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INTERNAL MEDICINE REVIEW
CORE
CURRICULUM
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- Describe the clinical manifestations and treatments of diseases encountered in Internal Medicine and effectively narrow the differential diagnosis list by utilizing the most appropriate medical studies
- Apply the competence and confidence gained through participation in this activity to both a successful Board exam-taking experience and daily practice

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INTERNAL MEDICINE REVIEW

CORE CURRICULUM

SIXTEENTH EDITION

Book 1 of 5

Topics in this volume:

Gastroenterology

Infectious Disease

Robert A. Hannaman, MD
Editor in Chief

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- National Guideline Clearinghouse: http://www.guideline.gov/
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INTERNAL MEDICINE REVIEW

CORE CURRICULUM

SIXTEENTH EDITION

GASTROENTEROLOGY

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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

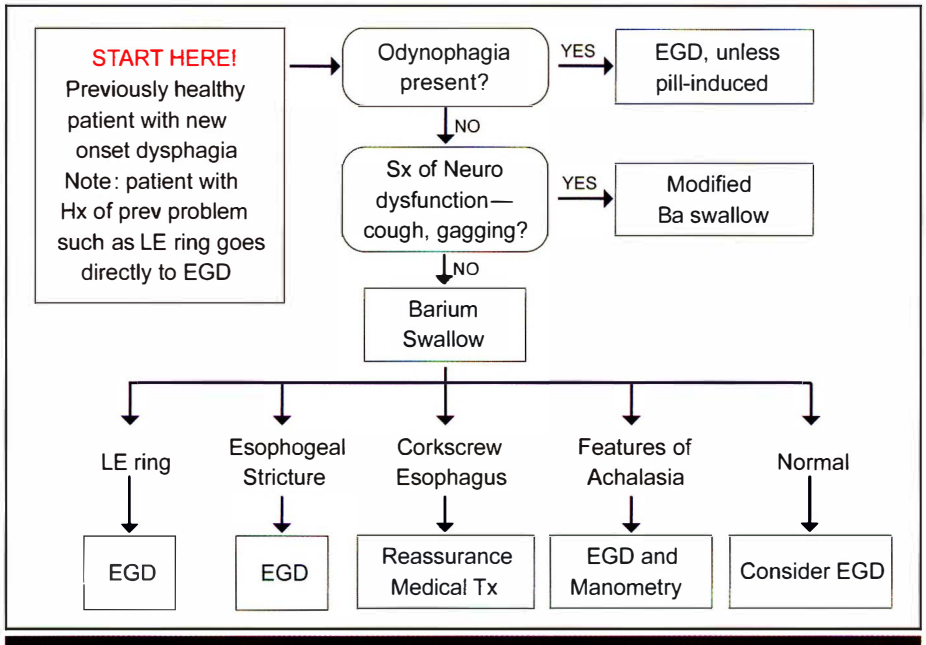
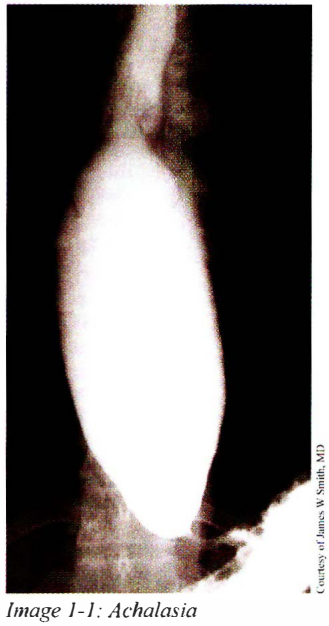


Figure 1-1: Dysphagia Workup



Courtesy of James W Smith, MD

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.

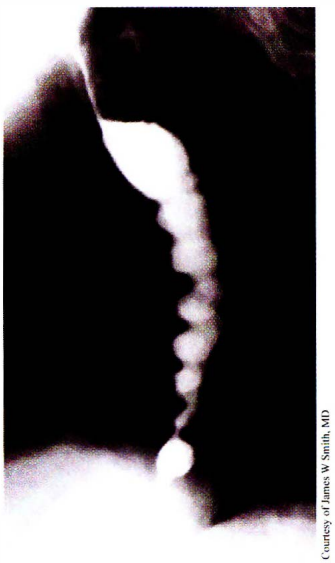

Courtesy of James W Smith, MD

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.

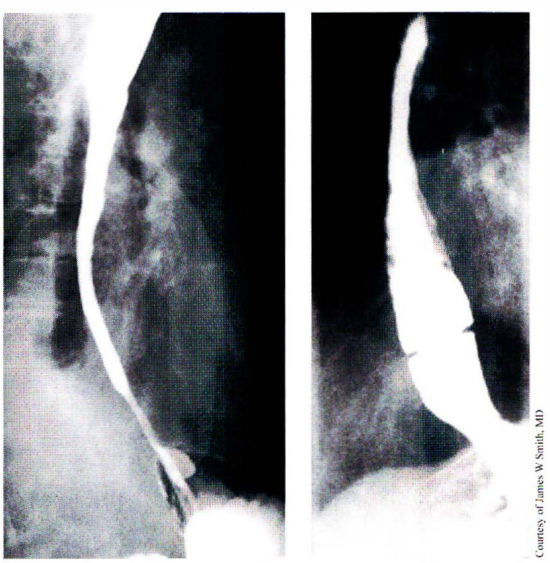


Image 1-3: Severe esophageal stricture on the left; Schatzki ring on the right

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.

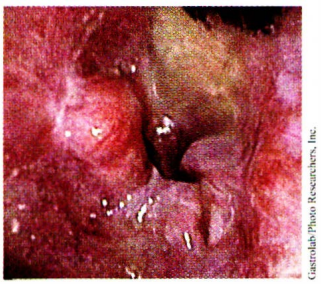


Image 1-4: Esophageal cancer

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).

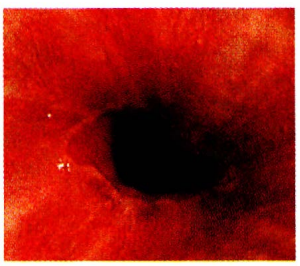


Image 1-5: Esophagitis

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.

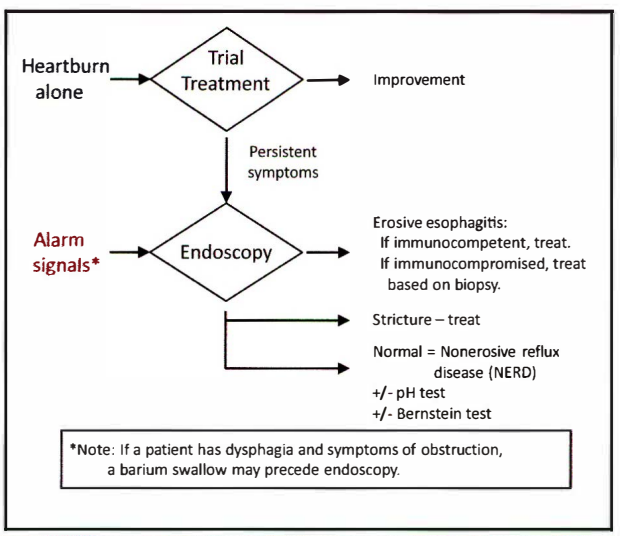


Figure 1-2: Workup of Suspected GERD

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).

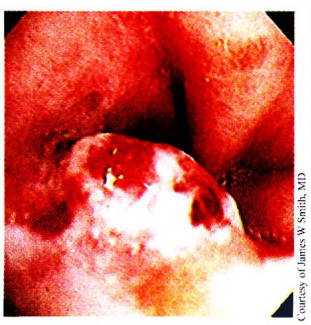


Image 1-6: Barrett esophagus

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.

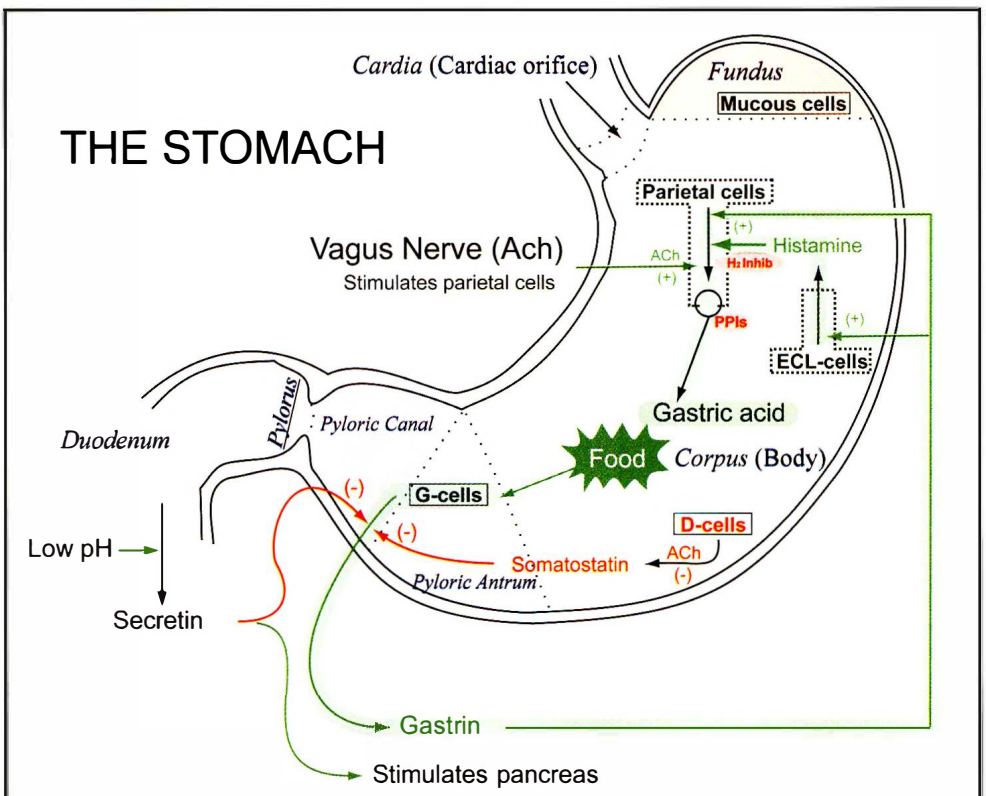


Figure 1-3: Stomach Physiology

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.

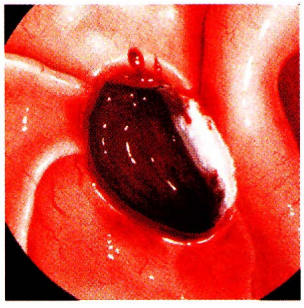


Image 1-7: Acute erosive gastritis

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.

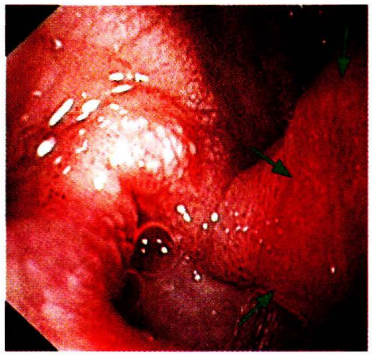


Image 1-8: Duodenal ulcer

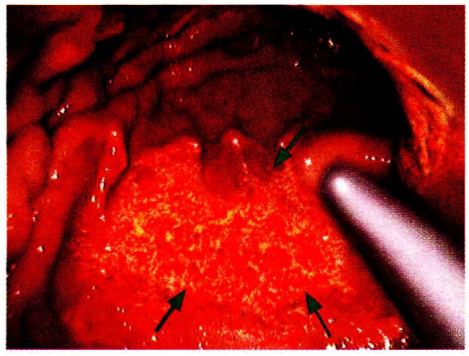


Image 1-9: Gastric ulcer

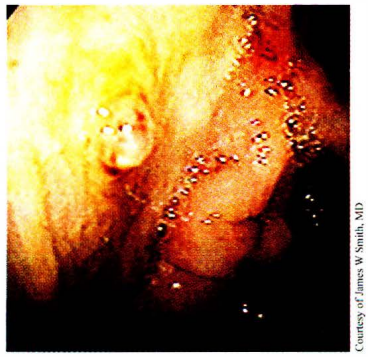


Image 1-10: Ulcer with visible vessel

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.

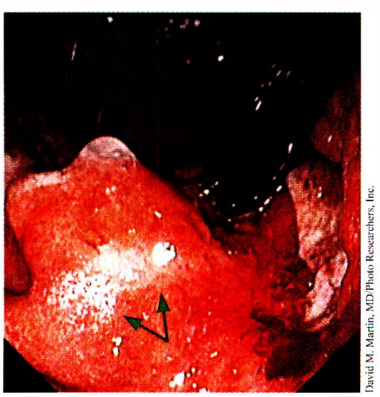


Image 1-11: Gastric adenocarcinoma

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

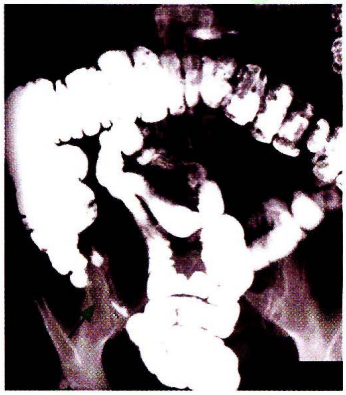


Image 1-12: Crohn colitis with "string sign" in RLQ

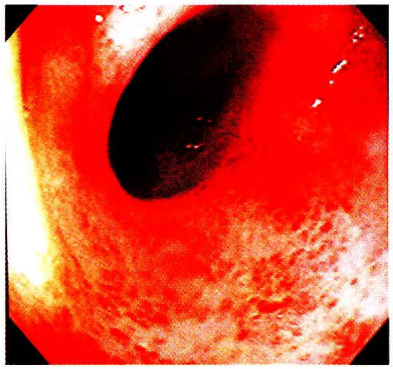


Image 1-13: Crohn proctitis

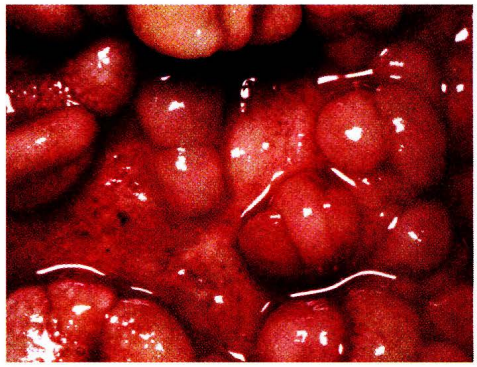


Image 1-14: Crohn disease with submucosal edema causing cobblestone appearance

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%.

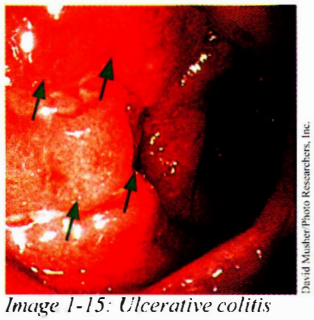


Image 1-15: Ulcerative colitis

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.

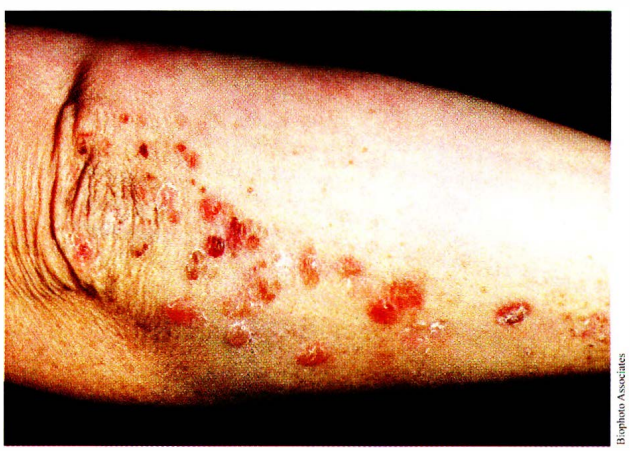


Image 1-16: Dermatitis herpetiformis

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.

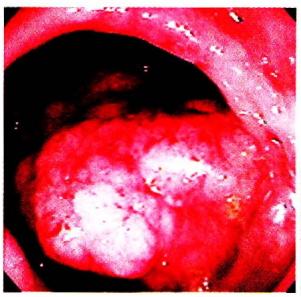


Image 1-17: Colon cancer

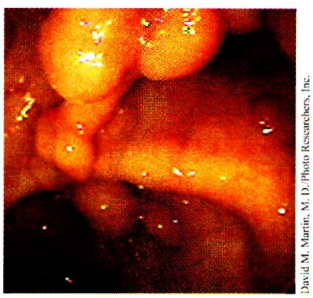


Image 1-18: Polyps in the colon

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

QuickQuiz

- 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.

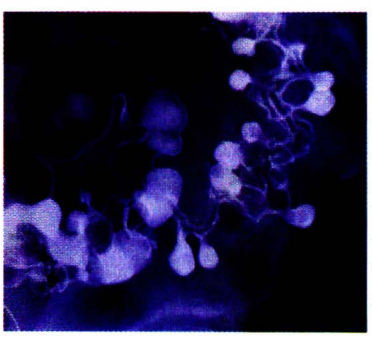


Image 1-19: Intestinal diverticulosis, x-ray

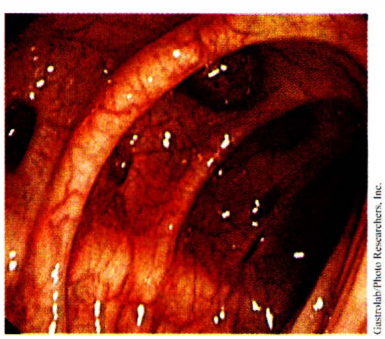


Image 1-20: Diverticular disease

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.

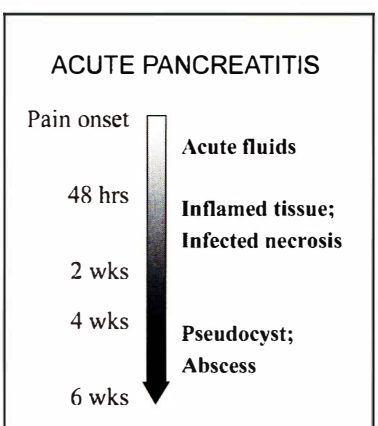


Figure 1-4: Timeline of Complications

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.

QuickQuiz

- 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.

QuickQuiz

- 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.

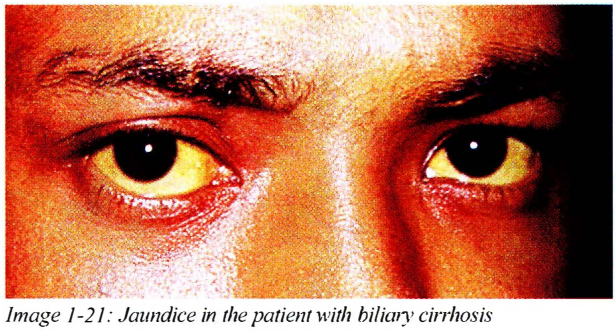
Later, patients develop jaundice, hyperpigmentation, inflammatory arthropathy, keratoconjunctivitis and/or xerostomia, and accelerated osteoporosis. Patients can develop xanthomas and xanthelasma from associated hypercholesterolemia, but this does not convey increased risk of CAD (not an atherosclerogenic 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.

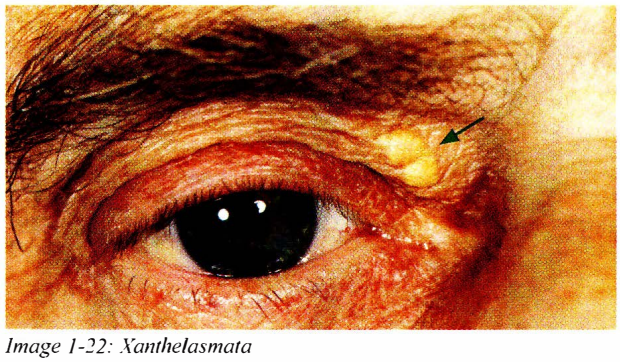
Incidental discovery of a 2–5x increase in serum alkaline phosphatase has been the primary reason for the increase in PBC diagnoses. High levels of alkaline phosphatase occur in up to 95% of patients with PBC.

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.

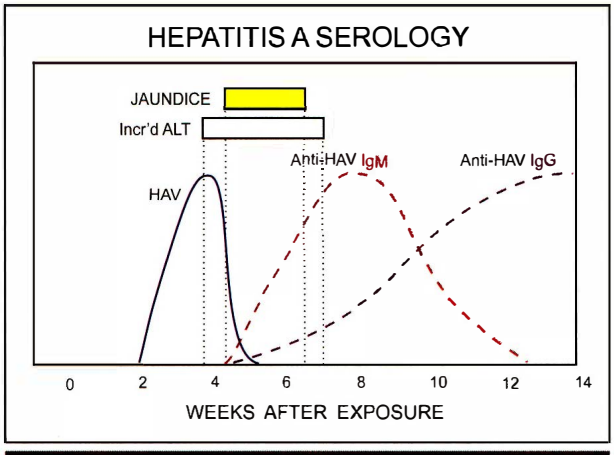


Figure 1-5: Hepatitis A Serology vs. Time after Exposure

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.

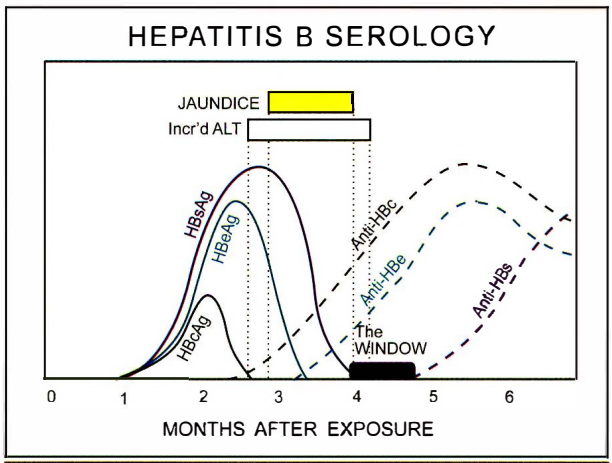


Figure 1-6: Hepatitis B Serology vs. Time after Exposure

- 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.

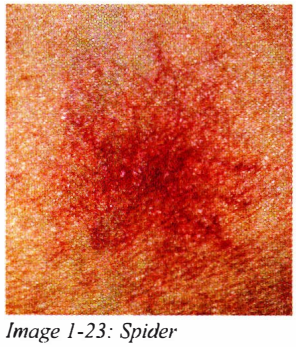


Image 1-23: Spider telangiectasia

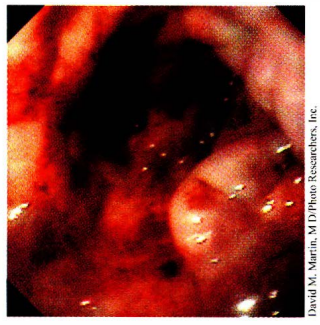


Image 1-24: Esophageal varices

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

QuickQuiz

- 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!

QuickQuiz

- 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.

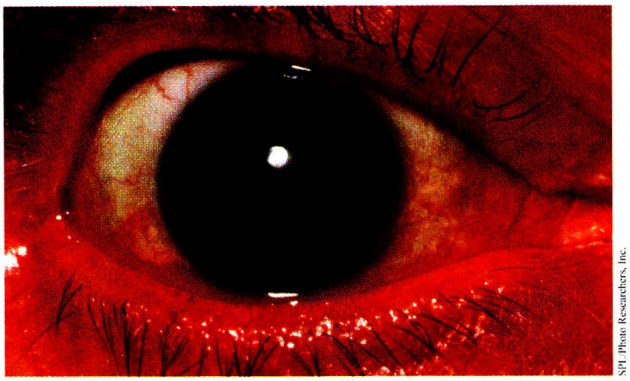
LIVER DISEASE DURING PREGNANCY

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.



SPL Photo Researchers, Inc.

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}.

Quick Quiz

- 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.

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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*,

Quick Quiz

- 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

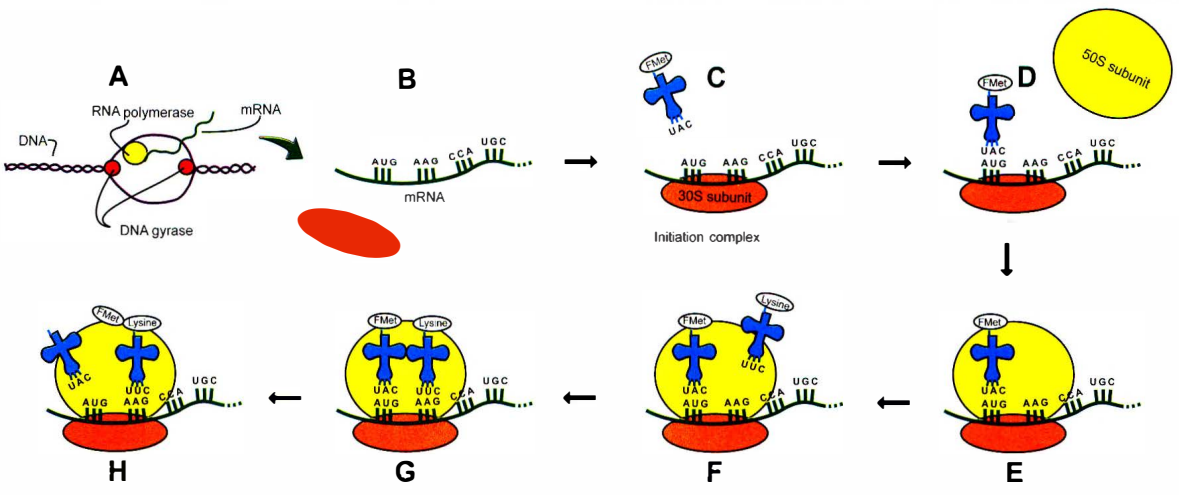
Most antibiotics work by subverting bacterial protein synthesis (Figure 2-1), folate metabolism, or the bacterial cell wall or cell membrane. First, let's review protein synthesis; then we'll tackle how specific antibiotics block it.

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

Quick Quiz

- 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.

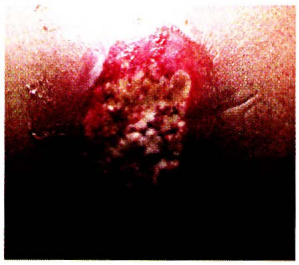
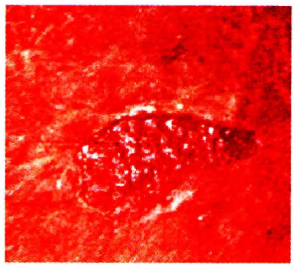


Image 2-1: Carbuncle on buttock



Courtesy of Vgaikwad, 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.

QuickQuiz

- 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).

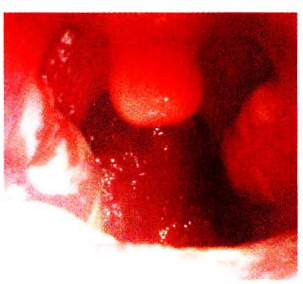


Image 2-3: Streptococcal pharyngitis

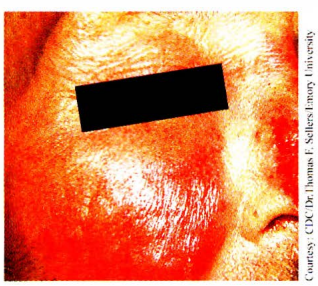


Image 2-4: Erysipelas

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.

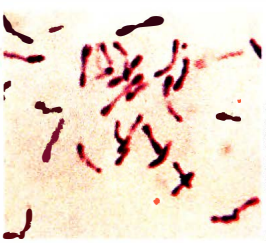

Courtesy: CDC/Dr. P. B. Smith

Image 2-5: C. diphtheriae

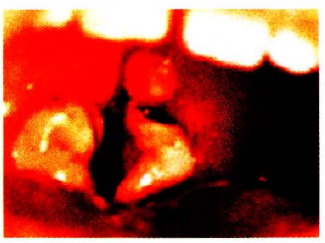


Image 2-6: Pharyngeal pseudomembrane

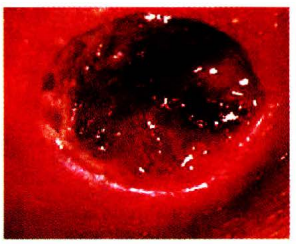


Image 2-7: Anthrax ulcer (painless)

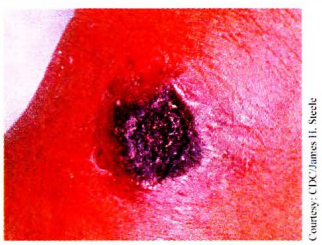

Courtesy: CDC/James H. Steele

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.

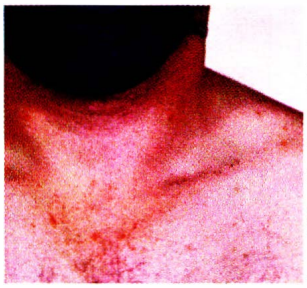
Non-typhoidal *Salmonella* are a fairly common cause of diarrhea. Because the bacteria are not host-specific to humans, like *S. typhi*, they can be found in many different, non-human host animals. *Salmonella* may be spread by frozen foods (especially chicken), milk, and eggs. Peanut butter and alfalfa 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.



Courtesy: CDC/Armed Forces Institute of Pathology/ Charles N. Farmer

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.

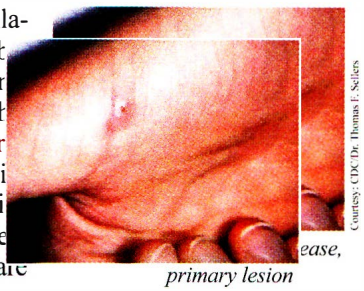
Typically, patients with tularemia present with a history of sudden onset of fever, chills, myalgias, and arthralgias, followed by an irregular ulcer at the site of inoculation that may persist for months. Regional lymphadenopathy develops, and these nodes may necrose and suppurate. If pneumonia occurs, 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.


Courtesy: CDC/Dr. Thomas F. Sellers

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.

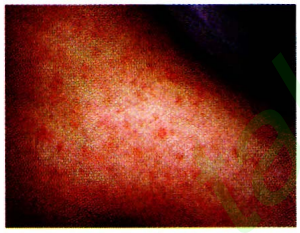


Image 2-11: Rocky Mountain spotted fever

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

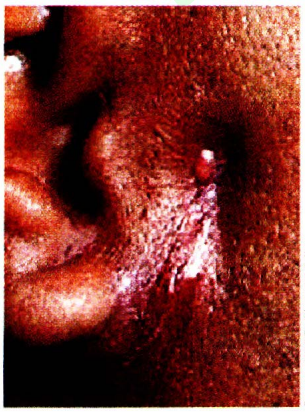

Courtesy, CDC/Dr. Thomas F. Sellers

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

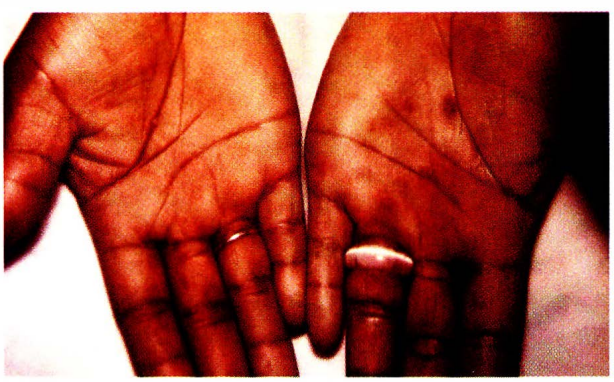

Courtesy: CDC

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.

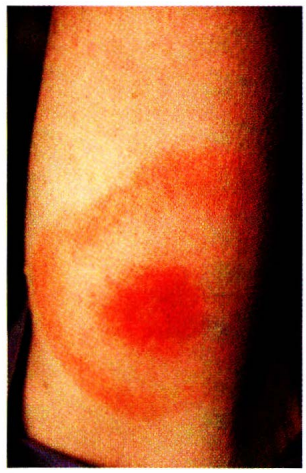
Diagnosis of Lyme Disease

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

Quick Quiz

- 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.

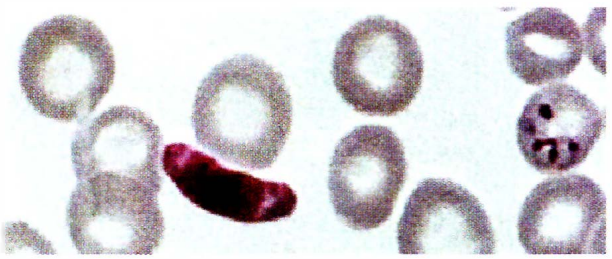


Image 2-15: P. falciparum, "banana-shaped gametocytes"

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

Quick Quiz

- 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.

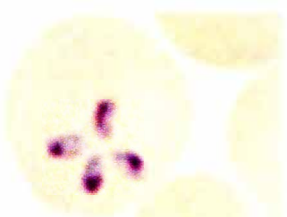


Image 2-16: Maltese cross—Babesia microti

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.

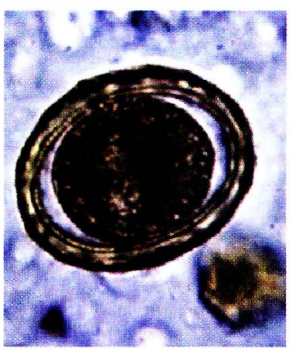


Image 2-17: Roundworm egg

Courtesy of CDC

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.

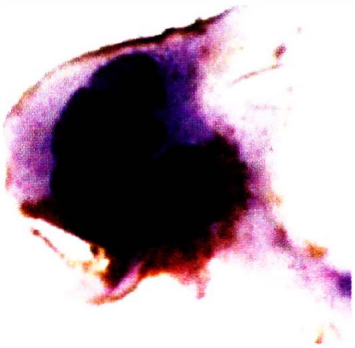


Image 2-19: Multinucleated giant cell

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.

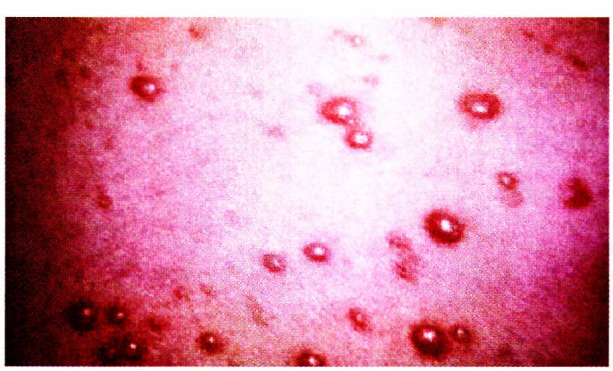


Image 2-20: VZV: Chicken pox

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.

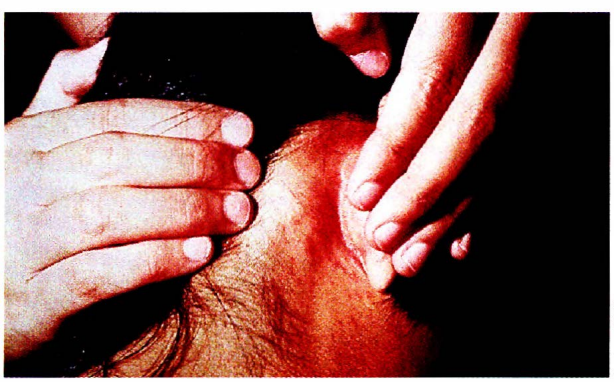


Image 2-21: Rubella infection with postauricular adenopathy

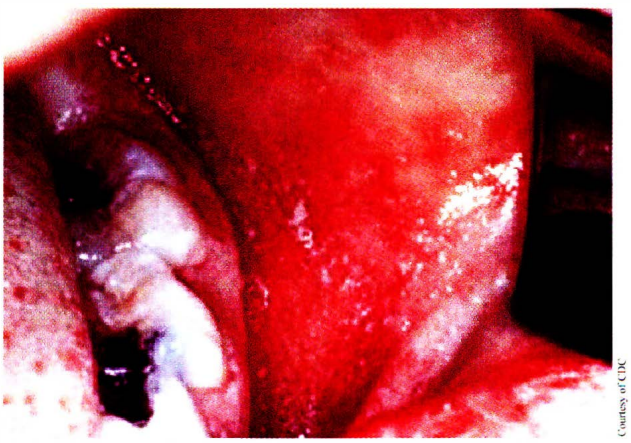


Image 2-22: Measles; Koplik spots, small white spots that occur before the rash

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*).

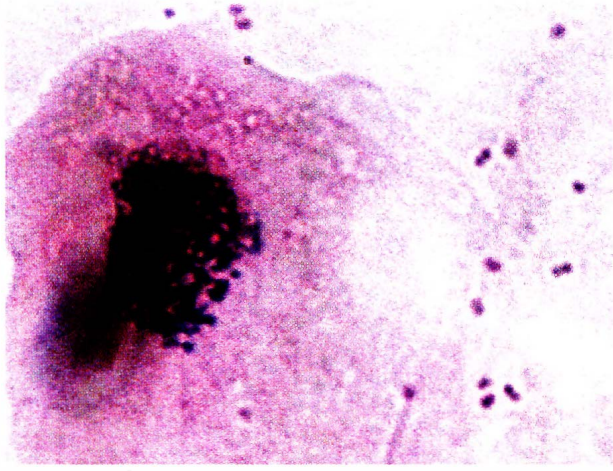


Image 2-23: Gram-negative diplococci—these are extracellular; require intracellular for Dx

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.

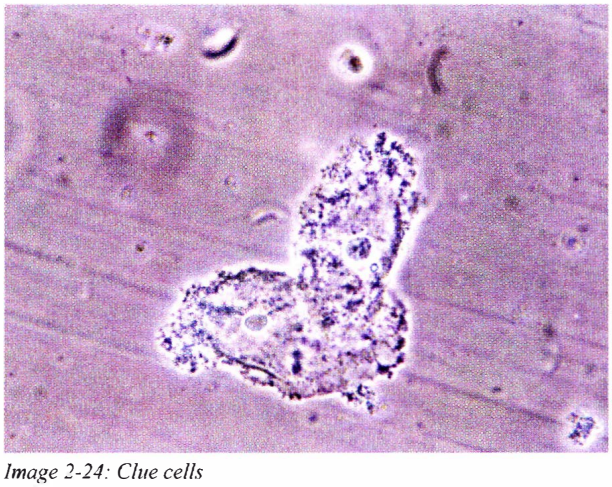


Image 2-24: Clue cells

- 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

- 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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