clonus, twitching, and tremors. Symptoms can be mild to rapidly fatal, depending on the amount of overstimulation.

Treatment of Severe PD

More severe symptoms are commonly treated with **L-dopa + carbidopa**. L-dopa acts as a precursor for dopamine synthesis in the basal ganglia. The carbidopa blocks conversion of L-dopa to dopamine in the periphery, a desirable effect because peripheral dopamine does not cross the blood-brain barrier. Additionally, peripheral dopamine causes side effects such as postural hypotension and nausea. Carbidopa does not help with the central side effects of L-dopa that emerge after several years. Note that L-dopa absorption may be reduced by dietary protein.

Although L-dopa is the most effective drug for PD, its use is withheld as long as possible, especially in younger patients, to delay the onset of complications that are common with chronic use---especially dyskinesias and motor fluctuations.

Direct dopamine receptor agonists (ropinirole, pramipexole, and rotigotine) and COMT inhibitors (entacapone or tolcapone) are added to reduce the overall daily dose of L-dopa, to even out the serum levels of this drug, and to provide more continuous dopamine receptor stimulation.

The older dopamine agonists (bromocriptine, cabergoline, and pergolide) may have ergot-related adverse effects, including a risk of valvular heart disease. Cabergoline should not be used to treat patients with Parkinson's; it remains available for treatment of prolactinomas.

Neural tissue transplants may result in "runaway dyskinesias" and are currently not recommended for PD.

Complications of PD therapy include the following:

- End-of-dose "wearing off" effects (due to short half-life of L-dopa).
- Unpredictable "on-off" fluctuations that are characterized by unpredictable loss of L-dopa treatment effect and dyskinesias (50% of patients after 3–5 years).
- Psychiatric symptoms develop in 30% of patients treated with L-dopa or dopamine receptor agonists. These symptoms include agitation, confusion, hallucinations, and delusions. Older patients with cognitive impairment are especially at risk. Approximately 17% of patients treated with a dopamine agonist develop an impulse control disorder.

Know that patients who develop psychosis with L-dopa treatment sometimes require a reduction or a switch in their meds to control their behavior. These patients are especially susceptible to development of a neuroleptic malignant-like syndrome with the switch or dose reduction. This syndrome is sometimes termed "Parkinsonism hyperpyrexia" and presents with hyperthermia, delirium, muscular rigidity, and autonomic instability. "Drug holidays" are no longer used in Parkinson patients for this same reason.

PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy (PSP) is similar to Parkinson disease in that patients have bradykinesia, abnormal gait, increased muscle tone, and later develop dementia.

The disease has its onset typically in the 6th decade (range: 45–75 years of age), with some combination of difficulty in balance, abrupt falls, visual and ocular disturbances, slurred speech, dysphagia, and changes in personality. Ultimately, the characteristic syndrome of supranuclear ophthalmoplegia, pseudobulbar palsy, and axial dystonia develops. Patients typically do not have a tremor.

Within 2 years, these patients develop the classic symptom of a vertical ophthalmoplegia, typically with initial impairment of downgaze, progressing to complete ophthalmoplegia in all directions. Subsequently, patients

- What is a potential side effect of anticholinergic drugs when used to treat Parkinson's?
- Ropinirole is associated with what side effects?
- Selegiline can cause serotonin syndrome when combined with what other drugs?
- What is the clinical presentation of serotonin syndrome?
- What is a potential complication of an L-dopa dose reduction in a patient with Parkinson psychosis?
- What is the classic eye finding of progressive supranuclear palsy?
- What is the clinical presentation of essential tremor? What improves it?
- What causes tardive dyskinesia? How is TD treated?

have trouble reading, eating, and walking down stairs. There is a gradual stiffening and extension of the neck. Within another 2–3 years, they may be unable to walk because of marked imbalance.

The treatment is palliative, aimed to improve the quality of life. These patients commonly die of aspiration pneumonia due to severe dysphagia.

TREMORS

Overview

Based on when the tremor occurs, it can be called either static or kinetic:

- Static tremors occur at rest, or when the head and extremities are held in a fixed position (termed "postural tremor").
- Kinetic tremors occur during voluntary movement. Of these, action tremors persist unchanged throughout voluntary movement and generally disappear at rest. Intention tremors occur with target-directed movement and worsen as the movement unfolds.

Tremor syndromes often include both static and kinetic tremors; e.g., the "essential tremor" includes both postural and action tremors.

Exaggerated Physiologic Tremor

Usually, normal patients have an unrecognizable physiologic tremor that has a frequency of ~ 10 Hz. This normal tremor can be aggravated by anxiety, fright, hyperthyroidism, metabolic states such as hypoglycemia, drug withdrawal states, and certain drugs (SSRIs, corticosteroids, tricyclics, theophylline, β-agonists, nicotine, and caffeine). This tremor can be postural or seen with action.

Essential Tremor

Essential tremor is the most common type of non-physiologic tremor and is often familial. In familial cases, it seems to be transmitted as an autosomal dominant trait, with variation in age at onset and severity. It affects the hands as a postural and action tremor with a frequency of 4–8 Hz. It also can be a higher frequency and affect the head and chin as a "yes, yes" or "no, no" postural tremor. There may be an associated vocal tremor. Essential tremor is typically benign but sometimes results in functional disability. Note that a postural tremor of the head is very unlikely to be due to Parkinson's and is more often essential tremor. Parkinson tremors that affect the face usually involve the lips or jaw only.

The frequency of essential tremor is typically decreased transiently by drinking alcohol, and you can often diagnose an essential tremor when patients tell you that their tremor improves after an alcoholic drink. Propranolol and primidone are effective in reducing the limb tremors.

Gabapentin and topiramate reduce limb tremors a little also, but both have many side effects. In severe cases, botulinum toxin and deep-brain stimulation surgery can be tried.

TARDIVE DYSKINESIA

Tardive dyskinesia (TD) is mostly a result of long-term antipsychotic drug use. The only way to be certain to avoid TD is to keep patients off chronic antipsychotics, but this cannot be accomplished in many patients with chronic psychosis.

Some "atypical antipsychotics" (2nd generation drugs), particularly clozapine and quetiapine fumarate (Seroquel®), are less likely to cause TD. Clozapine can cause bone marrow toxicity.

Tardive dyskinesia consists of many involuntary movements, including dystonia, chorea, athetosis, and tremor. The face, tongue, lips, eyelid, and bulbar muscles are most often involved, but neck, shoulder, and spine muscles with arching of the back may also be seen.

Clonazepam is a useful benzodiazepine for patients with mild tardive dyskinesias and anxiety. Extract of ginkgo biloba has also recently been shown to be effective for reducing tardive dyskinesia in patients with schizophrenia. Some patients may benefit from the presynaptic dopamine-depleting drug, reserpine; however, side effects of this drug may include depression, orthostatic hypotension, and parkinsonism. Severe TD cases can be treated with botulinum toxin. Deep-brain stimulation surgery can be used in the most severe cases that require continued use of antipsychotic drugs.

OTHER MOVEMENT DISORDERS

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome is an unusual response to antipsychotics (both "typical" and "atypical" antipsychotics), resulting in hyperthermia, rigidity, diaphoresis, autonomic instability, and altered mental status with a risk of rhabdomyolysis-induced renal failure. Occasionally, other drugs, such as metoclopramide and promethazine, can also have the same effect. Labs often show leukocytosis, electrolyte disturbances, and elevated CK levels.

This syndrome may occur days, weeks, or months after neuroleptic treatment is begun. It carries a mortality rate of 15–30% if not recognized and treated promptly. [Know:] Patients with Parkinson's who acutely discontinue their dopa therapy (or reduce dose) can develop this syndrome.

Treatment of neuroleptic malignant syndrome consists of immediate discontinuation of any offending drug; use of a direct dopamine agonist such as bromocriptine, amantadine, or dantrolene; and supportive therapy, including adequate hydration and scrupulous pulmonary toilet. If rigidity is sufficient to affect ventilation, the patient should be sedated and paralyzed. Patients who require neuroleptics may have recurrence of neuroleptic malignant syndrome if the drugs are restarted.

Hemifacial Spasm

Hemifacial spasm is a motor analog to trigeminal neuralgia (tic douloureux). 80% of patients have a tortuous, dilated basilar artery (basilar dolichoectasia) that loops around and irritates the facial nerve! Other causes include aneurysm, acoustic neuroma, and, rarely, MS.

Botulinum toxin (Botox®) injections are customarily the best treatment. Some patients have benefitted from surgery to separate the facial nerve from direct contact with the basilar artery (microsurgical decompression). Occasionally, carbamazepine, baclofen, and gabapentin may be effective.

Gilles de la Tourette Syndrome

Gilles de la Tourette syndrome is a developmental neuropsychiatric disorder characterized by chronic (> 1 year duration) multiple motor tics and 1 or more vocal tics. Motor tics may be simple, including eye blinking or rolling, facial grimacing and head or limb jerking, or complex, including semi-purposeful movements such as tapping, jumping, and copying the gestures of others (echopraxia). Vocal tics may also be simple, such as sniffing, snorting, grunting, and coughing, or complex, including utterance of words or phrases, obscenities (coprolalia), or imitating the speech of others (echolalia). Onset is commonly between 2 and 15 years of age. Many patients have comorbid attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, learning disorders, or conduct disorders.

Diagnosis is clinical and requires confirmation of both motor and vocal tics by a skilled observer.

Clonidine is recommended as 1st line treatment. If the tics are severe enough to interfere with daily functioning, typical neuroleptics (e.g., fluphenazine, pimozide, haloperidol), atypical neuroleptics (e.g., risperidone, ziprasidone, olanzapine), or the partial dopamine agonist aripiprazole may be used. CNS side effects such as moodiness and depression are more common with the typical neuroleptics, while the newer atypical drugs cause more weight gain and metabolic syndrome.

Milder tics and/or associated ADHD may respond to clonidine or guanfacine. More severe ADHD can be treated with stimulants such as methylphenidate; newer data show that these drugs may not exacerbate tics as previously thought, although close monitoring is necessary. Focal tics have been treated with botulinum toxin.

Focal Dystonias

Focal or segmental dystonias are intermittent, brief, or prolonged spasms or contractions of a group of adjacent muscles that place the body part in a forced and unnatural position.

Table 11-8: Causes of Acute Unilateral Blindness (Amaurosis Fugax)

Age	Disease	Etiology	Clinical Course	Exam	Outcome
Older (> 50)	Anterior ischemic optic neuropathy	< 60: atherosclerosis > 60: giant cell arteritis	Nonprogressive	Optic disk infarction	From normal to complete blindness
	Central retinal vein occlusion	Vascular disease or venous thrombosis	Nonprogressive	Hemorrhagic retinopathy	Usually some visual impairment
	Central retinal artery occlusion	Embolic or thrombotic	Nonprogressive	Cherry red spot	Only ~ 25% maintain useful vision
Younger (< 40)	Optic neuritis	Multiple sclerosis	Progressive (hours to days)	Marcus Gunn pupil; optic disc pallor	90% recover completely
	Migraine	Neurovascular	Resolves rapidly	Normal	Normal vision

QuickQuiz

- What is the clinical presentation of neuroleptic malignant syndrome?
- What comorbidities are associated with Tourette syndrome?
- What antihypertensive drug is used to treat tics in Gilles de la Tourette syndrome?
- What are causes of acute unilateral blindness (a.k.a. amaurosis fugax) in older patients?
- What do flashes followed by decreased vision suggest?
- What 4 symptoms are associated with narcolepsy?

3 focal dystonias are commonly asked about:

1) Blepharospasm is bilateral, forceful involuntary eye closure and may occur as an isolated syndrome or as part of Meige syndrome.
2) Meige syndrome is a combination of blepharospasm and oromandibular dystonia (involuntary jaw opening and jaw movements).
3) Spasmodic torticollis occurs when spasms of neck and shoulder muscles turn the head to one side.

A few oral drugs may offer mild relief: benzodiazepines, baclofen, anticholinergics, and sometimes antidopaminergics. However, botulinum toxin is now the treatment of choice, providing much more reliable but temporary relief when injected directly into the affected muscles. It requires repeat injections q 2–5 months.

MISCELLANEOUS DISORDERS

ACUTE-ONSET UNILATERAL BLINDNESS

[Know all of the following.] See Table 11-8 for a summary.

In older patients, acute onset of unilateral blindness (a.k.a. amaurosis fugax) is usually due to any of the following:

- Anterior ischemic optic neuropathy (AION), which may be:
  - Arteritic (secondary to giant cell arteritis)
  - Non-arteritic (less severe outcome)
- Retinal vein occlusion (secondary to diabetic retinal vascular disease)
- Retinal artery occlusion (from thrombus or emboli from the carotid artery or heart)

In the younger patient, think optic neuritis, but sometimes it can be from migraine. Migraine-induced blindness typically resolves rapidly, whereas blindness due to any of the other mentioned causes is prolonged or permanent.

Ischemic optic neuropathy, optic neuritis, and papilledema all can present with swollen discs with fundal splinter hemorrhages. Remember: Temporal (giant cell) arteritis also causes diplopia and jaw claudication.

"Malingering" as a cause of blindness (mono/bi) can be ruled out with evoked action potentials.

DIPLOPIA

Weak or paralyzed eye muscles cause "ophthalmoplegia" and manifest as diplopia. It can be a result of disease in the muscle itself, in the nerve that stimulates the muscle, or in the neuromuscular junction (myasthenia gravis).

A reminder of diseases that may present with diplopia (we have covered most of these separately):

- 3rd and 6th cranial nerve palsies
- Myasthenia gravis
- Graves disease
- Wernicke encephalopathy
- Miller Fisher variant of GBS
- Botulism
- Tick paralysis
- Infections/Masses that affect the cavernous sinus

If you see diplopia with pain:

- Think disease in the eyeball if pain is localized in the eye.
- Think myopathy or orbital processes if pain is present with movement of the eye. Influenza is a classic cause of orbital myopathy.

Optic neuritis may also cause pain on eye movement, but it does not cause diplopia!

VISUAL FIELD DEFECTS

Scotomas

Scotomas are alterations in an isolated area of the visual field with loss or dimness of vision. Do a complete ophthalmologic exam on any patient with any type of scotoma.

Acephalic migraine (migraine without headache) can cause "fortification scotomas" that constantly change in size and may be bilateral.

Moore's lightning streaks occur in older patients upon entering a darkened area. They are caused by the vitreous pulling on the retina; they are benign.

Retinal detachment causes flashes followed by decreased vision (from blood) or increased floaters. This is an ophthalmological emergency.

Bitemporal Hemianopsia

Bitemporal hemianopsia is the term for blindness in the lateral half of both visual fields. It has several causes:

- Pituitary adenomas (This is the one we all remember.)
- Craniopharyngioma
- Meningioma
- Aneurysm of the circle of Willis
- Sarcoidosis (rare)
- Metastatic carcinoma (rare)

COMPLEX REGIONAL PAIN SYNDROME

This syndrome causes extreme tenderness, pain, swelling, dysesthesias, and vasomotor instability in an extremity after a traumatic injury.

NARCOLEPSY

Narcolepsy is caused by a selective loss of hypocretin in the hypothalamus, the etiology of which is currently unknown. More than 85% of Caucasian and Japanese patients with narcolepsy-cataplexy syndrome have a specific HLA haplotype that includes HLA-DR1501 (formerly called DR15 or DR2) and HLA-DQB1-0602 (formerly DQ1 or DQ6).

Narcolepsy tetrad:

1) Narcolepsy
2) Cataplexy (3/4 of patients! With excitement, limbs become flaccid, often resulting in falls.)
3) Hypnagogic hallucinations (occurring as patient falls asleep)
4) Sleep paralysis (on waking)

Narcolepsy is treated with modafinil or armodafinil (non-amphetamine drugs) stimulants such as methylphenidate or methamphetamine (many side effects and addictive potential) or sodium oxybate, especially in more severe cases with associated cataplexy. Cataplexy may also be treated with tricyclics (e.g., imipramine, clomipramine, or protriptyline) or the selective serotonin reuptake inhibitors (e.g., venlafaxine or fluoxetine).

FOR FURTHER READING

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Dermatology

COMMON SKIN PROBLEMS

ATOPIC DERMATITIS (ECZEMA)

Atopic dermatitis ([AD]; Image 12-1) is a chronic inflammatory skin condition with a relapsing and remitting course which usually begins in infancy or childhood and becomes less severe with age. 85% of all cases present at < 5 years of age and the onset is rare after age 30. It is characterized by dry skin and pruritus. Subsequent scratching leads to more inflammation and lichenification (thickening and hardening of the skin, with exaggeration of its normal markings) as well as more itching and scratching ("itch-scratch" cycle). It is often associated with a personal or family history of eczema, allergic rhinitis, or asthma. Elevated IgE levels and eosinophilia are commonly seen. In adults, the most common areas involved include the wrists, and antecubital and popliteal fossas. They may also develop erythematous and edematous pruritic patches on the head and neck. These may crust and then "weep," at least partly from scratching.

Flares can be precipitated by clothing (particularly wool fibers), emotional stress, aeroallergens (dust mites and pollen), and infections. *S. aureus* is often present in severe cases and eczema herpeticum, caused by herpes simplex virus, can cause a severe disseminated infection. Occasionally, oral antibiotics are given to decrease colonization of *S. aureus* and thus shorten the course of the disease.

Hydration, water-trapping agents, and topical corticosteroids are the mainstays of treatment for AD. Mid- or high-potency topical corticosteroids are used for the trunk and extremities, while low-potency topical corticosteroids are recommended for the face to lessen the risk of skin atrophy and striae. Also, patients must be educated to avoid rubbing or scratching the skin lesions.

Tacrolimus (Protopic®) and pimecrolimus (Elidel®) are topical immunosuppressants (calcineurin inhibitors) that

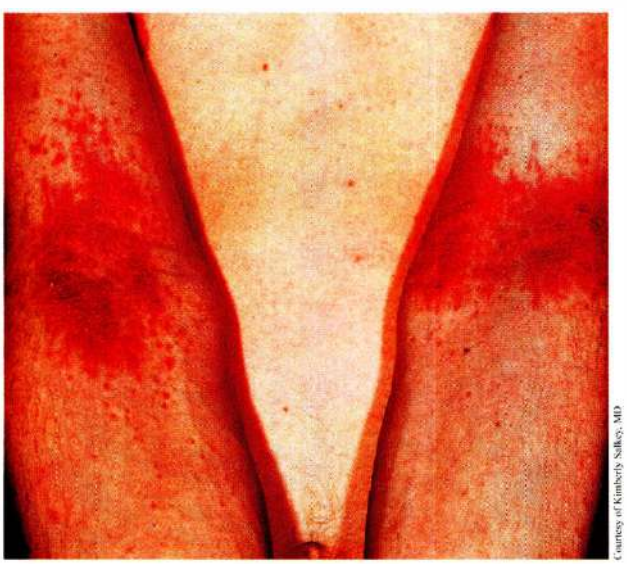


Image 12-1: Antecubital fossa with atopic dermatitis

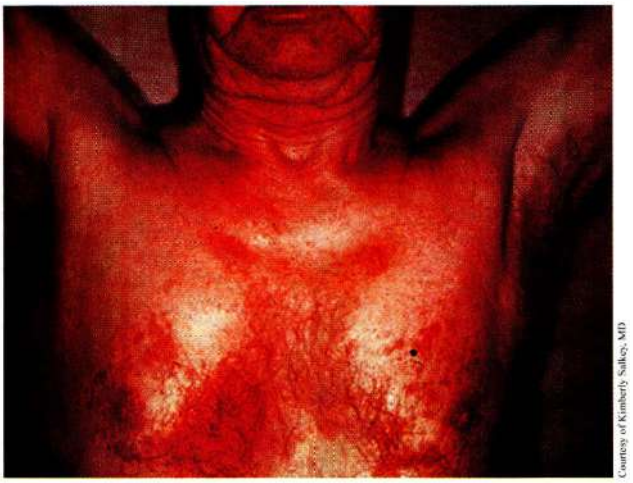


Image 12-2: Seborrheic dermatitis

are effective alternatives to topical corticosteroids. Since these do not cause skin atrophy, they are especially good for facial lesions. There is a potential risk of skin cancer or T-cell lymphoma, so these agents are 2nd line for intermittent treatment of atopic dermatitis. These agents should be avoided in HIV+ patients or anyone with a weakened immune system.

Use oral cyclosporine, azathioprine, mycophenolate mofetil, or methotrexate for severe AD that does not respond to conservative therapy. Ultraviolet light therapy may also be used in this setting. Oral corticosteroids are rarely indicated for acute flares.

SEBORRHEA

Seborrheic dermatitis affects 2–5% of the population and is a chronic condition that manifests as a yellow, greasy scale overlying erythematous patches or plaques (Image 12-2). Pruritus is variable. It affects areas where sebaceous glands are most active and especially involves the scalp (dandruff), eyebrows, paranasal area, and external auditory canals, although the chest, axilla, and groin areas may also be involved. There is a strong association with *Malassezia furfur*, but it is unknown if this fungus is a cause or result of the dermatitis.

Seborrheic dermatitis is common in patients with HIV/AIDS and Parkinson disease.

Treatment of seborrheic dermatitis: frequent washing and an antidandruff shampoo. The active ingredients in these shampoos are selenium sulfide, zinc pyrithione, salicylic acid, or tar. The antimicrobial shampoos include ketoconazole or ciclopirox.

Use low-potency topical corticosteroids in combination with ketoconazole cream for skin disease. Topical calcineurin inhibitors (tacrolimus and pimecrolimus) can be used as steroid sparing agents.

INTERTRIGO

Intertrigo is an irritant dermatitis found in the macerated skin folds (inframammary, axilla, groin) of obese

patients. It presents with tender, brightly erythematous, moist patches in the skin folds. *Candida* can secondarily infect these areas. Suspect *Candida* when satellite papules extend beyond the main lesion. Also rule out tinea cruris and erythrasma, which can mimic nonspecific intertrigo. These can be ruled out with a KOH test and Wood's lamp, respectively.

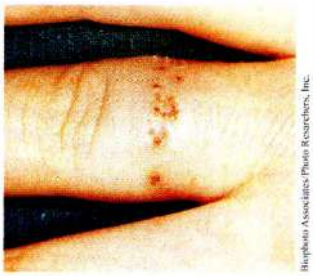


Image 12-3: Contact dermatitis caused by ring with nickel

Treat intertrigo with topical antifungals and drying agents (antifungal powders, aluminum sulfate products, corn starch). Avoid the use of talcum powder in the genital area of women because of the potential increased risk of ovarian cancer. Weight loss is crucial to prevent recurrences.

CONTACT DERMATITIS

Contact dermatitis can be caused by a chemical irritant (80% of cases), or it can be of allergic origin (20% of cases; [Image 12-3]). The most common irritants are soapy water, rubbing alcohol, and common household cleaners. Sufficient exposure to these irritants causes dermatitis in every individual. For irritant contact dermatitis, prior sensitization is not required.

The allergic type of contact dermatitis is due to a T-cell–mediated, delayed-type hypersensitivity reaction (Type IV hypersensitivity) in the skin. Patients must become sensitized to the antigen with one or many exposures. After sensitization and upon re-exposure, the skin develops a pruritic lesion in 1/2 to 2 days. The most common allergens are nickel, chromium, neomycin, and oleoresin urushiol (poison oak, poison ivy, and poison sumac).

1st line treatment is identifying and removing the offending allergen. Symptomatic treatment includes cool compresses, Burow's solution (aluminum acetate dissolved in water, 1:40), and topical corticosteroids. If the reaction is severe or involves the face, give systemic corticosteroids. Patch testing is the gold standard to identify contact allergens and can be used if the contact allergen is not obvious. In patch testing, multiple suspected allergens are applied to the patient's back under occlusive dressings. After 48 hours, the dressings are removed and the area is examined for evidence of delayed hypersensitivity reactions.

ACNE

Acne Vulgaris

The clinical manifestations of acne vulgaris are:

- Open ("blackheads") and closed ("whiteheads") comedones
- Papules
- Pustules
- Cystic lesions

Comedonal acne is noninflammatory acne and develops in early adolescence. The pathogenesis involves occlusion of the follicles.

Inflammatory acne occurs as a reaction to several factors, including *Propionibacterium acnes* within the follicle, ruptured follicular epithelium with leaking of sebum, and the immunologic response to these factors. Acne severity is genetic and hormonal, with an imbalance between estrogens and androgens. However, contrary to popular belief, most patients with acne do not overproduce androgens. The likely etiology is locally hyperresponsive sebaceous glands to androgens (hence the genetic predisposition for many).

However, in women with polycystic ovary syndrome (PCOS), acne is a common but not specific external manifestation of increased serum androgens. PCOS occurs in 5–10% of all women, and about 1/3 of women with acne have PCOS.

Factors that may exacerbate acne include cosmetics, oils, repetitive mechanical trauma (scrubbing), clothing (turtlenecks, bra straps, and sports helmets), humidity, and heavy sweating. Diet is a controversial cause; some studies have shown an association with milk intake (exacerbating) and low-glycemic diets (ameliorating). Stress appears to worsen acne severity.

Acne vulgaris differs from rosacea by the presence of comedones (not seen in rosacea) and the lack of telangiectasia (seen in rosacea). See Image 12-4 through Image 12-6.

Treatment of Acne Vulgaris

Comedonal (noninflammatory) acne: Topical retinoids are drugs of choice for comedonal acne. These include adapalene, tretinoin, and tazarotene. These are generally applied at night because they can be deactivated by sunlight (adapalene is an exception). Note: Tazarotene (Tazorac®, Avage®) is contraindicated in pregnancy!

Side effects are mainly skin irritation (start at a low dose and apply 2–3 times per week) and photosensitivity. Other agents for comedonal acne include topical salicylic acid, azelaic acid, and glycolic acid; all 3 have anticomedonal activity.

Mild inflammatory acne (Image 12-4): Benzoyl peroxide in combination with topical erythromycin or clindamycin is used to treat the *P. acnes* of inflammatory acne. The combination therapy decreases development of resistance, and commercial preparations are available that have both products. Topical retinoids are also useful adjuncts. Topical dapsone, an effective antimicrobial agent, was initially approved by the FDA in 1955; in 2009, it was remarketed with the trade name Aczone®.

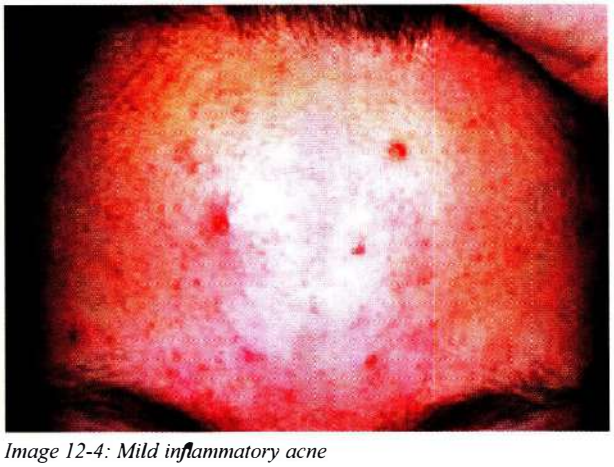
Moderate-to-severe inflammatory acne (Image 12-5): This requires oral antibiotics such as tetracycline, doxycycline, and minocycline in addition to the above

Quick Quiz

- What is the clinical presentation of seborrhea?
- What is the clinical presentation of intertrigo?
- Contact dermatitis is an example of what type of hypersensitivity reaction?
- What are the serious side effects of isotretinoin?
- How can you tell the difference between rosacea and acne vulgaris?

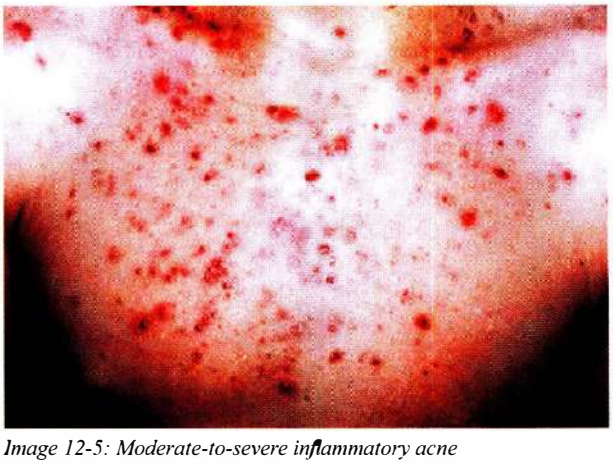
topical therapy. The high prevalence of *P. acnes* resistance to erythromycin has led to decreased use of this agent. TMP/SMX is recommended in selected refractory cases.

Isotretinoin (Amnesteem®, Claravis®, Sotret®; 1.0 mg/kg/d) is highly effective in severe nodulocystic, scarring, or resistant cases but is also a powerful teratogen. The use of isotretinoin is restricted to physicians who have registered with the electronic FDA system (called the "iPLEDGE™ program") and requires multiple steps in order to prescribe (e.g., 2 pregnancy tests, 2 forms of birth control). Serious side effects include pseudotumor cerebri (especially if used with tetracyclines), depression and psychosis, pancreatitis, marked hypertriglyceridemia, hearing loss, night vision loss, and skeletal abnormalities.



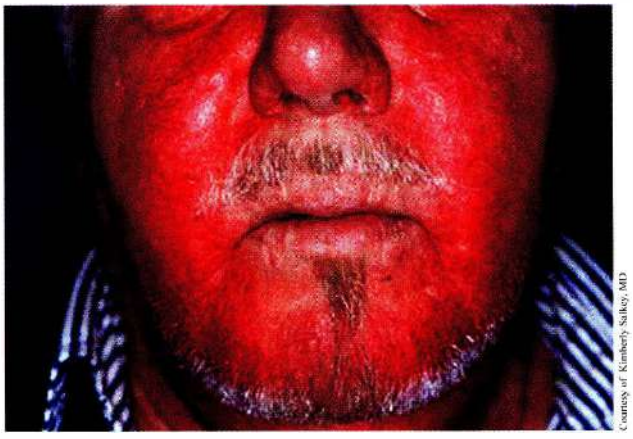
James Cavallini/Photo Researchers, Inc.

Image 12-4: Mild inflammatory acne



Biophoto Associates/Photo Researchers, Inc.

Image 12-5: Moderate-to-severe inflammatory acne



Courtesy of Kimberly Salkey, MD

Image 12-6: Acne rosacea

If oral isotretinoin is used, all other acne treatments must be stopped. Again, concurrent use of oral isotretinoin and the family of tetracycline antibiotics can cause pseudotumor cerebri.

Oral contraceptive therapy is used in PCOS to decrease androgen excess and to regulate menstrual cycles. Spironolactone, which has anti-androgen effects, is also used as hormonal therapy in combination with oral contraceptives.

Acne Rosacea

Acne rosacea (Image 12-6) is a lifelong condition that primarily affects fair-skinned, middle-aged patients and presents with erythema, telangiectasias, and acne-like lesions on the central face. It is more common in women, but more severe in men. It includes 4 main subtypes:

1) **Erythematotelangiectatic** (vascular): flushing, facial erythema, and telangiectasias
2) **Papulopustular**: facial erythema with transient papules/pustules
3) **Phymatous**: thickened skin, nodules, rhinophyma (bulbous nose)
4) **Ocular**: watery/bloodshot appearance, lid/periocular erythema

Patients may have a flushing reaction to various stimuli (e.g., alcohol, stress, spicy foods) even before the lesions appear. Once the rosacea manifests, the flush may become permanent. Trigger avoidance is recommended. Treatment is topical metronidazole, azelaic acid, sulfur/sulfacetamide preparations, or oral tetracycline antibiotics. The latter may be particularly helpful for the papulopustular and ocular subtypes.

Rhinophyma is more common in elderly men and may require surgical therapy. Telangiectasias can be treated with laser therapy. Know how to distinguish acne vulgaris from rosacea. Rosacea does not have comedones and may have telangiectasias, unlike acne vulgaris.

HIDRADENITIS

Hidradenitis suppurativa (acne inversa), which affects approximately 1% of the population, is a chronic

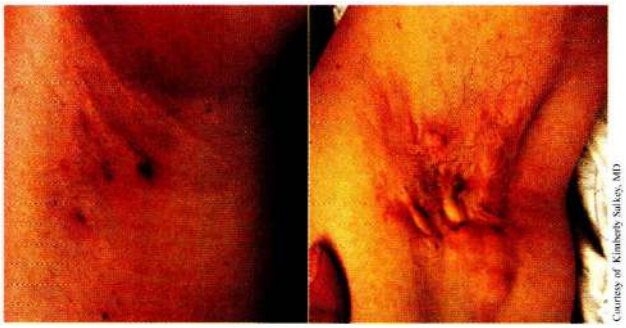


Image 12-7: Hidradenitis suppurativa; mild vs. severe

inflammatory scarring process involving apocrine gland-bearing areas such as the axillae and the groin/perianal regions (Image 12-7). It typically develops after puberty and manifests as painful, deep-seated nodules, sinus tracts, and abscesses. The abscesses are usually sterile, but can become secondarily superinfected. While it occurs in both sexes (women > men, 4:1)—women tend to have more axillary and vulvar involvement while perianal involvement is more common in men. Smoking and obesity correlate with severity of disease.

The disease process begins with dilated, occluded follicles (comedones) that often have multiple openings. Subsequently, the disease can range from mild to severe (induration, scarring, pitting, and draining abscesses).

Treatment for hidradenitis should be guided by disease severity and is often challenging. If applicable, smoking cessation and weight loss should be recommended. Avoid deodorants (antiperspirants are okay), tight synthetic clothing, and prolonged exposure to hot, humid environments. Early disease should be treated with 1% topical clindamycin and intralesional steroids. Treat acute infections with incision, drainage, and packing. Late disease should be treated with either oral tetracycline or oral clindamycin-rifampin. More severe disease may require immunosuppressants such as infliximab or etanercept, which are anti-TNF-α-inhibitors. Anti-androgens and zinc gluconate are controversial with limited data to support their use. For severe refractory lesions, complete surgical excision is definitive therapy, but laser therapy is also increasingly being used.

MOUTH FINDINGS

[Know all of these!]

Hyperpigmented gingiva is seen in Addison disease.

Koplik spots (Image 12-8) are small white papules on an erythematous base, which are found on the buccal mucosa in patients with measles. These usually precede the skin lesions by several days.

Oral hairy leukoplakia (Image 12-9) most commonly occurs in patients with HIV/AIDS. It manifests as asymptomatic white plaques along the sides of the tongue. This is due to Epstein-Barr virus in the superficial layers of the tongue's squamous epithelium. In contrast to *Candida*, it can't be scraped off!

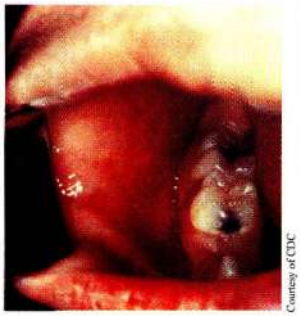


Image 12-8: Koplik spots

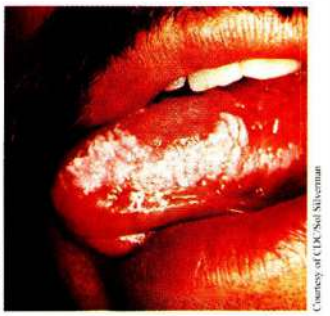


Image 12-9: Oral hairy leukoplakia

Erythroplakia consists of erythematous plaques. About 90% of cases are either dysplastic or carcinomatous, so distinction from leukoplakia, which is generally benign, is crucial.

Peutz-Jeghers syndrome (multiple intestinal hamartomatous polyps) should be ruled out in patients with melanotic pigmentation (lentigines) on the lips and buccal mucosa.

Beefy red tongue (glossitis) is seen in pernicious anemia and various B vitamin deficiencies. It also can be associated with glucagonomas—discussed under Skin Cancer and Skin Findings on page 12-14.

Macroglossia (big tongue) is associated with multiple myeloma, primary amyloidosis, lymphoma, hemangioma, acromegaly, hypothyroidism, angioedema, and Down syndrome.

White lesions: candidiasis, hairy leukoplakia (AIDS), lichen planus. Lichen planus also causes ulceration and lace-like patches (Wickham striae).

"Geographic" tongue an idiopathic inflammat condition that results the loss of filiform pap lae. It has the appearar of migratory denuded r patches that resemble map. It is asymptoma and benign (Image 12-1 but is associated w psoriasis.

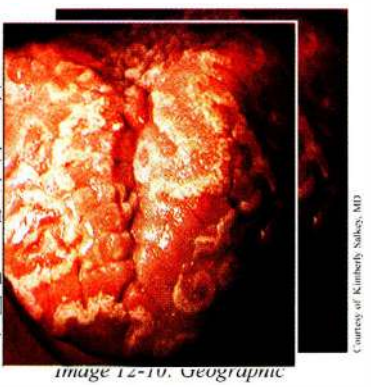


Image 12-10: Geographic tongue

"Strawberry" tongue is due to inflamed tongue papillae and is associated with scarlet fever, toxic shock syndrome, and Kawasaki disease (mucocutaneous lymph node syndrome commonly seen in children).

"Bald" tongue is atrophy of the lingual papillae associated with pellagra, iron deficiency anemia, pernicious anemia, and xerostomia (dry mouth commonly seen in Sjögren syndrome, lymphoma, mumps, and sarcoidosis; may occasionally be idiopathic).

Quick Quiz

- What finding on the buccal mucosa can be seen with measles? Describe and name the finding.
- What viral infection causes hairy leukoplakia?
- A beefy red tongue is seen with which underlying disease states? Macroglossia?
- What adverse cutaneous reactions are associated with phenytoin?

CUTANEOUS DRUG REACTIONS

The following are the most frequent drug-associated skin changes. [Know all of them.]

Penicillin (PCN):
- Immediate hypersensitivity reaction; anaphylaxis (IgE)
- Delayed hypersensitivity reaction; immune complex reaction, such as vasculitis or morbilliform eruption

Tetracyclines: photosensitivity (demeclocycline > doxycycline > tetracycline > minocycline). Other drugs commonly associated with photosensitivity include: fluoroquinolones, sulfonamides, and amiodarone.

NSAIDs: urticaria/angioedema in 1%, asthma in 0.5%, and may cause photosensitivity or toxic epidermal necrolysis (TEN).

Phenytoin:
- Hypersensitivity syndrome: rash, facial edema, lymphadenopathy, and hepatitis
- Various skin reactions, including erythema multiforme
- Hypertrophied gums (also commonly caused by cyclosporine, nifedipine, and amlodipine; also seen in M3 and M4 subtypes of AML) and hirsutism

Corticosteroids: skin changes, including striae, atrophy, telangiectasia, pigmentary changes, and acne-like lesions.

Warfarin: necrotic patches (necrosis) of skin appearing 3–10 days after starting warfarin, typically occurring in patients with unknown protein C deficiency. Lesions classically affect areas with the highest fat deposition such as the breasts, buttocks, thighs, and abdomen.

Radiocontrast dye: This can cause urticaria/erythema (1:15 incidence), and rarely (1:1,000 incidence) a severe anaphylactoid reaction (not IgE mediated). There is a 30% chance of a repeat reaction in someone with a history of prior reaction to contrast dye, and often the second presentation is more severe. Prophylaxis with antihistamines (H_1 +/– H_2 blockers) and corticosteroids (start 1–2 days prior) decrease the incidence of this reaction 10-fold.

Gadolinium: a contrast material used for MRI. It has been associated with nephrogenic systemic fibrosis (NSF), a fibrotic disease of the skin and internal organs similar but distinct from systemic sclerosis (scleroderma) in that it typically spares the face. Patients with ESRD or a GFR < 30 mL/min are at the highest risk. There is no good treatment, so prevention is paramount. Don't give gadolinium to a patient with stage 4 or worse CKD!

ACE inhibitors: Angioedema occurs in only 0.5% of patients treated with an ACE inhibitor. However, because such a large number of patients receive this drug, it is one of the most common causes of isolated angioedema. Angioedema can occur at any time during treatment with ACE inhibitors. Angiotensin receptor blockers (ARBs) rarely cause angioedema. However, they should be used cautiously in patients who have a previous history of angioedema with ACEI use. Careful consideration should be used in this scenario making sure that the benefit outweighs the risk (e.g., systolic heart failure, significant proteinuria).

DRESS syndrome––drug reaction with eosinophilia and systemic symptoms––carries a mortality rate of about 10%. Patients commonly present with a morbilliform rash, facial swelling, fever, lymphadenopathy, ↑ LFTs, and hepatomegaly. The majority of cases have associated eosinophilia. Anticonvulsants and allopurinol are the most common drugs implicated. Treatment requires removal of the offending medication. Systemic steroids are commonly prescribed, although data supporting their effectiveness is controversial.

INFLAMMATORY SKIN DISORDERS

NOTE

Many of the disorders described here are presented in more detail in Rheumatology, Book 3.

PSORIASIS

Overview

Psoriasis is a response triggered by T lymphocytes in the skin. The epidermis becomes hyperproliferative, producing more skin at a faster rate than normal. Trauma or irritation of normal skin commonly induces lesions of psoriasis at the site (Koebner phenomenon).

All types of psoriasis can be precipitated/exacerbated by stress, sunburn, infection (virus, strep pharyngitis), lithium, and beta-blockers). Obesity is associated with psoriasis, and significant weight loss may lead to clinical improvement.

Types of Psoriasis

Plaque psoriasis is the most common type (Image 12-11). It presents in young adults with well-defined, stable, slow-growing, erythematous skin lesions with distinctive mica-like (silvery) scales. Pruritus

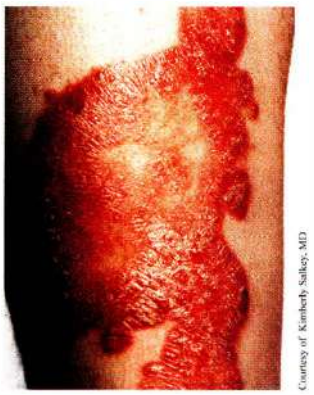


Image 12-11: Plaque psoriasis

is variable (absent to severe), with patients usually having mild itching. It is typically symmetric and occurs on extensor surfaces of the knees and elbows, the sacral area, and the scalp. (See Psoriatic Arthritis in Rheumatology, Book 3.)

Guttate (eruptive) psoriasis is an abrupt eruption of multiple small lesions (3–10 mm in diameter), and usually occurs on the trunk of children or young adults with no previous history of psoriasis. Streptococcal pharyngitis is a known trigger of guttate psoriasis.

Flexural (inverse) psoriasis affects skinfold areas. It is called inverse because it is not on the extensor surfaces.

There are 2 rare, especially severe types of psoriasis:

1) Erythrodermic psoriasis
2) Pustular psoriasis

Erythrodermic psoriasis is an exfoliative reaction in which the entire surface of the skin becomes red, warm, and scaly—and the patient is unable to control body temperature. (Hypo/hyperthermia is common.) Dehydration, hypoalbuminemia, and anemia of chronic disease are common sequelae.

Pustular psoriasis has many small pustules, often coalescing to form "psoriatic lakes of pus." There are 2 forms:

1) The localized form affects only the palms and soles. It is associated with DIP joint arthritis.
2) The rare, generalized form (von Zumbusch type) is the most severe form of psoriasis and may occur with the erythrodermic type. Sudden withdrawal of systemic corticosteroids is a well-described inciting event.

Nail Changes

The most specific nail finding is an "oil spot" on the nails. "Ice-pick" pitting of the nails is also common. These pits are usually in small groups on the nail. Thickened nails and onycholysis (separation of distal nail from the nail bed) are also common in psoriasis (Image 12-12). Having pitted nails in association with onycholysis is fairly specific for psoriasis and more strongly associated with psoriatic arthritis.

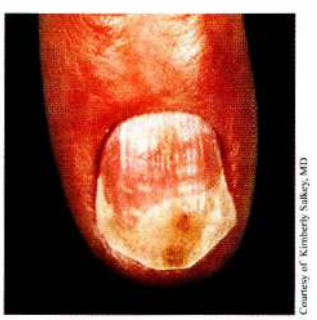


Image 12-12: Pitted nail with onycholysis

Drugs Used to Treat Psoriasis

[Know all of these.]

Topical corticosteroids: Plaques are usually treated with topical corticosteroids. Long-term use of high-potency steroids may cause thinning of the skin, striae, and steroid-induced rosacea on the face. They are best avoided on the face and intertriginous areas. To increase their effectiveness, topical steroids can be occluded with cellophane or a plastic wrap. Oral corticosteroids may actually worsen the disease by causing a "rebound flare." (See pustular psoriasis above.)

Tar is a time-honored treatment and is often still used in a compounded preparation with a corticosteroid. Tar preparations stain clothes but are well tolerated.

Calcineurin inhibitors: topical tacrolimus (Protopic®) and topical pimecrolimus (Elidel®). These are often used for facial and intertriginous areas where high-potency steroids should generally be avoided. Be aware of the FDA boxed warning for a potential increased risk of lymphoma and skin malignancy.

Retinoids (vitamin A derivatives):

- Tazarotene gel (Tazorac, Avage) decreases the hyperkeratosis or thick scales associated with psoriasis. Main side effect is skin irritation.
- Acitretin (Soriatane®), a 2nd-generation oral retinoid, is used for the severe forms of all types. It is extremely toxic and has a similar side effect profile to isotretinoin. (See moderate-to-severe inflammatory acne under Treatment of Acne Vulgaris on page 12-2.)

Do not use either drug in women with child-bearing potential. Important: The FDA has placed a 3-year post-dosing moratorium on pregnancy with acitretin.

Vitamin D_3 analog: These agents are less effective than high-potency topical steroids, but don't cause thin skin or striae:

- Calcipotriene (Dovonex®, a synthetic vitamin D_3 analog) is usually too irritating to apply to the face and intertriginous areas.
- Calcitriol (Vectical®, a synthetic vitamin D_3 analog in an ointment base) is less irritating.
- Treatment of extensive psoriasis with vitamin D analogs may result in hypercalcemia, so the maximum doses for calcipotriene and calcitriol are 100 gm and 200 gm per week, respectively.

Immunosuppressants: Methotrexate (MTX) and cyclosporine are both very effective for extensive severe psoriasis.

- Methotrexate can cause severe liver and pulmonary toxicity, as well as bone marrow suppression. Do not give MTX to patients with a history of alcohol abuse, liver disease, or severe kidney impairment (the drug is excreted renally).

Quick Quiz

- Nail pitting with onycholysis is a fairly specific finding for what dermatologic disorder?
- Which drugs should be added to the regimen for patients with psoriatic arthritis?
- Characterize the malar rash of systemic lupus.

- Cyclosporine is associated with renal toxicity and hypertension and is recommended only for short-term "rescue" use. Fair-skinned Caucasians with a prior history of treatment with psoralen and ultraviolet A (PUVA) should generally not be treated with cyclosporine because they have a much greater risk for developing squamous cell carcinoma.

Biologic immunomodulators: These are newer, effective treatments for psoriasis:

- TNF-alpha inhibitors: etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®)
- IL-12 and IL-23 blocker: ustekinumab (Stelara®)

Ultraviolet light may be added to the above treatments or used as monotherapy. UVB (290–320 nm) therapy is often used. Narrow-band (NB) UVB (311 nm) is possibly more effective than the broader spectrum treatment and is generally the treatment of choice. But, it requires more expensive equipment and a longer duration of therapy per session.

PUVA (oral psoralen + UVA light [320–400 nm]) is also very effective and is usually given to those who fail UVB. UVA penetrates more deeply than UVB and is less likely to burn (hence, the photosensitizing psoralen), but it is associated with accelerated photoaging, an increased likelihood of skin cancer (squamous cell carcinoma), and possibly melanoma in fair-skinned Caucasians. Future treatment with cyclosporine increases this risk.

Any patient with psoriatic arthritis is at risk for permanent joint damage and should be treated with a disease-modifying oral/injectable agent (cyclosporine, methotrexate, or the biologics). See Rheumatology, Book 3.

Treatment of Psoriasis

Recommended treatment for psoriasis depends on the severity of disease. The severity of psoriasis is defined not only by the extent of body surface area (BSA) involvement (< 5% being considered mild, 5–9% moderate, and ≥ 10% severe) but also by involvement of the hands, feet, facial, or genital regions. Involvement of these locations may interfere significantly with activities of daily living, irrespective of the amount of BSA involved.

Limited disease (< 5%): Treat with hydration and water trapping agents. Use high-potency or ultra–high-potency topical corticosteroids for no longer than 4 weeks. Taper to a mid-potency agent and add a vitamin D analog for maintenance. For the scalp use a tar shampoo and/or topical steroid lotions. For more sensitive areas like the face, axillae, and genitalia, use:

- low-potency corticosteroids,
- topical tacrolimus or pimecrolimus,
- calcitriol, or
- topical retinoids (tazarotene).

If the patient fails to respond, UV-based or short-term systemic therapy can be used.

Moderate disease (5–9%): Treatment is the same as for limited except that UV light therapy is routinely used, typically NB-UVB. PUVA can be used for those who fail UVB therapy. Depending on morbidity associated with the disease, consider treatment with systemic agents such as methotrexate, acitretin (Soriatane), or a biologic.

Widespread/severe disease (≥ 10%): NB-UVB is recommended, with consideration of PUVA for failures. Treat with methotrexate, cyclosporine, or a biologic. Combinations of these therapies can also be used. The combination of UVB or PUVA with acitretin is especially effective for pustular psoriasis.

Guttate psoriasis: Treat with UVB +/– topical steroids. Treat any streptococcal infection.

Flexural psoriasis: Treat with low-potency topical corticosteroids or topical tacrolimus/pimecrolimus.

LUPUS

Systemic lupus erythematosus (SLE): Malar (or butterfly) rash occurs in about half of acute SLE patients and rarely occurs in patients without systemic symptoms. Classically, this rash involves both cheeks and extends across the bridge of the nose, sparing the nasolabial fold. The malar rash is erythematous and either flat or slightly edematous and often occurs after sunlight exposure (photosensitivity). No scarring. Acne rosacea may mimic a malar rash, but can be distinguished by prominent telangiectasias, papules/pustules, and the lack of systemic symptoms.

Patients can get a red, scaly rash on the backs of the hands, usually between the joint spaces of the fingers (spares the knuckles), as opposed to dermatomyositis, where the rash is over the knuckles (Gottron papules) and spares the spaces between. Patchy and diffuse nonscarring alopecia is common in SLE. More on SLE in Rheumatology, Book 3.

Subacute cutaneous lupus erythematosus (SCLE) is a distinct subset of lupus characterized by erythematous macules/papules that evolve into papulosquamous plaques on sun-exposed areas. Like the acute rash of SLE, but in contrast to discoid lupus, these lesions heal without scarring. Many patients are seropositive for SSA/SSB antibodies. Patients uncommonly have significant systemic manifestations.

Chronic cutaneous lupus erythematosus (discoid lupus): Discoid lesions are erythematous and raised with tightly adherent scales. They cause atrophic scarring. They usually occur on sun-exposed areas, including the face, scalp, neck, and ear canals. Only 5% of discoid lupus patients develop SLE. However, patients with SLE who develop discoid lupus lesions tend to have a very good prognosis devoid of significant renal manifestations.

Intralesional corticosteroids are especially effective for discoid lupus. 1st line oral therapy includes antimalarials, such as hydroxychloroquine. More aggressive systemic therapy with immunosuppressants (MTX, azathioprine) is used in severe cases or for treatment of SLE with significant systemic involvement.

SYSTEMIC SCLEROSIS (SCLERODERMA)

Scleroderma localized to the skin only = morphea. Morphea is characterized by plaques that become sclerotic with a hypopigmented center and erythematous border. It usually occurs in children or young adults. It can be just a few lesions (localized morphea) or widespread with some confluence (generalized morphea).

Patients with systemic sclerosis (SSc) are classified into 2 major subtypes depending on the extent of skin sclerosis:

1) Limited sclerosis
2) Diffuse sclerosis

Limited SSc (previously CREST) is a grouping of symptoms that has limited systemic involvement, most commonly manifesting as skin thickening distal to the elbows and knees but sometimes affecting the face and neck. Patients classically present with several to all of the **CREST** features: **c**alcinosis cutis (small tender nodules on the fingers), **R**aynaud syndrome, **e**sophageal dysmotility, **s**clerodactyly of the fingers, and **t**elangiectasias. Anti-centromere antibody (ACA) is specific for limited SSc and is seen in about 50% of patients. Patients who are ACA+ tend to develop more severe digital ischemia and pulmonary hypertension.

Diffuse SSc is the progressive form of SSc that leads to diffuse skin thickening and is more likely to have multiorgan involvement (Image 12-13). This subset is characterized by rapid skin involvement of trunk, face, upper arms, and thighs. It is frequently associated with anti-Scl 70 (antitopoisomerase-I) or anti-RNA polymerase III antibodies and is more likely to develop interstitial lung disease and scleroderma renal crisis.

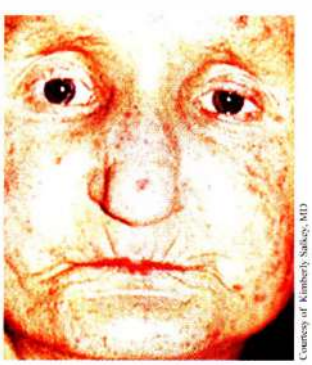

Courtesy of Kimberly Salkey, MD

Image 12-13: Systemic sclerosis

Raynaud phenomenon eventually develops in almost all patients with SSc. In limited SSc, Raynaud's usually occurs several years before other signs and symptoms become apparent, while in diffuse SSc, the Raynaud's typically occurs simultaneously with the other manifestations.

Nailfold capillary changes (but not in the actual nails) are commonly seen in both subtypes and correlate with severity of disease.

There are no proven disease-modifying treatments for SSc.

SARCOIDOSIS

Sarcoidosis is an immune-related noncaseating granulomatous disease that often affects the lungs, lymph nodes, eyes, and skin. It is most common in northern European countries (e.g., Sweden, Denmark). In the U.S., however, sarcoidosis most commonly affects African-Americans. Skin involvement is seen in about 25% of patients. Sarcoidosis is a great mimicker of other disorders, including many dermatologic diseases.

Lesions are divided into 2 categories: specific and nonspecific. Specific lesions have noncaseating granulomas on biopsy, while nonspecific skin lesions do not have granulomas and are considered reactive.

Specific sarcoid skin lesions are most commonly found on the head, neck, and upper back. Specific lesions include:

- Erythematous papules mainly around the face (the most common presentation)
- Scar sarcoidosis presenting as granulomatous changes in a healing skin wound or scar tissue (e.g., laceration, tattoo)
- Plaque-like lesions
- Micropapular lesions

Nonspecific skin lesions:

- Erythema nodosum (see next) is the most common nonspecific skin lesion seen in sarcoidosis and signals a good prognosis. Sarcoidosis is one of the most common causes of E. nodosum. Do not biopsy E. nodosum in sarcoidosis for diagnosis—the histopathology will just show a panniculitis (inflammation of the fat) and not granulomas.
- Löfgren syndrome is an acute form of sarcoidosis that presents with E. nodosum, bilateral hilar adenopathy, and arthritis, and is frequently accompanied by fevers. It is usually self-limiting and requires only supportive care.

Lupus pernio is a type of sarcoidosis that has skin changes ranging from violaceous lesions on the tip of the nose and earlobes to large purple nodules/tumors on the face and fingers. It has a slow onset and almost never resolves! It is associated with chronic disease and extrapulmonary involvement.

Treat cutaneous sarcoid with topical corticosteroids, intralesional steroid injections, antimalarials, and methotrexate. Lesions typically respond to treatment for pulmonary sarcoid.

QuickQuiz

- What are the manifestations of limited systemic sclerosis?
- What skin findings are associated with sarcoidosis?
- What are the skin manifestations of dermatomyositis?

ERYTHEMA NODOSUM

Erythema nodosum (Image 12-14) consists of red, warm, very tender nodules that are usually bilateral, symmetrical, and classically located on the shins. It is more common in women than men. Causes of erythema nodosum [Know!]:

- Sarcoidosis (common)
- Inflammatory bowel disease
- Infection (TB, streptococcal, deep fungal)
- Drugs (especially oral contraceptives, sulfas, and penicillins)

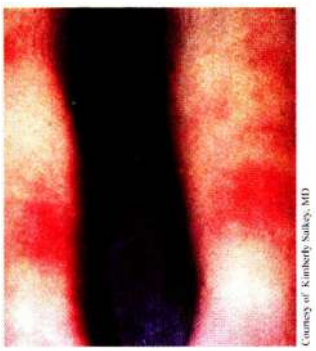


Image 12-14: Erythema nodosum

Worldwide, streptococcal infection is likely the most common cause of erythema nodosum. Treatment includes supportive therapy and NSAIDs.

DERMATOMYOSITIS

Buzzwords: periorbital heliotropic rash (+/– periorbital edema; [Image 12-15]). This is a violaceous (purple), sometimes scaly rash around the eyes.

Patients also manifest photodistributed, erythematous, scaly plaques—similar to psoriasis. Gottron sign is macular erythema over the dorsal aspects of the interphalangeal/metacarpophalangeal joints or over the elbows and knees.

Gottron papules, an extension of Gottron sign, are flat-topped, reddish-to-violet, sometimes scaling papules; sometimes, they just look like "cigarette paper" crinkling of the skin over the knuckles (MCP, PIP, and/or DIP). Gottron papules are the most specific finding with dermatomyositis. They may be described only as a "rash" or "eruption" over the knuckles (Image 12-16). Again, this contrasts to the finger rash in SLE that spares the knuckles. "Mechanic's hands" are bilateral symmetric areas of hyperkeratotic scale most commonly on the lateral fingers or on the palm. This finding is associated with antisynthetase syndrome, anti-Jo-1 antibodies, and interstitial lung disease.

Patients have symmetric proximal muscle weakness, but may present solely with cutaneous disease, termed amyopathic dermatomyositis.

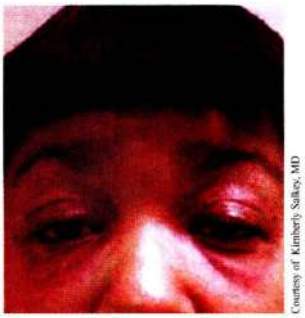


Image 12-15: Periorbital heliotropic rash

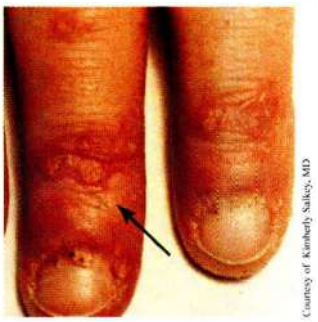


Image 12-16: Gottron papules

Treatment is corticosteroids. This is typically given for 1 year in a slowly tapering dose. A steroid-sparing drug (azathioprine or methotrexate) is sometimes started with initial treatment; other clinicians start it when there is failure to respond to prednisone.

Antimalarials (hydroxychloroquine) help with the skin disease but do nothing for the muscle disease. IV gamma-globulin may be effective in patients who do not respond to the other medications. Trials are examining the effectiveness of rituximab in the treatment of dermatomyositis.

Remember: In older patients, dermatomyositis may be a paraneoplastic phenomenon. (GU/ovarian, GI, lung, and lymphoma are most common.) All patients should be offered age-appropriate cancer screening. Patients who test positive for anti-p155/p-140 are at particularly high risk of cancer.

REACTIVE ARTHRITIS

Reactive arthritis is an immunologic reaction to an infection elsewhere in the body and typically occurs 1--4 weeks after a genitourinary or gastrointestinal infection. The classic triad of urethritis, conjunctivitis, and asymmetric arthritis is seen in less than 1/3 of patients. Cutaneous manifestations are common and include keratoderma blennorrhagicum and mucocutaneous genital lesions and/or mouth ulcers.

Keratoderma blennorrhagicum (Image 12-17) classically presents as papules/pustules with central erosion and characteristic crusting on the palms and soles and can be indistinguishable from pustular psoriasis.

Circinate balanitis presents as an erythematous pustular or plaque-like lesion on the glans or shaft of the penis.

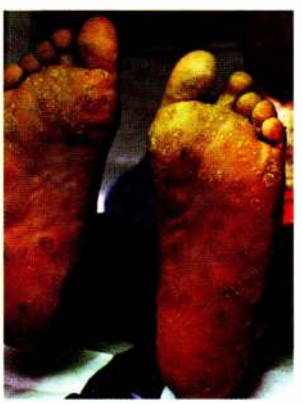


Image 12-17: Keratoderma blennorhagicum

VASCULITIS

Vasculitis presents most classically as palpable purpura, usually starting on the legs. Palpable purpura is the extravasation

of RBCs into the skin and is commonly caused by a small vessel vasculitis. Skin biopsy typically displays "leukocytoclastic vasculitis." There are many causes of cutaneous vasculitis, including infection (viral, bacterial, etc.), collagen vascular disease, and drug reactions. Up to 50% of self-limited cutaneous cases may be idiopathic. Always look for extracutaneous manifestations, especially kidney involvement. If a young patient presents with arthralgias, abdominal pain, renal disease, and palpable purpura, think IgA vasculitis (formerly Henoch-Schönlein purpura).

PYODERMA GANGRENOSUM

Pyoderma gangrenosum is an inflammatory ulcer typically occurring on the legs (Image 12-18). It is most commonly associated with inflammatory bowel disease, but can also be seen with rheumatoid arthritis and hematologic dyscrasias. Although a skin biopsy is not diagnostic, it serves to exclude other causes for ulceration. The classic presentation is a deep ulceration with an inflamed border that overhangs the ulcer. Treating the colonized bacteria usually does not help. Patients often complain of pain out of proportion to the clinical appearance of the lesion. Pathergy, the appearance of ulcers or lesions at sites of cutaneous trauma, is a common phenomenon.

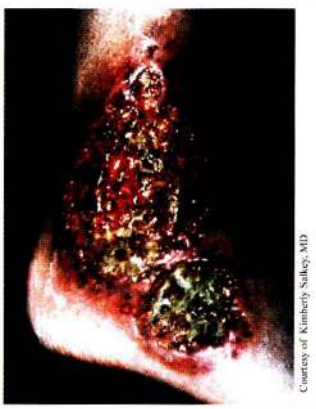


Image 12-18: Pyoderma gangrenosum

In idiopathic cases, 1st line treatment is corticosteroids. Otherwise, treat the underlying disorder.

SWEET SYNDROME

Sweet syndrome is an inflammatory disorder that is also referred to as acute febrile neutrophilic dermatosis. It may be idiopathic or associated with an underlying disease (most commonly AML) or medication (e.g., GCSF). Patients have high fever and painful red plaques, ~ 1 inch in diameter, typically on the upper extremities, trunk, neck, and face. A skin biopsy shows a dense, but benign neutrophilic infiltrate. Like in pyoderma gangrenosum and Behçet's pathergy, the lesions respond dramatically to corticosteroids. Potassium iodide and colchicine may also be used as 1st line agents.

VITAMIN DEFICIENCIES

VITAMIN/MINERAL DEFICIENCIES

Deficiency of B_{12}, folate, or niacin may cause diffuse hyperpigmentation, as well as hair and nail changes.

Niacin deficiency results in pellagra (remember the 3 **D**s: **d**ermatitis (photosensitive areas), **d**iarrhea, and **d**ementia). Isoniazid and carcinoid can also induce pellagra symptoms. Isoniazid is a competitive inhibitor of nicotinamide-adenine dinucleotide (niacin precursor) and also impairs pyridoxine functioning, which is essential for niacin synthesis from tryptophan.

Tryptophan can be metabolized to niacin or serotonin by 2 separate pathways. In carcinoid most of the L-tryptophan is diverted to the production of serotonin, leaving the patient at risk for niacin deficiency.

Zinc deficiency causes an irritant eczematoid red rash that has a predilection for periorificial (perioral, periocular, anogenital) and acral areas (hands and feet).

Iron deficiency is commonly associated with hair loss and fragile longitudinal nail ridges.

Vitamin C deficiency can result in follicular hyperkeratosis, especially on the posterolateral aspect of the arms, resembling keratosis pilaris. The hairs within these plugged follicles become curled, resulting in "corkscrew hairs." Perifollicular purpura develops as the disease advances.

SKIN INFECTIONS

BACTERIAL SKIN INFECTIONS

Much of the following and all treatments are covered more fully in Infectious Disease, Book 1.

Corynebacterium

Erythrasma is a well-defined, red lesion with some slight scaling. It is usually found in the axilla, groin, and toe webs. In obese women, it is seen under the breasts. Gram-positive *Corynebacterium minutissimum* is frequently isolated from the lesion (especially after it has become scaly or macerated). DDx: tinea cruris, *Candida*, and intertrigo (an irritant dermatitis found in the skin folds of obese patients). Diagnosis: Erythrasma fluoresces bright red (attributed to coproporphyrin III) with the Wood's lamp (ultraviolet light). Treat with benzoyl peroxide or topical erythromycin +/– an "-azole" antifungal cream. In severe cases, oral erythromycin or tetracycline may be used.

Staphylococcus aureus

Impetigo: *S. aureus* is by far the most common cause of impetigo, which starts as an erythematous, vesicular lesion that quickly becomes pustular and crusty ("honey-colored crust"). Impetigo is highly contagious and patients generally don't appear systemically

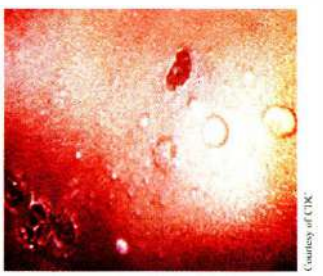


Image 12-19: Bullous impetigo

QuickQuiz

- Pyoderma gangrenosum is associated with what systemic illness?
- How does zinc deficiency manifest on the skin?
- What 2 organisms can cause impetigo?
- How does SSSS differ from toxic epidermal necrolysis?
- Characterize the lesions of disseminated gonorrhea.

ill. The face and exposed areas are most commonly affected. Methicillin-resistant *Staphylococcus aureus* (MRSA) is the cause of many community outbreaks of impetigo. When impetigo, an infection of the epidermis, extends into the dermis, it is called ecthyma. Treatment is covered in Infectious Disease, Book 1.

Bullous impetigo usually occurs in young children < 2 years old and presents with the acute onset of large, loose bullae (Image 12-19). An exotoxin/exfoliatin toxin causes cleavage of the epidermis.

Staphylococcal scalded skin syndrome (SSSS) primarily affects newborns and children < 5 years of age; it rarely affects immunocompromised adults. Patients with SSSS present with tender, red, peeling skin due to circulating toxins from localized staph infection or colonization, generally occurring at a non-skin site (sinuses; umbilicus in infants). Skin changes are similar to those seen in toxic epidermal necrolysis (noninfectious; rather, a side effect of drugs), so consider it during the workup. The skin in SSSS separates much more superficially than in toxic epidermal necrolysis. The peeling skin is caused by a similar exotoxin or exfoliatin toxin as seen in bullous impetigo (localized form of SSSS); however, it circulates systemically in SSSS. Treatment includes debridement of necrotic superficial epidermis, topical antibiotics for bullous impetigo lesions, and oral antibiotics for more severe/widespread disease.

Toxic shock syndrome (TSS): *S. aureus* and *S. pyogenes* are the causes of TSS. TSS presents with abrupt development of fever, hypotension, and multiorgan system failure. Patients have a diffuse painless macular erythroderma ("sunburn") rash (acute phase) followed by desquamation of the palms and soles during the convalescent phase. Patients are commonly < 30 years of age, and mucosal involvement is typical. In contrast to streptococcal TSS, blood cultures are usually negative. Treatment includes supportive care and systemic antibiotics.

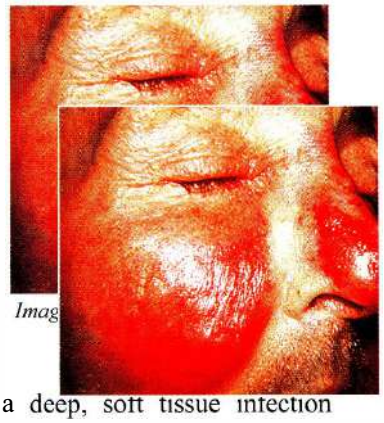
Folliculitis (inflammation of the follicle) and **furuncles** (deep folliculitis or "boil") are typically caused by *S. aureus*. Be aware that folliculitis associated with hot tub use is often caused by *Pseudomonas*, not staph.

Streptococcus pyogenes (Group A Strep)

Impetigo: Group A strep is a cause of impetigo a skin infection confined to the epidermis. Also see *S. aureus*, above.

Ecthyma starts as an impetigo and then becomes deeper, causing shallow ulcerations.

Erysipelas is an explosive superficial infection (often caused by group A strep) that is confined to the dermis and spreads quickly through skin lymphatics (Image 12-20). There is a clearly demarcated area of redness that is often palpable, indicating infection. It usually starts from a superficial abrasion, typically around the central face, with erythema and swelling. Lymphangitic spread with red streaking is seen.


Imag

Necrotizing fasciitis is a deep, soft tissue infection involving subcutaneous fat and fascia. Unlike erysipelas, it does not have a distinct border and can be difficult to diagnose early. There are 2 types: Type I, the most common type, is a polymicrobial infection (including anaerobes) seen in immunocompromised patients, such as diabetics. Type II is generally caused by group A strep or MRSA and most commonly affects healthy individuals. The LRINEC score is a helpful tool to use when there is concern for necrotizing fasciitis. This is a surgical emergency, and there is a high mortality rate even with appropriate medical and surgical intervention.

Scarlet fever primarily presents in children with pharyngitis and "scarlatina"—a fine, red, sandpaper-like rash that is more prominent in skinfolds (Pastia's lines) and involves the trunk and extremities, but spares the palms and soles. "Strawberry tongue" also commonly presents in the acute phase. During the convalescent stage, desquamation of the palms and soles occurs.

Streptococcal toxic shock syndrome (TSS) causes symptoms similar to staphylococcal TSS (described above). Treatment is with IV penicillin (PCN) + clindamycin +/– IVIG. In contrast to staphylococcal TSS, blood cultures are usually positive.

Strep throat: PCN is far and away the best treatment for a known group A strep throat infection. Give oral PCN (x 10 days) or IM benzathine PCN. Give erythromycin for PCN-allergic. Clindamycin is often added to PCN when there is serious infection (to decrease toxin production), such as necrotizing fasciitis or toxic shock.

Gonococcus and Meningococcus

Disseminated gonococcal infection causes a few (typically < 12) hemorrhagic pustules on the extremities,

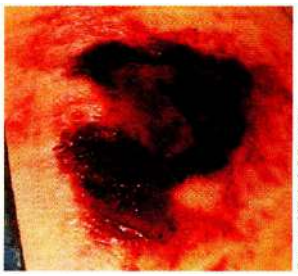


Image 12-21: Ecthyma gangrenosum

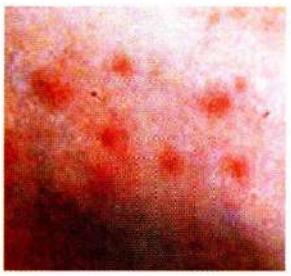


Image 12-22: Rocky Mountain spotted fever (medial foot)

often around the joints. Culture of the skin lesions is typically negative. Cultures should be taken from the initial site of infection (oral mucosa, cervix, urethra, or rectum), because they have a much higher yield.

Meningococcemic skin signs start as macular or petechial lesions and evolve to large purpura. Purpura fulminans consists of purpura, ecchymoses, and confluent map-like gray-to-black necrotic skin lesions. It is associated with severe infection and diffuse intravascular coagulation.

Pseudomonas

Pseudomonas causes a variety of skin infections. It is the cause of "hot tub folliculitis." Normal chlorine levels may prevent the possibility or growth of infection with this organism. The pustules from hot tub folliculitis are usually around the buttocks and thighs and resolve without treatment in 1 week. 5% acetic acid compresses can be used for symptomatic relief. Pseudomonal septicemia causes small, dark-centered (necrotic) papules. In a very ill, neutropenic patient, this papule can evolve to ecthyma gangrenosum—a necrotic ulcer with an erythematous rim (Image 12-21).

Animal Bites

S. aureus, *Eikenella*, and *Pasteurella multocida* often cause infection from dog and cat bites. Human bite infections are caused by multiple bacteria and can cause severe infection.

Treatment: Clean and lavage well and give AM/CL (amoxicillin-clavulanate) as prophylaxis and treatment. Don't forget tetanus vaccine if due.

RICKETTSIAL SKIN INFECTIONS

Rocky Mountain spotted fever is usually heralded by several days of fever. Then the patient gets small lesions, which progress in distribution from peripheral to central (centripetal) and in type from macular to petechial to purpuric. As you can see from Image 12-22, the skin findings can be deceivingly nondescript. See Infectious Disease, Book 1, for treatment.

SPIROCHETAL SKIN INFECTIONS

The first stage of **Lyme disease** is often associated with erythema migrans (Image 12-23). Typically, this is a slowly (over about 1 week) enlarging, annular erythematous rash with a clear center (looks like a bullseye). Occasionally, the center is not clear.

Syphilis: A chancre (painless ulcer at site of inoculation) indicates primary syphilis. Diffuse scaling papules on the palms and soles, trunk, penis, and mucosal surfaces suggest secondary syphilis, as does condyloma lata. Gummas occur in tertiary syphilis, and are painless, indurated, nodular, or ulcerative lesions.

VIRAL SKIN INFECTIONS

Warts (verrucae) are caused by any one of more than 60 types of human papillomaviruses (HPV), and they often resolve spontaneously. However, because of their unsightly appearance, patients usually request treatment, which typically involves some form of tissue destruction.

- Verruca vulgaris is the common wart; treat it with liquid nitrogen, topical acids, CO_2 laser, etc.
- Verruca plana is the flat wart.
- Verruca plantaris is the plantar wart (Image 12-24). Initial treatment may consist of a strong acid (trichloroacetic acid), concentrated (40%) salicylic acid plaster, liquid nitrogen, or laser.
- Condylomata acuminata are anogenital warts. They are often caused by HPV 6 and 11. They are sometimes caused by HPV 16, 18, and 31—the oncogenic HPV types (associated with cancer of the cervix). Treat them with podophyllin, trichloroacetic acid, liquid nitrogen, or CO_2 laser. Podophyllin is teratogenic, so do not give it to pregnant patients. A newer treatment for condyloma acuminatum is topical imiquimod (Aldara®).

[Know.] Molluscum contagiosum is caused by a poxvirus. It consists of smooth, umbilicated, pearly papules (Image 12-25). It usually occurs in children (anywhere on the body except palms and soles), but you may also see it in the pelvic area of sexually active young adults—and it is common in AIDS patients (can be sexually transmitted). Molluscum contagiosum often resolves spontaneously except in immunosuppressed patients (e.g., AIDS).

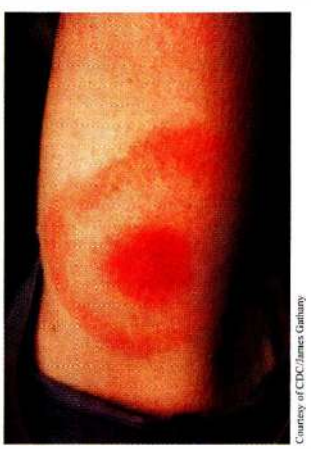


Image 12-23: Erythema migrans

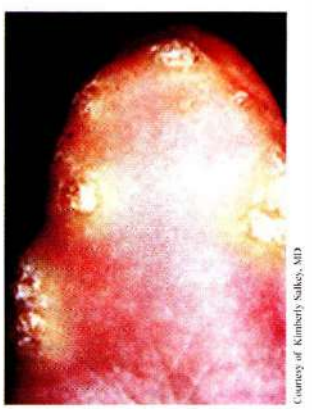


Image 12-24: Plantar wart

Quick Quiz

- What is the significance of finding a lesion of ecthyma gangrenosum on physical exam?
- Which antibiotic is used to treat a cat bite?
- Characterize the rash of erythema migrans.
- Molluscum contagiosum, if seen in an adult, should raise your suspicion for what immunodeficiency?
- How does the dose of acyclovir differ when the drug is used to treat varicella and herpes simplex infections?

[Know.] **Measles** (rubeola) has several stages. The prodromal stage lasts 3--4 days with fever, malaise, sinus discharge, and a hacking cough. Koplik spots (pathognomonic) often appear on the palate from 1 to several days before the onset of rash. As the Koplik spots begin to disappear, a red maculopapular rash starts on the face and behind the ears and quickly spreads downward and outward with the densest concentration of lesions from the face to the shoulders. The palms/soles are affected last. Lesions gradually fade in order of appearance and may have some desquamation.

Rubella (German measles, 3-day measles) is benign except when it occurs in pregnant women. The rash is similar to measles but lasts only 3 days. Congenital rubella results in a variety of serious birth defects:

- heart malformations,
- ocular defects,
- microcephaly,
- intellectual disability,
- deafness,
- TTP, and
- bone problems.

Varicella-zoster virus (VZV) causes two diseases: chicken pox and herpes zoster (shingles). Both diseases present with vesicles on an erythematous base. Herpes zoster is reactivation of VZV in a person who has had chicken pox.

Chicken pox: Incidence is decreased now due to routine vaccination of children. Rash is initially maculopapular and rapidly progresses to vesicles and then to scabbed lesions. These tend to come in "crops" over 2--4 days.

Herpes zoster: grouped vesicles along a dermatome with focal pain. Older age and immunosuppression are risk factors. If given within 72 hours of onset, antiviral therapy with acyclovir, famciclovir, or valacyclovir decreases the length of the disease and the likelihood of progression to post-herpetic neuralgia. A herpes zoster vaccine is approved as primary prevention for all patients > 50 years of age and those who have already had an episode of herpes zoster.

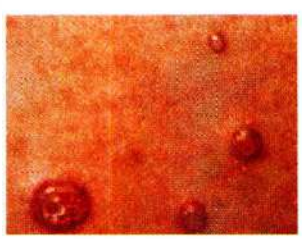


Image 12-25: Molluscum contagiosum

In the immunocompromised, treat both chicken pox and herpes zoster with intravenous acyclovir at higher doses than what is used to treat herpes simplex infections.

FUNGAL INFECTIONS

Dermatophytes (*Microsporum*, *Epidermophyton*, and *Trichophyton*) cause superficial fungal infections (outer layer of skin) and are named according to the site involved:

- Tinea capitis (scalp ringworm)
- Tinea corporis (common ringworm, Image 12-26)
- Tinea cruris (jock itch)
- Tinea unguium/onychomycosis (nails, Image 12-27)
- Tinea pedis (athlete's foot, Image 12-28)

The diagnosis is often made clinically, but can be confirmed with potassium hydroxide (KOH) test on skin scrapings, which reveals branching filamentous hyphae.

Candidiasis is a deeper fungal infection that causes red patches in intertriginous areas. Candidiasis of the mouth (thrush) causes white semi-adherent plaques on the tongue and mucosa. Unlike hairy leukoplakia, these can be scraped off. Vaginal candidiasis has similar plaques with cheesy discharge.

Most fungal skin infections are controlled by topical antifungal creams. Miconazole, clotrimazole, and topical terbinafine (Lamisil®) are used. Tinea capitis and tinea unguium (onychomycosis) are exceptions and must be

Image 12-26: Tinea corporis

Image 12-27: Tinea unguium or onychomycosis

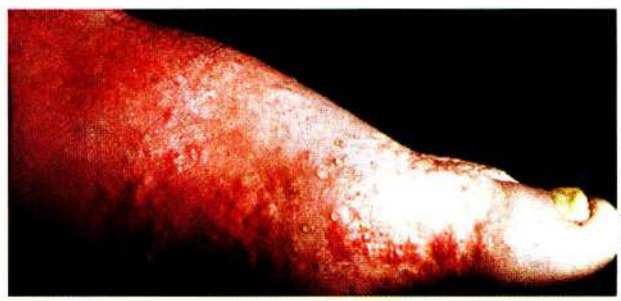


Image 12-28: Tinea pedis (athlete's foot)

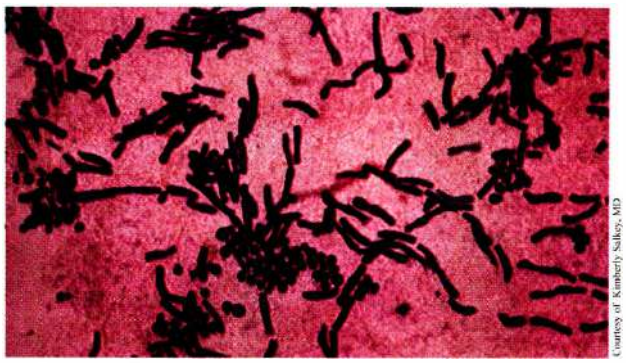


Image 12-29: Tinea versicolor

treated with **oral** anti-fungals. Tinea capitis requires oral griseofulvin, terbinafine, or itraconazole. Treat tinea unguium with systemic terbinafine, itraconazole, or fluconazole.

Tinea versicolor (pityriasis versicolor) is caused by *Malassezia globosa* or *Malassezia furfur* (Image 12-29). Skin infection results in hypopigmented or hyperpigmented (depending on the patient's skin tone/color) spreading macules, usually on the upper torso and upper arms. KOH skin scraping: **spaghetti and meatballs**. Treatment: imidazole creams, selenium sulfide or ketoconazole shampoo, and/or oral itraconazole.

PARASITIC SKIN INFECTIONS

Lice outbreaks occur in schools, nursing home communities, and camps.

Head lice (*Pediculus humanus capitis*): The recommended pesticide-based topical treatment (applied to hair and left on for 10 minutes) is over-the-counter **permethrin** cream 1% (Nix® cream rinse) because it kills both lice and eggs. It is approved for **head** lice only. Other topical medications that can be used include 1% lindane shampoo (2nd line because of neurotoxicity) and pyrethrin + piperonyl butoxide (RID®, etc.). These do not kill the eggs and require another treatment a week later. In the U.S., **resistance** is **growing** against **all** common pesticide-based preparations. Removal of nits (eggs) with a fine-toothed comb following the application of all treatments is **critical** for successful treatment.

A newer treatment that is as effective as RID but contains **no** neurotoxic pesticides is **benzyl alcohol lotion 5%** (Ulesfia®). It kills by suffocating the lice. It is safe in children older than 6 months.

Treatment for **resistant** head lice:

Malathion is a highly effective prescription **topical** agent. **Ivermectin** (yes, the drug that kills heartworms in dogs; Stromectol®) is the strongest drug; it is given **orally** as 2 doses, 1 week apart. It is considered a 2nd line alternative to malathion.

Body lice (*Pediculus humanus corporis*; [Image 12-30]) live in clothes and are on the body only when feeding. Treatment is bathing and careful **laundering** of clothes and bed linens. 1% lindane lotion or pyrethrin + piperonyl butoxide are used if body lice are found on the seams of clothing.

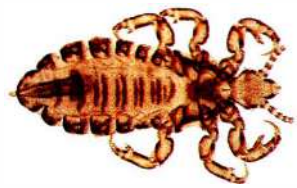


Image 12-30: Body louse

Pubic lice (*Pthirus pubis*): The crab louse is **sexually transmitted** and can also infect the eyelashes. Crab lice are **rarely** transmitted by fomites. Itching is the most common manifestation of infection. Exam may reveal bluish macules (maculae ceruleae) in the groin area. Treatment is similar to that of head lice. Use topical permethrin or pyrethrin + piperonyl butoxide. Wash bedding and clothing in hot water and use a hot dryer.

Scabies is caused by a mite (*Sarcoptes scabiei*) that **tunnels** into the skin to lay eggs (Image 12-31). It is spread by **skin-to-skin contact**—does not live > 48 hours without a host! It should be considered in anyone with unexplained generalized itching, particularly hospitalized or institutionalized patients. Diagnosis is made by microscopic visualization of the mite, feces, or eggs from skin scrapings.

Treat with 5% permethrin applied to **all** areas of the body from the head down and washed off after 8–14 hours. A second dose in 7 days is recommended. Use oral ivermectin for severe or recalcitrant cases with a repeat dose in 2 weeks. Lindane has CNS toxicity, so do not use during pregnancy, in infants, or in young children. Permethrin (Category B) can be used in pregnancy. Precipitated sulfur is also considered safe in pregnancy, but may be less effective. Wash all linens in hot water.

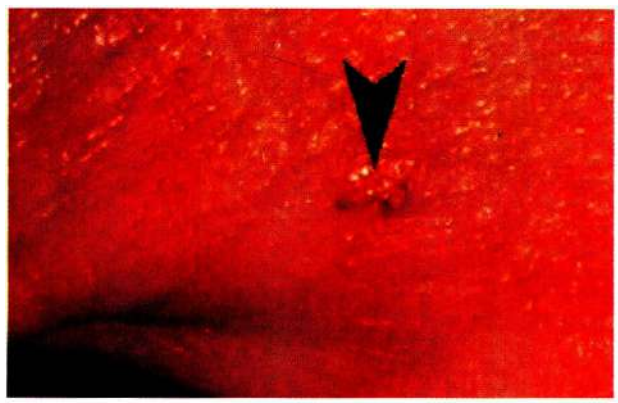


Image 12-31: Scabies tunnel

SKIN CANCER AND SKIN FINDINGS

Basal cell carcinoma (BCC) arises from epidermal basal cells and is the most common form of skin cancer, especially in **Caucasians** (Image 12-32). The usual type of BCC is characterized by translucent pearly papules, often with telangiectatic vessels. It spreads by **local extension** and, when large enough, gets a "**rodent-eaten**" appearance.

QuickQuiz

- What are the treatments for head lice? What topical treatment is not pesticide-based?
- What is the metastatic potential for basal cell carcinoma?
- On which areas of the body does squamous cell cancer have the highest rate of metastasis?
- For melanoma, what measurement is most important when determining prognosis?

BCC is caused by ultraviolet (UV) radiation from sun exposure. It is typically found on sun-exposed areas such as the head and neck, but it may appear elsewhere.

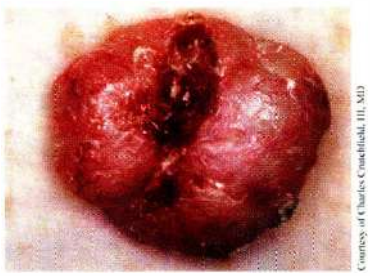


Image 12-32: Basal cell carcinoma

Know that the metastatic potential of BCC is < 0.1%. BCCs are typically surgically removed.

Squamous cell carcinoma (SCC): From keratinizing epidermal cells, SCC occurs especially in fair-skinned persons and on sun-exposed areas, like the dorsum of hands, forearms, ears, and lower lip (Image 12-33). In contrast to the low metastatic potential of BCC, SCC has a 0.3–5.0% metastatic potential—and even higher when it appears on the ear (11%) and lower lip (13%)! The metastatic rate of recurring tumors is 30%, and the rate in SCC originating from scars approaches 40%. Other risk factors associated with a higher rate of metastases include: size > 2 cm, depth > 4 mm and Clark level IV or V, poorly differentiated lesions, and immunocompromised hosts (transplant patient). SCCs are generally removed surgically.

Actinic keratosis is precancerous lesions that can develop into SCC. SCC *in situ* (Bowen disease) is a non-invasive form of SCC. Both of these types of lesions can be treated with cryotherapy, topical 5-flourouracil, topical imiquimod, and surgical excision.

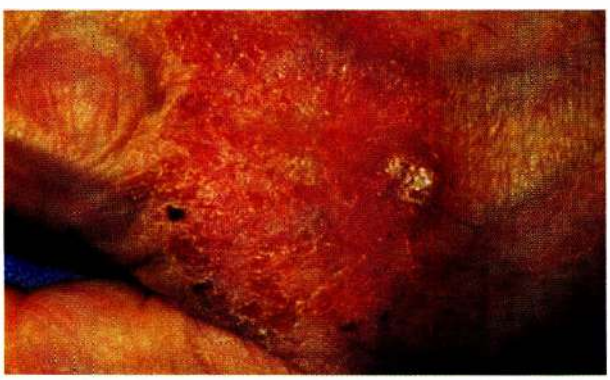


Image 12-33: Squamous cell carcinoma of the hand

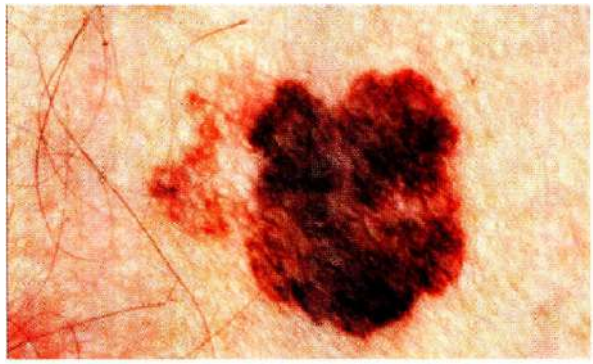


Image 12-34: Malignant melanoma—superficial spreading

Melanoma: This also tends to occur more commonly in fair-skinned people, especially those who had severe sunburns in childhood (Image 12-34). There has been a 300% increase in incidence of melanoma in the past 40 years. Other risk factors are dysplastic nevi (described below), a family history of melanoma, a high number of ordinary nevi, a congenital nevus, and immunosuppression. It is almost always completely curable if caught early enough.

Think "**ABCDE**" when assessing a lesion that might be malignant melanoma:

- **A**symmetry
- **B**orders are irregular
- **C**olor variation
- **D**iameter > 6 mm is suspicious
- **E**levated or **e**volving lesions are more suspicious

Prognostic factors include age (< 50 years) of the patient, location of the lesion (on the trunk), and (most important) the depth of the lesion. Lesions < 0.76 mm in depth have 99% five-year survival; those > 3.6 mm have < 50% five-year survival.

If the lesion is < 0.76 mm, you may safely excise the melanoma with a 1-cm, tumor-free margin. (Previously, a 5-cm margin was recommended.) Lesions over 0.76 mm in depth should be referred for evaluation for a sentinel lymph node procedure.

[Know.] Dark-skinned individuals can also get melanoma. The lesions tend to be in acral areas (palms, soles, and nail beds). Hutchinson nail sign is an important clinical clue to subungual melanoma, which is typified by extension of brown or black pigment from the nail bed, matrix, and nail plate to the adjoining cuticle and proximal or lateral nail folds.

Dysplastic nevi are "odd-looking" moles and may even look like melanomas (Image 12-35). They are markers for a propensity to develop malignant melanoma. However, most melanomas arise *de novo* and not in a preexisting

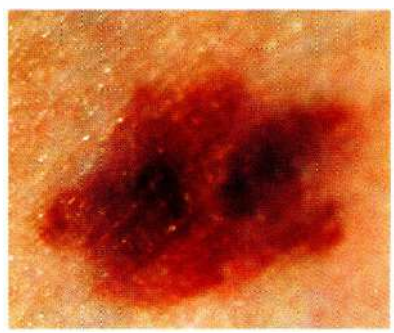


Image 12-35: Dysplastic nevus

DERMATOLOGY

nevus. Removing all moles does not prevent melanoma development. Standard of care is close follow-up and monitoring, utilizing photographic documentation. If a patient with a dysplastic nevus has 2 relatives with malignant melanoma, the patient has a 300x chance of getting malignant melanoma!

Mycosis fungoides and **Sézary syndrome** are the main forms of cutaneous T-cell lymphoma. Mycosis fungoides can be mistaken for psoriasis or eczema. Sézary syndrome has peripheral blood involvement in addition to the skin manifestations, and is associated with a poorer prognosis.

Paget disease of the breast is something to consider anytime there is a persistent (despite treatment), unilateral, oozing, eczematous plaque in the area of the areola. It is virtually always due to underlying intraductal breast cancer, and is due to retrograde extension of the tumor. By far, the most common causes of an acute eczema-type rash on an areola are contact dermatitis or skin irritation. Especially consider Paget disease if there is no response to treatment.

Peutz-Jeghers syndrome consists of multiple hamartomatous polyps + melanotic pigmentation (lentigines) on the lips + buccal mucosa. Even though these polyps are hamartomas, there is still some risk of cancer because an occasional adenoma occurs. Note that healthy, darkly pigmented people and those with Addison disease may have similar intraoral dark spots.

Glucagonomas (secreting pancreatic alpha-cell tumors) secrete excessive amounts of glucagon and can cause a beefy red tongue (think **GL**ucagonoma = **GL**ossitis), angular cheilitis, and a necrolytic migratory erythematous rash. Patients with glucagonomas may develop the "4 **D**s": **d**iabetes, **D**VT, **d**epression, and **d**ermatitis. Weight loss is characteristic.

Metastases to the skin: The 4 cancers that most commonly have cutaneous metastases are lung cancer, GI cancer, melanoma, and breast cancer in women.

Macroglossia associated with pinch purpura (purpura and ecchymosis develop after pressure or rubbing); strongly suggests amyloidosis.

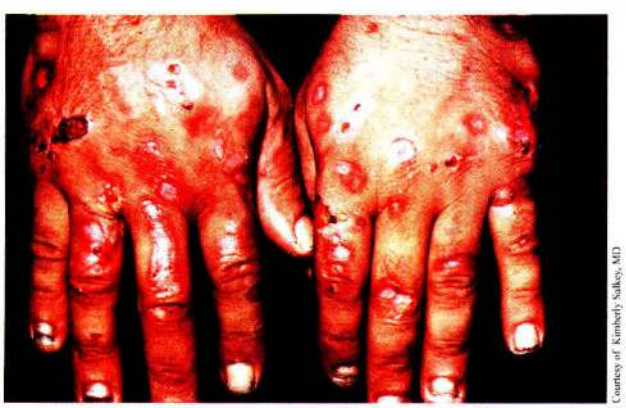


Image 12-36: Porphyria cutanea tarda (PCT)

BLISTERING LESIONS

Porphyria cutanea tarda (PCT) (Image 12-36, Image 12-37) is the most common type of porphyria. PCT causes hyperpigmentation, tense blisters in sun-exposed areas, milia, skin fragility, and increased facial hair. PCT is caused by a congenital or acquired decreased activity of uroporphyrinogen decarboxylase (UROD), which allows a buildup of phototoxic porphyrins in the skin. Symptoms can be induced by ingestion of estrogen or alcohol! Many patients have associated hepatitis C. Lab results usually show an increased serum Fe, ALT, and AST. To screen, check for increased urinary coproporphyrins and uroporphyrins. Patients may have dark or pink urine.

Treatment is the same as for hemochromatosis: regular phlebotomies. Iron may inhibit the activity of UROD. By decreasing iron stores with phlebotomy, the activity of UROD increases, resulting in porphyrins being metabolized quickly, thus preventing them from building up in the skin. Antimalarials (hydroxychloroquine) are also effective by helping to mobilize porphyrins. They are typically used when phlebotomy is contraindicated. PCT due to HCV resolves with treatment of hepatitis.

Porphyria variegata (variegate porphyria) is also known as South African porphyria. It is called variegate because patients can present in a variety of ways. They can have acute episodes like acute intermittent porphyria (AIP), chronic skin manifestations like PCT, or both. Patients may get blisters on sun-exposed areas and have mechanical fragility of the skin. These patients may also have abdominal pain, polyneuropathies, and mental disturbances.

The symptoms are due to a deficiency of protoporphyrinogen oxidase, which leads to the build-up of excess porphyrins. Treatment of acute attacks is the same as for AIP: glucose and hematin. Glucose and hematin theoretically work by inhibiting ALA synthase and preventing the accumulation of toxic precursors. Differential diagnosis: Note that AIP presents similarly to variegate porphyria, except without the skin changes. PCT (above) presents with the skin changes but without the neuro/mental changes!

Epidermolysis bullosa: Patients have blistering after minor skin trauma, caused by congenital structural defects of the skin. The skin splits at the junction of

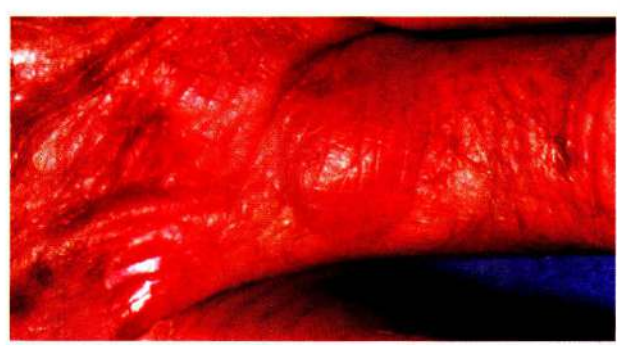


Image 12-37: Porphyria cutanea tarda (PCT) with blisters

Quick Quiz

- What are the main forms of cutaneous T-cell lymphoma? Which has the worse prognosis?
- What are the "4 Ds" that patients with glucagonomas develop?
- Characterize the skin findings associated with porphyria cutanea tarda.
- What type of hepatitis is associated with porphyria cutanea tarda?
- What is the pathognomonic lesion for erythema multiforme? Which virus is often the cause?

the epidermis and the dermis. There are many different classifications. All classifications are genetically transmitted, and each is due to a specific gene mutation. The major classifications include epidermolysis bullosa simplex (EBA), which affects the keratin genes *KRT5* and *KRT14*; junctional epidermolysis bullosa (JEB), which affects the laminin and collagen genes; and dystrophic epidermolysis bullosa (DEB), which affects the collagen VII gene.

Nikolsky sign: Slight lateral pressure on the skin causes sloughing of the epidermis. It is positive in pemphigus vulgaris, toxic epidermal necrolysis (TEN), and staphylococcal scalded skin syndrome (SSSS). It is negative in bullous pemphigoid.

Bullous pemphigoid causes recurrent crops of tense, deep, intact blisters (Image 12-38). Older individuals are usually affected. The disease process is classified as a type II hypersensitivity reaction and can appear similar to urticaria when it starts. It has an autoimmune etiology with formation of anti-basement membrane antibodies. Precipitating events include exposure to UV light, radiation therapy, and certain drugs including furosemide, ibuprofen, captopril, and penicillamine. Therapy includes topical (mild disease) and systemic corticosteroids and immunosuppressants.

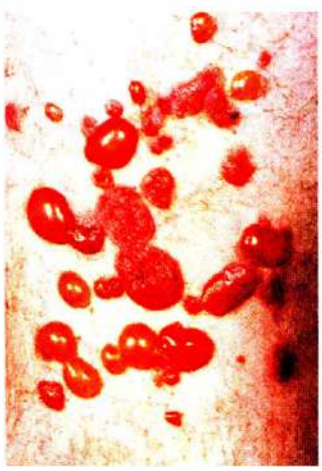


Image 12-38: Bullous pemphigoid

Pemphigus vulgaris (Image 12-39) is an autoimmune disease with intraepidermal antibodies against desmosomes. This causes acantholysis (the separation of epidermal cells from each other due to decreased cohesion), which results in the formation of large, superficial, loose bullae that peel off and leave denuded skin. Oral mucosal involvement is common, and any cutaneous area can be affected. Treatment of pemphigus vulgaris is similar to that of bullous pemphigoid.

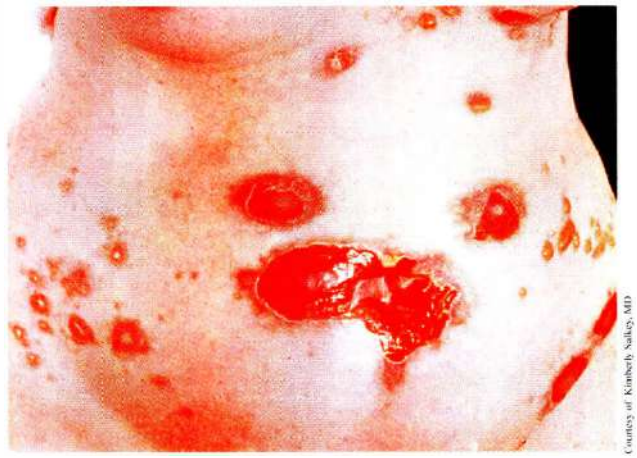


Image 12-39: Pemphigus vulgaris

Erythema multiforme consists of well-defined lesions varying from annular to targetoid (Image 12-40). Palms and soles are frequently involved, and mucous membranes may be affected. The "target" lesions are pathognomonic for erythema multiforme. It is caused by herpes simplex virus, *Mycoplasma*, and drugs (NSAIDs, penicillins, etc.). Treatment involves antimicrobial therapy if a causative organism is found (e.g., *Mycoplasma*) or removal of an offending medication. Herpes associated EM is often recurrent, and patients may benefit from suppressive antiviral therapy.

Stevens-Johnson syndrome is a severe form of erythema multiforme, and some authors consider it part of the spectrum of toxic epidermal necrolysis. It is usually caused by a drug and, by definition, affects < 10% of the body surface area (BSA). Treatment requires removal of the offending drug and supportive care. Corticosteroids are controversial and should be used for only a very short time, if at all.

Toxic epidermal necrolysis (TEN) is considered a variant or more severe form of Stevens-Johnson syndrome. It is caused by a hypersensitivity reaction to a drug (e.g., allopurinol, anticonvulsants, NSAIDs, sulfa, and antibiotics). Like SSSS, it results in a peeling

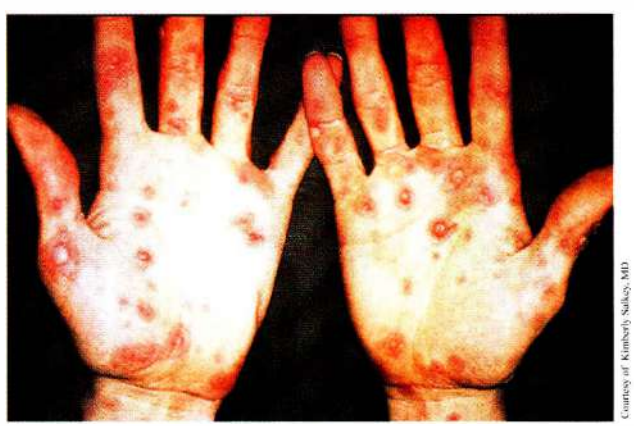


Image 12-40: Erythema multiforme

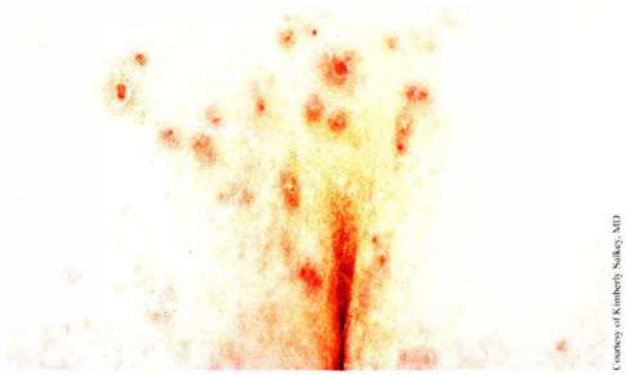


Image 12-41: Dermatitis herpetiformis

or exfoliation of large areas of skin, but it occurs at a deeper level than SSSS. By definition, it affects > 30% of the BSA. Treatment requires removal of the implicated drug, aggressive skin care, and supportive care in an intensive care burn unit. Patients with toxic epidermal necrolysis do poorly, and mortality can be as high as 40%.

Dermatitis herpetiformis (DH) is a skin disease where pruritic vesicular lesions appear on the extensor surfaces and mid-to-lower back. Lesions are caused by IgA deposition in the dermal papillary tips (Image 12-41). Given the extreme pruritus, intact vesicles are often not apparent. It is associated with celiac disease (gluten-sensitive enteropathy). DH and celiac disease can both be treated with a gluten-free diet. Alternatively, dapsone can be used to treat DH but is not effective for celiac disease.

ROUND LESIONS

Granuloma annulare is an idiopathic, annular, ringworm-like lesion without scaling, which typically appears on the distal portion of the extremities (Image 12-42). It often occurs in children and young women. It usually is self-limited, disappearing in months to a few years. Other treatment options include topical or intralesional corticosteroids.

Nummular eczema consists of small, circular (nummular = coin-shaped), pruritic lesions that are more common on the extremities and are often associated with dry skin and atopy. They are very common in the elderly and have no pathologic significance. Rule out fungal infection. Treat with mid-to-high–potency topical steroids.

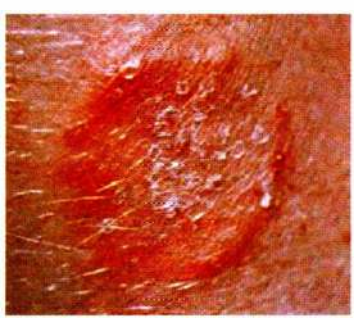


Image 12-42: Granuloma annulare

Pityriasis rosea is a rash common in children and young adults. Its etiology is unknown but it may be infectious in origin (possibly human herpesvirus 6 or 7). The disease is self-limited, typically lasting 4–8 weeks.

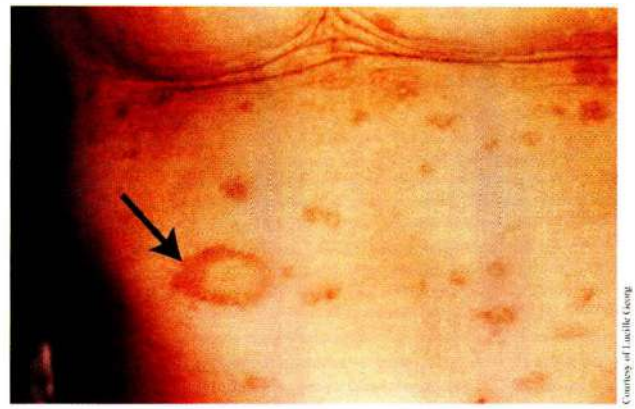


Image 12-43: Herald patch of pityriasis rosea

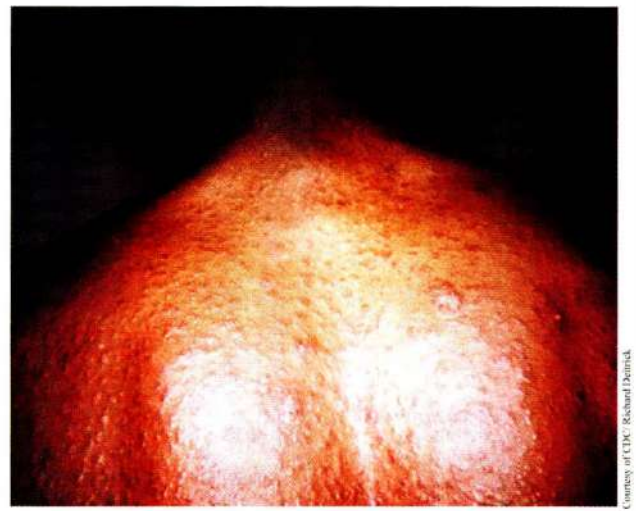


Image 12-44: Pityriasis rosea; generalized rash

A herald patch precedes subsequent pityriasis rosea lesions by 1–2 weeks (Image 12-43). This patch is sometimes confused with tinea corporis (Image 12-26 on page 12-13) Subsequently, small, pruritic papulosquamous oval lesions with the long axis parallel to skin folds and rib lines develop in a "Christmas tree" pattern usually on the trunk (Image 12-44). All the lesions typically have a "collarette of scale" at the margin. Treatment is symptomatic. Note: Tinea versicolor (pityriasis versicolor) has no relationship with pityriasis rosea.

Urticaria (hives) are raised pruritic welts on the skin that can be the manifestation of an allergic reaction. The lesions may have a smooth or irregular border. Aspirin is a common cause of urticaria. They can be a manifestation of a connective tissue disease, viral infection, or may be idiopathic. Treatment is primarily with antihistamines.

PIGMENT CHANGES

Vitiligo is an autoimmune disease which causes destruction of melanocytes resulting in depigmentation (Image 12-45). It usually occurs in healthy persons, but, rarely, it may also be part of a polyglandular autoimmune (PGA) syndrome. With a PGA, there may be any of the following: DM, autoimmune thyroid disease (hyper or hypo), Addison disease/adrenal insufficiency,

Quick Quiz

- With what GI disorder is dermatitis herpetiformis associated?
- What is characterized by a "Christmas tree" pattern and a herald patch?
- What skin finding might you see with a polyglandular autoimmune deficiency syndrome?
- Hyperpigmented areas of the axilla are associated with what underlying disease states?
- What diseases are on the short list of causes of black lesions?
- What is the significance of eruptive xanthomas?

hypoparathyroidism, and pernicious anemia. Anytime you see a patient with vitiligo, think of these possibilities and screen appropriately!

Tuberous sclerosis is uncommon and autosomal dominant. It is associated with seizures, intellectual disabilities, periungual fibromas, and hypopigmented (ash-leaf) macules. You can see these macules best with a Wood's lamp. Adenoma sebaceum manifests in these patients as numerous mid-facial papules, which are actually angiofibromas.

Café-au-lait spots are brown macules that occur in association with neurofibromatosis type 1 (von Recklinghausen disease) and McCune-Albright disease. To a lesser degree, café-au-lait spots occur in people with no disease (1–2 spots are normal and common). In neurofibromatosis, 78% of patients have > 6 spots—and 95% have at least one spot > 1.5 cm. In McCune-Albright disease, the spots have a more irregular outline.

Acanthosis nigricans is hyperpigmented skin with a thickened, velvety appearance, noticed mostly in the skin folds (Image 12-46). Involvement of the axilla is commonly shown as an example. It rarely is familial. Although you typically see this in obese patients, it is also associated with GI cancer, many endocrinopathies, and several autoimmune problems.

Image 12-45: Vitiligo

Malignant acanthosis nigricans is severe and progressive and is usually associated with gastric adenocarcinoma.

Associated endocrinopathies include Cushing disease, hyper/hypothyroidism, acromegaly, and diabetes mellitus. Overuse of niacin may also cause acanthosis nigricans!

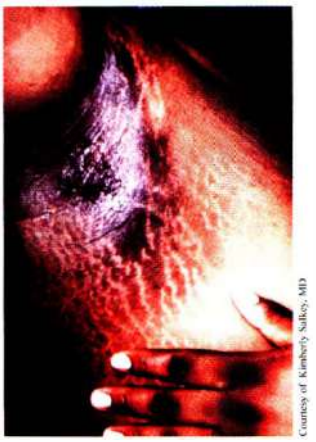


Image 12-46: Acanthosis nigricans

Diffuse hyperpigmentation may occur in primary biliary sclerosis, scleroderma, Addison disease, hemochromatosis (a grayish/bronze coloration), and with the use of the cancer drug busulfan. Other causes include porphyria cutanea tarda, malabsorption and/or Whipple syndrome, pellagra (niacin deficiency), B_{12} deficiency, and folate deficiency. Check for metastatic melanoma in "slate-blue" patients!

Hyperpigmentation in sun-exposed areas can be caused by amiodarone, porphyria cutanea tarda, and phenothiazines. Hyperpigmentation is diffuse but darker in sun-exposed areas in pellagra, biliary sclerosis, and scleroderma. Methotrexate can cause reactivation of sunburn.

Black lesions: Consider the following when you see black lesions:

- Rhinocerebral mucormycosis
- Anthrax
- Ecthyma gangrenosum
- Emboli to distal extremities
- Melanoma/Lentigo
- Warfarin skin necrosis

PRURITUS

The most common cause of itching in elderly patients is dry skin. Other causes seen across the age spectrum include:

- Hyper- or hypothyroidism
- Malignancy (think lymphoma—especially Hodgkin's, but also breast cancer)
- Iron deficiency (even if patient is not anemic)
- Polycythemia rubra vera (aquagenic pruritus)
- Chronic (but not acute) renal failure
- Cholestatic liver disease
- Diabetes mellitus

AIDS-RELATED SKIN LESIONS

All skin conditions become more common in HIV/AIDS. AIDS-related lesions include the following: xerosis (dry skin), seborrheic dermatitis (in virtually all patients!), telangiectasias, herpes simplex, herpes zoster, folliculitis, Kaposi sarcoma (KS), and oral candidiasis. Patients with HIV/AIDS can also get condyloma acuminatum (HPV), molluscum contagiosum (poxvirus), and bacillary angiomatosis. Bacillary angiomatosis resembles KS but is caused by a gram-negative bacillus, *Bartonella henselae* (same etiologic agent of cat-scratch disease).

Treat the seborrheic dermatitis with topical low-potency steroids +/– an antifungal shampoo.

The folliculitis is usually due to uncontrolled HIV infection, but it can also be due to a yeast, *Pityrosporum orbiculare*, or *Staphylococcus aureus*. Generally, treatment with antiretroviral therapy improves these rashes. If no organism is found, consider eosinophilic folliculitis (eosinophils seen on biopsy), which can occur in HIV/AIDS.

Oral "hairy" leukoplakia (Image 12-9 on page 12-4) is a corrugated tongue with white lesions along the side caused by the Epstein-Barr virus in immunocompromised HIV patients. It resolves with antiretroviral therapy and on physical exam, it cannot be scraped off the tongue.

Kaposi sarcoma usually presents as < 0.5-cm, purple/red/violet, macular/papular lesions, which are generally concentrated on the head/neck and lower extremities. It is common in patients with advanced HIV.

Herpes zoster is often refractory to treatment in patients with HIV/AIDS. Treat with acyclovir or famciclovir. Valacyclovir has been associated with thrombotic thrombocytopenic purpura in the immunocompromised, so it is not recommended.

Disseminated *Cryptococcus* infection may imitate molluscum contagiosum.

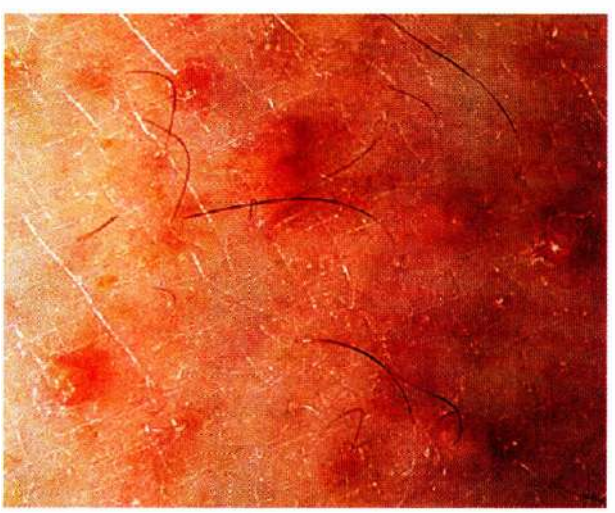


Image 12-47: Eruptive xanthomas in a diabetic

Image 12-48: Necrobiosis lipoidica diabeticorum

DIABETIC SKIN LESIONS

Eruptive xanthomas are due to severe hypertriglyceridemia. They are often seen in diabetic ketoacidosis. They appear abruptly as yellowish-red papules over the extensor surfaces and buttocks. These lesions resolve when the hyperglycemia is controlled (Image 12-47).

Necrobiosis lipoidica diabeticorum can be associated with diabetes in approximately 10–20% of cases (Image 12-48). It is a thin, atrophic, hyperpigmented plaque that appears on the shins. It is subject to trauma and ulceration and is thought to be due to microangiopathy.

Diabetic dermopathy (shin spots) are dark atrophic macules; they are common and often appear on the shins. They have no clinical significance.

FOR FURTHER READING

[Guidelines in blue]

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Part 2. Guidelines of care for the management and treatment of atopic dermatitis with topical therapies.

Part 3. Guidelines of care for the management and treatment of atopic dermatitis with systemic agents.

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