## Ascites Fluid Characteristics

<table>
<thead>
<tr>
<th><strong>Color</strong></th>
<th><strong>Description</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOODY:</strong></td>
<td>Trauma, iatrogenic (e.g., bx, paracentesis), malignancy (tumor eroding blood vessels, HCC is MCC of bloody), TB (rarely)</td>
</tr>
<tr>
<td><strong>MILKY:</strong></td>
<td>Chylos</td>
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<tr>
<td><strong>TURBID:</strong></td>
<td>Possible infection</td>
</tr>
<tr>
<td><strong>STRAW COLOR:</strong></td>
<td>Likely more benign causes</td>
</tr>
</tbody>
</table>

| **Bloody Ascites** | | |
|--------------------|----------------|
| Acitic fluid with RBC > 50,000 mm³ |

| **Neutrophils** | | |
|-----------------|----------------|
| ≥250/mm³: peritonitis (secondary or spontaneous bacterial) |

| **Total Protein** | | |
|-------------------|----------------|
| ≥2.5 g/dL (high-protein ascites) | |
| CHF, constrictive pericarditis, peritoneal carcinomatosis, TB, Budd-Chiari syndrome, fungal |
| <2.5 g/dL (low-protein ascites) | |
| Cirrhosis, nephrotic syndrome |

| **SAAG** | | |
|-----------|----------------|
| ≥1.1 g/dL (indicates portal hypertension) | |
| Presinusoidal: splenic or portal vein thrombosis, schistosomiasis |
| Sinusoidal (hepatic): cirrhosis, alcohol-related liver disease, liver METASTASIS. |
| Postsinusoidal: Cardiac ascites (RHF, cons peri), Budd-Chiari syndrome. |
| Pathophysiology: | |
| Cirrhosis (3 main theories): | |
| Arterial vasodilation hypothesis: (This is the most recent theory): Portal hypertension → vasodilation → reduced SVR and reduced MAP → Activation of endogenous vasoconstrictors, renal sodium and water retention, and renal vasoconstriction → hyperdynamic circulation |
| Underfill theory: argues that inappropriate splanchnic sequestration causes reduced intravascular volume and subsequent renal sodium and water retention |
| Overflow theory: States that the retention occurs without intravascular volume depletion. |
| Right-sided heart failure (RHF): backflow of blood obstructing the venous outflow of the liver (Therefore, |
especially pulmonary hypertension has a negative impact on the liver in the long run).

- **Budd-Chiari syndrome**: congestion of the portal/hepatic collateral veins and hypertrophy of the caudate lobe of the liver → compression of the sinusoids and intrahepatic IVC

- **<1.1 g/dL (absence of portal hypertension)**
  - **Hypoalbuminemia**
    - Nephrotic syndrome → primary renal sodium retention.
    - Severe malnutrition
    - Protein-losing enteropathy
  - **Malignancy** (e.g., peritoneal carcinomatosis): Various mechanisms of malignant-related ascites exist:
    - **Peritoneal carcinomatosis** (e.g., bladder ca, ovarian ca, and mesotheliomas) → blockage of **lymphatic** channels and increased vascular **permeability** → accumulation of peritoneal fluid (May occur in combination with liver metastases [especially with colonic, breast, pancreatic, and lung cancer] and therefore portal hypertension).
    - **Lymph obstruction** (by a **lymphoma**) → **chylous** ascites
    - If an underlying liver condition exists (typically HCC) → loss of synthetic liver function or **portal vein thrombosis**
  - **Infectious** (e.g., TB): production of protein-rich fluid from tubercles.
  - **Pancreatitis**: pancreatic fluid in the peritoneal cavity

**CHF** = congestive heart failure; **SAAG** = serum-ascites albumin gradient; **TB** = tuberculosis.

Ascites can be due to portal hypertensive (eg, cardiac ascites, cirrhosis) or non-portal hypertensive (eg, malignancy, pancreatitis, **nephrotic** syndrome, TB) causes. Assessment of color, neutrophil count, total protein, and the **serum-to-ascites albumin gradient** (SAAG) in ascitic fluid analysis can help to diagnose the etiology.

**SAAG** is useful to differentiate between portal and non-portal hypertensive etiologies. A SAAG <1.1 g/dL indicates portal hypertension while a SAAG >1.1 g/dL suggests other causes.

A patient with progressive abdominal distension and shifting dullness on examination has new-onset **ascites**, characterized by the accumulation of fluid within the peritoneal cavity. Ascites may occur in a variety of diseases (eg, peritoneal metastasis, congestive heart failure); however, in this patient with a history of heavy alcohol use and stigmata of chronic liver disease (eg, spider angioma, scleral icterus) on examination, it likely occurred from **cirrhosis**.
Cirrhosis is characterized by progressive liver fibrosis, which results in the formation of a high-resistance system (ie, **portal hypertension**). This results in the following alterations:

1. **Nitric oxide** and other vasodilatory factors are formed, possibly from bacterial products (eg, endotoxin) that accumulate due to the reduced host defenses (eg, impaired reticuloendothelial function) and increased portosystemic shunting (eg, decreased toxin clearance) seen with cirrhosis.

2. **Splanchnic vasodilation** occurs as a result, leading to significantly **decreased systemic vascular resistance** (SVR) and a compensatory increase in heart rate and cardiac output (hyperdynamic circulation).

3. The renin-angiotensin-aldosterone system (RAAS) is activated and antidiuretic hormone is released to maintain renal perfusion, leading to **retention of sodium and water**.

**Renin-angiotensin system (RAS)**
Hyperdynamic circulation and resistance to flow promote third spacing of fluids into the abdominal cavity while low oncotic pressure (ie, hypoalbuminemia due to impaired synthetic function) reduces fluid resorption from the interstitium. This results in a vicious cycle of hypervolemia and third spacing, promoting the formation of ascites.

Patients with ascites from cirrhosis have increased RAAS activity in response to the low SVR associated with splanchnic vasodilation. This results in increased circulating angiotensin levels (promoting renal vasoconstriction) and retention of urinary sodium (promoting volume retention). Although this compensatory mechanism is required to overcome the effects of splanchnic vasodilation, excessive renal vasoconstriction can cause renal hypoperfusion and kidney injury (eg, hepatorenal syndrome).

Severe hypothyroidism can lead to accumulation of mucopolysaccharides in the interstitial space, which promotes development of nonpitting edema (eg, myxedema), and ascites may occur. However, other signs of hypothyroidism would be expected (eg, cold intolerance, constipation, periorbital edema), and spider angioma and sclera icterus would not occur.

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**CHF** = congestive heart failure; **SAAG** = serum-ascites albumin gradient; **TB** = tuberculosis.
A patient with abdominal distension, weight gain, and a fluid wave has ascites. Although ascites can result from multiple disease processes, the most common etiology is **cirrhosis**, as suggested by this patient’s shrunken, nodular liver on ultrasound, stigmata of chronic liver disease (ie, scleral icterus, palmar erythema, spider angiomas), and history of heavy alcohol use.

Evaluation of **new-onset ascites** includes **diagnostic paracentesis** for fluid analysis. Ascitic fluid color assessment, total protein count, and serum-ascites albumin gradient (SAAG; calculated by subtracting the peritoneal fluid albumin concentration from the serum albumin concentration) are performed to confirm the underlying etiology. Patients with cirrhosis typically have clear, yellow-tinged ascites with low protein (<2.5 g/dL) and a high SAAG (≥1.1 g/dL).

**Cell count and differential** are also performed in all patients to rule out **spontaneous bacterial peritonitis**, a life-threatening infection of the ascitic fluid. Peritonitis symptoms usually include fever, abdominal pain, and mental status changes; however, findings may be subtle in early infection. The diagnosis is confirmed by an absolute polymorphonuclear cell count ≥250/mm³. Further testing is based on clinical presentation and is not required in patients with a presentation suggestive of ascites from cirrhosis.

<table>
<thead>
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<th>Miscellaneous ascitic fluid tests (perform when clinically indicated)</th>
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<tr>
<td><strong>Bilirubin</strong></td>
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<tr>
<td><strong>Glucose</strong></td>
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<td><strong>LDH</strong></td>
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Amylase

• ↑ In pancreatic ascites

Triglycerides

• ↑ In chylous ascites

Cytology

• Suspected malignant ascites

Gram stain and culture

• Suspected bacterial peritonitis

The ascites bilirubin level is elevated in the setting of a perforated biliary duct or bowel. Patients typically have brown (bilious) ascites, and present with sudden-onset, severe abdominal pain with peritoneal signs (eg, guarding).

Cytology should be performed for patients in whom there is a concern for underlying malignancy—usually those with persistently bloody ascites and cachexia. Yellow ascitic fluid is more suggestive of benign ascites from cirrhosis.

Fluid pH is obtained when assessing pleural fluid (ie, after a thoracentesis), and a low pH (<7.30) often indicates infection, malignancy, or rheumatoid effusion. pH does not have diagnostic value in a paracentesis.

Glucose and lactate dehydrogenase levels are obtained in patients with signs or symptoms concerning for infection, malignancy, or bowel perforation. These tests are less specific for infection than cell count and differential and are not indicated for routine screening. They are usually reserved for patients in whom there is high clinical suspicion (eg, fever, weight loss, severe abdominal pain).
<table>
<thead>
<tr>
<th>Spontaneous bacterial peritonitis</th>
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| **Clinical presentation** | • Temperature ≥37.8°C (100°F)  
  • Abdominal pain/tenderness  
  • AMS (abnormal connect-the-numbers test)  
  • HoTN, hypothermia, paralytic ileus with severe infection |
| **Diagnosis from ascitic fluid** | • PMNs ≥250/mm³  
  • Positive culture, often GN organisms (eg, *E. coli*, *Klebsiella*)  
  • Protein <1 g/dL  
  • SAAG ≥1.1 g/dL |
| **Treatment** | • Empiric antibiotics - third-generation cephalosporins (eg, cefotaxime)  
  • Fluoroquinolones for SBP prophylaxis |

PMN = polymorphonuclear leukocytes; SAAG = serum-ascites albumin gradient; SBP = spontaneous bacterial peritonitis.

A patient has cirrhosis and ascites accompanied by fever and lethargy, a presentation concerning for spontaneous bacterial peritonitis (SBP) and hepatic encephalopathy. The asterixis (flapping hand tremor), ascites, and laboratory abnormalities are all manifestations of his underlying cirrhosis. SBP superimposed on cirrhosis can be a subtle presentation, requiring a low threshold of suspicion. Fever and subtle changes in mental status are the most common symptoms, while abdominal pain often less prominent than in peritonitis due to other causes.

For making the diagnosis, paracentesis is the test of choice with the main diagnostic criteria being a positive ascites fluid culture and neutrophil count of ≥250/mm³. Paracentesis should be done before antibiotic therapy is initiated as therapy often results in negative ascites cultures. Enteric organisms such as *Escherichia coli* and *Klebsiella* are the most commonly cultured organisms followed by the streptococcal species; empiric therapy usually includes a third-generation cephalosporin.

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There is nothing in this patient's presentation to suggest colon pathology. A barium enema or colonoscopy is unlikely to be helpful.

Diagnostic laparoscopy may rarely be required in patients with peritoneal signs on examination if imaging studies have not revealed a source. However, the paracentesis results can also help distinguish
between SBP and bacterial peritonitis secondary to other causes such as intestinal perforation or abscess.

Although fever and mental status changes are common signs in meningoencephalitis, a patient with ascites and abdominal pain should first be evaluated for SBP as it is much more prevalent in patients with cirrhosis. Lumbar puncture is much less likely to yield a diagnosis.

Serum AFP level is elevated in patients with hepatocellular carcinoma, which is a possibility in this patient given his underlying cirrhosis. However, his acute changes (fever and altered mental status) are more concerning for SBP, which should be ruled out first.

This patient’s presentation is consistent with **spontaneous bacterial peritonitis** (SBP), an ascitic fluid infection without an obvious intraabdominal surgical etiology. SBP is most likely due to either intestinal bacterial translocation directly into the ascitic fluid or hematogenous spread to the liver and ascitic fluid (due to other bacterial infections).

Patients with cirrhosis are often relatively hypothermic, and any temperature ≥37.8 C (100 F) warrants investigation. Other manifestations of SBP may include **diffuse abdominal discomfort/tenderness** and/or mental status changes. The Reitan trail test, a timed connect-the-numbers test similar to children’s connect-the-dots pictures, is excellent for use in detecting **subtle mental status changes** sometimes present in patients with cirrhosis and SBP. Hypotension, hypothermia, or paralytic ileus (dilated loops of bowel on x-ray) indicate severe SBP. As the vast majority of cases of SBP are associated with cirrhosis, the serum-ascites albumin gradient (SAAG) is usually ≥1.1 g/dL (a SAAG <1.1 g/dL makes SBP unlikely). Ascitic fluid with a polymorphonuclear leukocyte (PMN) count ≥250/mm³ and positive peritoneal fluid culture confirm the diagnosis.

Patients with chronic alcohol use can develop acute pancreatitis with diffuse abdominal pain and ileus, but nausea and vomiting are common in these patients and the pain frequently radiates to the back.

Alcoholic hepatitis can also present similarly to SBP with fever, right upper quadrant abdominal pain, and peripheral leukocytosis. However, alcoholic hepatitis does not usually cause diffuse abdominal pain and decreased bowel sounds. Encephalopathy is seen only in severe cases.

The absence of free air under the diaphragm on x-ray makes bowel perforation less likely in this patient. Ascites separates the visceral and parietal peritoneal surfaces and prevents development of a rigid abdomen, even with organ perforation. As a result, presentation of secondary peritonitis (ascitic infection due to a surgically treatable intraabdominal
source such as perforated peptic ulcer) can be difficult to distinguish from SBP.

Small bowel obstruction (SBO) may present with diffuse abdominal pain and dilated loops of small bowel, but nausea and vomiting are much more common and bowel sounds tend to be high-pitched initially. Dilated loops of large bowel would not be expected with SBO (although air in the colon can sometimes be seen with partial SBO).
Alcoholic liver disease and hepatitis C are the most common causes of cirrhosis.

Macrocytic anemia, parotid enlargement (fatty infiltration), and AST:ALT ratio ≥2:1 suggest alcohol as the cause of cirrhosis.

Patients with compensated cirrhosis typically either are asymptomatic or have nonspecific symptoms (e.g., fatigue, generalized weakness,
intermittent N). In contrast, those with decompensated cirrhosis may have jaundice, pruritus, upper gastrointestinal bleeding, abdominal distension due to ascites, or confusion due to hepatic encephalopathy.

If the initial evaluation (history, examination, basic laboratory studies) reveals clinical findings consistent with alcohol liver disease, further evaluation for an underlying cause is not indicated. Instead, management goals should include identifying and treating reversible factors and potential complications (eg, variceal hemorrhage, hepatocellular carcinoma). Esophageal varices are the major cause of morbidity and mortality and can occur in 30%-60% of patients with cirrhosis. As a result, all patients with cirrhosis should undergo screening endoscopy to exclude varices, determine risk of variceal hemorrhage, and indicate strategies for prevention of hemorrhage.

If US revealed no liver masses suggestive of HCC, there is no need for CT scan of the abdomen to visualize potential masses. However, all patients with cirrhosis should have a screening US every 6 months.

A1AT deficiency should be suspected in patients with evidence of early onset obstructive lung disease or liver disease. However, liver disease in patients with AAT deficiency typically presents at a young age (eg, 10-30), and testing for AAT deficiency is not necessary in those with cirrhosis who have a clear history of and supporting laboratory evidence for heavy alcohol use.

Although liver biopsy is the gold standard for confirming cirrhosis, it is not required if the clinical findings (eg, presentation, laboratory findings, radiology studies) strongly suggest both cirrhosis (eg, ascites, portal hypertension) and its cause (eg, alcohol history, AST:ALT ratio), as in this patient.

The serum ammonia level is usually checked in patients with cirrhosis and suspected hepatic encephalopathy. In patients without clinical evidence of encephalopathy (eg, confusion, neurologic impairment, sleep disturbances), screening ammonia levels should not be checked routinely as they are neither sensitive nor specific.

Hemochromatosis should be suspected in patients with skin hyperpigmentation and liver function abnormalities. Other common manifestations are diabetes and arthralgia.

A patient with hepatic cirrhosis has developed ascites (ie, peritoneal fluid on ultrasound). Given his heavy alcohol intake and history of alcoholic hepatitis, this presentation suggests decompensated alcoholic cirrhosis.
Cirrhosis develops in the setting of chronic liver disease (eg, alcohol use, as in this patient), which leads to progressive hepatic fibrosis and regenerative nodule formation. Although advanced cirrhosis is irreversible, many patients have concurrent alcohol-related liver inflammation and active fibrogenesis that improves with abstinence from alcohol. In addition, abstinence leads to a reduction in portal pressure, which can make ascites more diuretic-responsive and ultimately aids in its resolution. Alcohol cessation also carries a significant survival benefit compared with patients who continue to drink and should be recommended in all patients with cirrhosis. Baclofen has been shown to decrease alcohol cravings in patients with alcoholic liver disease and can help with cessation.

In patients with cirrhosis, the renin-angiotensin-aldosterone system counteracts the effects of splanchnic vasodilation to prevent systemic hypotension. Because ACE inhibitors blunt this important compensatory response, they should be avoided in all patients with cirrhosis.

Nonselective beta blockers are used to prevent bleeding in patients with known esophageal varices; however, they can be harmful in patients with ascites due to progressive hypotension. In this patient with ascites and no known esophageal varices, nonselective beta blockers should be avoided.

Diuretics (eg, spironolactone, furosemide) can improve ascites by inducing natriuresis and are considered first-line therapy in addition to alcohol abstinence and a low-sodium diet. However, they would not be expected to reverse liver inflammation.

Ursodeoxycholic acid prevents the accumulation of toxic bile acids in the liver and can effectively reverse liver inflammation in patients with primary biliary cholangitis. However, it has no role in the management of alcoholic cirrhosis.
Patients with small varices that demonstrate bleeding risk factors or those with medium or large esophageal varices should receive primary prophylaxis to prevent bleeding.

Primary prophylaxis can be achieved either with endoscopic variceal ligation (EVL) or administration of a nonselective beta blocker such as propranolol or nadolol. Nonselective beta blockers reduce portal venous pressure by blocking the adrenergic vasodilatory response of the mesenteric arterioles, which results in unopposed alpha-adrenergic tone, vasoconstriction, and reduced portal blood flow. The choice of beta blocker or EVL depends on patient preference and the size of the varices (EVL is preferred for larger varices).

Lactulose and rifaximin are treatments for HE, which commonly presents with confusion, neurologic impairment (eg, asterixis), or sleep disturbances. However, unlike variceal bleeding, hepatic encephalopathy does not typically require primary prophylaxis.

Furosemide and spironolactone are first-line therapy for ascites due to cirrhosis. Large-volume therapeutic paracentesis is indicated in case of respiratory compromise or significant abdominal discomfort.
ACE inhibitors do not have a role in the management of cirrhosis.

**Compensated** cirrhosis without evidence of complications (eg, variceal hemorrhage, encephalopathy) is not a sufficient criterion for transplantation. In general, abstinence from alcohol for ≥6 months is required.

A transjugular intrahepatic portosystemic shunt (TIPS) is often used as salvage therapy in patients with refractory ascites or esophageal varices who have failed endoscopic or medical management.
Initial treatment of suspected variceal bleeding includes **volume resuscitation**, through 2 to 3 large-bore peripheral intravenous lines. Prophylactic **antibiotics** (eg, ceftriaxone) should be given to cirrhotic patients with gastrointestinal bleeding to decrease infectious complications, recurrent bleeding, and mortality. **Somatostatin analogues** (eg, octreotide) inhibit the release of vasodilator hormones, which leads indirectly to splanchnic vasoconstriction and decreased portal flow.

Urgent **endoscopy** (within 12 hours) can diagnose and treat (eg, endoscopic band ligation, sclerotherapy) active bleeding. Patients with uncontrolled bleeding require temporary balloon tamponade (eg, Sengstaken-Blakemore, Minnesota, Linton-Nachlas tubes) as a short-term measure until more definitive therapy, including transjugular intrahepatic portosystemic shunt (TIPS) or shunt surgery. Patients without further bleeding after endoscopy can be monitored and receive secondary prophylaxis (**beta blocker**) with repeat endoscopic band ligation 1-2 weeks later.
Recombinant factor VIIa is effective in treating some types of hemophilia. However, current studies have not shown significant benefit for correcting coagulopathy in active variceal bleeding. Fresh frozen plasma is commonly used for correcting coagulopathy of liver disease, but it increases the risk of volume overload and may not adequately correct the coagulopathy.

Current guidelines suggest keeping the hemoglobin >9 g/dL in variceal hemorrhage. This patient should have serial blood counts drawn and may require transfusion if the hemoglobin decreases to <9 g/dL.

Platelet transfusions are generally reserved for patients with active bleeding and platelet count <50,000/mm³.

This patient has evidence of cirrhosis (eg, spider angioma, nodular coarse liver, varices), likely from chronic hepatitis C. He is found to have medium-sized, nonbleeding esophageal varices. Variceal hemorrhage develops in approximately one third of all patients with varices and is a major cause of morbidity and mortality. Most cirrhotic patients should undergo diagnostic upper endoscopy to assess for varices and to determine their risk of hemorrhage. Those with (medium- or large-sized) varices, such as this patient, generally should be started on a nonselective beta blocker.

Nonselective beta blockers (eg, propranolol, nadolol) are recommended to decrease progression to large varices and the risk of variceal hemorrhage. They are thought to act by decreasing adrenergic tone in mesenteric arterioles, which results in unopposed alpha-mediated vasoconstriction and decreased portal venous flow. Endoscopic variceal ligation is an alternate primary preventive therapy in patients with contraindications to beta blocker therapy.
ACE inhibitors have not been shown to reduce variceal bleeding or improve outcomes in cirrhosis, and they have no role in the management of patients with esophageal varices.

Endoscopic sclerotherapy is an effective treatment for actively bleeding esophageal varices. It is not recommended for primary prophylaxis of variceal hemorrhage.

H2 histamine receptor blockers have not been shown to reduce progression or bleeding complications in patients with cirrhosis and varices.

Octreotide is a long-acting somatostatin analogue that causes splanchnic vasoconstriction and reduced portal blood flow by inhibiting the release of glucagon. It is used in the treatment of active variceal bleeding and has no role in primary prophylaxis.

A patient has numerous findings suggestive of alcoholic cirrhosis of the liver. Cirrhosis of any type leads to progressive loss of liver function, which can be divided into 3 categories: synthetic (production of clotting factors, cholesterol, and proteins); metabolic (metabolism of drugs and corticosteroids, including detoxification); and excretory (bile excretion).

In patients with cirrhosis, spider angioma and palmar erythema both arise from hyperestrinism due to impaired hepatic metabolism of circulating estrogens, a process that begins in the cytochrome P450 system. Circulating estrogens affect vascular wall dilation. Spider angioma consists of a central, dilated arteriole surrounded by smaller radiating vessels. Palmar erythema is a result of increased normal speckling of the palm due to increased vasodilation, especially at the thenar and hypothenar eminences. Other manifestations of hyperestrinism in patients with cirrhosis include gynecomastia, testicular atrophy, and decreased body hair in males.

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Caput medusae arise from the dilation of superficial veins on the abdominal wall due to portal hypertension (PH). PH results from increased resistance to portal flow at the sinusoids and leads to increased pressure at the portosystemic collateral veins in the anterior abdomen, rectum, and distal esophagus. This then predisposes to esophageal varices, rectal varices, and caput medusae. Similarly, PH causes enlargement of the spleen (which drains into the portal vein via the splenic vein) due to vascular congestion of the red pulp.
Dupuytren contracture occurs when the palmar fascia thickens and shortens, deforming the hand. It is usually most notable initially in the fourth and fifth digits and occurs due to fibroblast proliferation and collagen deposition, which are likely worsened by oxidative stress from increased free radical production.

The liver is the primary site of protein synthesis, and the cirrhotic liver typically produces insufficient amounts of proteins, including albumin. Hypoalbuminemia leads to both a decrease in the intravascular oncotic pressure and fluid shifts to the extravascular space, predisposing to edema of the lower extremities.

This patient with pedal edema, ascites (shifting dullness), bilateral gynecomastia, and spider angiomata likely has cirrhosis and portal hypertension. Other clinical features that suggest cirrhosis include palmar erythema, caput medusa, and splenomegaly. The most common causes of cirrhosis in the United States include viral hepatitis (C more than B), chronic alcoholism, nonalcoholic fatty liver disease (NAFLD), and hemochromatosis.

The initial evaluation of patients with suspected cirrhosis consists of obtaining a medical history, including inquiring about medications, social habits (eg, alcohol use, drug use, high-risk sexual activity), and family history (eg, to exclude hemochromatosis). Given this patient's history of intravenous drug use, the most likely cause of his cirrhosis is an infection with viral hepatitis (which, along with alcohol use, accounts for ~50% of cases of cirrhosis). He has no significant alcohol history. He is not overweight and is therefore unlikely to have NAFLD. His family history is unknown, but he has no stigmata of hemochromatosis (eg, bronze diabetes, cardiomyopathy, arthropathy). Laboratory studies, including viral hepatitis serologies and iron studies, should be obtained. If these are unrevealing, the patient may require further investigation for the less common causes of cirrhosis.

Amlodipine can cause pedal edema, but not cirrhosis. Medications (eg, methotrexate, isoniazid) can cause cirrhosis, but this is less common.

Cor pulmonale can cause fatigue and leg edema but not gynecomastia or spider angiomata; it would be unlikely in the absence of other...
manifestations (eg, exertional dyspnea, syncope, angina, loud second heart sound, prominent a wave).

Hypothyroidism can cause fatigue, pleural and pericardial effusions, ascites, and pedal edema; however, these findings are rare in the absence of severe hypothyroidism (eg, cold intolerance, constipation, weight gain, bradycardia, goiter). Hypothyroidism would be unlikely to cause gynecomastia or spider angiomata.

Lung cancer could lead to fatigue, weight loss, anorexia, edema of the legs, and ascites in patients with advanced disease (eg, metastatic compression of the lymphatics, peritoneal carcinomatosis), but it would not likely cause gynecomastia or spider angiomata.

Nephrotic syndrome can cause anasarca but is not usually associated with spider angiomata or gynecomastia.

<table>
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<th>Management of ascites in cirrhosis</th>
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<tr>
<td><strong>Initial evaluation</strong></td>
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<tr>
<td>• Imaging for confirmation (eg, abdominal ultrasound)</td>
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<tr>
<td>• Diagnostic paracentesis to confirm etiology &amp; rule out infection</td>
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<tr>
<td>○ SAAG, cell count &amp; differential, total protein</td>
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<tr>
<td><strong>Medical therapy</strong></td>
</tr>
<tr>
<td>• Spironolactone with furosemide</td>
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<tr>
<td>• Alcohol abstinence, sodium restriction</td>
</tr>
<tr>
<td>• Avoid ACE inhibitors, angiotensin receptor blockers, NSAIDs</td>
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<tr>
<td><strong>Refractory ascites</strong></td>
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<tr>
<td>• Large-volume paracentesis</td>
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<tr>
<td>• Transjugular intrahepatic portosystemic shunt</td>
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This patient with a history of heavy alcohol use has new-onset ascites and a shrunken liver on ultrasound, suggesting decompensated cirrhosis. Portal hypertension in cirrhosis leads to hemodynamic changes (eg, splanchnic vasodilation) that promotes fluid and sodium retention, ultimately resulting in ascites and peripheral edema.

The workup of ascites is directed at confirming the underlying etiology and ruling out infection. In addition to imaging (eg, abdominal ultrasound), a diagnostic paracentesis should be performed in all patients. Ascites from cirrhosis is usually yellowish or straw-colored; analysis reveals low total protein (<2.5 g/dL) and a high serum-ascites albumin gradient (≥1.1). Cell count and differential should be obtained to rule out spontaneous bacterial peritonitis (ie, neutrophil count ≥250/mm³).
Management includes **sodium restriction** as well as **spironolactone** and **furosemide**, which improve both ascitic fluid retention and peripheral edema. These medications are usually used concurrently to increase the efficacy of natriuresis and prevent electrolyte disturbances. **Alcohol abstinence** is also important since cessation improves portal hypertension and decreases ascites. Large-volume paracentesis or transjugular intrahepatic portosystemic shunt may be required for refractory ascites.

Fluid restriction is used to treat hypervolemic hyponatremia. Although hyponatremia can develop in cirrhosis, fluid restriction is not indicated in patients with normal sodium levels, such as this patient.

Although spironolactone is occasionally used by itself in patients prone to hypokalemia, furosemide monotherapy is usually avoided in cirrhosis because it is less effective in this population and predisposes to electrolyte wasting.

Patients with cirrhosis have low mean arterial pressure due to splanchnic vasodilation and are dependent on the renin-angiotensin-aldosterone system to help normalize blood pressure and renal perfusion. ACE inhibitors (eg, lisinopril) and angiotensin receptor blockers blunt this critical response and promote organ hypoperfusion in this group. These medications should be avoided in patients with cirrhosis.

Periodic large-volume paracentesis is used in those whose condition fails to improve with diuretics or who develop diuretic-related side effects (eg, acute kidney injury, electrolyte disturbances). It is invasive and not recommended prior to a trial of spironolactone and furosemide.

**Hepatic Hydrothorax**: Transudative, occurs much more commonly on the **right** side due to the less muscular** hemidiaphragm.** Patients have dyspnea, cough, pleuritic chest pain, and hypoxemia. Diagnosis involves documentation of the effusion (eg, chest x-ray) and testing to exclude other causes (eg, thoracentesis, echocardiogram).

Treatment involves salt restriction and diuretic administration. Therapeutic thoracentesis could be attempted in patients with prominent symptoms. Chest tube placement should be avoided as it can result in large-volume protein, fluid, and electrolyte losses as well as other severe complications (eg, renal failure). The definitive option for treatment is liver transplantation, although this may not be appropriate for all patients depending on other factors.

Tense ascites can result in dyspnea and decrease the range of diaphragmatic excursion due to increased intraabdominal pressure, but this is unlikely to cause right-sided dullness and decreased breath sounds.
<table>
<thead>
<tr>
<th>HEPATIC ENCEPHALOPATHY (HE)</th>
<th><strong>Hepatic encephalopathy</strong></th>
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| **Precipitating factors**    | • Drugs (eg, sedatives, narcotics)  
• Hypovolemia (eg, diarrhea)  
• Electrolyte changes (eg, hypokalemia)  
• ↑ Nitrogen load (eg, GI bleeding)  
• Infection (eg, pneumonia, UTI, SBP)  
• Portosystemic shunting (eg, TIPS) |
| **Clinical presentation**     | • Sleep pattern changes  
• Altered mental status  
• Ataxia  
• Asterixis |
| **Treatment**                 | • Correct precipitating causes (eg, fluids, antibiotics)  
• ↓ Blood ammonia concentration (eg, lactulose, rifaximin) |

**GI** = gastrointestinal; **SBP** = spontaneous bacterial peritonitis; **TIPS** = transjugular intrahepatic portosystemic shunt; **UTI** = urinary tract infection.

A patient with likely cirrhosis (heavy alcohol use, ascites, thrombocytopenia) now has progressive confusion, slurred speech, and asterixis (flapping tremor with outstretched hands), which is suggestive of hepatic encephalopathy (HE). HE refers to impaired central nervous system function in patients with cirrhosis and is due in part to ammonia neurotoxicity from impaired liver function. Treatment involves identifying any underlying precipitant (eg, infection, sedative medications, gastrointestinal bleed) and lowering serum ammonia.

Nonabsorbable disaccharides (eg, lactulose, lactitol) are preferred for lowering serum ammonia. Colonic bacteria metabolize lactulose to short-chain fatty acids (eg, lactic acid, acetic acid). This acidifies the colon to stimulate conversion of the absorbable ammonia to the nonabsorbable ammonium (an ammonia trap) and causes bowel movements (which facilitates fecal nitrogen excretion). The medication is titrated to produce 2 or 3 semiformed stools daily.

Broad-spectrum antibiotics would be appropriate in a patient with a suspected or confirmed infection, which would generally present with fever, elevated leukocyte count, and other signs of infection (eg, tachycardia).

Chlordiazepoxide is a long-acting benzodiazepine used to treat alcohol withdrawal, which would usually cause autonomic instability (eg, tachycardia, hypertension) along with mental status changes.
Dantrolene is used in neuroleptic malignant syndrome and malignant hyperthermia. Patients with these conditions usually have severe muscle rigidity, fever, and tachycardia.

Hypertonic saline is usually used in patients with hyponatremia and severe symptoms (eg, coma, seizure). A serum sodium level of 132 mg/dL is mild hyponatremia, which is not uncommon in patients with cirrhosis (hypervolemic hyponatremia) and would be an unlikely cause of this patient’s symptoms.

Thiamine is used to treat and prevent Wernicke encephalopathy, which may be seen in alcoholics due to poor dietary intake of thiamine. It presents as altered mental status, ataxia, and nystagmus, but asterixis is not generally present.

A high-protein diet is generally not recommended in patients with cirrhosis as it can precipitate HE by causing increased serum ammonia levels.

A patient with **cirrhosis** has lethargy, confusion, and asterixis (flapping tremor with outstretched hands) suggestive of **hepatic encephalopathy (HE)**. HE refers to impaired central nervous system (CNS) function in patients with cirrhosis and is due in part to the neurotoxicity from ammonia (NH₃) in the setting of impaired liver function.

In this patient, HE was likely triggered by the recent initiation of **diuretic** therapy. This, along with poor oral intake, led to **low intravascular volume** (hypotension, dry mucous membranes) with:

- **Hypokalemia**, which can exacerbate HE as the resultant intracellular acidosis (excreted intracellular potassium replaced by...
hydrogen ions to maintain electroneutrality) causes increased \( \text{NH}_3 \) production (glutamine conversion) in renal tubular cells

- **Metabolic alkalosis** (elevated bicarbonate), which can also exacerbate HE as it promotes conversion of ammonium (\( \text{NH}_4^+ \)), which cannot enter the CNS, to \( \text{NH}_3 \), which can enter the CNS

As a result, patients with HE and hypokalemia require prompt **potassium repletion** in addition to intravascular **volume repletion**. Disaccharides (eg, lactulose, lactitol) are also administered to lower \( \text{NH}_3 \) levels.

Patients with cirrhosis tend to be malnourished; therefore, dietary protein restriction is generally not recommended. Protein-free diets can cause a negative nitrogen balance and increase mortality. Protein restriction is generally limited to patients who have required transjugular intrahepatic portosystemic shunting (TIPS).

Lorazepam can be used to treat alcohol withdrawal; however, this patient does not have typical manifestations of withdrawal (eg, tachycardia, hypertension, tremor).

Neomycin is a nonabsorbable antibiotic used to treat HE in patients unresponsive to lactulose and those unable to tolerate rifaximin.

TIPS is performed when a patient has ascites that does not respond to medical therapy (eg, diuretics) or has ongoing active or recurrent variceal bleeding even after appropriate treatment with upper endoscopy. TIPS is associated with HE in up to 35% of patients due to (\( \text{NH}_3 \)-rich) blood bypassing the liver.

**CLOSTRIDIUM SEPTICUM INFECTION**

This patient with acute acalculous cholecystitis has bacteremia with *C. septicum*, a gram-positive, spore-forming colonic bacterium. Although this pathogen rarely causes bacteremia and invasive infection (eg, gas-gangrene, tissue necrosis), the risk is significantly increased in those with **colonic malignancy**. This is because tumor cells frequently undergo anaerobic glycolysis, which creates an adequate environment for the germination of *C. septicum* spores; and tumors damage the colonic mucosa, which allows sporulated bacteria to translocate into the bloodstream.

About 30% of patients with *C. septicum* bacteremia have colon cancer; therefore, **colonoscopy** is required for those with no history of the tumor. Bacteremia with group D streptococci, particularly *Streptococcus bovis*, is also strongly associated with colon cancer and should prompt screening colonoscopy.
Cystoscopy is sometimes indicated for patients who have recurrent gram-negative bacteremia (eg, *E coli*) in the setting of bladder voiding symptoms.

*Staphylococcus aureus* bacteremia should prompt transthoracic echocardiogram (TTE) because the organism often seeds native (undamaged) and damaged valves. Although *S bovis* bacteremia is also strongly associated with infective endocarditis (and should prompt TTE), clostridial species do not typically attack the heart or heart valves; therefore, screening echocardiography is generally not necessary.

<table>
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<th>GASTRIC CANCER</th>
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*Helicobacter pylori* infection plays a critical role in the pathogenesis of extranodal marginal zone B cell lymphomas (low-grade B cell lymphoma of MALT) of the stomach. It is present in 90% of patients with tumors. Chronic inflammation from *H pylori* infection results in stimulation of large numbers of antigen-dependent B and T cells in the gastric lamina. The **chronic activation** and proliferation eventually results in a **monoclonal population** of B cells that no longer depends on normal stimulatory pathways for growth.

As a result, all patients with MALT lymphomas should be tested for *H pylori infection*, and patients with a **positive** result who have early-stage MALT lymphoma should undergo *H pylori* **eradication therapy** (eg, quadruple therapy). The majority of patients achieve **complete remission** with antibiotic treatment. Patients with **more advanced malignancies** or with *H pylori*-negative tumors should be considered for **RTX**, **immunotherapy** (eg, rituximab), or single-agent **CTX**.

Various environmental factors such as **cigarette smoking**, **high salt intake**, and consumption of **N-nitroso compounds** (found in processed meats and cheeses) are associated with increased risk for gastric adenocarcinoma but not MALT lymphomas.

**NSAIDs** appear to be a **protective** factor for gastric adenocarcinoma, with longer use associated with greater reductions in risk.

Although **Sjögren syndrome** and **Hashimoto thyroiditis** are associated with an **increased** risk for **MALToma**, **pernicious anemia** is **not**. Instead, **pernicious anemia** is related to an **increased** risk of gastric adenocarcinoma and gastric **carcinoid** tumors.
A patient's presentation – episodic pounding sensation (due to flushing and associated rise in pulse rate), chronic diarrhea, weight loss, and valvular heart disease with tricuspid regurgitation – is consistent with carcinoid syndrome. Carcinoids are well-differentiated neuroendocrine tumors (NETs) found most commonly in the distal small intestine, proximal colon, and lung, with a strong propensity for metastasis to liver. These tumors can secrete several products including histamine, serotonin, and vasoactive intestinal peptide that are metabolized in the liver. In patients with liver metastasis, these hormones are released directly into the systemic circulation, leading to carcinoid syndrome.

**Episodic flushing** is the hallmark of carcinoid syndrome and occurs in almost 85% of patients. Severe flushing may be associated with hypotension and tachycardia. **Secretory diarrhea** may be accompanied by abdominal cramping. Other common features include **cutaneous telangiectasias**, **bronchospasm**, and **tricuspid regurgitation**. Pathognomonic plaque-like deposits of fibrous tissue occur most commonly on the endocardium on the right side of the heart, leading to tricuspid regurgitation and right-sided heart failure. Elevated 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) can confirm the diagnosis in most patients.

<table>
<thead>
<tr>
<th><strong>Clinical manifestations</strong></th>
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<tbody>
<tr>
<td>Skin: flushing, telangiectasias, cyanosis</td>
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<tr>
<td>Gastrointestinal: diarrhea, cramping</td>
</tr>
<tr>
<td>Cardiac: valvular lesions (right &gt; left side)</td>
</tr>
<tr>
<td>Pulmonary: bronchospasm</td>
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<tr>
<td>Miscellaneous: Niacin deficiency (dermatitis, diarrhea &amp; dementia)</td>
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<tr>
<th><strong>Diagnosis</strong></th>
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<tr>
<td>Elevated 24-hour urinary excretion of 5-HIAA</td>
</tr>
<tr>
<td>CT/MRI of abdomen &amp; pelvis to localize tumor</td>
</tr>
<tr>
<td>OctreoScan to detect metastases</td>
</tr>
<tr>
<td>Echocardiogram (if symptoms of carcinoid heart disease are present)</td>
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<tr>
<th><strong>Treatment</strong></th>
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<tbody>
<tr>
<td>Octreotide for symptomatic patients &amp; prior to surgery/anesthesia</td>
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<tr>
<td>Surgery for liver metastases</td>
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Patients with chronic thromboembolic disease and recurrent pulmonary emboli typically have symptoms of progressive dyspnea and decreased exercise tolerance. There is usually a history of deep venous thrombosis or a prior thromboembolic event.

Right-sided infective endocarditis (IE) is often associated with intravenous drug use. Patients with IE typically have constitutional symptoms (fever, malaise, and arthralgias), vascular or immunologic phenomena, and a new valvular regurgitant murmur. However, flushing and chronic diarrhea are not symptoms of IE.

Myxomatous valve disease occurs due to weakening of the connective tissue of valvular structures. It most commonly affects the mitral valve, resulting in mitral valve prolapse. Although the tricuspid valve may be affected by myxomatous degeneration, symptoms of flushing and diarrhea are more suggestive of carcinoid syndrome.

Patients with primary pulmonary hypertension typically have exertional symptoms including chest pain, dyspnea, decreased exercise tolerance, and/or syncope. These patients do not have any associated flushing, weight loss, or diarrhea.

Systemic lupus erythematosus (SLE) typically has skin (butterfly rash and photosensitivity), musculoskeletal (arthralgias), hematologic (cytopenias), cardiac (pericarditis), renal, and neurologic manifestations (cognitive defects, seizures). However, isolated tricuspid regurgitation is not a frequent presentation of SLE.

AST and ALT are distributed widely throughout the body, with AST present and very active in the liver, heart, kidney, and skeletal muscle. While ALT is also present in reduced quantities in the kidney, heart, and skeletal muscle, it is predominantly found in the liver and is therefore more specific for hepatocyte injury.

A patient has a mild (< 250 U/L), asx elevation of his serum transaminases. The first step in the evaluation of his condition should be a careful screening for all hepatitis risk factors, including drug and alcohol intake, travel outside the United States, blood transfusions, or high-risk sexual practices. This aspect of the patient's history will provide insight as to whether the transaminase elevation could be caused by alcohol, medications (eg, NSAIDs, antibiotics, HMG-CoA reductase inhibitors, antiepileptic drugs, antituberculous drugs, herbal preparations), or viral agents.

After thoroughly questioning the patient about his history and having him discontinue all alcohol and drug use, the next step in the evaluation
process would be to repeat the liver function tests. If the transaminases persist in being elevated over a six-month period, they are categorized as chronic. Testing for viral hepatitis B and C, hemochromatosis, and fatty liver should then be undertaken to further evaluate chronically elevated transaminases. If these tests prove unremarkable, a search for muscle disorders (eg, polymyositis) and thyroid disease should be made.

An ultrasound of the abdomen would not be particularly enlightening in a patient with asxaminotransferase elevation unless gallbladder pathology was suspected.

<table>
<thead>
<tr>
<th>NAFLD</th>
<th>Nonalcoholic fatty liver disease (NAFLD)</th>
</tr>
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| **Definition** | • Hepatic steatosis on imaging or biopsy  
• Exclusion of significant alcohol use  
• Exclusion of other causes of fatty liver |
| **Clinical features** | • Mostly asymptomatic  
• Metabolic syndrome  
• ± Steatohepatitis (AST/ALT ratio <1)  
• Hyperechoic texture on ultrasound |
| **Treatment** | • Diet & exercise  
• Consider bariatric surgery if BMI >35 |

ALT = alanine aminotransferase; AST = aspartate aminotransferase.

This patient’s presentation (hepatocellular injury in the absence of viral hepatitis or autoimmune disease) is most consistent with nonalcoholic fatty liver disease (NAFLD). Affected patients are typically middle-aged, obese, and have features of the metabolic syndrome (eg, central obesity, diabetes mellitus, hyperlipidemia, hypertension). NAFLD can range from bland steatosis to inflammation and necrosis (steatohepatitis) to fibrosis and cirrhosis. Histologically, NAFLD can resemble alcohol-induced liver disease (macrovesicular fat deposition, peripheral displacement of nuclei) but occurs in patients with minimal or no alcohol history.

NAFLD can be due to increased transport of free fatty acids (FFA) from adipose tissue to the liver, decreased oxidation of FFA in the liver, or decreased clearance of FFA from the liver (due to decreased VLDL production). It is frequently related to peripheral insulin resistance leading to increased peripheral lipolysis, triglyceride synthesis, and hepatic uptake of fatty acids. Hepatic FFA increases oxidative stress and production of proinflammatory cytokines (eg, tumor necrosis factor-alpha).
Insulin decreases lipolysis in adipose cells. Insulin resistance, as seen in most patients with NAFLD, leads to increased lipolysis and FFA release. FFA are then transported to the liver, where they participate in pathogenesis of NAFLD and further contribute to insulin resistance by impairing insulin-dependent glucose uptake and increasing hepatic gluconeogenesis.

......

Some patients with type 2 diabetes can have increased glucagon production. Although glucagon increases gluconeogenesis and glycogenolysis, it does not play a role in hepatic fat accumulation.

Cushing syndrome can contribute to insulin resistance and NAFLD, but it would be unlikely in this patient with near lifelong obesity.

Hepatic glycogen synthesis is usually decreased in type 2 diabetes and does not play a role in hepatic steatosis.

......

NAFLD, defined as hepatic steatosis in the absence of other causes of secondary hepatic fat accumulation (eg, alcohol). The incidence of NAFLD has risen along with the increase in obesity, with nearly half of obese patients demonstrating some degree of steatosis on liver biopsy.

Most patients with NAFLD have hepatomegaly, but other stigmata of chronic liver disease are rarely seen. Liver markers typically show mild elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), with an AST/ALT ratio <1. Diagnosis is often made based on laboratory and imaging findings (eg, hyperechoic texture on ultrasound), but it can be confirmed with liver biopsy. Hepatic fibrosis develops in 40% of individuals with NAFLD, and cirrhosis in 10%-15%. The foundation of management includes weight loss and control of metabolic risk factors. It is generally safe to continue statin therapy in patients with NAFLD.

The hepatic steatosis in NAFLD resembles that found in alcoholic liver disease. However, alcoholic liver disease is characterized by AST predominance (AST/ALT ratio 2:1) in contrast to the parallel rise in NAFLD. In addition, alcoholic liver disease is unlikely with light to moderate alcohol intake (<15 drinks/wk for men, <10/wk for women). A standard drink is equivalent to 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof spirits (1 oz = 30 mL).

ANA titers are a sensitive marker for autoimmune hepatitis, and antismooth muscle titers are relatively sensitive and specific. This patient has negative titers for both autoantibodies.
This patient underwent a **Roux-en-Y gastric bypass**, which bypasses most of the stomach by creating a small gastric pouch, a gastrojejunal (GJ) anastomosis, and a jejunojejunal anastomosis. Weight loss results from restricting food consumption (smaller gastric pouch) and inducing malabsorption as nutrients can only be absorbed in the common limb (where food from the alimentary limb meets pancreatic enzymes/bile acids from the biliopancreatic limb).

The procedure is associated with several postoperative **complications**. This patient likely has **stomal (anastomotic) stenosis**, caused by progressive narrowing of the GJ anastomosis that leads to obstruction of gastric pouch outflow. This complication usually occurs within the first year after surgery, likely due to local tissue ischemia and ulceration. Patients typically have **progressive symptoms** including nausea, **postprandial vomiting**.
gastroesophageal reflux, and dysphagia, to the point of not tolerating liquids. Diagnosis requires visualization of the GJ anastomosis via **esophagogastroduodenoscopy (EGD)**, during which balloon dilation can be performed to open the narrowing. Patients sometimes require surgical revision if balloon dilation fails.

Rapid emptying of food, especially highly osmotically active simple carbohydrates (eg, corn syrup), from the gastric pouch can cause dumping syndrome due to abrupt transfer of fluid from the circulatory system into the intestines. In addition to abdominal pain, nausea, and diarrhea, patients typically have hypotension and tachycardia accompanied by diaphoresis, lightheadedness, or syncope. None of these symptoms are present in this patient.

A gastric emptying scan is the test of choice for gastroparesis, which can present with postprandial pain, vomiting, and early satiety. However, recent bypass surgery renders this test inaccurate and raises suspicion for outlet obstruction that must be investigated with EGD.

RUQ US is useful in diagnosing cholelithiasis, which is a common complication after Roux-en-Y, especially in the setting of rapid weight loss. However, severe reflux and regurgitation are not typical of symptomatic cholelithiasis.

Marginal ulcers can occur at the GJ anastomosis and can present symptomatically like stomal stenosis. These ulcers can be treated with proton pump inhibitors, but their presence should first be confirmed by EGD; empiric therapy is not appropriate.
JAUNDICE

A patient's icterus and positive urine bilirubin assay are consistent with elevated conjugated bilirubin. She likely has Dubin-Johnson syndrome, a rare, benign, hereditary condition resulting in chronic or fluctuating conjugated hyperbilirubinemia due to a defect in hepatic excretion into the biliary system. It is typically discovered in puberty or early adulthood. Episodes of jaundice can be triggered by intercurrent illness, pregnancy, or the use of oral contraceptives. Liver function tests are otherwise normal, and urine studies may demonstrate bilirubinuria. If a liver biopsy is performed as part of the evaluation, it typically demonstrates a grossly black liver with dark, lysosomal pigments on histology.

An understanding of the bilirubin metabolism pathway clarifies how a positive urine bilirubin assay reflects a buildup of conjugated bilirubin. Conjugated bilirubin is water soluble and readily excreted in urine. Despite this, no bilirubin is typically seen on urinalysis because conjugated bilirubin is usually degraded in the intestines. However, in the presence of hepatobiliary disease or a defect in hepatic bilirubin excretion,
levels of conjugated bilirubin rise, with some excreted in the urine (positive urine bilirubin).

In contrast, unconjugated bilirubin is highly insoluble and cannot be excreted in urine. Excess unconjugated bilirubin (eg, due to hemolysis) undergoes metabolism to eventually form urobilinogen, which is mostly recycled. However, increased levels of urobilinogen also result in excretion in feces and urine (positive urine urobilinogen).

.....

Choledocholithiasis typically results in right upper quadrant or epigastric pain, nausea, and vomiting. Laboratory analysis shows a significant elevation in alkaline phosphatase and a milder elevation in transaminase levels, in addition to hyperbilirubinemia.

Decreased bilirubin glucuronidation such as in Gilbert syndrome results in unconjugated hyperbilirubinemia.

Drug-induced liver injury may occur due to many medications, including oral contraceptives; however, chronic injury due to oral contraceptive use is more likely to present with elevations of both alkaline phosphatase and serum bilirubin.

Hemolytic anemias such as hemoglobinopathies or autoimmune anemias result in elevations in unconjugated bilirubin and urinary urobilinogen.

Patients with hereditary hemochromatosis typically have multiple symptoms, including fatigue, arthralgias, hyperglycemia, and skin hyperpigmentation. In addition, liver transaminases are frequently abnormal.
Patients with viral hepatitis typically have multiple symptoms, including fatigue, nausea, right upper quadrant pain, and jaundice. Transaminases are significantly elevated and are accompanied by hyperbilirubinemia.

The next appropriate step in management for patients with predominantly **cholestatic pattern** is to obtain an abdominal **ultrasound** to assess hepatic parenchyma and biliary ducts. The presence of biliary dilatation is suggestive of extrahepatic cholestasis; the absence of biliary dilatation suggests intrahepatic cholestasis.

.........

Endoscopic retrograde cholangiopancreatogram (ERCP) is usually performed in patients when initial ultrasonography or CT scan suggests the presence of obstruction due to cholelithiasis or malignancy. ERCP in these settings can be both diagnostic and therapeutic by relieving obstruction and facilitating biliary drainage.

Examination of the peripheral blood smear is useful in the evaluation of patients with suspected hemolytic anemias. However, patients with hemolysis have elevated unconjugated (indirect) hyperbilirubinemia.

Measurement of serum iron, transferrin saturation, and ferritin levels is useful in the diagnosis of iron overload syndromes, including hereditary hemochromatosis. Patients with hereditary hemochromatosis have progressive iron deposition in the liver and elevated serum aminotransferases (AST and ALT).

Patients with acute viral hepatitis typically have marked elevation of serum aspartate and alanine aminotransferase levels. Chronic viral hepatitis can be associated with mild to moderate elevation of serum aminotransferases. This patient has normal aminotransferase levels and is unlikely to have viral hepatitis as a cause of hyperbilirubinemia.
Typically, increased direct bilirubin levels are suggestive of hepatobiliary disease (eg, cirrhosis, hepatitis) because bilirubin conjugates are shunted into the plasma when excretion into bile is slowed. In contrast, elevated unconjugated (indirect) bilirubin levels (as in this patient) typically indicate increased bilirubin formation (eg, hemolysis) or reduced bilirubin conjugation.

This patient likely has Gilbert syndrome, a familial disorder caused by reduced bilirubin glucuronidation. Clinical manifestations include intermittent jaundice due to a mild, predominantly unconjugated hyperbilirubinemia (<3 mg/dL) without evidence of hemolysis (eg, normal haptoglobin). Jaundice may be triggered by fasting or consumption of a fat-free diet, physical exertion, febrile illness, stress, or menstruation. Presumptive diagnosis can be made when unconjugated hyperbilirubinemia persists with repeat testing but liver function tests, complete blood count, blood smear, and reticulocyte count are normal. Management involves reassurance and supportive care.

Patients with hereditary hemochromatosis (eg, skin hyperpigmentation, diabetes, elevated iron studies and transaminases) should undergo phlebotomy to avoid iron overload.
| Ursodeoxycholic acid is frequently used for the treatment of symptomatic hepatobiliary disorders such as primary biliary cholangitis (eg, fatigue, pruritus) or gallstone disease (eg, right upper quadrant pain). |
| WHIPPLE’S DISEASE | Whipple’s disease is a rare multi-systemic illness. It is an infectious disease caused by the bacillus *Tropheryma whippelii*. It is most commonly seen in white men in the fourth-to-sixth decades of life, and often presents with weight loss. Gastrointestinal symptoms include abdominal pain, diarrhea, and malabsorption with distension, flatulence, and steatorrhea. Extraintestinal manifestations include migratory polyarthritis, chronic cough, and myocardial or valvular involvement leading to congestive failure or valvular regurgitation. Later stages of the disease may be characterized by dementia and other central nervous system findings, such as supranuclear ophthalmoplegia and myoclonus. Intermittent low-grade fever, pigmentation and lymphadenopathy may also be occasionally seen. PAS-positive material in the lamina propria of the small intestine is a classical biopsy finding. Celiac disease, although associated with malabsorption, is not associated with pigmentation and lymphadenopathy. Tropical sprue is a chronic diarrheal disease, possibly of infectious origin, that should be considered in patients who have lived for more than a month in a tropical area. |
| DIARRHEA | Typical features of *giardiasis* include diarrhea acquired during international travel, abdominal cramps, foul-smelling stools, bloating, and benign findings on abdominal examination. *Giardia duodenalis* (sometimes noted as *G. lamblia* or *G. intestinalis*) is common in rural areas and developing countries, and has an incubation period of 1-2 weeks. It is most commonly transmitted by contaminated water but can be foodborne or transmitted person-to-person via a fecal-oral route. Most patients are ax; however, a significant minority of those who do develop clinical illness may go on to develop chronic giardiasis characterized by malabsorption, weight loss, or persistent GI distress. The preferred confirmatory test for giardiasis is a stool antigen assay (direct immunofluorescence or ELISA). Stool microscopy for oocysts and trophozoites can also identify the organism and is useful in resource-poor settings or if other parasitic organisms are suspected. Some facilities also offer a NAAT. Metronidazole is the preferred treatment. Asymptomatic carriers do not usually need treatment. |
A short course of ciprofloxacin is advised for empiric treatment of traveler’s diarrhea (most commonly due to *Escherichia coli*).

A patient with chronic nonbloody diarrhea and weight loss after multiple abdominal surgeries most likely has **secretory diarrhea**. Diarrhea can be divided into 3 main categories: **watery**, **fatty**, and **inflammatory**. **Watery diarrhea** can be further broken down into **osmotic**, **secretory**, and **functional**. Hallmarks of secretory diarrhea include larger daily stool volumes (>1 L/day) and diarrhea that **occurs even during fasting or sleep**. Secretory diarrhea most commonly occurs when luminal ion channels are disrupted in the gastrointestinal tract, resulting in a state of active secretion.

A helpful tool in distinguishing osmotic from secretory diarrhea is the **stool osmotic gap** (SOG), which calculates the difference between plasma osmolality (considered equivalent to measured stool osmolarity) and double the sum of sodium and potassium ions in stool (corresponding to calculated stool osmolality):

\[
\text{SOG} = \text{plasma Osm} - 2 \times (\text{stool Na} + \text{stool K})
\]

= measured stool Osm – calculated stool Osm

In **osmotic** diarrhea, nonabsorbed and unmeasured osmotically active agents are present in the gastrointestinal tract. These ions result in an **elevated** osmotic gap (SOG >125 mOsm/kg). By contrast, **secretory** diarrhea is due to increased secretions of ions; therefore, the difference between plasma osmolality and measured fecal sodium and potassium is significantly **reduced** (SOG <50 mOsm/kg).

Common causes of secretory diarrhea include **bacterial** infections (eg, *Vibrio cholera*), **viral** infections (eg, rotavirus), congenital disorders of ion transport (eg, CF), **early ileocolitis**, and **postsurgical changes**. Secretory diarrhea can occur after **bowel resection** or **cholecystectomy** when unabsorbed bile acids reach the colon and result in the direct stimulation of luminal ion channels. In addition, resection of the ileocecal area reduces the ability of the intestines to actively absorb sodium ions against the electrochemical gradient.

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Factitious diarrhea: psychiatric disturbances and is most commonly seen in women with a work history in health care. Depending on the laxative abused, the SOG can be **elevated** (eg, lactulose) or **negative** (eg, sulfate-containing laxative).
Inflammatory diarrhea is usually accompanied by either grossly bloody stools or positive occult blood testing. Patients also commonly report systemic symptoms such as fatigue and fever. Intestinal dysmotility disorders, such as chronic intestinal pseudo-obstruction and IBS, frequently have associated fatigue, nausea, and vomiting. Neither is associated with diarrhea during fasting.

Osmotic diarrhea is caused by the ingestion of osmotically active, poorly absorbable substances and is characterized by an elevated SOG.

**Clostridium difficile** is a GP, anaerobic bacterium that causes infectious diarrhea in the nosocomial and outpatient settings. Hardy antibiotic-resistant spores are ingested and convert to fully functional bacilli in the colon. Although the organism is noninvasive, pathogenic strains produce exotoxins ("enterotoxin" A and "cytotoxin" B) that penetrate colonic epithelial cells, resulting in apoptosis and the loss of tight junctions. Carriage of toxigenic *C difficile* is common (8%-15%), but extensive proliferation is usually required to reach exotoxin levels that are pathogenic.

The single greatest risk factor for *C difficile*-associated diarrhea is recent antibiotic use (eg, fluoroquinolones, clindamycin, cephalosporins, penicillins), which disrupts the normal colonic flora (eg, *Bacteroides*), freeing nutrients and eliminating a crucial epithelial barrier. Other common risk factors include:

<table>
<thead>
<tr>
<th>Risk factors</th>
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| Recent antibiotics  
| Hospitalization  
| PPI  
| Sever comorbid illness (e.g., IBD [even at young age])  |

<table>
<thead>
<tr>
<th>Clinical presentation</th>
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</table>
| Profuse diarrhea (most common)  
| Fulminant colitis or toxic megacolon  |

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Stool PCR</td>
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<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral vancomycin or fidaxomicin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infection control</th>
</tr>
</thead>
</table>
| Hand hygiene with soap & water  
| Contact isolation  
| Sporicidal disinfectants (eg, bleach)  |

PCR = polymerase chain reaction; PPI = proton pump inhibitor.
- **Gastric acid suppression** - alter the colonic microbiome, which increases the risk of *C difficile* proliferation.
- Hospitalization - *C difficile* transmission is MC in the hospitalized setting, particularly when patients are severely ill.
- **Advanced age (eg, >65)** - Older individuals often have diminished colonic immunity and greater exposure to antibiotics, PPIs, and hospital environments.

*C difficile* colitis usually manifests with watery diarrhea (≥3 stools/day), abdominal pain, cramping, N/V, low-grade fever, and leukocytosis (~15,000/mm³). Overt melena and bright red blood per rectum are rare (unlike ulcerative colitis, which usually causes small-volume bloody stools). The abdomen is usually diffusely tender. Diagnosis is typically made with stool assay for *C difficile* exotoxin genes via polymerase chain reaction. Treatment involves the cessation of the inciting antibiotic (if possible), infection control (contact precautions), and antimicrobial therapy with oral vancomycin or fidaxomicin. Oral metronidazole was previously used as first-line therapy but is no longer recommended due to greater risk of recurrence.

**Pelvic splanchnic nerve** damage is usually due to abdominal surgery or spinal trauma. Constipation, not diarrhea, is a common consequence.

Steatorrhea: Patients typically develop pale, foul-smelling, voluminous watery diarrhea, but do not generally have low-grade fever and leukocytosis.

<table>
<thead>
<tr>
<th>Treatment of <em>Clostridioides difficile</em> infection</th>
</tr>
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<tbody>
<tr>
<td><strong>Initial episode</strong></td>
</tr>
<tr>
<td>• Vancomycin PO</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>• Fidaxomicin</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
</tr>
<tr>
<td>• First recurrence</td>
</tr>
<tr>
<td>o Vancomycin PO in a prolonged pulse/taper course</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>o Fidaxomicin if vancomycin was used in initial episode</td>
</tr>
<tr>
<td>• Multiple recurrences</td>
</tr>
<tr>
<td>o Vancomycin PO followed by rifaximin (or above regimens)</td>
</tr>
<tr>
<td>o Fecal microbiota transplant</td>
</tr>
</tbody>
</table>
Fulminant (eg, HoTN/shock, ileus, megacolon)

- Metronidazole IV plus high-dose vancomycin PO (or PR if ileus is present)
- Surgical evaluation

**IV = intravenous; PO = per mouth; PR = per rectum.**

A patient presents with new-onset white blood cell elevation and confusion, in association with recent antibiotic use, watery diarrhea, and mild abdominal tenderness, suggesting possible *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI). Risk factors for CDI include recent hospitalization, advanced age, or antibiotic use (most commonly fluoroquinolones, penicillins, cephalosporins, and clindamycin). Unexplained leukocytosis in hospitalized patients should raise suspicion for CDI, even without diarrhea. CDI can range from mild watery diarrhea to fulminant colitis with toxic megacolon.

Diagnosis is usually confirmed with stool studies for *C difficile* toxin (eg, polymerase chain reaction). Treatment options for initial infection include oral vancomycin or fidaxomicin. Patients with fulminant disease (eg, hypotension, ileus, megacolon) should be treated with high-dose PO vancomycin and IV metronidazole; if ileus is present, vancomycin may be given rectally.

Asymptomatic funguria is common in patients with longstanding indwelling urinary catheters, but actual symptomatic fungal urinary tract infections are unusual. In cases of uncomplicated asymptomatic funguria, catheters can be replaced, but empiric antifungal agents are generally unnecessary.

Aminoglycosides (eg, gentamicin) treat resistant gram-negative bacteria. However, this patient was improving clinically and had *Escherichia coli* sensitive to ciprofloxacin. This patient's antibiotic use and gastrointestinal symptoms make *C difficile* colitis more likely than worsening urinary tract infection.

In patients with CDI, inciting antibiotics (eg, ciprofloxacin) should be stopped as soon as possible, with patients switched to antibiotics that are less frequently associated with CDI. Intravenous vancomycin is used to treat resistant gram-positive organisms. However, this would not treat her *E coli* bacteremia. In addition, intravenous vancomycin is not excreted into the colon and is **not** effective against CDI.
Surgical consult is required in patients with fulminant CDI (eg, hypotension, ileus, toxic megacolon). However, this patient has mild to moderate colitis without acute peritoneal signs on examination.

| A patient has watery diarrhea that developed after beginning chemotherapy. In association with a normal complete blood count and negative tests for *Clostridioides difficile* and fecal occult blood, this presentation is consistent with chemotherapy-related diarrhea (CRD). Many chemotherapeutic agents (eg, fluorouracil and irinotecan—both of which are used to treat metastatic pancreatic cancer) exert a direct cytotoxic effect on intestinal mucosa, resulting in decreased fluid absorption and increased electrolyte secretion. As with this patient, CRD often results in secretory diarrhea, which is voluminous, watery, and persistent despite periods of fasting (eg, nocturnal diarrhea). Osmotic diarrhea, which occurs only after eating, may also occur due to damage of the brush border enzyme system (eg, lactase deficiency causing lactose intolerance).

Management of CRD includes oral hydration and antidiarrheal therapy with loperamide or diphenoxylate-atropine. Severe diarrhea may warrant hospital admission for intravenous fluid and electrolyte repletion. Because chemotherapy is a risk factor for infection (particularly with *C difficile*), all patients with persistent diarrhea should undergo laboratory evaluation (eg, complete blood count, serum chemistry) and stool testing (eg, *C difficile* stool studies, fecal occult blood) prior to a presumptive diagnosis of CRD.

Cholestyramine is sometimes used to treat chronic diarrhea related to bile acid malabsorption, which can also cause secretory diarrhea. However, it typically occurs after surgical resection of the small bowel or gallbladder. Although bile acid malabsorption can occasionally develop as a side effect of chemotherapy (eg, due to ileal damage), a trial of loperamide is typically the initial step in CRD management; if chronic diarrhea persists, further evaluation for bile acid malabsorption or empiric treatment with cholestyramine can be considered.

Metronidazole, followed by paromomycin, is used to treat intestinal amebiasis, which causes bloody diarrhea, fever, and abdominal pain. It typically occurs after travel to an endemic area (eg, Central America).

Pancrelipase is used to treat steatorrhea due to pancreatic exocrine insufficiency, which usually is caused by chronic pancreatitis. Although
exocrine insufficiency may rarely occur in those with pancreatic cancer, steatorrhea (ie, bulky diarrhea with visible fat globules) would be expected. Both prednisone and sulfasalazine are used to treat inflammatory bowel disease (eg, ulcerative colitis). However, inflammatory bowel diseases typically causes abdominal pain, hematochezia, anemia, and leukocytosis.

LAXATIVE ABUSE

A patient's presentation is concerning for factitious diarrhea, specifically laxative abuse. Factitious diarrhea has a female predominance, and most patients are employed in the health care field and have a history of multiple hospitalizations. Diarrhea associated with laxative abuse is typically described as watery, frequent (10-20 bowel movements daily), and voluminous. Nocturnal bowel movements and abdominal cramps are common accompanying symptoms.

Although diarrhea (including factitious diarrhea) can lead to metabolic acidosis, metabolic alkalosis is a common and classic finding in laxative abuse. Several mechanisms likely contribute, including the profound hypokalemia as a result of increased loss of potassium in the stool. This then impairs chloride reabsorption and affects chloride-bicarbonate exchange, increasing serum bicarbonate concentrations (metabolic alkalosis). Patients may also have hypermagnesemia if a magnesium-containing laxative is used.

Diagnosis is supported by a positive stool screen for diphenolic (eg, bisacodyl) or polyethylene-containing laxatives. Diagnosis is further suggested by the characteristic colonoscopy finding of melanosis coli, which is dark brown discoloration of the colon with pale patches of lymph follicles that can give the appearance of alligator skin. Melanosis coli can develop within a few months of the onset of regular laxative ingestion and can similarly disappear if laxative use is discontinued. If melanosis coli is not seen on gross inspection, histological examination may demonstrate the pigment in the macrophages of the lamina propria.

.......
In addition to diarrhea, carcinoid syndrome (which would cause elevated urine 5-hydroxyindoleacetic acid levels) presents with cutaneous flushing, venous telangiectasia, bronchospasm, and cardiac valvular abnormalities. Although VIPomas are associated with diarrhea during fasting and dehydration, patients typically describe tea-colored stools and have hypokalemia with hypochlorhydria. VIPomas are not associated with melanosis coli.

Patients with low cortisol levels (eg, adrenal insufficiency) may have hypotension and chronic diarrhea; however, hyponatremia, hyperkalemia, and metabolic acidosis are the common metabolic abnormalities associated with the condition.

C. difficile–associated diarrhea is associated with the healthcare setting (eg, antibiotic exposure). However, classic findings on colonoscopy are bowel wall edema, erythema, and friability (eg, pseudomembranous colitis), not melanosis coli.

Parasitic causes of persistent diarrhea, including *Giardia*, *Cryptosporidium*, and *Entamoeba histolytica*, are more common in patients with a history of immunosuppression or travel. None of them cause melanosis coli.

<table>
<thead>
<tr>
<th>SICKLE CELL ANEMIA</th>
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| This patient underwent a long plane flight and developed a **spleenic infarction**, an uncommon condition that usually arises in the setting of acute splenic artery (or subbranch) occlusion; possible underlying etiologies include a hypercoagulable state, embolic disease, or hemoglobinopathy. In this patient, a mild hemoglobinopathy such as **sickle cell trait** is most likely given the mild intravascular hemolysis (eg, elevated reticulocyte count, indirect hyperbilirubinemia), normal hemoglobin level, and negative past medical history for pain crises (making sickle cell disease unlikely).

Sickle hemoglobin mutations are often linked to Sub-Saharan Africa but are also common in other regions that have a high burden of malaria, including Central/South America, the Caribbean, the Middle East, the Mediterranean, and **India**. Most patients with sickle cell trait (eg, one altered beta-hemoglobin chain) are asymptomatic and considered benign carriers; however, certain stressors, such as **flying at high altitude** or dehydration due to **alcohol consumption**, can sometimes lead to intravascular hemolysis, tissue ischemia (eg, splenic infarction), and/or vasoocclusive pain. **Hemoglobin electrophoresis** is diagnostic.

24-hour ECG monitoring can diagnose atrial fibrillation, which can cause splenic infarction due to atrial thromboembolism. However, atrial
fibrillation would be unusual in a 24-year-old and does not typically cause reticulocytosis or bilirubinemia.

Blood cultures can diagnose infective endocarditis, which can cause splenic infarction due to septic thromboembolism. However, most patients are ill (eg, fever, chills, anorexia, weight loss) and cardiac murmur is usually present on examination.

Bone marrow biopsy can diagnose hematopoietic malignancies such as myelofibrosis, which may cause splenic infarction due to venous occlusion from congestive splenomegaly. However, myelofibrosis typically presents in older adults and causes splenomegaly (a hallmark feature not seen in this patient).

Factor V Leiden mutation is a common cause of thrombosis in middle-aged adults and typically causes venous thromboembolism, which can occasionally lead to splenic infarction. However, signs of intravascular hemolysis are not typically present.

CHOLANGITIS

Primary biliary cholangitis (PBC)

<table>
<thead>
<tr>
<th>Pathogenesis</th>
<th>Autoimmune destruction of intrahepatic bile ducts</th>
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</table>
| Clinical features | Affects middle-aged women  
| | Insidious onset of fatigue & pruritus  
| | Progressive jaundice, hepatomegaly, cirrhosis  
| | Cutaneous xanthomas & xanthelasmas |
| Laboratory findings | Cholestatic pattern of liver injury (↑↑ ALP, ↑ ATs)  
| | Antimitochondrial antibody  
| | Severe hypercholesterolemia |
| Treatment | Ursodeoxycholic acid (delays progression)  
| | Liver transplantation for advanced disease |
| Complications | Malabsorption, fat-soluble vitamin deficiencies  
| | Metabolic bone disease (osteoporosis, osteomalacia)  
| | Hepatocellular carcinoma |

Typical features of primary biliary cholangitis (PBC [previously called PB cirrhosis]), include pruritus, fatigue, hepatomegaly, elevated serum bilirubin, and a positive antimitochondrial antibody (AMA) assay. PBC is a progressive autoimmune disease characterized by destruction of the intrahepatic bile ducts, leading to cholestasis (bile stasis) and cirrhosis. It is commonly associated with severe hyperlipidemia, which may manifest with xanthelasmas (soft yellow plaques on the eyelids) due to accumulation of lipid-filled macrophages in the dermis. This hyperlipidemia is characterized by elevation of HDL out of proportion to...
LDL and does not appear to significantly increase the risk for atherosclerosis. It is most common in middle-aged women and has an insidious onset. Pruritus and fatigue are usually the first symptoms. As the disease progresses, jaundice, steatorrhea, hepatomegaly, eyelid xanthelasma, portal hypertension, and osteopenia may develop.

Other complications of PBC include malabsorption with associated nutrient deficiencies and hepatocellular carcinoma. In addition, patients may develop metabolic bone disease manifesting as osteoporosis or osteomalacia. Calcium and vitamin D levels in these patients are typically normal, suggesting that the bone disease is not due to malabsorption, but the precise etiology is not clear.

A RUQ US distinguishes intrahepatic (no biliary tract dilation) from extrahepatic (biliary tract dilation; eg, due to gallstones) cholestasis. If ultrasound suggests intrahepatic cholestasis (as with this patient), the next step is to obtain serum anti-mitochondrial antibody titers, which have high sensitivity and specificity for PBC.

Complications can include severe hyperlipidemia (with xanthelasma) and metabolic bone disease. PBC is often associated with other autoimmune disorders (eg, autoimmune thyroid disease).

Ursodeoxycholic acid (UDCA) is used in a number of cholestatic disorders and is the drug of choice in PBC. UDCA is a hydrophilic bile acid that decreases biliary injury by the more hydrophobic endogenous bile acids. It also increases biliary secretion and may have additional anti-inflammatory and immunomodulatory effects. UDCA delays histologic progression in PBC and may improve symptoms and possibly survival. It should be initiated as soon as the diagnosis is made, even in asx patients. Treatment is less effective in advanced disease, and many patients will go on to require liver transplantation.

Autoimmune hepatitis is associated with elevated titers of antinuclear antibodies and anti-smooth muscle antibodies. It is characterized by fluctuating hepatocellular injury (ie, elevated transaminases) rather than cholestasis. First-line treatment includes oral glucocorticoids.

Statins cause a hepatocellular rather than cholestatic pattern of injury, characterized by elevated liver transaminases (ALT, AST). AFP is used to screen for hepatocellular carcinoma in patients with chronic viral hepatitis or cirrhosis.

Liver transplantation is the definitive cure for progressive PBC but is indicated only in those with severe liver damage or cirrhosis.
Glucocorticoids are used for autoimmune hepatitis, which is characterized by elevated liver transaminases and a positive ANA titer. Glucocorticoids are ineffective in PBC.

-------------

Ascending cholangitis is a possible complication of extrahepatic biliary obstruction (eg, common bile duct stone) and typically presents acutely with Charcot triad (eg, fever, jaundice, right upper quadrant pain).

Bile salt diarrhea occurs in patients with terminal ileal disease (eg, ileal resection, Crohn ileitis). Impaired bile absorption in the ileum leads to increased bile salts in the colon, resulting in diarrhea (cholerheic diarrhea).

PSC is an inflammatory disorder of the intrahepatic and extrahepatic biliary tree associated with IBD. Patients with ulcerative colitis and PSC are at increased risk for colorectal cancer.

A1AT: The absence of pulmonary symptoms/signs makes emphysema unlikely

**RCM** and liver cirrhosis may be seen in patients with hemochromatosis due to excessive iron deposition in tissues. Other findings typically include skin hyperpigmentation and diabetes mellitus ("bronze diabetes").

### Evaluation of elevated alkaline phosphatase

- **AMA positive**: Abnormal hepatic parenchyma on ultrasound
  - Liver biopsy
- **AMA negative**: Normal liver ultrasound
  - Consider liver biopsy, ERCP, observation

**AMA** = antimitochondrial antibody; **ERCP** = endoscopic retrograde cholangiopancreatogram; **GGT** = gamma-glutamyltransferase; **RUQ** = right upper quadrant.

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### Primary sclerosing cholangitis

<table>
<thead>
<tr>
<th>Clinical features</th>
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<tbody>
<tr>
<td>• Fatigue &amp; pruritus</td>
<td></td>
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<tr>
<td>• Majority of patients asymptomatic at time of diagnosis</td>
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<tr>
<td>• About 90% of patients have underlying inflammatory bowel disease, mainly ulcerative colitis</td>
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<tr>
<th>Laboratory/imaging</th>
<th></th>
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<tbody>
<tr>
<td>• Cholestatic liver function test pattern (serum aminotransferases typically &lt;300 U/L)</td>
<td></td>
</tr>
<tr>
<td>• Multifocal stricturing/dilation of intrahepatic &amp;/or extrahepatic bile ducts on cholangiography</td>
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</table>

<table>
<thead>
<tr>
<th>Liver biopsy</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>• Fibrous obliteration of bile ducts with concentric replacement by connective tissue in an &quot;onion-skin&quot; pattern</td>
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</table>

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<thead>
<tr>
<th>Complications</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Intrahepatic &amp;/or extrahepatic biliary stricture</td>
<td></td>
</tr>
<tr>
<td>• Cholangitis &amp; choledolithiasis (cholesterol &amp;/or pigment stones)</td>
<td></td>
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<tr>
<td>• Cholangiocarcinoma (10%-15% lifetime risk)</td>
<td></td>
</tr>
<tr>
<td>• Cholestasis (eg, ↓ fat-soluble vitamins, osteoporosis)</td>
<td></td>
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<tr>
<td>• Colon cancer</td>
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</tbody>
</table>

PSC: inflammation, fibrosis, and stricturing of intrahepatic and extrahepatic bile ducts. Affected individuals frequently have coexisting UC. PSC is often asymptomatic but may present with fatigue and pruritus. Continued bile duct destruction leads to cholestatic complications (eg, fat-soluble vitamin deficiencies, osteoporosis), end-stage liver disease, and portal hypertension.

Elevated ALP, inflammatory markers (eg, ESR), increased IgM, and positive PANCA. ERCP or MRCP confirms the diagnosis by showing multifocal narrowing (red arrows) with intrahepatic and extrahepatic duct dilation (black arrows). Liver biopsy is typically not necessary but classically shows intrahepatic ductular obliteration with lymphocytic infiltration and periductular "onion-skin" fibrosis.
Although patients with PSC may experience acute cholangitis, the absence of fever or significant jaundice makes this diagnosis less likely.

Drug-induced hepatotoxicity can present as acute or chronic hepatitis (predominately elevated serum aminotransferases), cholestasis, or a mixed pattern. However, oral 5-aminosalicylic acid and corticosteroid enemas are usually not associated with hepatotoxicity.

Lack of hepatomegaly and weight loss makes metastatic liver ca unlikely.

Polyarteritis nodosa is a necrotizing vasculitis that affects medium-sized arteries and presents with systemic symptoms (eg, fever, malaise, weight loss), neuropathy, arthralgias/myalgias, cutaneous findings (eg, livedo reticularis), and renal disease. The hepatobiliary system is rarely affected and there is no association with antineutrophil cytoplasmic antibodies or ulcerative colitis.

Primary biliary cholangitis (primary biliary cirrhosis) can present similar to PSC; however, it classically affects middle-aged women and has no association with ulcerative colitis. Patients frequently have positive serum antimitochondrial antibodies.

### Acute cholangitis

<table>
<thead>
<tr>
<th><strong>Etiology</strong></th>
<th>Ascending infection due to biliary obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical presentation</strong></td>
<td>Fever, jaundice, RUQ pain (Charcot triad) ± Hypotension, AMS (Reynolds pentad)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Cholestatic liver function abnormalities o ↑ Direct bilirubin, ALP o Mildly ↑ aminotransferases Biliary dilation on abdominal US or CT scan</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Antibiotic coverage of enteric bacteria Biliary drainage by ERCP within 24-48 hr</td>
</tr>
</tbody>
</table>

**Acute cholangitis** (AC) occurs in the setting of biliary stasis, which is MCly caused by** gallstones, malignancy,** or **stenosis**. Elevated intrabiliary pressure allows for disruption of the bile-blood barrier and translocation of bacteria from the hepatobiliary system into the bloodstream.
Diagnostic findings reflect biliary obstruction, with US or CT scan demonstrating **dilation of the intrahepatic and CBD**. In addition to leukocytosis with left shift, laboratory results characteristically demonstrate **direct hyperbilirubinemia**, elevated ALP, and elevated GGT. ATs are typically only mildly elevated.

Supportive care, broad-spectrum antibiotics, and biliary drainage, preferably by **endoscopic retrograde cholangiopancreatography** with sphincterotomy, are the mainstays of treatment. Other options for biliary decompression include percutaneous transhepatic cholangiography with drain placement and open surgical decompression.

...........

Acetaminophen overdose is typically characterized by markedly elevated transaminases (>3000 U/L). In addition, the hyperbilirubinemia is primarily **indirect**, and **fever is atypical**.

**PSC** is characterized by short, annular strictures alternating with a normal bile duct ("beads on a string") visible on ultrasound. Although it has a cholestatic pattern on liver function studies, patients are frequently asymptomatic or have chronic fatigue and pruritus on presentation. Acute hypotensive illness and leukocytosis are not typical.

A patient's presentation is consistent with acute **cholangitis**. The classic Charcot triad of **fever, right upper quadrant (RUQ) pain**, and **jaundice** (not noted in this patient, although it may develop with worsening hyperbilirubinemia) is only seen in 50%-75% of patients; Reynolds pentad (additional hypotension and altered mental status) is classically associated with severe disease. Acute cholangitis is a life-threatening infection that typically develops in the setting of biliary obstruction, which enables bacteria to enter the ampulla and biliary tree. Common etiologies include choledocholithiasis, malignancy, primary sclerosing cholangitis, and biliary interventions that result in incomplete bile drainage.

In addition to **leukocytosis** with a left shift, classic laboratory findings include **direct hyperbilirubinemia** and elevated alkaline phosphatase (reflecting cholestasis). An anion gap metabolic acidosis (AGMA) commonly occurs from **lactic acidosis** with severe sepsis. The imaging modality of choice is a RUQ abdominal ultrasound, which demonstrates **common bile duct dilation** or evidence of biliary obstruction (eg, choledocholithiasis). Management includes broad-spectrum antibiotics, aggressive intravenous fluid resuscitation, and relief
of the biliary obstruction with either endoscopic retrograde cholangiopancreatography or percutaneous drainage.

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Acetaminophen overdose and viral hepatitis also cause nausea/vomiting, RUQ pain, hyperbilirubinemia, and occasionally an AGMA; however, transaminases elevations are expected to be in the thousands.

Diabetic ketoacidosis (DKA) also presents with abdominal pain, hyperglycemia, AGMA, and glucosuria. Although this patient is at high risk of DKA, the urinary ketones are normal, making DKA unlikely. In addition, hyperbilirubinemia is unexpected, and the abdominal pain due to DKA (which is possibly due to ileus or electrolyte abnormalities) is not classically localized to the RUQ. This patient’s hyperglycemia without DKA is likely due to infection.

Alcohol toxicity can cause alcoholic hepatitis, which also causes fever, RUQ pain, and jaundice. However, it typically causes a transaminase elevation with an aspartate aminotransferase to alanine aminotransferase ratio of ≥2.

Acute mesenteric artery occlusion would cause severe abdominal pain and lactic acidosis, but a direct hyperbilirubinemia is unexpected, and this patient lacks typical risk factors (eg, peripheral artery disease, arrhythmias).

Necrotizing pancreatitis presents with severe abdominal pain radiating to the back along with nausea and vomiting. Gallstone pancreatitis can sometimes occur with concurrent cholangitis; however, the lipase would be expected to be elevated.
### ACUTE PANCREATITIS

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Clinical features of acute pancreatitis</th>
</tr>
</thead>
</table>
| Chronic alcohol use               | • Etiology:  
| Gallstones                        | - Acute epigastric abdominal pain often radiating to the back                 |
| Hyperlipidemia (types I, IV & V)  | • ↑ Amylase/lipase >3 times normal limit                                       |
| Drugs (e.g., didanosine, azathioprine, valproic acid) | • Abdominal imaging showing focal or diffuse pancreatic enlargement with heterogeneous enhancement with intravenous contrast (CT) or diffusely enlarged & hypoechogenic pancreas (ultrasound) |
| Infections (e.g., cytomegalovirus, Legionella, Aspergillus) | Other findings:  
| Trauma                            | • Nausea, vomiting, leukocytosis                                              |
| Iatrogenic (post-ERCP)            | • Severe disease with possible abdominal tenderness, fever, tachypnea, hypoxemia & hypotension |
|                                   | • ALT level >150 units/L → biliary pancreatitis                               |
|                                   | Complications:  
|                                   | • Pleural effusion                                                           |
|                                   | • Ileus                                                                      |
|                                   | • Pancreatic pseudocyst/abscess/necrosis                                      |
|                                   | • Acute respiratory distress syndrome                                         |

US may show focal enlargement. Risk factors: hyperTG (3rd MCC). Drugs (e.g., HCTZ) The serum triglyceride level generally must be **>1,000 mg/dL** to be considered a potential cause of pancreatitis. The yellow-red papules on this patient’s arms and shoulders suggest eruptive xanthomas, which are due to subcutaneous fat deposition. Eruptive xanthomas are usually associated with marked hypertriglyceridemia (>1,000 mg/dL), typically due to familial hypertriglyceridemia (which may also explain the patient’s father’s myocardial infarction at age 42). A **fasting serum lipid profile** can determine if hypertriglyceridemia is the underlying cause of this patient’s xanthomas and pancreatitis.

Early in pancreatitis, the pancreas synthesizes digestive enzymes but cannot secrete them. These enzymes leak out of the acinar cells into the systemic circulation. Amylase rises within 6-12 hours of symptom onset and may remain elevated for 3-5 days. Lipase rises within 4-8 hours of
symptom onset but remains elevated longer than amylase (8-14 days). As a result, lipase is more useful and sensitive than amylase for diagnosis (especially in alcoholics and patients presenting later in the disease course).

Imaging is not required for diagnosis in patients with typical abdominal pain and significantly elevated amylase and/or lipase. Contrast-enhanced computed tomography scan of the abdomen may be performed in patients with unclear diagnosis or in those who fail to improve with conservative management (to identify infection or necrosis).

Drug-induced pancreatitis (mnemonic SIADH): common drugs associated with pancreatitis include:

1. Seizure meds (e.g., valproate)
2. Immunosuppressive agents (azathioprine)
3. Antibiotics (metronidazole, tetracycline)
4. Diuretics (furosemide, thiazides)
5. Drugs for IBD (sulfasalazine, 5-ASA)
6. HIV-related medications (didanosine, pentamidine)

Drug-induced pancreatitis is usually mild. Patients typically develop nausea, vomiting and abdominal pain radiating to the back. Laboratory results usually show elevated serum amylase and lipase. The CT scan reveals swelling of the pancreas with prominent peripancreatic fluid and fat-stranding (red arrow). Supportive treatment with fluids and electrolyte replacement is recommended.

ERCP is usually done to evaluate biliary pancreatitis. Although patients with biliary pancreatitis may sometimes have a normal ultrasound (especially if the stone is passed), they typically have an elevated alanine aminotransferase (ALT) level (>150 U/L). Normal ALT level makes biliary pancreatitis less likely. ERCP should also be considered in patients with >1 episode of acute pancreatitis of unknown cause.

Early ERCP for suspected biliary pancreatitis may decrease morbidity and mortality. ERCP is also effective for evaluating patients with recurrent pancreatitis or draining pancreatic pseudocysts.

Acute pancreatitis has been associated with viruses (e.g., mumps, HBV, HIV, coxsackievirus, CMV, HSV), but patients often develop other characteristic findings of particular viral infections. Viral serology is

| Drug-induced pancreatitis (mnemonic SIADH): common drugs associated with pancreatitis include: |
| 1. Seizure meds (e.g., valproate) |
| 2. Immunosuppressive agents (azathioprine) |
| 3. Antibiotics (metronidazole, tetracycline) |
| 4. Diuretics (furosemide, thiazides) |
| 5. Drugs for IBD (sulfasalazine, 5-ASA) |
| 6. HIV-related medications (didanosine, pentamidine) |
generally not recommended as the significance of a positive result is unknown, and there is no potential treatment for most of these viruses.

Cannabis use has been associated with case reports of acute pancreatitis, but it would not cause eruptive xanthomas. Other illicit drugs usually do not cause acute pancreatitis.

Acute mesenteric ischemia: does not usually cause the abnormal pancreatic findings seen on this patient’s abdominal CT scan.

<table>
<thead>
<tr>
<th>Acute pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td>• Chronic alcohol use (~40%)</td>
</tr>
<tr>
<td>• Gallstones (~40%)</td>
</tr>
<tr>
<td>• Hypertriglyceridemia</td>
</tr>
<tr>
<td>• Drugs (eg, azathioprine, valproic acid, thiazides)</td>
</tr>
<tr>
<td>• Infections (eg, CMV, <em>Legionella, Aspergillus</em>)</td>
</tr>
<tr>
<td>• Iatrogenic (post-ERCP, ischemic/atheroembolic)</td>
</tr>
<tr>
<td><strong>Clinical presentation</strong></td>
</tr>
<tr>
<td><strong>Diagnosis (requires 2 of the following)</strong></td>
</tr>
<tr>
<td>• Acute epigastric pain radiating to the back</td>
</tr>
<tr>
<td>• Amylase or lipase &gt;3 times normal limit</td>
</tr>
<tr>
<td>• Abnormalities on imaging consistent with pancreatitis</td>
</tr>
<tr>
<td><strong>Other findings</strong></td>
</tr>
<tr>
<td>• ALT level &gt;150 U/L suggests biliary pancreatitis</td>
</tr>
<tr>
<td>• Severe disease: Fever, tachypnea, hypoxemia, hypotension</td>
</tr>
</tbody>
</table>

*ALT = alanine aminotransferase; CMV = cytomegalovirus; ERCP = endoscopic retrograde choangiopancreatography.*

A patient’s abdominal pain, nausea, and elevated lipase are consistent with **acute pancreatitis**. He has no history of alcohol use, and his ultrasound reveals no gallstones. His pancreatitis is likely due to **cholesterol emboli**. Patients with risk factors for aortic atherosclerosis (eg, hypercholesterolemia, diabetes, peripheral vascular disease) who undergo **cardiac catheterization** or a vascular procedure are at increased risk for cholesterol emboli as a result of vascular manipulation. These emboli can occlude blood vessels and cause the following:

- Skin manifestations: Livedo reticularis (reticulated, mottled, discolored skin), blue toe syndrome
- Kidney manifestations: **Acute kidney injury**
- Gastrointestinal manifestations: **Pancreatitis**, mesenteric ischemia
Supportive care (eg, pain control, intravenous fluids, bowel rest) is recommended for uncorrectable causes of acute pancreatitis (eg, hypotension, ischemia, viruses, atheroembolism). Most acute pancreatitis attacks are self-limiting and improve in 4-7 days with conservative management. This patient should receive nothing by mouth except essential medications (ie, antiplatelet therapy to prevent stent thrombosis); early refeeding can be considered if the patient's condition improves (eg, decreasing pain).

Elective cholecystectomy is generally indicated for patients with gallstones and biliary colic or cholecystitis. Endoscopic retrograde cholangiopancreatography is indicated for sphincterotomy and stone removal in patients with gallstone pancreatitis and cholangitis or in those who have high surgical risk for cholecystectomy. This patient has no gallstones or common bile duct dilation on ultrasound.

Prophylactic antibiotics are not routinely used in patients with acute pancreatitis unless there is evidence of necrotizing pancreatitis with local infection (which is not seen on this patient's CT scan).

Glucocorticoids have no role in management of uncomplicated acute pancreatitis.

<table>
<thead>
<tr>
<th>Drugs associated with drug-induced pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesics</strong></td>
</tr>
<tr>
<td>• Acetaminophen</td>
</tr>
<tr>
<td>• NSAIDs</td>
</tr>
<tr>
<td>• Mesalamine, sulfasalazine</td>
</tr>
<tr>
<td>• Opiates</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
</tr>
<tr>
<td>• INH</td>
</tr>
<tr>
<td>• Tetracyclines</td>
</tr>
<tr>
<td>• Metronidazole</td>
</tr>
<tr>
<td>• TMP-SMZ</td>
</tr>
<tr>
<td><strong>Antiepileptics</strong></td>
</tr>
<tr>
<td>• Valproic acid</td>
</tr>
<tr>
<td>• Carbamazepine (CBZ)</td>
</tr>
<tr>
<td><strong>Antihypertensives</strong></td>
</tr>
<tr>
<td>• Thiazides, furosemide</td>
</tr>
<tr>
<td>• Enalapril, losartan</td>
</tr>
</tbody>
</table>
### Antivirals
- Lamivudine
- Didanosine

### Immunosuppressants
- Azathioprine, 6-MP
- Corticosteroids

### Others
- Asparaginase
- Estrogens

The diagnosis of **acute pancreatitis** requires ≥2 of the following 3 criteria:

- Severe **epigastric pain**
- Elevated serum lipase >3 times the upper limit of normal
- CT scan findings suggestive of **pancreatic inflammation**

Gallstones and alcohol abuse account for approximately 75% of all cases of acute pancreatitis. Hypertriglyceridemia, the third most common cause, typically occurs only when the triglyceride level exceeds 1,000 mg/dL. When these common etiologies have been ruled out, less common causes, including **drug-induced pancreatitis** (DIP), should be considered.

Recognizing DIP can be challenging because it may develop months after drug initiation and many medications have been implicated. **Diuretics**, including thiazides (eg, hydrochlorothiazide) and most loop diuretics (eg, furosemide), are among the most common offenders. These drugs may trigger pancreatitis via **hypersensitivity** to the sulfonamide molecule (a structural component of thiazides and most loop diuretics), **pancreatic ischemia** due to reduced blood volume, and/or **increased viscosity** of pancreatic secretions. Other medications associated with DIP include ACE inhibitors (eg, enalapril), statins (eg, simvastatin), and certain antibiotics (eg, isoniazid, trimethoprim-sulfamethoxazole), which may act through similar or other pathophysiologic mechanisms (eg, direct toxicity).

In addition to discontinuation of the offending agent, management of DIP is identical to that of other causes of acute pancreatitis, involving aggressive intravenous hydration, pain control, and diet advancement as tolerated.
Patients with gallstone pancreatitis should undergo timely cholecystectomy to help prevent additional episodes. ERCP can be used to remove gallstones obstructing the biliary tract, and it is indicated in patients with gallstone pancreatitis complicated by cholangitis. This patient has no laboratory evidence (eg, hyperbilirubinemia, elevated transaminases) or ultrasound findings (eg, gallstones, common bile duct dilation) to suggest gallstone pancreatitis, and no evidence of cholangitis (eg, jaundice, right upper quadrant pain).

Glucocorticoids are used to treat autoimmune pancreatitis, a relatively rare IgG4 mediated disorder. These drugs should not be initiated prior to diagnostic confirmation, which typically requires pancreatic biopsy in addition to a serum IgG4 level.

HIDA scan can demonstrate cystic duct obstruction in acute cholecystitis, which presents with fever, leukocytosis, and right upper quadrant pain. This test has minimal use in evaluating acute pancreatitis.
This patient’s presentation is consistent with acute severe pancreatitis that has progressed to multisystem organ dysfunction (eg, shock, renal failure, early respiratory failure). Most patients with acute pancreatitis have mild disease and recover with conservative management (eg, fluids, bowel rest, pain medication) in 3-5 days. However, nearly 15%-20% of patients can develop severe acute pancreatitis, defined as pancreatitis with failure of at least 1 organ. Clinical markers associated with increased risk for severe pancreatitis include age >75, alcoholism, obesity, C-reactive protein >150 mg/dL at 48 hours, and increased blood urea nitrogen (BUN)/Cr in the first 48 hours. Abdominal imaging (computed tomography scan or magnetic resonance cholangiopancreatography) is indicated for suspected severe pancreatitis to look for pancreatic necrosis and extrapancreatic inflammation, which also indicate severe acute pancreatitis.

Severe pancreatitis causes local release of activated pancreatic enzymes that enter the vascular system and increase vascular permeability within and around the pancreas. This leads to large volumes of fluid migrating from the vascular system to the surrounding retroperitoneum. Systemic inflammation also ensues as the inflammatory mediators enter the vascular
system. The net effect is widespread vasodilation, capillary leak, shock, and associated end-organ damage. Treatment usually involves supportive care with several liters of IV fluid to replace the lost intravascular volume.

Hypotensive episodes seen in severe pancreatitis could incite an underlying myocardial infarction. However, this patient has no signs or symptoms (eg, chest pain) suggesting myocardial infarction.

Narcotics (eg, meperidine) are often given for analgesia in acute pancreatitis. Narcotic overdose can cause respiratory depression, hypotension, and bradycardia. This patient’s tachycardia, crackles, abdominal distention, worsening BUN, and low urine output make severe pancreatitis with early multiorgan failure more likely.

Occult bleeding is unlikely to cause significant hypotension without resulting in anemia.

Pericardial effusion can be a complication of pancreatitis, but tamponade severe enough to cause cardiac failure would cause jugular venous distention (not seen in this patient’s physical examination).

Acute pancreatitis can be complicated by a peripancreatic pseudocyst, a fluid collection (containing pancreatic enzymes, blood, fluid, and tissue debris) surrounded by a necrotic or fibrous capsule. Pseudocysts typically take 3-4 weeks to develop after acute pancreatitis and would be a less likely cause of acute hypotension in this patient.

### CHRONIC PANCREATITIS

<table>
<thead>
<tr>
<th>Overview of chronic pancreatitis</th>
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<tbody>
<tr>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td>• Alcohol use, Smoking</td>
</tr>
<tr>
<td>• CF (common in children)</td>
</tr>
<tr>
<td>• Ductal obstruction (eg, malignancy, stones)</td>
</tr>
<tr>
<td>• Autoimmune</td>
</tr>
<tr>
<td>• FHx (e.g., hereditary pancreatitis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Chronic epigastric pain</strong> that worsens w/ meals with intermittent pain-free intervals</td>
</tr>
<tr>
<td>• <strong>Malabsorption</strong> - steatorrhea, weight loss</td>
</tr>
<tr>
<td>• <strong>Diabetes mellitus</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory results/imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Amylase/lipase can be normal &amp; nondiagnostic</td>
</tr>
<tr>
<td>• CT scan or MRCP can show calcifications, dilated ducts &amp; enlarged pancreas</td>
</tr>
</tbody>
</table>
Treatment

- Pain management
- Alcohol & smoking cessation
- Frequent, small meals
- Pancreatic enzyme supplements

MRCP = magnetic resonance cholangiopancreatography.

This patient's presentation suggests chronic pancreatitis (CP), most commonly due to chronic alcohol consumption (including prolonged use of socially acceptable amounts). CP typically presents with chronic epigastric abdominal pain that can radiate to the back and is partially relieved by sitting upright or leaning forward. Patients can have intermittent pain-free intervals lasting from months to a year. Early CP can present with acute attacks that become continuous as the condition progressively worsens.

Patients with CP develop progressive pancreatic inflammation that causes nonreversible exocrine and endocrine functional damage. Diarrhea, steatorrhea, and weight loss can develop due to fat malabsorption from reduced levels of exocrine pancreatic enzymes (eg, amylase, protease, lipase). CP eventually causes pancreatic endocrine failure with glucose intolerance or overt diabetes. Pancreatic calcifications seen on abdominal plain films or CT scan are helpful for establishing the diagnosis. In addition, CT scan helps exclude other etiologies (eg, pancreatic cancer, pseudocyst).

Fecal elastase is a noninvasive test with high sensitivity and specificity for severe pancreatic exocrine insufficiency. Elastase is a proenzyme (zymogen) produced in pancreatic acinar cells and activated by trypsin in the duodenal lumen; low levels indicate severe exocrine insufficiency. An alternate noninvasive test is serum trypsinogen, which would also be low in this setting. Treatment involves pancreatic enzyme replacement, which includes lipase to aid in fat digestion and improve steatorrhea.

The destruction of acinar and islet cells results in pancreatic exocrine insufficiency. Pancreatic secretion is stimulated by cholecystokinin (CCK). Normally, pancreatic enzymes breakdown CCK-releasing protein, thereby limiting CCK release. In patients with pancreatic insufficiency, pancreatic enzyme deficiency leads to the release of high volumes of CCK, resulting in a loop of pancreatic hyperstimulation. In association with pancreatic inflammation and ischemia, this results in the characteristic post-prandial abdominal pain common in patients with chronic pancreatitis.

Pancreatic enzyme supplementation, which typically contains lipase, protease, and amylase, helps alleviate pain by reducing pancreatic
hyperstimulation and improves nutrient digestion; additionally, fat malabsorption and steatorrhea (if present) typically improve. The ingestions of frequent, small meals that are low in fat may also improve pain. Secondary options for treating chronic pancreatitis pain include pregabalin, nortriptyline, and amitriptyline. Further management includes alcohol and tobacco cessation and treatment of diabetes (if present).

--------

A celiac plexus block (with glucocorticoids or alcohol) is useful for pancreatic cancer pain but has limited efficacy in chronic pancreatitis. In addition, there is increased risk for hypotension and infection.

ERCP with sphincterotomy and/or stent placement may improve pain in patients with evidence of an obstructed pancreatic duct, and surgery (eg, pancreatic resection) can be considered if ERCP is unsuccessful.

Although chronic pain medication may be required in patients who fail to obtain relief with pancreatic enzyme supplementation, opiate medications carry significant risks (eg, sedation, dependence). If the patient fails to respond to pancreatic enzyme supplementation, non-opiate therapy (eg, pregabalin, nortriptyline) is a more appropriate next step.

Mesenteric angiogram can diagnose chronic mesenteric ischemia, which can present with dull abdominal pain (usually after eating) and unintentional weight loss due to avoidance of food. Diarrhea and improvement in pain with position changes are uncommon.

In contrast to widespread inflammation in acute pancreatitis, CP causes patchy inflammation and fibrosis (burned-out pancreas) and can present with normal or only slightly elevated serum amylase and lipase. Abdominal imaging showing pancreatic calcifications is the best way to confirm CP.

**Treatment**

**General measures**

- **Abstinence** from alcohol and nicotine
- Small, regular meals (rich in carbohydrates, low in fat), supplementation with medium-chain triglycerides (MCT)
- Pancreatic enzyme **replacement** (with meals)
- Parenteral administration of fat-soluble vitamins (A, D, E, K) if necessary
- Endocrine insufficiency: Insulin administration
- For management of acute attacks see “Treatment” in acute pancreatitis.

**Pain management**
- **Analgesics:** NSAIDs, opioids for severe pain (e.g., long-acting fentanyl/morphine), low dose tricyclic antidepressants (e.g., amitriptyline)
- **Intractable pain**
  - Celiac ganglion block (offers temporary relief)
  - Endoscopic papillotomy + ductal dilation and stent placement + removal of stones, if present
  - Extracorporeal shock wave lithotripsy (ESWL): for intraductal stones

### Surgery
- **Indication:** if pancreatic cancer is suspected or in those with intractable pain
- **Procedures**
  - Pancreaticojejunostomy: if the main pancreatic duct is dilated (> 5 mm)
  - Resection of the affected part of the pancreas (distal pancreatectomy, Whipple's procedure)
  - Thoracoscopic bilateral splanchnicectomy

### Complications

#### Pancreatic pseudocysts
- **Definition:** encapsulated collection of pancreatic fluid which develops 4 weeks after an acute attack of pancreatitis; can occur in both acute and chronic pancreatitis
- **Pathophysiology:** pancreatic secretions leak from damaged ducts → inflammatory reaction of surrounding tissue → encapsulation of secretions by granulation tissue
- **Clinical features**
  - Often asymptomatic
  - **Painless** abdominal mass
  - Pressure effects
    - Gastric outlet obstruction (early satiety, non-bilious vomiting, abdominal pain)
    - Obstruction of the distal duodenum (bilious vomiting)
      - Results in steatorrhea
      - Bile duct obstruction with jaundice
- **Diagnostics:** abdominal ultrasound/CT/MRI → extrapancreatic fluid collection within well-defined wall/capsule, no solid cyst components detectable
- **Treatment:** Surgical/endoscopic cystogastrostomy/cystoduodenostomy/cystojejunostomy; US/CT-guided percutaneous drainage
- **Complications**
Infection → fever, abdominal pain, sepsis
Rupture → pancreatic ascites/pancreaticopleural fistula
Erosion into an abdominal vessel with hemorrhage into the cyst → sudden abdominal pain, signs of hemorrhagic shock

\textbf{Splenic vein thrombosis}
- Can occur in 10% of patients with chronic pancreatitis
- \textbf{Pathophysiology: inflammation} of the splenic vein → thrombus formation → left-sided portal hypertension → gastric varices
- \textbf{Clinical features}: can present with upper GI bleeding, ascites, and splenomegaly
- \textbf{Diagnosis}: ultrasound with doppler, CT/MR angiography
- \textbf{Treatment}
  - Acute: anticoagulation and/or \textbf{thrombectomy}
  - Chronic and symptomatic: splenectomy

\textbf{Pancreatic ascites}
- \textbf{Pathophysiology}: Ductal disruption (due to an acute attack of pancreatitis; pancreatic surgery/trauma) or a pseudocyst \textbf{leak/rupture} → pancreatic ascites
- \textbf{Clinical features}
  - Abdominal distension; variable abdominal pain; dyspnea; peripheral edema
  - \textbf{Free fluid} in the peritoneal cavity
- \textbf{Diagnosis}
  - Ascitic fluid analysis: \textbf{Exudate} with \textbf{high amylase levels} (>1000 IU/L)
  - ERCP: Demonstrates the site(s) of leak
  - CECT and MRCP can also demonstrate ascites and the site of leak; ERCP is preferred since treatment can be performed in the same sitting
- \textbf{Treatment}
  - Conservative management: Indicated in all patients; ~30% will require no further treatment
    - \textbf{Nil per oral}, IV fluids, parenteral nutrition
    - Somatostatin analogues (\textbf{octreotide})
    - Repeated ascitic taps
  - \textbf{Stenting} of the pancreatic duct: If ERCP demonstrates ductal disruption
  - Surgery: Indicated in patients with no improvement on conservative management for 4 weeks (See Pancreatic and hepatic surgery)
    - \textbf{Pancreatic resection}
    - Surgery for pancreatic pseudocyst
Dysphagia can be classified as oropharyngeal or esophageal. **Oropharyngeal dysphagia** presents with difficulty initiating swallowing due to inability to properly transfer food from the mouth to the pharynx. Underlying etiologies for oropharyngeal dysphagia can include stroke, advanced dementia, oropharyngeal malignancy, or neuromuscular disorders (eg, myasthenia gravis).

Patients with oropharyngeal dysphagia can also have associated coughing, choking, or nasal regurgitation on swallowing. Other complications can include aspiration pneumonia and weight loss. This patient's history of stroke with coughing and choking on swallowing suggests oropharyngeal dysphagia. Recurrent right lower lobe pneumonia suggests likely aspiration pneumonia. **Videofluoroscopic modified barium swallow study** is preferred initially in these patients to evaluate swallowing mechanics, degree of dysfunction, and severity of aspiration.
Esophageal motility studies and upper gastrointestinal endoscopy are typically used for evaluating esophageal dysphagia, which presents with a sensation of food getting stuck in the esophagus (not throat) a few seconds after a swallow but does not cause difficulty initiating swallowing.

Achalasia: Either primary (ie, loss of peristalsis in the distal esophagus with lack of lower esophageal sphincter relaxation) or pseudoachalasia due to esophageal cancer. Several clues point to pseudoachalasia (eg, narrowing of distal esophagus not due to denervation) caused by malignancy.

**Tobacco** use is a major risk factor for esophageal adenocarcinoma and SqCC; alcohol use is also an important risk factor for esophageal SqCC. **Significant weight loss, rapid symptom onset (<6 months), and presentation at age >60** all increase the likelihood of malignancy (by comparison, patients with achalasia have symptoms for approximately 5 years before receiving a diagnosis, and they typically only have mild weight loss). Tumor metastasis (eg, mediastinal LNs) or local involvement may give a radiologic appearance similar to that seen with a widened mediastinum. **Endoscopic evaluation** can differentiate between achalasia and pseudoachalasia. In achalasia, this evaluation usually shows normal-appearing esophageal mucosa and a dilated esophagus with possible residual material; in addition, it is generally possible to easily pass the endoscope through the lower esophageal sphincter (unlike in malignancy).

If endoscopy shows a malignancy, a CT scan can be performed for staging. CT scan can also be obtained if endoscopy is nonrevealing and there is still concern for malignancy.

Laparoscopic myotomy and pneumatic balloon dilation are the treatments of choice for patients with achalasia who are at low surgical risk. Options for patients at high surgical risk include botulinum toxin injection, nitrates, and calcium channel blockers. However, all these treatments should be considered only after malignancy is excluded and the diagnosis of achalasia is confirmed.
Achalasia

<table>
<thead>
<tr>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic dysphagia to solids &amp; liquids, regurgitation</td>
</tr>
<tr>
<td>• Heartburn, weight loss</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Manometry: ↑ LES resting pressure, incomplete LES relaxation, ↓ peristalsis of distal esophagus</td>
</tr>
<tr>
<td>• Barium esophagram: smooth “bird beak” narrowing at GEJ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Upper endoscopy to exclude malignancy</td>
</tr>
<tr>
<td>• Laparoscopic myotomy or pneumatic balloon dilation</td>
</tr>
<tr>
<td>• Botulinum toxin injection, nitrates &amp; CCB</td>
</tr>
</tbody>
</table>

Chronic dysphagia to both solids and liquids, regurgitation, difficulty belching, and mild weight loss are all common manifestations of achalasia. Other symptoms include chest pain and heartburn; therefore, many patients are initially diagnosed with gastroesophageal reflux. On average, patients have symptoms for approximately 5 years before receiving a diagnosis of achalasia.

Achalasia is due to impaired peristalsis of the distal esophagus and impaired relaxation of the lower esophageal sphincter (LES). This prevents food or liquid from passing through the LES until the hydrostatic pressure in the esophageal column is greater than the closing pressure of the sphincter. Being in the upright position increases the pressure in the esophagus and results in more effective swallowing.

Manometry is the most sensitive test and key to diagnosis. Barium esophagram, which may show a smooth “bird-beak” narrowing near the LES, can be helpful in patients with nondiagnostic manometry.

.........

Esophageal webs are most commonly located in the upper esophagus and only cause mild focal narrowing (dysphagia to solids but not liquids). They are often associated with iron deficiency (Plummer-Vinson syndrome).
Globus sensation is a diagnosis of exclusion and is characterized by the sensation of a lump in the back of the throat. It is a functional disorder and does not cause any abnormalities on barium esophagram.

Zenker diverticulum, caused by an outpouching at the cricopharyngeal level of the esophagus, most commonly occurs in patients age >60 and presents with dysphagia, halitosis, and fullness of the throat.

Supportive measures for UGIB include supplemental oxygen, bowel rest, and intravenous fluids through large-bore catheters. An intravenous proton pump inhibitor should also be administered for acid suppression. Packed red blood cell (PRBC) transfusion can increase oxygen-carrying capacity in patients with significantly low hemoglobin levels.

In general, **stable patients** without significant comorbid conditions should receive PRBC **transfusion** for hemoglobin **<7 g/dL**. A higher threshold of hemoglobin **<9 g/dL** can be considered for patients with acute coronary syndrome. Patients with active bleeding and hypovolemia may need PRBC transfusion at higher hemoglobin levels due to the initial hemoglobin concentration not fully reflecting blood loss. In addition, the hemoglobin level may drop significantly as blood volume is replaced by the infusion of crystalloid solutions and the mobilization of interstitial fluid.

**FFPs** contains all clotting factors and plasma proteins from one unit of blood. It is usually indicated for severe coagulopathy (eg, liver disease, disseminated intravascular coagulation) with active bleeding. Fresh frozen plasma is generally not needed to correct a minimally abnormal INR (<1.6), which is a common finding in gastrointestinal bleeding.

PPIs reduce rebleeding and the need for transfusions, and help stabilize clots in patients with UGIB. Histamine-2 blockers, such as famotidine, have not demonstrated such benefits and consequently are not recommended as first-line therapy for UGIB.

Platelet transfusions are typically given for a platelet count **<10,000/mm³** (increased risk of spontaneous hemorrhage) or for a platelet count **<50,000/mm³** with active bleeding.

Whole blood transfusion, which includes PRBCs in addition to plasma, may be used in patients with severe hemorrhage (eg, major trauma) requiring massive blood transfusions to assist in volume expansion.
### Diffuse esophageal spasm

<table>
<thead>
<tr>
<th><strong>Pathophysiology</strong></th>
<th>• Uncoordinated, simultaneous contractions of esophageal body</th>
</tr>
</thead>
</table>
| **Symptoms**        | • Intermittent *chest pain*  
|                     | • Dysphagia for solids & liquids                          |
| **Diagnosis**       | • Manometry: Intermittent peristalsis, multiple *simultaneous contractions*  
|                     | • Esophagram: "Corkscrew" pattern                       |
| **Treatment**       | • CCBs  
|                     | • Alternates: Nitrates or tricyclics                     |

This patient with intermittent *non-cardiac chest pain* and *dysphagia* has typical symptoms of diffuse *esophageal spasm* (DES). DES is characterized by *uncoordinated, simultaneous contractions* of the esophageal body, likely related to impaired inhibitory innervation in the esophagus. DES is frequently seen in association with emotional factors and functional gastrointestinal disorders. Symptoms often resemble those in achalasia (impaired esophageal motility with incomplete relaxation at the lower esophageal sphincter) and nutcracker esophagus (excessive tone at the lower esophageal sphincter).

The diagnosis of DES is challenging due to the episodic nature of clinical features. Esophageal manometry reveals intermittent peristalsis and *multiple* nonperistaltic *simultaneous contractions* of the middle and lower esophagus. The lower esophageal sphincter usually shows normal relaxation. Esophagram may show nonperistaltic contractions producing a "corkscrew esophagus" pattern, although this is neither sensitive nor specific. Endoscopy is usually normal. First-line treatment includes *calcium channel blockers* (eg, diltiazem), which relieve pain and reduce dysphagia.

......

Variant (Prinzmetal) angina is due to coronary artery spasm. Typical symptoms include episodic chest pain at rest. Patients may have normal ECG findings between attacks, with variable ST abnormalities during acute events. Variant angina does not explain the patient’s dysphagia.

Costosternal syndrome (costochondritis) usually occurs after repetitive activity. It is characterized by pain that is reproducible with palpation and
worsened with movement or position changes. It would not cause dysphagia.

Eosinophilic esophagitis is characterized by food impaction, dysphagia, or heartburn that does not respond to standard medications. Endoscopy usually reveals esophageal rings or strictures.

Globus sensation is a functional disorder of the esophagus characterized by the sensation of a foreign body in the throat. It is often worse when swallowing saliva and is frequently associated with anxiety. Pain, dysphagia, dysphonia, or systemic symptoms are not typical for globus and suggest another condition.

Zenker diverticulum is a disorder of the proximal esophagus and is generally asymptomatic, although it can cause a sensation of food sticking in the throat, halitosis, and regurgitation. Chest pain is not a typical symptom.

**DES**
Spontaneous pain, odynophagia for cold and hot food are suggestive of DES. Nitrates (and CCBs) relax not only myocytes in coronary vessels but also smooth muscle cells in the esophagus, thereby alleviating the pain. Esophagography may or may not show other anomalies (eg, corkscrew shape). Esophageal manometry should show repetitive, nonperistaltic, high-amplitude contractions, either spontaneously or after ergonovine stimulation.

Radiation of pain to the back and its precipitation by emotional stress make the diagnosis of motility disorder more likely than GERD. GERD MCly causes burning discomfort (heartburn) rather than radiating pain and is associated with esophagitis on endoscopy. Furthermore, if GERD were suspected, the patient should be started on an empiric trial of a PPI rather than 24-hour pH monitoring.

<table>
<thead>
<tr>
<th>ESOPHAGITIS</th>
<th>Medication-induced esophagitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug class</strong></td>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Anti-inflammatory agents</td>
<td>Aspirin &amp; many NSAIDs</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Alendronate, risedronate</td>
</tr>
<tr>
<td>Others</td>
<td>Potassium chloride (KCl), iron</td>
</tr>
</tbody>
</table>
Mucosal injury in pill esophagitis can be due to **acid effect** (eg, tetracyclines), **osmotic tissue injury** (eg, KCl), or disruption of normal gastroesophageal protection (eg, NSAIDs). Patients usually do not have prior esophageal disease, although pill esophagitis can be worse in those with concurrent GER.

Typical symptoms of pill esophagitis include **sudden-onset** odynophagia and retrosternal pain that can sometimes cause difficulty swallowing. It is MC in the mid-esophagus due to compression by the aortic arch or an enlarged left atrium. The diagnosis is usually made clinically but can be confirmed on endoscopy, which shows discrete ulcers with relatively normal-appearing surrounding mucosa. Treatment includes primarily stopping the offending medication to prevent future injury.

... Endoscopy in *Candida* esophagitis is characterized by white plaques, and most patients will also have oral thrush. These conditions are most common in immunocompromised patients.

**DES.** Patients typically have recurrent episodes of liquid/solid dysphagia and chest pain.

**GERD** typically causes recurrent or persistent burning pain in the upper abdomen and chest. Symptoms are worse following large meals or certain foods (eg, chocolate, peppermint) or when lying down. Symptoms are usually **subacute** to chronic rather than abrupt.

### Eosinophilic esophagitis

<table>
<thead>
<tr>
<th>Pathogenesis</th>
<th>• Chronic, immune-mediated esophageal inflammation</th>
</tr>
</thead>
</table>
| **Clinical features** | • Dysphagia  
• Chest/epigastric pain  
• Reflux/vomiting  
• Food impaction  
• Associated atopy |
| **Diagnosis** | • Endoscopy & esophageal biopsy (≥15 eosinophils per HPF) |
| **Treatment** | • Dietary modification  
• ± Topical glucocorticoids |

A patient has an esophageal **food impaction**, which most commonly occurs when food becomes trapped in the esophagus due to a preexisting abnormality (eg, ring, stricture). **Drooling, hypersalivation**, and an **inability to tolerate liquids** (eg, vomiting after drinking water) are cardinal symptoms. Food impaction can lead to esophageal perforation and requires **urgent upper endoscopy** with food bolus removal.
Although any physiologic or pathologic esophageal narrowing can predispose to food impaction, several features suggest that eosinophilic esophagitis (EoE) is the most likely underlying etiology. EoE commonly affects young men (age 20–30) and is frequently associated with other atopic conditions (eg, seasonal allergies, eczema, asthma). In addition to refractory heartburn despite a PPI (as seen in this patient), other common manifestations include intermittent solid food dysphagia and substernal chest or upper abdominal pain. More than 50% of patients have a history of food impaction, which typically occurs when progressive esophageal inflammation from untreated EoE leads to stricture formation.

The diagnosis of EoE is confirmed with esophageal biopsies demonstrating eosinophilic mucosal infiltration (eg, ≥15 eosinophils/hpf). If diagnosed early, EoE responds well to an elimination diet or topical glucocorticoids (eg, fluticasone, budesonide); stricture dilation may be required if there is no response to medical therapy.

Disordered oropharyngeal neuromuscular transmission can occur in ALS and multiple sclerosis. However, these disorders typically present with symptoms of oropharyngeal dysphagia (eg, coughing after eating, nasal regurgitation, aspiration) rather than esophageal food impaction.

Achalasia results from myenteric plexus degeneration, which causes incomplete relaxation of the lower esophageal sphincter. Patients with achalasia tend to present with progressively worsening dysphagia (solids and liquids), not a sudden food impaction.

Fibrosis and atrophy of esophageal smooth muscle occurs in systemic sclerosis; this leads to chronic, often severe GER and may result in strictures with food impaction. However, systemic sclerosis is expected to affect multiple organ systems; cutaneous (eg, skin thickening) and extracutaneous (eg, Raynaud phenomenon) findings would be expected.

Esophageal cancer can rarely cause food impaction, but it tends to affect elderly patients and presents with progressive dysphagia (from solids to liquids) and weight loss.
An elderly patient likely has overflow fecal incontinence due to fecal impaction. Fecal impaction is common in older patients with impaired mobility, inadequate fluid or dietary fiber intake, chronic constipation, or decreased sensation of stool in the rectal vault (eg, spinal cord injury, dementia). Urinary incontinence is also common due to pressure against the bladder.

The diagnosis of fecal impaction is typically apparent on DRE, although impaction in the proximal rectum may be apparent only on abdominal x-ray. Initial management includes manual disimpaction to break up the hard stool followed by enemas (eg, tap water, mineral oil) to dislodge the fecal fragments. Following acute treatment, a bowel regimen, including laxatives (eg, polyethylene glycol, lactulose) and dietary alterations (eg, increased intake of fluid and fiber), should be instituted.

Loperamide is used for symptomatic management of diarrhea.

Plain x-ray is the most appropriate initial imaging study for fecal impaction, when necessary. CT scan is useful for evaluating extrinsic intestinal compression, but it is not usually needed and would not be the first study.

Stool studies (eg, culture, microscopy for ova and parasites) are appropriate to evaluate for suspected infectious diarrhea, which presents with large-volume watery stools.
Anal manometry can provide information regarding anorectal neurologic dysfunction and is indicated for evaluation of chronic constipation and fecal incontinence. However, if the patient’s symptoms are likely attributable to known factors (ie, debilitation, opioid analgesics), and neurophysiologic studies are unlikely to add useful information. Disimpaction should be performed first.

AMBOSS

Treatment

- Identify and treat any underlying conditions (see differential diagnoses).
- **Approach in adults** [12]
  - Begin with lifestyle changes: high-fiber diet, increased fluid intake, and exercise
  - If constipation persists, start an osmotic laxative.
  - If osmotic laxatives are unsuccessful, add a stimulant laxative.
- **Approach in children** [9][3]
  - Infants 2 weeks to 6 months of age, without alarming features
    - May only require reassurance
    - Passage of stool is particularly variable in breastfed infants.
    - Parents who formula feed their children should be properly instructed on correct formula preparation.
    - Reassess in 2–4 weeks. [9]
    - If constipation persists, consider drug therapy (best initial: polyethylene glycol).
  - Children ≥ 6 months of age without suspected organic disease
    - Prompt laxative therapy (best initial: polyethylene glycol)
    - In combination with age-appropriate fiber, fluid, and physical activity requirements
    - Toilet training, if applicable
  - Maintenance therapy: laxative therapy (polyethylene glycol or lactulose) until constipation is resolved for at least 1 month (treatment should then be tapered gradually)
  - Further investigation to exclude an underlying disorder is warranted if there is a poor response to the treatments mentioned above or if constipation affects a child < 2 weeks of age.

Laxatives
<table>
<thead>
<tr>
<th>Class</th>
<th>Agent(s)</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Osmotic laxatives</strong></td>
<td>Polyethylene glycol (PEG): very effective and well-tolerated (best initial Tx)</td>
<td>Increase of osmotic pressure draws water into the intestinal lumen → stimulation of intestinal motility</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Glycerin</td>
<td>Lactulose is degraded by intestinal microbiota into lactic acid and acetic acid:</td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>Magnesium hydroxide</td>
<td>o Induces nitrogen (NH₄⁺) excretion</td>
<td>Magnesium salts: hypernatremia, hypermagnesemia</td>
</tr>
<tr>
<td></td>
<td>Magnesium citrate</td>
<td>o Used in the treatment of hepatic encephalopathy</td>
<td>Lactulose and sorbitol: severe flatulence</td>
</tr>
<tr>
<td></td>
<td>Lactulose</td>
<td></td>
<td>Osmotic laxative misuse is frequently seen in patients with bulimia nervosa</td>
</tr>
<tr>
<td></td>
<td>Sorbitol</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stimulant laxatives</strong></td>
<td>Senna</td>
<td>Stimulation of nitric oxide-mediated epithelial cell secretion of electrolytes into the colonic lumen</td>
<td>For short-term use only</td>
</tr>
<tr>
<td></td>
<td>Bisacodyl</td>
<td>Myenteric neuronal depolarization → colon contractions</td>
<td>Diarrhea: Stimulant laxatives may result in severe water and potassium loss.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Senna may result in <em>melanos</em> <em>t</em> * coli*.</td>
</tr>
<tr>
<td><strong>Emollient stool softeners</strong></td>
<td>Docusate</td>
<td>Emulsification (i.e., integration of water and fat) of stool → softening of stool → easier passage through the intestinal tract</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bloating, cramping</td>
</tr>
<tr>
<td><strong>Bulk-forming laxatives</strong></td>
<td>Methylcellulose: chemical compound derived from cellulose</td>
<td>Bulk-forming laxatives are <em>indigestible</em>, not systemically absorbed</td>
<td>Bloating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Soluble fibers increase water absorption in the intestinal lumen → stretching of the</td>
<td>Worsening constipation or ileus if the patient doesn’t take enough water with doses</td>
</tr>
</tbody>
</table>
Psyllium husks → stimulation of peristalsis
Polycarbophil

*Chronic laxative use may lead to dependency and/or hypokalemia, which can further reduce bowel motility!

**Complications**

- Fecal incontinence
- Fecal impaction
- Anal fissures
- Hemorrhoids
- Megacolon
- Urinary retention
- Pelvic floor damage in women

**Fecal impaction**

**Clinical features**

- Inability to defecate for days or weeks
- Normal bowel sounds
- Distended, tympanitic abdomen
- DRE: hard, impacted stools distending the rectum
- Tenesmus

**Diagnostics**

- Clinical diagnosis
- Abdominal x-ray (to rule out bowel perforation)
  - Findings:
    - Dilated bowel loops
    - Fecal shadows in the colon and rectum
    - Air-fluid levels may be visible.

**Treatment**

- Rule out bowel perforation.
- Manual disimpaction
• Administer osmotic enema (e.g., warm water enema or mineral oil enema).
• Consider the addition of stimulatory suppositories
• Prevention of recurrence
  o Start maintenance bowel regimen with osmotic laxative.
  o Stop contributing medications.
  o Lifestyle modifications
  o See treatment of constipation and laxatives.
• For severe cases, consult surgery.

**Opioid-induced constipation**

**Clinical features**

• Recent initiation of an opioid or dose adjustment
• New or worsening constipation
• Fecal impaction may be present
• Physical examination typically normal

**Diagnostics**

• Clinical diagnosis
• Rome IV diagnostic criteria for OIC
  o Recent initiation of opioid treatment or a dose increase
  o AND ≥ 2 of the characteristic clinical features of functional constipation:
    ▪ Passage of spontaneous bowel movement < 3 times/week
    ▪ Passage of hard or lumpy stool (more than 25% of defecations)
    ▪ Sensation of anorectal obstruction/blockage (more than 25% of defecations)
    ▪ Manual aid to evacuate stool necessary (more than 25% of defecations)
    ▪ Straining during attempts to defecate (more than 25% of defecations)
    ▪ Sensation of incomplete evacuation (more than 25% of defecations)
  o Loose stools are rarely present without the use of laxatives
• Consider x-ray of the abdomen to rule out fecal impaction

**Treatment**

• Similar to the treatment of primary constipation (see “Treatment” and “Laxatives” above)
Identify and treat any underlying organic cause.
- Lifestyle and dietary modification
- Evaluate the need for opiate therapy and discontinue/reduce dose if appropriate.
- Medical therapy
  - Laxative therapy
    - Osmotic laxative
    - and/or stimulant laxative
  - Options for laxative-refractory OIC:
    - Peripherally acting \( \mu \)-opioid receptor antagonists

*Discontinue any additional laxatives when initiating a peripherally acting \( \mu \)-opioid receptor antagonist.

**VITAMINS**

**Pellagra**: Pellagra ("rough skin" in Italian vernacular) is due to niacin deficiency and is characterized by the "3 Ds": dermatitis, diarrhea, and dementia:

- Dermatitis is primarily on sun-exposed areas of the body and is characterized by rough, hyperpigmented, scaly skin.
- Diarrhea is often associated with abdominal pain, nausea, and loss of appetite.
- Dementia is due to neuronal degeneration in the brain and spinal cord and can lead to memory loss, affective symptoms (eg, depressed mood in this patient), and psychosis.

Niacin is present in a broad variety of foods and can be synthesized endogenously from tryptophan. In developing countries, niacin deficiency is seen in populations that subsist primarily on corn products (niacin in corn occurs in a bound, unabsorbable form). In developed countries, it is primarily seen in patients with impaired nutritional intake (eg, alcoholism, chronic illness). Pellagra can also be seen occasionally in those with carcinoid syndrome (due to depletion of tryptophan) or Hartnup disease (congenital disorder of tryptophan absorption). Prolonged isoniazid therapy can interfere with metabolism of tryptophan and occasionally lead to pellagra.

......

AIP causes abdominal pain, vomiting, and diarrhea, often with neurologic symptoms (eg, agitation, paresthesias, confusion). Although AIP may be
triggered by isoniazid, the symptoms are episodic rather than chronic, chronic transaminase elevation is common, and it is more frequent in women than in men.

Isoniazid hypersensitivity can present as hives (maculopapular rash) with pruritus, fever, and hepatitis.

Seborrheic dermatitis is characterized by erythematous, scaly plaques affecting the scalp, face, chest, and intertriginous areas. It can be associated with dementia (eg, Parkinson disease). However, the hands are not typically affected, and it does not cause gastrointestinal symptoms.

SLE causes a photosensitive rash in a malar distribution. Central nervous system manifestations (eg, psychosis) can occur. Isoniazid can cause drug-induced lupus (eg, positive antinuclear antibodies) although rash is uncommon. With lupus, gastrointestinal involvement typically causes impaired motility, and diarrhea is not typical. In addition, this patient's diet makes pellagra more likely.

Ulcerative colitis (UC) causes bloody diarrhea as opposed to the watery diarrhea seen with pellagra. Although UC can have extraintestinal manifestations, associated skin findings include erythema nodosum and pyoderma gangrenosum, not scaly dermatitis.

### UGIB

Patients with upper (but not lower) GI bleeding often have an elevated blood urea nitrogen (BUN) and **elevated BUN/creatinine ratio**. Possible causes include increased urea production from intestinal breakdown of hemoglobin and increased urea reabsorption in the proximal tubule due to associated hypovolemia.

A patient has **upper gastrointestinal bleeding** with ongoing hematemesis and **altered mental status**. Given her history of cirrhosis and variceal band ligation, esophageal variceal hemorrhage is the most likely cause. Initial evaluation and management of patients with variceal hemorrhage should focus on maintaining adequate circulation, **preventing** and treating complications, and stopping the underlying cause of bleeding. Two large-bore catheters have been placed, crystalloid solution has been administered for volume resuscitation, and a packed red blood cell transfusion (which is indicated, despite a hemoglobin >7 g/dL, due to ongoing hemodynamic instability) is being prepared.

However, this patient's continued hematemesis (with clots) and depressed level of consciousness are a major risk for **aspiration**, which could quickly exacerbate her tenuous clinical status. While the patient awaits urgent endoscopic intervention, rapid sequence **endotracheal intubation** should
be performed to prevent airway compromise due to aspiration of blood. Intubation also assists gastroenterologists in performing an upper endoscopy, especially in patients unable to maintain their own airway.

Patients with cirrhosis and variceal bleeding should also receive prophylactic antibiotics to prevent spontaneous bacterial peritonitis and a somatostatin analog (eg, octreotide) to reduce variceal hemorrhage and improve hemostasis.

........

Although an abdominal x-ray can be very useful to identify gastrointestinal tract perforation (sudden, severe abdominal or chest pain, subcutaneous emphysema), it rarely provides helpful information in patients with gastrointestinal bleeding.

Diagnostic paracentesis could be considered at a later point to evaluate for spontaneous bacterial peritonitis, which can be a complicating factor in patients with cirrhosis and gastrointestinal hemorrhage. However, this is not as important as stabilizing the patient and attempting to stop the bleeding.

Nasogastric (NG) tube placement may help decompress the stomach and facilitate in the removal of blood for improved visualization prior to endoscopy. However, it is less important than securing the patient's airway and preventing a life-threatening complication.

Upper gastrointestinal endoscopy with variceal ligation or sclerotherapy is critical to stop this patient's variceal hemorrhage; however, in patients with significantly altered mental status and persistent hematemesis, it should be performed after the patient's airway is protected.
This patient has **minimal bright red blood per rectum (BRBPR)**. This symptom, characterized by small amounts of bright red blood on toilet paper after wiping, a few drops of blood in the toilet bowl after defecation, or small amounts of blood on the surface of the stool, is most often due to benign disorders such as **hemorrhoids** or rectal fissures. However, more serious disorders (eg, proctitis, rectal ulcers, colorectal polyps, cancer) are possible.

The evaluation of BRBPR depends on the patient's presentation and risk factors. Clinical factors associated with increased risk of serious disease include blood mixed with stool, systemic symptoms (eg, fever, weight loss), diarrhea, anemia, change in bowel habits, and abdominal pain. Age also correlates strongly with risk of malignancy in patients with BRBPR. Patients **age >50** are at elevated risk for colorectal cancer and should undergo **colonoscopy** unless they have had a normal colonoscopy within the last 2-3 years. Patients age 40-49 are at intermediate risk and could be considered for sigmoidoscopy as an alternative to colonoscopy. If the patient is **age <40** and has no other risk factors for colon cancer, office-based **anoscopy** or proctoscopy should be performed first. If no etiology is found, colonoscopy or sigmoidoscopy is then considered. Anoscopy is also useful in older patients to visualize a palpable abnormality found on physical examination.
Barium enema is occasionally used for colorectal cancer screening (often in addition to other procedures) in asymptomatic patients. It has low sensitivity for evaluating rectal bleeding.

This patient has gross blood confirmed on examination. Occult blood testing is not necessary.

**ANGIODYSPLASIA**

The clinical presentation of episodic **painless GI bleeding** suggests angiodysplasia. **Angiodysplasia** is characterized by dilated submucosal veins and AV malformations, and has an increased incidence **after age 60**. It may occur anywhere in the GI tract but is MC in the right colon. Angiodysplasia is more frequently diagnosed in patients with advanced **renal disease** and **vWD**, possibly due to the bleeding tendency associated with these disorders. Angiodysplasia may also be more common in patients with **aortic stenosis (AS)**, possibly due to acquired vW factor deficiency (from disruption of the vW multimers as they traverse the turbulent valve space induced by AS). Angiodysplastic bleeding has been reported to remit following aortic valve replacement.

Diagnosis of angiodysplasia is usually made on **endoscopic** evaluation (eg, upper GI endoscopy, colonoscopy). However, it is not uncommon for angiodysplasia to be missed on colonoscopy due to poor bowel preparation or location behind a haustral fold. Asx patients do not require treatment. Patients with anemia or gross or occult bleeding can be treated endoscopically, usually with **cautery**.

.............

**Colon cancer** can cause painless chronic bleeding. However, a cancer capable of causing gross bleeding (as seen in this patient) is unlikely to have been missed on colonoscopy and would likely have led to microcytic anemia (with mean corpuscular volume <80/µm³). It is more likely that angiodysplasia rather than colon cancer would be missed on colonoscopy.

**Diverticulosis** is also unlikely to have been missed on colonoscopy. In addition, bleeding from diverticula is frequently arterial, and typically results in passage of bright red blood. Maroon-colored stools are more characteristic of right colonic angiodysplasia.
**Hemorrhoids** cause bright red rectal bleeding, with blood on the surface of the stool or dripping into the toilet. They are usually apparent on rectal examination or during colonoscopy.

**Ischemic colitis** usually presents with sudden onset of abdominal pain and tenderness followed by rectal bleeding or bloody diarrhea within 24 hours.

**CHRONIC MESENTERIC ISCHEMIA (CMI)**

This patient with a history of vascular disease most likely has **chronic mesenteric ischemia** (CMI). CMI commonly presents with crampy, postprandial epigastric pain (intestinal angina), food aversion, and weight loss. Patients may also report N, D, and early satiety. The anginal pain frequently starts **within the FIRST HOUR** of eating and slowly resolves over the next 2 hours. The pathophysiology of the pain is most likely related to shunting of blood away from the small intestine to meet the increased demand of the stomach. In patients with **atherosclerosis**, the celiac or the superior mesenteric arteries may be narrowed and unable to dilate appropriately to maintain adequate blood flow to the intestines.

<table>
<thead>
<tr>
<th>Chronic mesenteric ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td>• Atherosclerosis (smoking, dyslipidemia)</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
</tr>
<tr>
<td>• Crampy, postprandial, epigastric pain</td>
</tr>
<tr>
<td>• Food aversion &amp; weight loss</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
</tr>
<tr>
<td>• Signs of malnutrition, abdominal bruit</td>
</tr>
<tr>
<td>• CT angiography (preferred), Doppler ultrasonography</td>
</tr>
<tr>
<td><strong>Management</strong></td>
</tr>
<tr>
<td>• Risk reduction (eg, tobacco reduction), nutritional support</td>
</tr>
<tr>
<td>• Endovascular or open surgical revascularization</td>
</tr>
</tbody>
</table>

Physical examination may show signs of **malnutrition** and may reveal an **abdominal bruit** in ~50% of patients, but can be otherwise unremarkable. Although abdominal x-ray and CT scans may demonstrate calcified vessels, diagnosis requires better visualization of the vessels. **CT angiography** is the preferred choice, although **Doppler USG** may also be helpful.

Treatment involves risk reduction (eg, tobacco cessation), nutritional support, and revascularization.

**Biliary colic:** The pain is often localized to the RUQ and **does not occur after every meal**. Significant weight loss is very rare.
Ventricular aneurysms (scarred myocardium following transmural myocardial infarction) predispose to **acute** mesenteric ischemia (rather than CMI) due to thrombus formation and embolization. The presentation of acute mesenteric ischemia is abrupt, with severe abdominal pain out of proportion to examination findings. Both in pathophysiology and acuity, acute mesenteric ischemia is analogous to acute myocardial infarction whereas CMI is similar to stable cardiac angina.

Pain accompanied by malabsorption may be due to chronic pancreatitis or Crohn disease (transmural intestinal inflammation). However, these diseases frequently produce abnormal CT scan and x-ray findings (e.g., pancreatic calcifications). In addition, if the patient does not have risk factors for pancreatitis (e.g., heavy alcohol use) it makes the dx unlikely. Crohn disease generally presents at an earlier age and usually causes RLQ pain.

### ACUTE LIVER FAILURE

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Acute liver failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis (e.g., HSV; CMV; hepatitis A, B, D &amp; E)</td>
<td></td>
</tr>
<tr>
<td>Drug toxicity (e.g., acetaminophen overdose, idiosyncratic)</td>
<td></td>
</tr>
<tr>
<td>Ischemia (e.g., shock liver, Budd-Chiari syndrome)</td>
<td></td>
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<tr>
<td>Autoimmune hepatitis</td>
<td></td>
</tr>
<tr>
<td>Wilson disease</td>
<td></td>
</tr>
<tr>
<td>Malignant infiltration</td>
<td></td>
</tr>
</tbody>
</table>

| Clinical presentation                                                  |                     |
| Generalized symptoms (e.g., fatigue, lethargy, anorexia, nausea)       |                     |
| Right upper quadrant abdominal pain                                    |                     |
| Pruritus & jaundice due to hyperbilirubinemia                          |                     |
| Renal insufficiency                                                    |                     |
| Thrombocytopenia                                                       |                     |
| Hypoglycemia                                                           |                     |

| Diagnostic requirements                                                |                     |
| Severe acute liver injury (ALT & AST often >1000 U/L)                  |                     |
| Signs of hepatic encephalopathy (e.g., confusion, asterixis)           |                     |
| Synthetic liver dysfunction (INR ≥1.5)                                  |                     |

**ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **CMV** = cytomegalovirus; **HSV** = herpes simplex virus.

The presence of HE differentiates ALF from acute hepatitis, which has a much better prognosis than ALF. In addition to varying degrees of HE, other common manifestations of ALF include fatigue, lethargy, nausea, vomiting, jaundice, pruritus, and right upper quadrant pain.

Chronic HBV carriers, such as this patient, typically remain asymptomatic without evidence of underlying liver disease (e.g., fibrosis). In the presence of HBV, acute **superinfection** with **HDV**
carries a high risk of ALF development, particularly in intravenous drug users.

Features of liver cirrhosis include fluid retention, jaundice, caput medusae, palmar erythema, muscle wasting, and gynecomastia. ALF includes some of these features (e.g., jaundice, fluid retention), but it is characterized by acute liver injury in a patient without cirrhosis.

This patient has **acute liver failure (ALF)** likely due to **acetaminophen toxicity** in the setting of chronic alcohol use. Diagnosis of ALF requires the triad of **elevated aminotransferases** (markedly elevated in this patient), signs of **hepatic encephalopathy** (confusion, somnolence, and flapping tremor consistent with asterixis in this patient), and **synthetic liver dysfunction** (evidenced by INR >1.5). Cirrhosis or underlying liver disease should not be present.

Acetaminophen toxicity is the most common cause of ALF in many developed countries and can be seen in intentional overdose (suicide attempt) or accidental overdose in patients taking multiple sources of acetaminophen (such as this patient). Toxicity results from overproduction of the toxic metabolite **N-acetyl-p-benzoquinone imine (NAPQI)**, which leads to hepatic necrosis. NAPQI is normally safely detoxified through **glucuronidation** in the liver, but this pathway becomes overwhelmed in overdose. **Chronic alcohol use** is thought to potentiate acetaminophen hepatotoxicity by depleting glutathione levels and impairing the glucuronidation process. On the other hand, **N-acetylcysteine** increases glutathione levels and binds to NAPQI, so it is an effective antidote for acetaminophen overdose when given early.

**Acute renal insufficiency** is common in ALF, especially when acetaminophen induced, due to the drug's direct renal tubular toxicity. **Hyperbilirubinemia** is common as well, but acetaminophen hepatotoxicity is characterized by relatively low serum bilirubin compared with that in other etiologies of ALF.

Acute alcoholic hepatitis typically causes mild to moderate aminotransferase elevation (<500 U/L) in patients who drink heavily (>100 g/day). The AST/ALT ratio is usually >2:1.

HCV causes chronic hepatitis and may lead to cirrhosis but is not typically associated with ALF. Hepatitis A, B, D, and E are more typical causes of ALF.
Ischemic hepatitis can result from severe hypotension (eg, shock liver) or Budd-Chiari syndrome (hepatic vein thrombosis) and is a potential cause of ALF. This patient has not had significant hypotension and lacks right upper quadrant pain, which is typically severe in Budd-Chiari syndrome.

Nonalcoholic steatohepatitis (NASH) is a chronic condition that is associated with metabolic syndrome and may lead to liver cirrhosis. Both nonalcoholic steatohepatitis and cirrhosis are characterized by normal to moderately elevated aminotransferase levels, and elevation >1000 U/L is not consistent with either diagnosis.

This patient has **acute liver failure (ALF)** due to **acetaminophen toxicity**. ALF is defined as severe acute liver injury without underlying liver disease and is characterized by elevated aminotransferases (often >1,000 U/L), **hepatic encephalopathy**, and **synthetic liver dysfunction** (defined as **prolonged prothrombin time [PT]** with INR >1.5). Approximately only half of patients with ALF will survive without **liver transplantation**. Reliable indicators of worsening ALF include rising serum bilirubin and PT, as seen in this patient. Acute renal insufficiency, likely due to decreased renal perfusion, is common and portends a lower chance of recovery without liver transplantation. The degree of hepatic encephalopathy is also of prognostic importance as grade III hepatic encephalopathy (characterized by marked confusion and incoherence) is associated with an only 40%-50% chance of spontaneous recovery. **Cerebral edema** is a potential complication of ALF that may lead to coma and brain stem herniation, and is the most common cause of death.

The ethical considerations are complicated regarding liver transplantation for ALF due to a suicide attempt; however, in a patient with reactive depression and no history of psychiatric illness or previous suicide attempt, liver transplantation is typically pursued if needed. In ALF due to acetaminophen toxicity, liver transplantation is firmly indicated in patients with grade III or IV hepatic encephalopathy, PT >100 seconds, and serum creatinine >3.4 mg/dL (as in this patient). One-year survival following liver transplantation for ALF is approximately 80%.

Liver biopsy is sometimes helpful in ALF of unclear etiology. This patient's ALF is due to acetaminophen toxicity and his condition is worsening. Close monitoring alone would not be appropriate, and liver biopsy is unlikely to prevent the need for liver transplantation.
This patient’s prolonged PT reflects coagulopathy due to ALF rather than due to vitamin K deficiency (often seen in patients with malnutrition). As a result, vitamin K supplementation will have limited effect on this patient’s coagulopathy.

Glucocorticoids are generally not indicated in ALF as they increase the risk of infection and have not demonstrated benefit in most etiologies of ALF. They may provide benefit in alcoholic hepatitis and in ALF due to autoimmune hepatitis.

| DRUG-INDUCED LIVER INJURY | Acute hepatitis w/ negative serologies → non-infectious more likely. INH can cause an idiosyncratic liver injury with a histological picture similar to viral hepatitis must be considered. Although extrahepatic hypersensitivity manifestations like rash, arthralgias, fever, leukocytosis, and eosinophilia are common in patients with drug-induced liver injury, they are characteristically absent in cases of isoniazid-induced hepatic cell injury. Drugs and toxins typically cause hepatic injury, either through direct toxic effects or through idiosyncratic reactions. The direct toxic effects are dose-dependent and have short latent periods. Examples of direct toxins include acetaminophen and substances found in the *Amanita phalloides* mushroom. Idiosyncratic reactions are not dose-dependent and have variable latent periods. Some examples of pharmacological agents that cause idiosyncratic reactions include isoniazid, chlorpromazine, and antiretroviral therapy. Drug-induced liver disease can also be broadly categorized according to morphology: cholestasis (eg, anabolic steroids), fatty liver (eg, valproate), hepatitis (e.g., INH), toxic or fulminant liver (eg, acetaminophen), or granulomatous (eg, allopurinol).

Oral contraceptives are unusual in that they can cause abnormalities in liver function tests without evidence of necrosis or fatty change. |
| HEPATITIS | **Ischemic hepatitis:** Ischemic hepatic injury, or shock liver: The hallmark of ischemic hepatopathy is a rapid and significant increase in the transaminases with modest accompanying elevations in total bilirubin and alkaline phosphatase. AST and ALT levels peak at 25 to 250 times the upper limit of normal and can reach >10,000 U/L. This reflects diffuse liver injury due to hypotension; as a result of the liver’s dual blood supply, diffuse injury is more common than focal infarction. In patients who survive the underlying cause of their hypotension (eg, septic shock, heart failure), liver enzymes typically return to normal within 1-2 weeks. |
Alcoholic liver disease typically causes less dramatic increases in the transaminases compared to those seen in this patient. The AST/ALT ratio is usually ~2, and the AST is rarely >300 units/L.

Granulomatous disorders (eg, tuberculosis, sarcoidosis) rarely cause massive transaminase elevations. Chronic hepatic damage is occasionally associated.

Iron overload may cause chronic hepatic dysfunction with low-grade elevations in the AST and ALT. Transfusion of 4 units of packed red blood cells would be unlikely to cause iron overload.

Autoimmune hepatitis may cause large increases in the AST and ALT. However, young women are more commonly affected, and the associated serum bilirubin increases are typically more dramatic.

### Clinical features of alcoholic hepatitis

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Laboratory/imaging studies</th>
</tr>
</thead>
</table>
| • Jaundice, anorexia, fever  
• Right upper quadrant &/or epigastric pain  
• Abdominal distension due to ascites  
• Proximal muscle weakness from muscle wasting (if malnourished)  
• Possible hepatic encephalopathy | • Elevated AST & ALT, usually <300 U/L  
• AST:ALT ratio ≥2  
• Elevated gamma-glutamyltransferase, bilirubin, &/or international normalized ratio  
• Leukocytosis, predominantly neutrophils  
• Decreased albumin if malnourished  
• Abdominal imaging may show fatty liver |

**Alcoholic hepatitis:** There is no evidence of ascites or cirrhosis (eg, spider angiomas, gynecomastia, asterixis). In addition, there would be no weight loss or systemic symptoms to suggest malignancy, and there are no signs of infection.

Alcoholic liver disease is generally characterized by modest elevations in AST and ALT, usually <300 IU/L and almost always <500 IU/L. A ratio of **AST to ALT >2** (thought to be due to hepatic deficiency of pyridoxal 5’-phosphate, an ALT enzyme cofactor) is very common in alcoholic liver
disease (>90% in one study). However, it is rarely seen with other forms of liver disease, in which ALT is typically higher than AST. This can be used as an important diagnostic marker. There is no correlation between the degree of elevation and liver disease severity.

Elevations in GGT, an enzyme present in liver and other cells, and in ferritin, an acute phase reactant, would likely be seen in alcoholic liver disease.

Macrocystic anemia, thrombocytopenia, and mild elevation in the INR. Alcohol use should be confirmed and quantified by first obtaining the patient's social history and discussing substance use. Patients with AH commonly have a history of chronic, heavy alcohol use (>7 drinks/day) and sometimes develop AH symptoms after an acute increase in consumption.

Methotrexate could cause elevated MCV, bone marrow suppression (anemia, thrombocytopenia), and liver function test abnormalities; however, an AST:ALT ratio ≥ 2:1 makes AH more likely.

Diagnosis is clinical and often does not require further studies in patients with consistent history and laboratory results. Patients with risk factors for diseases such as acute viral hepatitis require further investigation. Radiographic imaging may reveal fatty liver disease, cirrhosis, or ascites. Treatment involves abstinence, supportive care (eg, hydration and nutrition support), and acid suppression. Liver biopsy can be helpful if there is diagnostic uncertainty.

If marked elevations (>25 times the upper limit) of AST and ALT are present, toxin-induced (eg, acetaminophen), ischemic, or viral hepatitis should be suspected.

<table>
<thead>
<tr>
<th>AUTOIMMUNE HEPATITIS (AIH)</th>
<th>Autoimmune hepatitis</th>
</tr>
</thead>
</table>
| **Presentation** | • Asymptomatic  
  ○ Identified by abnormal LFTs  
• Symptomatic  
  ○ Fatigue, anorexia, nausea, jaundice  
  ○ Can progress to fulminant liver failure &/or cirrhosis  
• Often associated with other autoimmune disorders (eg, vitiligo, autoimmune thyroiditis, celiac disease) |
| **Laboratory findings** | • Hepatocellular pattern (↑↑ AST & ALT)  
• Hypergammaglobulinemia  
• Elevated autoantibodies |
This woman with persistent asymptomatic elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and a large gamma gap (total protein – albumin = >4 g/dL) has **autoimmune hepatitis** (AIH). AIH is thought to be triggered by environmental exposure in susceptible individuals; it occurs most commonly in **women** with comorbid autoimmune disease (eg, autoimmune thyroiditis, vitiligo).

The initial presentation is variable, with most patients presenting with constitutional symptoms (eg, fatigue, weight loss), abdominal pain, pruritus, and, possibly, cirrhosis (eg, jaundice, ascites). However, approximately 25% are **asymptomatic** and identified by routine blood work demonstrating a **hepatocellular pattern** of liver injury, with predominant **elevations in AST and ALT** and normal or mildly elevated alkaline phosphatase and bilirubin. High levels of autoantibodies (typically IgG) result in hypergammaglobulinemia and a **gamma gap**, a helpful characteristic feature (not seen in all cases). Positive serology (eg, anti–smooth muscle, anti–liver/kidney microsomal type 1, antinuclear antibodies) or hypergammaglobulinemia confirms the diagnosis.

----------

Alcoholic hepatitis also causes a hepatocellular pattern of injury, but an AST/ALT ratio of >2:1 is expected, and transaminases rarely exceed 300 U/L. In addition, patients typically have heavy alcohol use (5 or 6 drinks/day), fever, and jaundice. A gamma gap would be atypical.

Alpha1-antitrypsin deficiency (AATD) is an autosomal codominant condition leading to emphysema (typically presenting in patients in their 40s) and liver disease (eg, chronic hepatitis, cirrhosis). This patient does not have manifestations of emphysema (eg, cough, dyspnea) or a family history of liver disease, and a protein gap would not occur with AATD.

Although amlodipine can cause hepatotoxicity, this adverse effect is exceedingly rare, typically develops within weeks to months (rather than...
after >5 years), and is generally associated with a cholestatic pattern. An elevated gamma gap would not occur.

Hepatitis A causes a hepatocellular pattern of injury, but it typically presents with vomiting, fever, and abdominal pain; transaminases are generally >1,000 U/L and would be expected to normalize after 3 months.

Primary biliary cholangitis is an autoimmune disorder characterized by elevated antimitochondrial antibodies. Although PBC can be asymptomatic and mild AST and ALT elevation can be seen, a cholestatic picture is expected, with marked elevations in alkaline phosphatase (≥1.5x the upper limit of normal).

**HCV**

Chronic HCV infection is frequently asx, and many patients have only minimal laboratory abnormalities. Screening for HCV infection should be performed in selected populations (eg, history of IVDU).

Despite the introduction of direct-acting antiviral agents (eg, sofosbuvir-velpatasvir), which have dramatically improved the ability to achieve virologic cure, HCV management continues to involve strategies to prevent further liver damage. These strategies include alcohol avoidance and HAV and HBV vaccination (if the pt isn’t immunized).

Patients with HCV should also be evaluated to determine the presence of cirrhosis and, when appropriate, other associated risk factors (eg, esophageal varices).

Patients with evidence of cirrhosis and ascites should be started on a diuretic regimen to improve quality of life and minimize complications such as SBP.

Lamivudine (3TC) is a RTI sometimes used to treat HIV and chronic HBV co-infection.

Prednisolone is used to treat severe alcoholic hepatitis, which typically presents with fever, abdominal pain, jaundice, N, and V.

Weight loss is important for HCV patients overall health and is especially helpful in managing patients with NAFLD. However, in patients with HCV infection, vaccination for HAV and HBV is a mainstay of treatment that should be pursued first.

**AMBOSS:**

**Treatment**

**Acute hepatitis C**

- **Goal:** prevent transition to chronic infection!
**Treatment:** IFN-α or peginterferon-α (PEG-INF-α) for 6 months

*There is no post-exposure prophylaxis available!*

### Chronic hepatitis C

#### Treatment goals
- Complete cure
- Eradication of HCV RNA in serum as defined by SVR (sustained virologic response)

#### Treatment regimens
- Chosen based on viral genotype, history of antiviral treatment, and degree of liver fibrosis
- Combination of two **direct-acting antivirals** (DAAs)
  - **Ledipasvir + sofosbuvir** for 12 weeks (genotypes 1, 4, 5, 6)
  - **Sofosbuvir + velpatasvir** for 12 weeks (all 6 genotypes)
- Interferon + ribavirin
  - May be used in the treatment of genotypes 2 and 3
  - Interferon-based treatment is still used for cases of treatment failure.
  - Ribavirin on its own may be combined with DAAs to increase antiviral activity.
- In addition to any treatment regimen, give **vaccinations for hepatitis A and B**

*IFN and ribavirin are associated with severe side effects and teratogenicity!*

### Complications
- Rarely fulminant hepatitis (liver failure)
- Liver cirrhosis
- Hepatocellular carcinoma
- Secondary hemochromatosis

### Special patient groups

#### Considerations in pregnancy
- **Vertical transmission** approx. 3–5%
  - C-section does not lower risk of transmission
  - Avoid amniocentesis or the use of fetal scalp electrode (↑ risk)
  - HCV-infected patients may breastfeed as normal
- **Postpartum treatment**
Currently available medication regimens are contraindicated
Give the infant vaccinations for hepatitis A and B

**HBV**

A patient’s new-onset symptoms (eg, fatigue, nausea/abdominal pain, dark urine) and abnormal liver function tests (eg, elevated serum transaminases, hyperbilirubinemia) in the setting of unprotected sex with multiple partners is concerning for **acute hepatitis B infection**. The first serologic marker to appear in the serum with acute hepatitis B is HBsAg, which appears usually 4-8 weeks after infection. IgM anti-HBc appears shortly thereafter, which is around the time clinical symptoms occur and patients develop elevations in hepatic aminotransferase levels (often >25 times the normal limit).

There can be a time lag (weeks to months) between the disappearance of HBsAg and the appearance of anti-HBs, which is termed the **window period**. IgM anti-HBc may be the only detectable marker for acute hepatitis B infection during this period. As such, HBsAg and anti-HBc are the most appropriate diagnostic tests for acute hepatitis B infection as
these are both elevated during initial infection and anti-HBc will remain elevated during the window period.

HBcAg is not detectable in serum and is therefore not useful for establishing the diagnosis.

HBeAg is a good indicator of infectivity but is a poor test for acute hepatitis B infection as levels typically fall early in the course of the disease.

Testing for HBsAg and anti-HBs can miss the diagnosis of acute hepatitis B infection in patients who are in the window period.

Although hepatitis B virus DNA may be detectable prior to the appearance of HBsAg or HBeAg, this test is generally not performed to diagnose acute infection. Instead, hepatitis B virus DNA is obtained in patients with chronic hepatitis B to determine candidacy for antiviral therapy or monitor response to treatment.

A patient's serologic test results are consistent with resolved hepatitis B virus (HBV) infection. Individuals who are immune to HBV due to natural infection are positive for anti-HBs and negative for HBsAg. They are also positive for IgG anti-HBc because they form antibodies directed against the HBV core antigen. The HBV vaccine contains HBsAg, which stimulates production of anti-HBs and confers immunity in the host. However, the vaccine does not contain the core antigen so antibodies are not made against it and patients are consequently anti-HBc negative.

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>HBeAg</th>
<th>IgM anti-HBc</th>
<th>IgG anti-HBc</th>
<th>Anti-HBs</th>
<th>Anti-HBe</th>
<th>HBV DNA</th>
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<tbody>
<tr>
<td><strong>Acute HBV</strong></td>
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<td><strong>Early phase</strong></td>
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<td>++ +</td>
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<td><strong>Window phase</strong></td>
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<tr>
<td><strong>Recovery phase</strong></td>
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<td>Like +</td>
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<tr>
<td>Chronic HBV carrier</td>
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<tr>
<td>Acute flare of chronic HBV</td>
<td>+</td>
<td>Likely +</td>
<td>+</td>
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<tr>
<td>Vaccinated for HBV</td>
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<td>Immune due to natural HBV infection</td>
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</table>

- **anti-HBc** = hepatitis B core antibody; **anti-HBe** = hepatitis B e antibody; **anti-HBs** = hepatitis B surface antibody; **HBeAg** = hepatitis B e antigen; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus.

Serological markers for the hepatitis B virus include the following:

- **HBsAg**: The first serologic marker detected in the serum after inoculation. It precedes the onset of clinical symptoms and elevation of serum aminotransferases. It also remains detectable during the entire symptomatic phase of acute hepatitis B and suggests infectivity.

- **Anti-HBs**: Appears in the serum after either successful HBV vaccination or clearance of HBsAg, and remains detectable for life in most patients. It indicates non-infectivity and immunity. However, there is a time lag between the disappearance of HBsAg and the appearance of anti-HBs; this is termed the "window period."

- **HBeAg**: This antigen is detectable shortly after the appearance of HBsAg and indicates active viral replication/infectivity. It is associated with the presence of HBV DNA. HBeAg tends to
disappear shortly after aminotransferase levels peak and before HBsAg is eliminated; it is followed by the appearance of anti-HBe.

- **Anti-HBe**: This marker suggests cessation of active viral replication and low infectivity.

......

Acute hepatitis B infection is characterized by the presence of HBsAg and IgM anti-HBc. In contrast, chronic hepatitis B infection is defined by the presence of HBsAg in the serum for >6 months.

The recovery phase of hepatitis B infection is characterized by the presence of anti-HBs, anti-HBc (predominantly IgG), and anti-HBe.

**AMBOSS**

**Treatment**

**Acute hepatitis B**
- Supportive care
- For treatment of acute liver failure, see "Complications" below

**Chronic hepatitis B**
- **Antiviral treatment**
  - Indication: chronic active hepatitis B (see “Diagnostics” above) with evidence of liver inflammation (ALT ≥ 2 times upper limit) or cirrhosis
  - Goals
    - Reduce HBV DNA below detectable levels
    - Seroconversion of HBeAg to anti-HBe
    - Reverse liver disease
  - Nucleoside/nucleotide analogs: indicated for patients with both decompensated and compensated liver disease and nonresponders to interferon treatment
- Tenofovir is commonly the drug of choice
- Entecavir
  - Pegylated interferon alfa (PEG-IFN-a): especially in younger patients with compensated liver disease
  - Regimen is shorter than nucleoside/nucleotide analogs
- Contraindications
  - Decompensated cirrhosis
  - Psychiatric conditions
  - Pregnancy
  - Autoimmune conditions
  - Leukopenia or thrombocytopenia
- Coinfection with HDV is best treated with PEG-IFN-a.

- **Surgical treatment**
  - Liver transplantation
    - In cases of end-stage liver disease due to HBV
    - In cases of fulminant hepatic failure (emergent transplantation)

### Complications

**Hepatitis D virus infection**
- Epidemiology: 5% of all chronically infected HBV patients are carriers of the hepatitis D virus.
- Pathogen: Hepatitis D virus (HDV)
  - Incomplete viral particle resembling a viroid
  - Defective single-stranded RNA virus
  - Utilizes the HBsAg coat of HBV for propagation
- Transmission: sexual, parenteral, perinatal (only possible in combination with HBV)
- Course
  - Coinfection: more severe acute hepatitis, but 90% rate of convalescence
  - Superinfection of a chronic HBsAg carrier: ↑ risk of liver cirrhosis
  - In rare cases, fulminant hepatitis

**Acute liver failure**
- **Definition:** rapidly worsening liver function resulting in coagulopathy and hepatic encephalopathy
  - Fulminant liver failure: onset of hepatic encephalopathy within 8 weeks of initial symptoms (e.g., jaundice)
  - Subacute liver failure: onset within ≤ 26 weeks
- **Etiology**
  - Drugs/toxins
- Acetaminophen toxicity (most common)
  - Phenytoin, halothane, isoniazid
  - *Amanita phalloides*
  - Aflatoxin
  - Further risk factors: alcohol, cocaine
    - Viral hepatitis: hepatitis A, B, E, or B + D, CMV
    - Vascular disorders: Budd-Chiari syndrome, ischemic hepatitis
    - Pregnancy-related: HELLP syndrome, acute fatty liver of pregnancy
    - Others: autoimmune hepatitis, Wilson's disease
- **Clinical features**
  - Jaundice
  - Signs of hepatic encephalopathy: altered mental state, asterixis
  - Symptoms of cerebral edema: nausea, vomiting, confusion
- **Diagnostics**
  - Laboratory findings: ↑ PT with INR ≥ 1.5, often ↑↑ ALT and AST, ↑ bilirubin level, and platelet count ≤ 150,000/mm³
  - Further diagnostics: depending on the suspected underlying cause
    - Viral serologies
    - Toxicology screening (e.g., acetaminophen level)
    - Autoimmune hepatitis serology
    - RUQ abdominal ultrasound
- **Treatment**
  - Early transfer to a liver transplant center
  - Intravenous N-acetylcysteine
  - Address/prevent complications: e.g., cerebral edema, encephalopathy, coagulopathy, renal failure, and infection
  - Address underlying cause: e.g., antiviral treatment for hepatitis B, steroids for autoimmune hepatitis, or delivery for HELLP syndrome
  - Liver transplantation is the only therapeutic option for patients without sufficient regeneration of hepatocytes.
- **Prognosis:** The mortality rate without liver transplantation ranges from 30% (acetaminophen toxicity) to 80% (non-acetaminophen-related liver failure).

**Long-term complications of hepatitis B**
- Liver cirrhosis
- Hepatocellular carcinoma (HCC)
- Reactivation of previous HBV infection due to immunosuppression
Prevention

- **Pre-exposure vaccination:** recommended for all unvaccinated individuals (see immunization schedule)
- **Post-exposure prophylaxis (PEP) for hepatitis B**
  - Goal: prevention of HBV infection
  - Indication: exposure to HBV (e.g., percutaneous, ocular, mucosal)
  - Administration
    - Documented vaccine responder with HBsIgG ≥ 10 mIU/mL: no intervention needed
    - Documented non-responder: Administer two doses of hepatitis B immune globulin (HBIG) separated by 1 month
    - Unvaccinated individuals or incompletely vaccinated: simultaneous administration of hepatitis B immune globulin (HBIG) and hepatitis B vaccine (see also perinatal hepatitis B) and completion of original vaccination series
    - Vaccinated with 3 doses of hepatitis B vaccine but postvaccination anti-HBs status is unknown or anti-HBs <10 mIU/mL:
      - 1 dose of HBIG and
        - Administration of 3 consecutive doses of the hepatitis B vaccine and retest of anti-HBs level or alternatively
        - Administration of 1 dose of the vaccine and retest for anti-HBs in 1-2 months and if needed 2 additional doses and then retest anti-HBs level.

Special patient groups

**Perinatal hepatitis B**

Whereas maternal hepatitis B infections rarely cause fetal complications during pregnancy, the risk of perinatal transmission is high, especially if the maternal viral load is increased. If an infant becomes infected, the risk of developing chronic hepatitis is 90%.

- Maternal screening for HBsAg should be performed on all women at the first prenatal visit.
- Management for HBsAg-positive mothers
  - In mild disease and/or low HBV DNA levels, therapy may be delayed until after birth
  - In severe disease (e.g., cirrhosis) and/or high HBV DNA, therapy with nucleoside/nucleotide analogs (especially tenofovir) is commonly recommended
- Delivery: spontaneous vaginal delivery possible
  - Newborn immunization: within 12 hours of birth (first dose of hepatitis B vaccine series plus 1 dose of HBIG)
  - Breastfeeding: allowed as long as passive-active postexposure prophylaxis was given
  - Infected newborns:
    - Usually asymptomatic, but up to 90% risk developing chronic infection and significant risk of cirrhosis and progression to hepatocellular carcinoma if left untreated
    - Serum studies:
      - Normal or only slightly elevated transaminases
      - High viral replication rate

*Interferon therapy is contraindicated during pregnancy!

<table>
<thead>
<tr>
<th>WILSON DISEASE</th>
<th>Wilson disease</th>
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<tbody>
<tr>
<td><strong>Pathogenesis</strong></td>
<td>• AR mutation of ATP7B → hepatic copper accumulation → leak from damaged hepatocytes → deposits in tissues (eg, basal ganglia, cornea)</td>
</tr>
<tr>
<td><strong>Clinical findings</strong></td>
<td>• Hepatic (acute liver failure, chronic hepatitis, cirrhosis) • Neurologic (parkinsonism, gait disturbance, dysarthria) • Psychiatric (depression, personality changes, psychosis)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>• ↓ Ceruloplasmin &amp; ↑ urinary copper excretion • Kayser-Fleischer rings • ↑ Copper content on liver biopsy</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>• Chelators (eg, D-penicillamine, trientine) • Zinc (interferes with copper absorption)</td>
</tr>
</tbody>
</table>

The combination of liver disease (eg, elevated liver enzyme results) and neuropsychiatric symptoms (eg, tremors, involuntary movements) in a young adult is highly suggestive of Wilson disease (WD, hepatolenticular degeneration), a rare, AR disease most often identified in individuals age 5-35. It results from impaired copper transportation with resultant accumulation in tissues, including the liver and brain. In younger patients, liver disease predominates, whereas neurologic symptoms are more prominent in older patients.

Liver dysfunction ranges from asymptomatic liver function abnormalities to hepatitis to cirrhosis. Neuropsychiatric symptoms include parkinsonism, dysarthria, choreoathetosis, ataxia, personality changes, and depression. The diagnosis is suggested by low serum ceruloplasmin with increased urinary copper excretion or Kayser-Fleischer rings (golden brown or greenish rings encircling the iris).
Treatment focuses on removing accumulated copper and preventing re-accumulation. First-line medications include copper chelators (eg, D-penicillamine, trientine). **Oral zinc**, which interferes with copper absorption, may be used for **maintenance therapy**. For patients with fulminant hepatic failure or drug-resistant disease, liver transplantation is curative.

A1ATD can result in obstructive lung disease, liver dysfunction (eg, cirrhosis), and **skin disease**. Patients who smoke are at very high risk of early onset emphysema.

Hemochromatosis is characterized by iron overload. Common clinical manifestations include liver disease, hyperpigmentation, DM, arthropathy, and **cardiac enlargement**.

Huntington disease is a genetic disorder with marked neuropsychiatric manifestations such as chorea, parkinsonism, dementia, and personality changes. Symptom onset usually occurs in midlife.

Multiple system atrophy describes a series of neuromotor disorders that share a common set of symptoms, including parkinsonism, urogenital dysfunction (eg, erectile dysfunction), autonomic dysfunction (eg, orthostatic hypotension), and ataxia.

Serotonin syndrome most commonly occurs within the first 24 hours of starting or adjusting the dose of a medication with serotonergic activity. It is associated with autonomic instability, agitation, diaphoresis, hyperreflexia, clonus, and rigidity.

**Treatment**

**General management**

- Low-copper diet: avoid foods such as **organs, shellfish, nuts, and chocolate**
- Regular check-ups: liver biochemical tests every 6 months if disease is stable
- Liver transplantation in cases of fulminant liver failure

**Medical therapy**

- **Initial therapy: chelating agents**
  - Penicillamine: side effects in ~ 30% of cases (e.g., sensitivity reactions)
  - Alternatives: trientine or zinc salts
- **Maintenance therapy: zinc salts** or low dose chelating agents
<table>
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<tr>
<th><strong>Treatment with a chelating agent should be administered gradually over the course of 3 to 6 months, as mobilizing the copper stored in tissues too rapidly may exacerbate neurological symptoms!</strong></th>
</tr>
</thead>
</table>

**LIVER METASTASIS**

This patient— with abdominal pain, microcytic anemia, positive fecal occult blood, and hepatomegaly with a hard edge on liver palpation—has typical features of gastrointestinal malignancy, likely colon cancer, metastatic to the liver. The liver is the most common site of metastasis in colon cancer. The moderate abnormalities in hepatic markers in this case (elevated alkaline phosphatase and slightly elevated aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) are more suggestive of infiltrative or cholestatic disease than of hepatocellular injury. The patient also has a small pleural effusion on the left that may be malignant. (Hepatic hydrothorax due to cirrhosis usually occurs on the right.) This patient should have a CT of the abdomen with intravenous contrast to evaluate for malignancy.

*******

In alcoholic cirrhosis, the liver is often shrunken and the edge is not palpable. Also, in hepatocellular injury due to alcohol, AST is characteristically greater than ALT, usually by a multiple of 1.5-2.0.

Autoimmune hepatitis is typically seen in young to middle-aged women and may present as acute or chronic hepatitis. There is significant hepatocellular injury, with transaminases often above 1,000 U/L.

Hemochromatosis is an autosomal recessive disease resulting in multiorgan dysfunction from systemic iron overload. The most common sequelae include cirrhosis, heart failure, diabetes, hypogonadism, and arthritis. It is typically associated with significant elevations in transaminases.

Left ventricular failure does not directly cause hepatomegaly, though it may eventually lead to right heart failure. Pulmonary hypertension and right heart failure may lead to congestive hepatopathy. In such cases, other signs of right ventricular failure will be present: peripheral edema, elevated jugular venous pressure, positive hepatojugular reflux, and an S3 on cardiac exam.

Nonalcoholic steatohepatitis (NASH) is often asymptomatic and manifests as hepatomegaly with elevated transaminases. Imaging will reveal fatty infiltration of the liver. The leading causes of NASH are obesity, diabetes mellitus, and hypertriglyceridemia. This patient's hard hepatomegaly, anemia, and positive fecal occult blood in the setting of minimal transaminase elevations are more consistent with metastatic disease.
Cirrhotic and noncirrhotic portal hypertension may result in ascites and significant peripheral edema. Other signs of portal hypertension include esophageal varices, spider nevi, palmar erythema, and caput medusa. Thrombocytopenia and coagulopathy are often seen.

**SARCIOIDOSIS**

<table>
<thead>
<tr>
<th>Manifestations of sarcoidosis</th>
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<tbody>
<tr>
<td><strong>Pulmonary</strong></td>
</tr>
<tr>
<td>• Hilar LAD*</td>
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<tr>
<td>• Interstitial infiltrates</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
</tr>
<tr>
<td>• Papules, nodules &amp; plaques</td>
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<tr>
<td>• Erythema nodosum*</td>
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<tr>
<td><strong>Ophthalmologic</strong></td>
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<tr>
<td>• Anterior &amp; posterior uveitis</td>
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<tr>
<td>• Keratoconjunctivitis sicca</td>
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<td><strong>Neurologic</strong></td>
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<tr>
<td>• Facial nerve palsy</td>
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<tr>
<td>• CDI</td>
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<tr>
<td>• Hypogonadotropic hypogonadism</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
</tr>
<tr>
<td>• AV block</td>
</tr>
<tr>
<td>• Dilated or restrictive cardiomyopathy</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>• HSM</td>
</tr>
<tr>
<td>• Asymptomatic LFT abnormalities</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>• Hypercalcemia</td>
</tr>
<tr>
<td>• Peripheral lymphadenopathy</td>
</tr>
<tr>
<td>• Parotid gland swelling</td>
</tr>
<tr>
<td>• Polyarthritis*</td>
</tr>
<tr>
<td>• Constitutional symptoms (fever*, malaise)</td>
</tr>
</tbody>
</table>

*Manifestations of Löfgren syndrome.

AV = atrioventricular; LFT = liver function test.
A relatively asx man has HSM and LFTs showing mixed cholestatic and hepatocellular abnormalities. Given his associated hypercalcemia and hilar LAD (suggested by radiographic findings), this presentation is consistent with extrapulmonary sarcoidosis.

Sarcoidosis is a multisystemic, inflammatory granulomatous disease. Asx liver involvement (eg, abnormal LFTs, hepatomegaly) is common (~65%). Patchy infiltration by noncaseating granulomas can cause cholestatic (eg, mild alkaline phosphatase elevation) followed by hepatocellular (eg, mild aminotransferase elevations) changes. Reticuloendothelial granulomatous infiltration can also cause splenomegaly.

Other common sarcoidosis findings seen in this patient include lung involvement (>90%), with radiographs showing evidence of hilar lymphadenopathy (eg, described as upper lobe reticulonodular opacities, diffuse or nodular parenchymal infiltrates), and hypercalcemia (due to vitamin D conversion by macrophages in granulomas).

Biopsy of the most accessible lesion (eg, liver, enlarged LN) can establish the diagnosis.

Excessive iron accumulation from hereditary hemochromatosis, which commonly affects middle-aged men, can cause infiltrative liver disease, resulting in hepatosplenomegaly and transaminase elevations (primary hepatocellular pattern). However, lung involvement and hypercalcemia would not be expected.

Amyloidosis, a multisystem condition characterized by insoluble fibril deposition, can affect the liver, causing hepatomegaly and elevated alkaline phosphatase. However, this patient lacks other associated findings.
of amyloidosis, such as easy bruising and bleeding, peripheral edema (nephrotic syndrome), or anemia. In addition, hypercalcemia would not be expected.

HSM and elevated ALP (primary cholestatic pattern) can be seen in patients with primary biliary cholangitis (PBC), a condition involving T-lymphocyte-mediated bile duct destruction. However, jaundice (eg, scleral icterus) is common, lung involvement is not seen, and >90% of patients with PBC are women.

A1AT deficiency can cause early-onset lung emphysema, liver cirrhosis, and panniculitis. Elevated transaminases and cough can be presenting symptoms. However, chest imaging characteristically shows changes (eg, bullae) at lung bases, rather than the upper lobe opacities seen in this patient, LFTs typically show a primary hepatocellular pattern, and hypercalcemia would not be expected.

<table>
<thead>
<tr>
<th>ATROPHIC GASTRITIS</th>
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| A patient with hypothyroidism, chronic postprandial abdominal pain, and macrocytic anemia likely has **autoimmune metaplastic atrophic gastritis** (AMAG). AMAG is an autoimmune disorder that affects women>M; patients with other autoimmune conditions (eg, T1DM, autoimmune thyroid disease) are at increased risk. AMAG is characterized by the presence of antibodies toward parietal cells, resulting in atrophy and metaplasia of the gastric corpus, **hypochlorhydria**, and **unchecked gastrin production**; and toward intrinsic factor, resulting in vitamin B\(_{12}\) deficiency.

Therefore, the diagnosis should be suspected in patients with **macrocytic anemia** (due to vitamin B\(_{12}\) deficiency) who have suggestive epidemiologic characteristics (eg, female, autoimmune conditions) and GI features. Patients often develop **dyspepsia** with **postprandial abdominal pain**, bloating, N, heartburn, or **regurgitation**; the pathophysiology may be related to changes in **gastroduodenal motility**, **visceral sensitivity**, or **acid secretion**. Other laboratory findings include **elevated serum gastrin levels**; IDA may occur as hypochlorhydria leads to reduced iron bioavailability. Because AMAG is associated with an increased risk for **gastric adenocarcinoma** and **neuroendocrine tumors**, **routine surveillance endoscopy is indicated**.

**.........**

**Functional dyspepsia** can present with **postprandial abdominal pain and bloating**, whereas **IBS** leads to changes in bowel frequency and/or caliber along with abdominal cramps. Both diseases are functional disorders and are not associated with laboratory abnormalities; the
Presence of anemia (macrocytic or otherwise) requires workup for an alternative diagnosis.

**Gastroparesis** can cause postprandial abdominal pain, but V and early satiety would also be expected. It is more common in patients with uncontrolled diabetes or **scleroderma** and in **chronic opiate users**. Macrocytic anemia would be atypical.

Small intestinal bacterial overgrowth (**SIBO**) can be caused by small bowel dysmotility (eg, scleroderma, diabetes). SIBO can cause macrocytosis due to bacterial consumption of vitamin B₁₂; however, this diagnosis is **unlikely in the absence of diarrhea**.

### IDA

The evaluation of **iron deficiency anemia** (IDA) varies according to age group and patient-specific factors such as family history of colon cancer or presence of associated symptoms (eg, diarrhea in celiac disease).

New IDA in elderly patients should be considered to be from **gastrointestinal (GI) blood loss** (eg, polyps, cancer, angiodysplasia) until proven otherwise. In the clinical setting fecal occult blood tests (FOBTs) are frequently performed in patients before a diagnosis of iron deficiency is established with laboratory testing. When positive, FOBTs may guide the decision to perform colonoscopy and endoscopy in elderly patients, regardless of iron levels. However, a single negative FOBT is not sufficient to exclude occult GI bleeding. Elderly patients with IDA should be evaluated with **colonoscopy and endoscopy** despite a single negative FOBT, especially if no other obvious source of chronic blood loss is identified.

When severe, it is associated with GI angiodysplasia causing occult GI bleed. However, normal S2 splitting essentially excludes severe aortic stenosis.

Radioisotope scans are useful in determining the source of active bleeding but are not diagnostic in the absence of an active bleed. They are typically used in acute (not chronic) GI blood loss when the source of bleeding remains unidentified on colonoscopy and endoscopy.
A patient has symptomatic anemia with macrocytic red blood cells, hypersegmented neutrophils, and normal methylmalonic acid level indicating folic acid deficiency.

Folate is obtained from nutritional sources such as meats and leafy vegetables. Unlike cobalamin (vitamin B₁₂), body stores of folate are minimal, and deficiency occurs quickly if dietary intake wanes. This is rare in developed countries due to the fortification of flour with folic acid; however, patients with severe alcohol abuse and poor nutrition may become deficient in as little as 5-6 weeks.

Both folic acid and cobalamin deficiency impair DNA synthesis in cells with rapid turnover. Manifestations most commonly arise in the hematopoietic cells of the bone marrow and include:

- Megaloblastic anemia – macrocytic (mean corpuscular volume >100 µm³) red blood cells with peripheral smear evidence of hypersegmented neutrophils
- Low/normal reticulocyte count – inability to increase red blood cell production to respond to anemia
- Pancytopenia - if deficiency is severe
- Hyperhomocysteinemia – decreased metabolism of homocysteine

Unlike cobalamin deficiency, folic acid deficiency is associated with normal methylmalonic acid levels and no neurologic manifestations.

Cobalamin deficiency may occur with intestinal bacterial overgrowth (competes for cobalamin) or pernicious anemia (lack of intrinsic factor). Cobalamin deficiency typically takes years (not months) to develop, and the methylmalonic acid level would be high (not normal).

Myelodysplasia is a hematopoietic neoplasm that may cause macrocytic anemia with thrombocytopenia and leukopenia. However, peripheral blood smear usually shows dysplastic granulocytes that are hypogranulated and hyposegmented (not hypersegmented).

Pancreatic insufficiency reduces the absorption of fat-soluble vitamins (A, D, E, and K). Although vitamin K deficiency may impair the coagulation pathway (eg, bruising, petechiae) and vitamin E deficiency may cause hemolytic anemia, neither results in megaloblastic anemia.
**VITAMIN B12 DEFICIENCY**

This patient’s omeprazole use, lower extremity paresthesia, and diminished light touch/vibration sensation in the feet raise strong suspicion for **vitamin B₁₂ deficiency**. Because vitamin B₁₂ is an essential cofactor for DNA synthesis and myelin formation, deficiency usually manifests with hematologic (eg, megaloblastic anemia) and/or neurologic abnormalities. Common neurologic findings include subacute combined degeneration of the dorsal columns (eg, **impaired proprioception/vibrioception**) and the lateral corticospinal tracts (eg, positive Babinski reflex), but patients often first develop symmetric **lower extremity paresthesia** due to myelinated peripheral nerve damage.

Vitamin B₁₂ is ingested bound to animal protein and must be liberated in the stomach by **pepsin**, which is activated from pepsinogen by **gastric acid**. Therefore, patients on long-term **proton pump inhibitor** therapy (eg, omeprazole) sometimes develop vitamin B₁₂ deficiency due to achlorhydria. **Older** patients are particularly at risk. The diagnosis is usually made with **serum vitamin B₁₂ level**, but methylmalonic acid or homocysteine testing may be necessary if this test is inconclusive.

HIV can cause a distal symmetric polyneuropathy that generally begins with tingling and numbness in the bilateral feet. However, all sensory modalities are typically diminished (not just light touch and vibration), reflexes are generally impaired, and neuropathic pain is usually prominent.

Neurologic manifestations (eg, peripheral neuropathy, paresthesias) can develop in multiple myeloma (MM), which is diagnosed by serum protein electrophoresis. However, they are typically due to plasmacytoma infiltration or paraneoplastic effects and are not usually present at initial diagnosis. MM is unlikely in this patient with no other suggestive features (eg, bone pain, anemia). Most patients with neurologic manifestations of MM have significant neuropathic pain and mixed sensory and motor abnormalities.

Urine heavy metal testing can diagnose lead poisoning, which is often associated with peripheral neuropathy. However, peripheral motor neurons are primarily affected; therefore, most patients have motor weakness (eg, wrist or ankle drop).

Chronic hepatitis C virus infection can cause mixed cryoglobulinemia, which is associated with peripheral neuropathy. However, most cases are marked by both sensory and motor abnormalities; and patients often have palpable purpura and arthritis or arthralgias. This patient’s acid suppression and signs of dorsal spinal cord injury make vitamin B₁₂ deficiency more likely.
Lynch syndrome (eg, HNPCC) is an AD cancer syndrome that predisposes individuals to colorectal cancer and other malignancies. Genetic testing should be performed in patients with a strong family history of colon cancer (eg, ≥3 relatives involving multiple generations). The condition is due to a germline mutation in a DNA mismatch repair gene. Once the diagnosis of Lynch syndrome is established, patients should undergo screening for colon cancer with colonoscopy.

In addition to colon cancer, patients are at extremely high risk for endometrial carcinoma. Endometrial cancer screening with annual endometrial biopsy should begin at age 30-35. Ovarian cancer risk is also increased and may present at a relatively younger age. Therefore, prophylactic TAH-BSO is recommended at age 40 or earlier if childbearing is complete.

Breast carcinoma can be caused by BRCA1 and BRCA2 gene mutations, which also impart an increased risk of ovarian cancer. It is unclear if patients with Lynch syndrome have an increased incidence of breast cancer.

Clear cell renal carcinoma and pheochromocytoma can be due to VHL syndrome. This syndrome is also AD but is not associated with colon carcinoma.

MEN 1 and MEN 2: both syndromes are AD, but colon cancer is not a feature.

**AMBOSS:**

**Diagnostics**

Lynch syndrome should be suspected if there is a positive family history based on the Amsterdam II criteria. Genetic testing confirms the diagnosis.
Family history
The Amsterdam II criteria are used to identify individuals who are likely to be mutation carriers for Lynch syndrome.

Amsterdam II criteria
Presence of at least three relatives with a Lynch syndrome-associated cancer; all the following criteria should be present:

- One should be a first-degree relative of the other two
- At least two (>2) consecutive generations affected
- At least one (>1) relative with a diagnosis <50 years of age
- Exclude cases of FAP
- Verify tumors with pathological examination.

*3-2-1 rule: (3 affected family members, 2 generations, 1 relative under 50 years of age).

Genetic testing
- First test: tumor microsatellite instability (MSI) and/or immunohistochemical staining (IHC)
  - Low MSI/stable microsatellite and normal IHC: rules out Lynch syndrome
  - High MSI and/or abnormal IHC: requires further evaluation
- Confirmatory test: germline testing via DNA sequencing
  - Detection of mutations in DNA repair genes (MLH1, MSH2, MSH6, and PMS2)

Colorectal cancer
- For diagnosis of CRC, see colorectal cancer.

*Lynch syndrome typically manifests with colorectal cancer of the proximal colon, with only a few adenomatous polyps, in contrast to familial adenomatous polyposis, in which hundreds of adenomatous polyps are present.

Treatment
- Surgery
  - Subtotal colectomy with ileorectal anastomosis
  - Total colectomy with ileostomy
  - Total colectomy with ileorectal anastomosis
- Immunotherapy with an immune checkpoint inhibitor (pembrolizumab or nivolumab) may be used for high MSI
or mismatch repair deficient (dMMR) metastatic colorectal cancer. [5][6]

- For more specific guidelines regarding management, see colorectal cancer.
- For women with Lynch syndrome, prophylactic hysterectomy and bilateral salpingo-oophorectomy should be offered when they are no longer of child-bearing age.

**Prevention**

- **Genetic counseling**
  - Genetic testing is generally not recommended for at-risk individuals < 18 years of age.
  - Genetic screening should be initiated 10 years before the earliest manifestation of the condition in the family.

- **Cancer screening:** for Lynch syndrome patients with a confirmed mutation or who meet Amsterdam criteria
  - Colonoscopy: every 1–2 years, starting at 20–25 years of age, or 2–5 years before the earliest recorded case of a tumor in the family (only if it occurred before 25 years of age), whichever comes first [8]
  - Annual pelvic examination with transvaginal sonography and endometrial biopsy starting at 30–35 years of age or 3–5 years before the earliest reported case of a tumor in the family
  - Annual upper endoscopy with biopsy of the gastric antrum starting at 30–35 years of age
  - Annual physical exam and urinalysis

- **Total colectomy:** not generally recommended in patients with normal endoscopy
### Familial Adenomatous Polyposis (FAP)

A patient with a family history of colonic polyps and osteomas and an alteration in the tumor suppressor gene adenomatous polyposis coli has **familial adenomatous polyposis** (FAP). Patients with classic FAP can develop >1000 polyps and **almost universally develop colorectal cancer** (CRC) if left untreated; some patients may have an attenuated form with a slightly decreased risk of CRC. As a result, **increased screening** and elective proctocolectomy are the standard of care, rather than screening as recommended for the general population.

Guidelines generally recommend annual screening sigmoidoscopies for children starting at age 10-12, followed by **annual colonoscopies** once colorectal adenomas are detected or if the patient is age ≥50. Patients with the attenuated version of FAP can have a delayed start of screening (age 25) and longer screening intervals (1-2 years). In addition to colonoscopies, patients with FAP should also undergo regular screening for upper gastrointestinal tract tumors.

Proctocolectomy should be performed in patients who initially present with CRC or adenomas with high-grade dysplasia. Other indications for colorectal surgery include severe symptoms from colonic neoplasia (eg, hemorrhage) or a significant increase in polyp number during the screening interval. In patients with classic FAP who do not have any of the above findings, surgery does not need to be performed urgently and may be delayed until early twenties.

Regular aspirin or NSAIDs use has been associated with reduced risk for colon cancer in patients with average risk; however, it has not been shown to decrease risk in patients with FAP.

Screening or monitoring patients with carcinoembryonic antigen for CRC is not recommended due to the poor sensitivity for early-stage disease. It is most helpful in monitoring patients who have been diagnosed with CRC.

Annual fecal occult blood testing or CT colonography every 5 years (not annual CT scan with oral contrast) are appropriate options for patients with an average risk for CRC. However, neither is a sufficient strategy for patients with increased risk (eg, FAP, Lynch syndrome).

### CRC Screening

The United States Preventive Services Task Force (USPSTF) strongly encourages routine **colon cancer screening** in all patients age ≥50; the American Cancer Society recommends screening starting at age 45. Screening methods include:

- High-sensitivity stool-based testing (eg, fecal occult blood testing [FOBT] or fecal immunochemical testing [FIT] annually)
- Direct visualization techniques (eg, colonoscopy every 10 years, flexible sigmoidoscopy every 5 years),
- A combination (eg, flexible sigmoidoscopy every 10 years with FIT annually).

These strategies decrease colon cancer mortality. Colonoscopy is the most sensitive and specific test, but it is also the most costly and expertise-dependent.

Colonoscopy at age 50 is appropriate for patients with average colon cancer risk based on USPSTF recommendations (Choice B). However, this patient's family history places him at increased risk, and he requires screening at an earlier age. Patients with a history of colon cancer in a first-degree relative should be screened at age 40 or 10 years before the age of the relative's diagnosis (whichever comes first). This patient's father was diagnosed with colon cancer at age 50, and he should begin screening at age 40.

An exercise ECG stress test is a useful diagnostic study in patients with a moderate risk of coronary artery disease based on symptoms and risk factors. Although this patient has risk factors for coronary artery disease, he is currently asymptomatic and would not benefit from a stress ECG at this time.

This patient with a heavy smoking history and a family history of lung cancer is at increased risk for lung cancer. Sputum cytology does not effectively screen for lung cancer or decrease mortality from the disease. Low-dose chest CT is recommended yearly for lung cancer screening in patients who are age 55-80, have a ≥30-pack-year smoking history, and are currently smoking or quit within the past 15 years. This patient has a 30-pack-year history (eg, 2 packs a day for 15 years), but lung cancer screening is only recommended age 55-80.

<table>
<thead>
<tr>
<th>Recommended test</th>
<th>Low-dose chest CT scan</th>
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<tbody>
<tr>
<td>Recommended interval</td>
<td>Yearly</td>
</tr>
<tr>
<td>Age for screening</td>
<td>55-80</td>
</tr>
</tbody>
</table>
| Eligibility | • Patient has ≥30-pack-year smoking history **AND**  
|            | • Patient is a current smoker or quit smoking within the last 15 years |
| Termination of screening | • Age >80 **OR**  
|            | • Patient successfully quit smoking for ≥15 years **OR**  
|            | • Patient has other medical conditions that significantly limit life expectancy or ability/willingness to undergo lung cancer surgery |

The USPSTF guidelines conclude that there is currently insufficient evidence on screening for thyroid disease in asymptomatic patients with a family history of thyroid disease.

**COLONIC POLYPS**

Colon polyps are grossly visible protrusions from the flat mucosal surface of the intestine. They can be categorized as neoplastic (having malignant potential) and non-neoplastic. Adenomas (adenomatous polyps) are considered neoplastic polyps; findings that suggest a greater risk of malignant transformation (usually warranting more aggressive colonoscopic surveillance) include:

- Predominance of **villous** features (long glands on histologic examination), particularly in the presence of **high-grade dysplasia**
- Large **size** (eg, >1 cm)
- High **number** (eg, >3 concurrent adenomas)
In addition, **sessile** (nonpedunculated) adenomatous polyps are associated with an increased risk of synchronous advanced neoplasia and often require careful follow-up to ensure complete removal.

Non-neoplastic polyps, including hyperplastic polyps (arising from hyperplastic mucosal proliferation), hamartomatous polyps (eg, juvenile polyps, Peutz-Jeghers polyps), inflammatory pseudopolyps, and submucosal polyps (eg, lipomas, lymphoid aggregates), have low malignant potential and generally do not require enhanced surveillance.

### Pancreatic adenocarcinoma

<table>
<thead>
<tr>
<th><strong>Risk factors</strong></th>
<th><strong>Pancreatic adenocarcinoma</strong></th>
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<tbody>
<tr>
<td>Smoking</td>
<td>• Smoking</td>
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<tr>
<td>Hereditary pancreatitis</td>
<td>• Hereditary pancreatitis</td>
</tr>
<tr>
<td>Nonhereditary chronic pancreatitis</td>
<td>• Nonhereditary chronic pancreatitis</td>
</tr>
<tr>
<td>Obesity &amp; lack of physical activity</td>
<td>• Obesity &amp; lack of physical activity</td>
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<tr>
<th><strong>Clinical presentation</strong></th>
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<tbody>
<tr>
<td>Systemic symptoms (eg, weight loss, anorexia) (&gt;85%)</td>
<td>• Systemic symptoms (eg, weight loss, anorexia) (&gt;85%)</td>
</tr>
<tr>
<td>Abdominal pain/back pain (80%)</td>
<td>• Abdominal pain/back pain (80%)</td>
</tr>
<tr>
<td>Jaundice (56%)</td>
<td>• Jaundice (56%)</td>
</tr>
<tr>
<td>Recent-onset atypical diabetes mellitus</td>
<td>• Recent-onset atypical diabetes mellitus</td>
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<tr>
<td>Unexplained migratory superficial thrombophlebitis</td>
<td>• Unexplained migratory superficial thrombophlebitis</td>
</tr>
<tr>
<td>Hepatomegaly &amp; ascites with metastasis</td>
<td>• Hepatomegaly &amp; ascites with metastasis</td>
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<tr>
<th><strong>Laboratory studies</strong></th>
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<tbody>
<tr>
<td>Cholestasis (↑ alkaline phosphatase &amp; direct bilirubin)</td>
<td>• Cholestasis (↑ alkaline phosphatase &amp; direct bilirubin)</td>
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<tr>
<td>↑ Cancer-associated antigen 19-9 (not as a screening test)</td>
<td>• ↑ Cancer-associated antigen 19-9 (not as a screening test)</td>
</tr>
<tr>
<td>Abdominal ultrasound (if jaundiced) or CT scan (if no jaundice)</td>
<td>• Abdominal ultrasound (if jaundiced) or CT scan (if no jaundice)</td>
</tr>
</tbody>
</table>

This patient’s worsening epigastric pain and weight loss in the setting of idiopathic chronic pancreatitis suggest **pancreatic cancer**. The presentation and workup vary depending on tumor location. Classic manifestations include **weight loss** and insidious onset of gnawing **abdominal pain** (usually epigastric and radiating to the back), which is worse at night, with eating, or when lying supine.
• Cancers in the **head** of the pancreas (60%-70%) typically present with **jaundice** (common bile duct obstruction, elevated alkaline phosphatase and bilirubin) and steatorrhea (pancreatic exocrine insufficiency or pancreatic duct blockage). In patients with these findings, abdominal **ultrasound** is preferred for detecting pancreatic head tumors and excluding other potential causes of biliary obstruction (eg, choledocholithiasis).

• Cancers in the body and tail usually do **not** present with obstructive jaundice. **Abdominal CT scan** with contrast is preferred (more sensitive and specific) as it can delineate necrosis within the pancreas and identify distant metastases; it also helps exclude other conditions. Ultrasound is less sensitive for visualizing the pancreatic body and tail (due to overlying bowel gas) and for detecting smaller (<3 cm) tumors.

...............  

**CA 19-9**, a tumor marker associated with pancreatic cancer, is not recommended for screening due to variable sensitivity and low specificity. Normal levels do not rule out pancreatic cancer.

**ERCP** is more invasive than CT scan, and is reserved for patients with **cholestasis** (from the tumor compressing the biliary system) who may require an intervention (eg, stenting).

**Pancreatic enzyme** replacement therapy is typically titrated based on the patient's clinical symptoms and stool fat content.

**Plain abdominal radiographs** may show calcifications in chronic pancreatitis, but are not useful for diagnosing pancreatic cancer. In addition, calcifications are rarely seen in idiopathic pancreatitis.

**Opioid therapy** may be necessary in some patients with chronic pancreatitis. However, reassurance and symptomatic management are not appropriate in this patient with suspected pancreatic cancer.

The **secretin test** directly measures the ability of pancreatic ductal cells to produce bicarbonate. It is useful in diagnosing chronic pancreatitis, but not helpful in evaluating possible pancreatic cancer.
This patient’s presentation is consistent with typical GERD. Patients with typical GERD require upper gastrointestinal (GI) endoscopy if they have alarm symptoms (dysphagia, odynophagia, weight loss, anemia, GI bleeding, or recurrent vomiting) or are men age >50 with chronic (>5 years) symptoms and cancer risk factors (eg, tobacco use). Patients with esophagitis on endoscopy can receive treatment depending on the diagnosis (eg, autoimmune disease, Barrett’s esophagus). Patients without esophagitis on endoscopy usually require further evaluation (eg, esophageal manometry).

Patients with typical GERD symptoms who do not meet initial endoscopy criteria can receive an initial trial of daily proton pump inhibitor (PPI). Patients with refractory symptoms should try another PPI or increase the use of PPI to twice daily. Patients with persistent symptoms likely require further testing such as endoscopy or esophageal pH monitoring. This patient’s presentation (age >50, unintentional weight loss, dysphagia, tobacco use) warrants initial endoscopy (rather than PPI or H2 blockers) to assess for complications of GERD.
Esophageal manometry and pH monitoring should be considered in patients with persistent GERD symptoms or normal upper GI endoscopy to assess for other conditions (eg, motility disorders) that can occasionally mimic GERD.

*H pylori* can cause gastric and duodenal ulcers. Testing is indicated in patients with active or past history of peptic ulcer disease. Routine screening and empiric treatment for *H pylori* infection may also be considered for patients who have dyspepsia but not GERD.

A patient's presentation – chronic gastroesophageal reflux with new dysphagia and symmetric lower esophageal narrowing – suggests esophageal (peptic) stricture. Chronic gastroesophageal reflux disease (GERD) predisposes to Barrett's esophagus (intestinal metaplasia of the lower esophagus) and esophageal strictures. Both conditions are consequences of the body's reparative response to chronic gastric acid exposure and can occur simultaneously. Benign strictures affect 5%–15% of patients with GERD. Other causes of peptic strictures include radiation, systemic sclerosis, and caustic ingestions.

Strictures typically cause slowly progressive dysphagia to solid foods without anorexia or weight loss. As they progress, they can actually block reflux, leading to improvement of heartburn symptoms (as seen in this patient). Strictures tend to appear as symmetric, circumferential narrowing on barium swallow. Nonetheless, in any case of stricture in the setting of Barrett's esophagus, biopsy is necessary to rule out adenocarcinoma. This is usually accomplished via endoscopy which may be diagnostic and therapeutic (dilation is performed if no malignancy is detected).

Achalasia is an esophageal motility disorder that presents with dysphagia (both solids and liquids) and regurgitation of undigested food or saliva. Barium swallow typically shows aperistalsis, poor emptying of
barium, dilation of the proximal esophagus (caused by retention of food), and narrowing in a "bird beak" pattern at the gastroesophageal junction.

Adenocarcinoma typically occurs in patients who have had GERD symptoms for >20 years. Early symptoms of esophageal cancer are subtle and include retrosternal discomfort, mild dysphagia to solid foods, and/or a burning sensation. Barium swallow generally shows asymmetric narrowing of the esophageal lumen.

A hiatal hernia is a protrusion of the stomach above the diaphragm. These patients may have GERD and are also at risk for Barrett’s esophagus, peptic strictures, and adenocarcinoma. Barium swallow shows gastric folds protruding above the diaphragm.

Vascular rings are uncommon congenital anomalies in which aortic arch vessels encircle the trachea and/or esophagus. Patients may present in infancy with symptoms of airway obstruction, though some patients do not present until adulthood. In adult cases, dysphagia is usually the presenting complaint. There is not a strong association with GERD or Barrett’s esophagus.

| HERPES ZOSTER |
|-----------------
| A patient with burning, localized pain and regional hyperesthesia/allodynia, in the context of recent cancer treatment, has common features of herpes zoster (shingles). Pain from shingles may precede the onset of the classic vesicular rash by several days, during which the diagnosis may not be obvious. The possibility of shingles should be considered in patients with regional pain who have no conclusive evidence of disease in the local internal organs.

Shingles may occur at any age, but it is most common after age 50 and the risk increases with age. It is frequently triggered by severe physical stress (such as cancer treatment, as in this patient) or immunosuppressed states, but many cases are spontaneous. Shingles develops when there is reactivation of the varicella zoster virus in a dorsal root ganglion, where it has remained dormant since a past chickenpox infection. This results in pain and a vesicular rash in a dermatomal distribution along the course of the nerve. In some cases, patients may develop persistent hypersensitivity of afferent pain fibers leading to chronic pain known as post-herpetic neuralgia. Treatment with antiviral medications (acyclovir, valacyclovir, or famciclovir) in the first few days of a shingles outbreak can shorten the duration of symptoms and decrease the risk of post-herpetic neuralgia.

......

Ascites is seen MCly in patients with advanced liver disease (cirrhosis) or chronic kidney disease. This patient has no liver abnormalities noted in the
history or examination findings, and development of ascites would be unexpected.

Black stools (melena) are a typical symptom of upper gastrointestinal hemorrhage (above the ligament of Treitz). Peptic ulcer would be the most likely explanation. Although ibuprofen increases the risk of ulcer, this patient had symptoms prior to taking the medication.

Patients with recent malignancy would be at increased risk for a number of pulmonary conditions, such as pulmonary embolism or pneumonia, which could cause referred pain to the abdomen. However, this patient’s abdominal hyperesthesia is not consistent with a pulmonary disorder.

Fever and jaundice in association with right-sided abdominal pain would suggest the possibility of acute cholangitis. Cholangitis is most often associated with biliary obstruction, usually due to gallstones. In the absence of nausea or right upper-quadrant tenderness, biliary obstruction is less likely.

Patients with impending bowel perforation, as in acute appendicitis, often develop initial symptoms in the periumbilical area. Abdominal examination should yield more specific clues to this possibility, and hyperesthesia would be unlikely.

Small-bowel obstruction (SBO) is a common cause of abdominal pain, but it most often occurs in patients with adhesions from prior abdominal surgery. It is usually associated with nausea and abnormal bowel sounds.

**DYSPEPSIA**

<table>
<thead>
<tr>
<th>Dyspepsia</th>
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<tbody>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>• Epigastric pain often described as “burning”</td>
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<tr>
<td>• ± Nausea, vomiting, epigastric fullness, heartburn</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td>• Functional (75%)</td>
</tr>
<tr>
<td>• Malignancy (eg, gastric, esophageal)</td>
</tr>
<tr>
<td>• Peptic ulcer, NSAIDs, <em>Helicobacter pylori</em> infection, GERD</td>
</tr>
<tr>
<td><strong>Workup</strong></td>
</tr>
<tr>
<td>• Age ≥60: Upper endoscopy</td>
</tr>
<tr>
<td>• Age &lt;60:</td>
</tr>
<tr>
<td>• Testing and treatment for <em>H pylori</em></td>
</tr>
<tr>
<td>• Upper endoscopy in high-risk patients (eg, overt GI bleeding, significant weight loss, &gt;1 alarm symptom)</td>
</tr>
</tbody>
</table>
A patient has dyspepsia (ie, burning intermittent epigastric pain and postprandial discomfort), postprandial bloating, and nausea associated with a positive stool guaiac. In association with her younger age (<65), absence of features concerning for malignancy (ie, dysphagia, regurgitation, weight loss, change in bowel habits), and history of living in an area with a high prevalence of infection (eg, parts of Asia), this presentation suggests *Helicobacter pylori* infection complicated by peptic ulcer disease.

*H pylori* is a urease-producing organism that commonly causes dyspeptic symptoms. It colonizes the stomach and induces excessive production of gastric acid by the parietal cells, which can eventually lead to duodenal ulcer formation. Other common symptoms of duodenal ulcers include nocturnal pain (due to circadian rhythm of gastric acid secretion), worsening of the pain with fasting, postprandial bloating, and nausea. Biopsy of the gastric antrum during endoscopy can confirm infection. In a patient without occult bleeding, noninvasive diagnostic testing, including stool antigen studies and urea breath testing, can be employed. Serology cannot distinguish between active and cleared infection and is not preferred.

Biliary cholesterol supersaturation is involved in cholesterol gallstone formation. Gallstones usually cause right upper quadrant pain, nausea, and diaphoresis. A positive stool guaiac is unexpected.

Although gastrin-secreting pancreatic tumors (eg, Zollinger-Ellison syndrome) can result in dyspepsia and duodenal ulcers, they are very rare and usually accompanied by chronic diarrhea and weight loss. This patient's history and normal bowel habits make *H pylori* infection more likely.

Primary biliary cholangitis, which occurs due to immune-mediated bile duct destruction, most frequently presents with chronic fatigue, pruritus, and jaundice.
Celiac disease leads to immune-mediated destruction of the intestinal villi. It can be asymptomatic or cause severe diarrhea, flatulence, or iron deficiency anemia; dyspepsia is uncommon.

Although both achalasia and gastroesophageal reflux disease (GERD) result from lower esophageal sphincter dysfunction and may cause dyspepsia, bleeding is not typical. In addition, achalasia typically presents with weight loss, dysphagia for solid foods, and regurgitation of undigested food. GERD presents with heartburn (retrosternal burning pain) and much milder regurgitation.

**PUD**

A patient with epigastric pain and intermittent melena most likely has a duodenal ulcer (DU). The pain of DU is often worse on an empty stomach (possibly due to unopposed gastric acid emptying into the duodenum) and improves with food (due to alkaline fluid secretion into the duodenum). By contrast, the pain of gastric ulcers is often worse after eating (due to increased acid secretion).

The majority of DUs are caused by either *H pylori* infection or nonsteroidal anti-inflammatory drugs (NSAIDs). Malignant ulceration should be considered with gastric ulcers but would be very unlikely in this young patient with DU. As this patient has no history of NSAID use, *H pylori* infection is the most likely etiology and can be confirmed with endoscopic biopsy or urea breath test. Management of DU due to *H pylori* requires the following:

- **Antisecretory therapy**, preferably a proton pump inhibitor (PPI) (eg, omeprazole, pantoprazole), and
- **Antibiotic eradication** (eg, amoxicillin plus clarithromycin)

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Compared to antisecretory therapy with antibiotic eradication, antisecretory therapy alone leads to reduced healing rates and a higher risk of recurrent ulcer in patients with *H pylori*-associated DU. Antisecretory therapy without antibiotics would be recommended for DU attributable to causes other than *H pylori*.

Heavy alcohol intake can contribute to hemorrhagic gastritis, but light alcohol intake likely does not affect the course of DU. Smoking appears to increase the risk of peptic ulcer in patients infected with *H pylori* but does not increase relapse following *H pylori* eradication.

Laparoscopic cholecystectomy is recommended for biliary colic (intermittent, severe right upper quadrant pain with nausea) or acute
cholecystitis. This patient's epigastric pain (relieved by food) and melena are unlikely to be due to symptomatic gallbladder disease.

NSAIDs can contribute to the risk of DU. Therefore, they are contraindicated during the acute management of DU and should be used with caution following confirmed ulcer resolution.

Selective vagotomy decreases gastric acid production by removing vagal input to the stomach. With antibiotic regimens for \textit{H pylori} and the advent of PPIs, selective vagotomy is used only in refractory cases.

A patient's epigastric abdominal discomfort and melena are likely due to \textbf{peptic ulcer disease (PUD)}. PUD refers to ulcerations in the stomach or duodenum that are most commonly caused by \textit{Helicobacter pylori} infection or nonsteroidal anti-inflammatory drugs. Patients may have epigastric pain, nausea, and/or early satiety in association with food. The classic symptoms of duodenal ulcer occur in the absence of a food buffer and can include epigastric pain 2-5 hours after meals, on an empty stomach, or at night. Patients can have melena due to processed blood from upper gastrointestinal (GI) bleeding (eg, proximal to the ligament of Treitz). In fact, PUD is one of the most common causes of upper GI bleeding. Diagnosis of PUD is made with upper GI endoscopy.

Colon cancer and diverticulosis are possible etiologies of lower GI bleeding that typically present with hematochezia as opposed to melena. Colon cancer may also result in changes in bowel habits (eg, constipation, changes in stool caliber).

Gastric cancer can cause melena and abdominal pain but is usually accompanied by weight loss and anorexia instead of weight gain.

Ulcerative colitis typically causes hematochezia as opposed to melena. Melena can occur with Crohn disease involving the upper GI tract or small bowel. Nonetheless, inflammatory bowel disease is typically accompanied by diarrhea and systemic symptoms (eg, fatigue, fever, weight loss), which are not evident in this patient.

Atherosclerotic vascular disease (eg, carotid stenosis) is a risk factor for chronic ischemic colitis and mesenteric ischemia. However, ischemic colitis is typically associated with hematochezia as opposed to melena. In addition, patients with mesenteric ischemia report pain that is exacerbated by eating, which often leads to food aversion and weight loss as opposed to weight gain.
Mallory-Weiss syndrome refers to hematemesis that occurs after repeated episodes of retching/vomiting and is often accompanied by epigastric or back pain. The absence of vomiting and hematemesis in this patient make the diagnosis unlikely.

A patient who developed occult GI hemorrhage days after being admitted to the ICU for septic shock likely has a stress-induced ulcer.

Stress ulcerations are exceedingly common in patients requiring ICU-level care, and typically develop within hours to days of severe physiologic stress. Risk factors include:

1. Shock,
2. Sepsis,
3. Coagulopathy,
4. Mechanical ventilation,
5. Traumatic spinal cord/brain injury,
6. Burns, and

The etiology is multifactorial and likely includes splanchnic hypoperfusion, reflux of bile salts, and accumulation of uremic toxins that impair formation of the protective mucosal layer around the stomach, allowing for mucosal injury and bleeding.

Stress ulcers typically form in the proximal stomach and duodenum and may result in generally Painless GI bleeding, which can be occult (eg, anemia, positive FOBT) or clinically obvious (eg, melena, hematemesis) with shock. Prophylactic acid suppressive agents (eg, PPIs, H2 blockers) are a mainstay in the prevention of stress ulcerations. However, they are typically reserved for high-risk patients (eg, bleeding diathesis, prolonged mechanical ventilation, recent GI bleed) due to the potential harms associated with these agents, including pneumonia and Clostridiodes (formerly Clostridium) difficile infection. Patients who develop ulcerations should receive PPIs and close monitoring; endoscopy may be required in those with clinically significant bleeding.

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Acute colonic ischemia is due to hypoperfusion and usually affects watershed areas (limited collateral flow) in the left colon (eg, splenic flexure, rectosigmoid junction). Therefore, it typically presents with
**crampy, left-sided abdominal pain** and overt hematochezia during or shortly after (<24 hours) episodes of hypotension.

*C difficile* infection is common in hospitalized patients on antibiotics but typically causes watery diarrhea associated with fevers and leukocytosis. Occult bleeding and a marked drop in hemoglobin would be rare.

**Diverticular disease** can cause painless bleeding but typically presents with gross hematochezia rather than occult bleeding. Occult bleeding in the setting of severe illness is more consistent with stress ulceration.

**PUD** often causes occult bleeding but typically begins with gnawing abdominal pain **over weeks to months**. The acute onset of bleeding after septic shock is more consistent with stress ulceration.

Use of NSAIDs w/ ASA → risk of IDA. Evaluation of this patient would likely include CBC, iron studies, and FOBT. If iron deficiency is confirmed, especially if there is evidence of ongoing blood loss, definitive diagnosis can be obtained with upper (and usually lower) GI **endoscopy**. Even mild iron deficiency should be evaluated thoroughly as low-grade GI bleeding may herald a later catastrophic hemorrhage.

Management typically includes withholding NSAIDs and aspirin and initiating antisecretory medication (PPIs).

Elderly patients may present additional challenges in evaluating acute anemia. Besides other potential comorbidities that can cause chronic anemia at baseline (eg, renal insufficiency, MDS, occult malignancy, nutritional deficiencies), a significant number of elderly patients will have a baseline anemia for which no etiology is apparent, the so-called "**idiopathic anemia of ageing**." They are also more likely to have additional comorbidities such as **CHF** or **chronic lung disease**, which make them poorly tolerant of even mild anemia.

Anemia of chronic disease (anemia of chronic inflammation) is caused by suppression of red cell production by inflammatory cytokines. It commonly occurs in inflammatory arthropathies (eg, rheumatoid arthritis, lupus) but is not associated with osteoarthritis.

Aplastic anemia is a disorder of bone marrow stem cells that is often induced by exposure to various drugs, chemicals, ionizing radiation, or viruses. It can also be idiopathic. The incidence increases with age, but it is significantly less common than iron deficiency anemia at
Undiagnosed hypothyroidism can also cause anemia, but the anemia of hypothyroidism is generally mild and less likely to be apparent on examination than iron deficiency anemia. Although biochemical vitamin B12 deficiency, as defined by low serum B12 levels, is relatively common, overt anemia due to B12 deficiency is significantly less common. The clinician may wish to measure B12 levels, especially in a patient with macrocytic anemia.

Acute erosive gastropathy is characterized by the development of severe hemorrhagic lesions after the exposure of gastric mucosa to various injurious agents or after a substantial reduction in blood flow. Aspirin decreases the protective prostaglandin production, and cocaine results in vasoconstriction, significantly reducing gastric blood flow. In addition, aspirin and alcohol cause direct mucosal injury, which decreases the normal protective barriers (eg, secreted mucins, bicarbonate), thereby permitting acid and other luminal substances (eg, proteases, bile acids) to penetrate into the lamina propria. This results in additional injury to the vasculature and subsequent hemorrhage. As in this case, patients frequently present with hematemesis and abdominal pain.

Aortoenteric fistula can present as massive, life-threatening gastrointestinal (GI) hemorrhage or as minimal bleeding (a common sentinel event of massive hemorrhage). However, this patient lacks typical risk factors for aortoenteric fistula, including older age, history of abdominal aortic aneurysm, prior GI interventions, or malignancy. Esophageal variceal bleeding is another common cause of upper GI bleeding, but it is usually seen in patients with cirrhosis. This patient is young, has a history of moderate alcohol consumption, and has no other findings suggestive of chronic liver disease (eg, ascites, spider angiomata, jaundice).

Both S aureus and Bacillus cereus produce heat-stable enterotoxins that can lead to significant vomiting after the consumption of contaminated food. However, this patient describes only minimal vomiting, and neither S aureus nor B cereus food-poisoning commonly leads to hematemesis. Pancreatitis may be caused by alcohol consumption; however, it typically causes severe abdominal pain (classically without hematemesis) and usually occurs after years of heavy alcohol abuse rather than a single event of binge drinking. Cocaine use is much more commonly associated with mesenteric ischemia than with acute pancreatitis.
Mallory-Weiss tears occur in the distal esophagus at the gastroesophageal junction after repeat bouts of retching and vomiting. Patients typically have a history of multiple episodes of nausea and vomiting preceding the onset of hematemesis, not concurrent with its first presentation (as in this patient).

### Diverticula Disease

<table>
<thead>
<tr>
<th>Etiology</th>
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<tbody>
<tr>
<td>• Diverticulosis: ↑ intraluminal pressure causing herniation through points of weakness (vasa recta penetration)</td>
<td></td>
</tr>
<tr>
<td>• Diverticular bleeding: injury to exposed vasa recta</td>
<td></td>
</tr>
<tr>
<td>• Diverticulitis: trapped food particles &amp; ↑ intraluminal pressure causing microperforation</td>
<td></td>
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<table>
<thead>
<tr>
<th>Symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diverticulosis: none</td>
<td></td>
</tr>
<tr>
<td>• Diverticular bleeding: painless hematochezia</td>
<td></td>
</tr>
<tr>
<td>• Diverticulitis: left lower quadrant pain, nausea, vomiting, fever</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diet high in red meat &amp; fat &amp; low in fiber</td>
<td></td>
</tr>
<tr>
<td>• Obesity, physical inactivity, smoking</td>
<td></td>
</tr>
</tbody>
</table>

Diverticula are outpouchings of the colonic wall that form at points of weakness, most commonly in the sigmoid colon. **Diverticulosis** is a common finding on endoscopy, and the incidence increases with age. Although diverticulosis is usually asymptomatic, potential complications include diverticular bleeding (due to injury to the colonic vasculature) or diverticulitis.

Acute diverticulitis occurs due to inflammation associated with microperforation of a diverticulum; it typically presents with **left lower quadrant pain**, nausea/vomiting, and fever. CT findings include focal thickening of the colon wall and pericolic fat stranding; diverticula are not always seen. Initial management includes antibiotics (eg, ciprofloxacin plus
metronidazole) and bowel rest. Because colonic malignancy may mimic the presentation and CT findings seen in diverticulitis, follow up **colonoscopy** (typically 4-8 weeks later) is often recommended to rule out malignancy and evaluate the extent of diverticulosis.

Diverticular diseases are strongly associated with **chronic constipation**; the increased colonic pressures in constipation may promote formation of diverticula, and conversely, the altered motility seen in diverticulosis may contribute to constipation. Diets high in **fruit and vegetable fiber** help prevent further complications of diverticulosis by softening the stool and preventing constipation. Physical activity is also inversely correlated with the risk of complications. Factors associated with an increased risk include heavy meat consumption, obesity, and smoking.

**.......**

In the past, patients with diverticulosis were advised to avoid nuts and seeds under the assumption that these hard objects may obstruct the diverticular lumen and precipitate acute diverticulitis. However, recent studies have found no link between intake of these foods and incidence of diverticulitis.

Daily low-dose aspirin is associated with a lower risk of colorectal cancer. However, frequent use of aspirin and nonsteroidal anti-inflammatory drugs is associated with a higher risk of diverticular complications.

Surgery is indicated for diverticulosis complicated by recurrent bleeding, perforation, peritonitis, or abscess that does not resolve with percutaneous drainage. Uncomplicated diverticulosis can otherwise be managed nonoperatively.

Frequent colonoscopy is indicated for patients at increased risk for colon cancer (eg, large or multiple adenomatous polyps, Lynch syndrome). In the absence of adenomas, patients with diverticulosis may return to a routine colon screening schedule.

Probiotic therapy is sometimes used for acute infectious diarrhea and functional gastrointestinal disorders. However, it has not demonstrated benefit in prevention of diverticular complications.

A patient has large-volume rectal bleeding most likely due to diverticulosis. **Diverticulosis** is the most common cause of gross lower gastrointestinal (GI) bleeding in adults. Diverticula are outpouchings of the colonic wall that form at points of weakness. The deformation in the colonic wall can cause weakness in the associated arterial supply and lead
to bleeding into the diverticular lumen. Diverticulosis is most common in the sigmoid colon, but diverticular bleeding is more common in the right colon.

Diverticular bleeding is typically **painless**, but large-volume bleeding may be associated with lightheadedness and hemodynamic instability. Low- or moderate-volume bleeding from the right colon will mix with stool and pass as dark or maroon-colored hematochezia. Large-volume hemorrhage can lead to passage of frank red blood. The diagnosis is confirmed on **colonoscopy**. Most cases of diverticular hemorrhage will **resolve spontaneously**, but a minority of patients will require endoscopic or surgical intervention.

Colonic angiodysplasia can cause painless bleeding in the right colon. However, it is significantly less common than diverticular hemorrhage. Angiodysplasia usually also causes low-volume (venous) bleeding, whereas diverticulosis can cause large-volume arterial hemorrhage.

Colon cancer tends to cause chronic occult blood loss, with abdominal pain, altered passage of stool, and weight loss. Gross bleeding is less likely.

Hemorrhoids cause painless rectal bleeding, with bright red blood in the toilet bowl or on the paper. Hemorrhoids rarely cause massive lower GI bleeding.

Ischemic colitis causes sudden onset of abdominal pain and tenderness, followed by rectal bleeding. It can occur due to inadequate perfusion of "watershed" areas of the colon (eg, splenic flexure) in the setting of nonocclusive ischemia or surgical or endovascular interventions.

Acute mesenteric thrombosis presents with abdominal pain out of proportion to physical findings, nausea/vomiting, and bloody diarrhea due to mucosal sloughing. Patients have numerous atherosclerotic risk factors.

Brisk upper GI bleeding (eg, due to peptic ulcer disease) can present with bright red blood per rectum; however, most patients with upper hemorrhage of that degree usually have hematemesis as well. This patient's nonbloody gastric aspirate makes an upper GI source less likely.
| PERFORATED VISCUS | Full-thickness erosion of a peptic ulcer through the stomach or duodenal wall releases both air and caustic (ie, pH ~1-2) gastric secretions/contents into the peritoneal cavity, quickly resulting in chemical peritonitis (eg, marked abdominal tenderness with guarding) and a systemic inflammatory response (eg, fever, tachycardia).---> diffuse abdominal pain.

Perforated viscus is primarily a clinical diagnosis; however, confirmation can often be made quickly via demonstration of subdiaphragmatic free air on upright x-ray of the chest and abdomen. When perforation is suspected and plain radiographs are negative, CT scan of the abdomen with IV contrast can help detect smaller amounts of free air or free fluid. However, CT scan should not delay surgical consultation and intervention, especially when peritonitis is present.

........

Mesenteric angiography can be used to evaluate for mesenteric ischemia. Acute mesenteric ischemia typically causes acute-onset, severe abdominal pain with a relatively benign abdominal examination (rather than diffuse tenderness and guarding) and hematochezia (rather than fecal occult blood).

NSAID avoidance and oral PPI are part of uncomplicated PUD management. In contrast, this patient has signs (eg, fever, peritonitis) concerning for complicated PUD (eg, perforation) and should remain NPO while awaiting radiologic confirmation of the diagnosis and/or definitive management.

Upper and lower gastrointestinal endoscopy should be considered in patients with occult gastrointestinal bleeding (eg, positive stool guaiac test); however, endoscopy is contraindicated if acute gastrointestinal perforation is suspected because air insufflation and instrumentation may worsen the perforation.
### IBS

<table>
<thead>
<tr>
<th>Clinical features of irritable bowel syndrome</th>
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</thead>
<tbody>
<tr>
<td><strong>Rome IV diagnostic criteria</strong></td>
</tr>
<tr>
<td>Recurrent abdominal pain/discomfort ≥1 day/week for past 3 months &amp; ≥2 of the following:</td>
</tr>
<tr>
<td>• Related to defecation (improves or worsens)</td>
</tr>
<tr>
<td>• Change in stool frequency</td>
</tr>
<tr>
<td>• Change in stool form</td>
</tr>
<tr>
<td><strong>Alarm features</strong></td>
</tr>
<tr>
<td>• Older age of onset (≥50)</td>
</tr>
<tr>
<td>• GI bleeding</td>
</tr>
<tr>
<td>• Nocturnal diarrhea</td>
</tr>
<tr>
<td>• Worsening pain</td>
</tr>
<tr>
<td>• Unintended weight loss</td>
</tr>
<tr>
<td>• Abnormal labs (e.g., IDA, electrolyte disorders, ↑ CRP)</td>
</tr>
<tr>
<td>• Positive fecal lactoferrin or calprotectin</td>
</tr>
<tr>
<td>• FHx of early colon cancer or IBD</td>
</tr>
</tbody>
</table>

**IBD** = inflammatory bowel disease.

**Irritable bowel syndrome (IBS):** a functional disorder characterized by recurrent abdominal pain (e.g., once a week for ≥ 3 months) and altered bowel habits (e.g., diarrhea, constipation) with symptoms that worsen (or improve) with bowel movements. Other common symptoms include bloating, flatulence, bletching, N, passage of mucus, and tenesmus. The etiology is poorly understood but likely involves visceral hypersensitivity and abnormal GI motility. It occurs most commonly in younger women (age <50) and is associated with fibromyalgia, depression, and anxiety. Symptoms worsen with psychosocial stressors.

IBS is the MC dx in north America, w/ a prevalence of 10-15%. IBS presents most commonly in young women as chronic, crampy abdominal pain with alternating episodes of constipation and diarrhea. It can also present with nonspecific symptoms such as GERD, dysphagia, early satiety, and chest pain. IBS is further subclassified as diarrhea-predominant, constipation-predominant, or mixed. IBS was previously considered a diagnosis of exclusion. However, patients with IBS symptoms based on the ROME III criteria, no alarm features, and no family history of IBD or CRC do not require extensive workup.

IBS is a clinical diagnosis; the w/u is directed at excluding organic disease and typically includes a CBC, inflammatory markers (e.g., ESR, fecal calprotectin), and, in patients with diarrhea-predominant disease, celiac serologies (e.g., serum IgA and antitissue transglutaminase levels). Further testing is not required unless alarm features are present that suggest an alternate diagnosis. These include older age of onset (age ≥50), GI bleeding, nocturnal diarrhea (suggests secretory diarrhea), unintended
weight loss, iron deficiency anemia, elevated inflammatory markers, or a family history of early colon cancer or IBD. This patient describes typical symptoms of IBS without alarm features and does not require further testing.

.......... A CT scan is indicated in patients with alarm features concerning for malignancy (eg, weight loss, older age) or chronic pancreatitis (eg, epigastric pain worse with eating, steatorrhea).

IBS is often episodic with alternating bowel habits and varying bowel movement frequency. Postprandial symptoms are common and likely due an exaggerated gastrocolic reflex.

A patient’s father who had colon cancer that was diagnosed early (age <50) is considered an alarming feature.

The presence of nocturnal diarrhea suggests secretory diarrhea. Unlike osmotic causes of diarrhea, patients with secretory diarrhea develop symptoms while fasting, often in the middle of the night. Etiologies include chronic infection, microscopic colitis, bile salt diarrhea, or a hormone-secreting tumor (eg, gastrinoma, VIPoma). Appropriate laboratory testing and a colonoscopy should be considered.

Jejunal aspiration can be used to diagnose small intestinal bacterial overgrowth, which causes bloating and chronic diarrhea but typically occurs in patients with risk factors (eg, scleroderma, intestinal dysmotility, abnormal anatomy).

Celiac dz: Atypical presentation includes minor abdominal complaints, iron deficiency anemia, increased transaminases, arthritis, or neurologic symptoms. Symptoms are strongly correlated to dietary intake of gluten-containing foods.

A patient has irritable bowel syndrome (IBS), which is characterized by recurrent abdominal pain typically related to or relieved by defecation and associated with changes in stool frequency or form. IBS can be subclassified as either constipation predominant (IBS-C, as in this patient), diarrhea predominant (IBS-D), or mixed (ie, both constipation and diarrhea). Other common symptoms include bloating, flatulence, nausea, and passage of mucus in the stool. IBS is most frequently diagnosed in young women, and psychiatric comorbidities (eg, anxiety, depression) are common.
The diagnosis is made clinically; laboratory abnormalities (eg, anemia, elevated inflammatory markers) or other alarm features (see table) are unexpected and should prompt evaluation for alternative diagnoses. Management of IBS includes reassurance and dietary modification. For IBS-C, fiber supplementation improves constipation and may reduce abdominal pain. IBS-D is usually treated with antidiarrheal agents such as loperamide.

Patients with IBS-D should be screened for celiac disease because both disorders may present with abdominal pain, diarrhea, and bloating; screening is not indicated in IBS-C. IBS-D is characterized by a predominance of loose and frequent stools, which is not the case in this patient.

Colonoscopy is recommended in patients with alarm features to evaluate for malignancy or inflammatory bowel disease. This young patient has classic symptoms of IBS, and colonoscopy is unnecessary.

An abdominal and pelvic CT scan is used to diagnose patients with features suspicious for diverticulitis (ie, left lower quadrant abdominal pain, fever, leukocytosis), malignancy (eg, weight loss, older age), or chronic pancreatitis (eg, steatorrhea, postprandial abdominal pain). Imaging is not required in patients with IBS without alarm features.

Fecal calprotectin testing can be used to identify inflammatory causes of diarrhea (eg, infection, inflammatory bowel disease) and may be of value in patients who have fever, leukocytosis, bleeding, or nocturnal diarrhea.

Although tricyclic antidepressants are effective for IBS-related abdominal pain, they are associated with side effects (eg, drowsiness, dry mouth) and should be reserved for those who fail to respond to more benign alternatives such as fiber supplementation.
This patient most likely has **microscopic colitis** (MC), an immune-mediated colitis characterized by watery, nonbloody diarrhea. MC is a secretory diarrhea and, unlike osmotic diarrhea, may occur during periods of fasting and/or at night. Other symptoms can include fecal urgency, incontinence, abdominal pain, fatigue, and weight loss. Blood and stool studies are usually unremarkable (eg, normal C-reactive protein and hemoglobin, negative FOBT). The diagnosis is confirmed with colonoscopy and biopsy; although the colon appears grossly normal, biopsy of the mucosa reveals a **mononuclear inflammatory infiltrate** within the **lamina propria**. The disease is divided histologically into 2 types:

- Collagenous colitis - characterized by a thickened **subepithelial collagen band**
- Lymphocytic colitis - characterized by high levels of intraepithelial lymphocytes

MC is likely due to an abnormal immune response to various gastrointestinal and external agents. Certain medications—including NSAIDs, PPIs, and SSRIs—have been associated with the development of MC, as has **smoking**. Those with other **autoimmune conditions** (eg, celiac disease, autoimmune thyroiditis) are at increased risk. Older women (age >60) are disproportionately affected.

Initial management of MC includes smoking cessation and withdrawal of triggering medications. If diarrhea persists, **budesonide** and antidiarrheal medications (eg, loperamide) can be considered.

Colonoscopy demonstrates intermittent ulcerations (cobblestone appearance), and histology reveals transmural ulcerations and granulomas.
Factitious diarrhea (ie, laxative abuse) is more common in women; however, endoscopy commonly demonstrates melanosis coli (brown discoloration of the colon).

<table>
<thead>
<tr>
<th>IBD</th>
<th>Crohn disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
</table>
| Involvement | • Anywhere mouth to anus (mostly ileum & colon)  
• Perianal disease with rectal sparing  
• Skip lesions | • Rectum (always) & colon  
• Continuous lesions |
| Microscopy | • Noncaseating granulomas | • No granulomas |
| Gross findings | • Transmural inflammation  
• Linear mucosal ulcerations  
• Cobblestoning, creeping fat  
• Anal fissures, skin tags and fistulas (perianal manifestations) | • Mucosal & submucosal inflammation  
• Pseudopolyps |
| Clinical manifestations | • Abdominal pain (often RLQ)  
• Watery diarrhea (bloody if colitis) | • Abdominal pain (varying locations)  
• Bloody diarrhea |
| Intestinal complications | • Fistulas, abscesses  
• Strictures (bowel obstruction) | • Toxic megacolon |

RLQ = right lower quadrant.

IBD is characterized by idiopathic and chronic GI inflammation, and the 2 major types are ulcerative colitis (UC) and **Crohn disease** (CD).

Several features are more **suggestive of CD** than UC and are helpful in differentiating between the 2 conditions:

- Involvement of multiple portions of the GI tract (extending from the mouth to the anus)
- Presence of **noncaseating granulomas** (up to 30% of patients with CD)
- Rectal sparing
- Fistula formation
### Crohn disease

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• GI: Abdominal pain, nonbloody diarrhea, oral ulcers, malabsorption, weight loss, fistula/abscess formation</td>
<td>• ↑ WBC, iron deficiency anemia, ↑ inflammatory markers</td>
<td>• 5-ASA drugs, corticosteroids, antibiotics</td>
</tr>
<tr>
<td>• Extraintestinal: MSK (arthritis), eye (e.g., uveitis, scleritis, episcleritis), skin (e.g., erythema nodosum, pyoderma gangrenosum)</td>
<td>• Endoscopy: Focal ulcerations adjacent to normal mucosa (cobblestoning), skip areas of disease</td>
<td>• Azathioprine</td>
</tr>
<tr>
<td></td>
<td>• Radiography: Strictures, bowel wall thickening</td>
<td>• Anti-TNF therapies</td>
</tr>
</tbody>
</table>

ASA = aminosalicylic acid; GI = gastrointestinal; MSK = musculoskeletal; TNF = tumor necrosis factor; WBC = white blood cell.

Other characteristic features of CD are transmural involvement of the colon, skip lesions (disease-free regions of GI tract), cobblestone appearance of the colon, fissures, intra-abdominal abscesses, malabsorption, and perianal disease. Extraintestinal manifestations include arthritis, skin lesions, and lung disease. CD commonly presents in patients age 15-40, and there appears to be a slight female predominance. Smoking is a risk factor. Diagnosis can be confirmed with endoscopy or other imaging studies that demonstrate consistent findings (e.g., strictures). Conversely, UC is more commonly characterized by bloody diarrhea and continuous involvement of the rectum and colon.

Diagnosis is confirmed with endoscopic or radiographic studies, and treatment involves immunosuppressive therapy.

Endoscopic evaluation (e.g., colonoscopy) is central to diagnosis of both CD and UC and frequently helpful in distinguishing them from each other.

Initial management of both CD and UC involves administration of 5-aminosalicylic acids and, frequently, corticosteroids. Maintenance therapy for both diseases may involve azathioprine or TNF-alpha inhibitor.

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Infectious colitis due to a number of bacteria (including *Yersinia*), parasites, or amoebae can closely mimic Crohn disease, especially if it
presents with ileitis. However, infectious colitis is a more acute process and does not involve the oral mucosa.

Pseudopolyps are growths due to chronic inflammatory disease. These are more commonly seen in UC but frequently seen in CD.

Intestinal amebiasis due to *Entamoeba histolytica* can also cause abdominal pain with chronic diarrhea and, rarely, perianal disease; however, stools are most commonly bloody and *E histolytica* would not explain this patient’s oral ulcers.

**UC** is associated with diffuse colitis with no skip lesions and presents with colicky abdominal pain and inflammatory diarrhea (eg, blood, mucus). However, gastrointestinal involvement is limited to the colon, and both oral and perianal disease would be unusual.

**TB** enteritis should be included in the differential of CD as it may present similarly with abdominal pain, diarrhea, strictures, and fistula. However, patients classically have fever, night sweats, and weight loss, and oral ulcers would be unusual.

Vasculitides such as PAN can present with recurrent abdominal pain and diarrhea, but the abdominal pain is frequently postprandial as a result of chronic mesenteric ischemia. Patients also commonly have multiple other manifestations, including skin (eg, erythema nodosum), renal, and neurologic disease (eg, mononeuropathy multiplex). Fistulas are not a common complication.

Similar to Crohn disease (CD), most patients first develop UC at age 15-40; however, there appears to be a bimodal distribution, with a second peak at age 50-80. UC is characterized by chronic idiopathic inflammation of the colon and rectum with intermittent exacerbations. Patients commonly have abdominal pain, **bloody diarrhea**, tenesmus, fecal incontinence, and, in more severe cases, weight loss. UC may be complicated by toxic megacolon. The most common **extraintestinal** manifestations include **arthritis** (seen in this patient), uveitis, episcleritis, erythema nodosum, and primary sclerosing cholangitis.

Laboratory findings can include leukocytosis, iron deficiency anemia, reactive thrombocytosis, and elevated inflammatory markers (eg, erythrocyte sedimentation rate [ESR]). **Endoscopy** may demonstrate **erythematous** and **friable mucosa** with **ulcers**, as seen in this patient. Exudates, edema, and spontaneous bleeding may also be evident. The lesions are usually **continuous** and circumferential (unlike in CD). Biopsy shows inflammation limited to the mucosa and submucosa.
(compared to transmural inflammation in CD) with crypt abscesses and crypt distortion.

It is slightly more frequent in males and individuals of Ashkenazi Jewish descent, with a peak incidence at age 15-25. UC invariably involves the **rectosigmoid colon**

Common extracolonic manifestations of UC include erythema nodosum and pyoderma gangrenosum in the skin, episcleritis, spondyloarthritis, and sclerosing cholangitis. In addition, the incidence of **colorectal cancer** is increased in patients with UC, with the risk proportionate to the **duration** and **extent** of disease. As a result, surveillance colonoscopy is advised in patients with UC even in the absence of symptoms (typically beginning 8-10 years after the initial diagnosis).

The risk of melanoma is increased in inflammatory bowel disease, and the risk of nonmelanoma skin cancer may also be elevated in patients treated with certain immunosuppressive agents. However, a dedicated surveillance program is not currently advised.

Toxic megacolon is a severe complication of UC that can lead to peritonitis and death, but no form of regular surveillance has been shown to prevent this complication.

Uveitis is an extraintestinal manifestation of UC but does not necessitate regular surveillance.

.........

Amebic colitis also commonly presents with bloody diarrhea, abdominal pain, and elevated inflammatory markers but is typically less acute. In addition, endoscopy commonly shows skip lesions as opposed to contiguous areas of inflammation and ulcers.

Patients with chronic colonic ischemia or small-vessel vasculitis can also present with bloody diarrhea and weight loss and may be initially misdiagnosed with UC. However, the significant elevation in ESR and the involvement of the rectum, which has a dual blood supply, make ischemia due to atherosclerosis less likely. Moreover, this patient’s lack of other
findings of small-vessel inflammation (eg, skin, pulmonary, or renal involvement) reduces the likelihood of vasculitis.

<table>
<thead>
<tr>
<th><strong>Ulcerative colitis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>• Bloody diarrhea</td>
</tr>
<tr>
<td>• Weight loss, fever</td>
</tr>
<tr>
<td><strong>Endoscopic findings</strong></td>
</tr>
<tr>
<td>• Erythema, friable mucosa</td>
</tr>
<tr>
<td>• Pseudopolyps</td>
</tr>
<tr>
<td>• Involvement of rectosigmoid</td>
</tr>
<tr>
<td>• Continuous colonic involvement (no skip lesions)</td>
</tr>
<tr>
<td><strong>Biopsy</strong></td>
</tr>
<tr>
<td>• Mucosal &amp; submucosal inflammation</td>
</tr>
<tr>
<td>• Crypt abscesses</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
</tr>
<tr>
<td>• Toxic megacolon</td>
</tr>
<tr>
<td>• Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>• Colorectal cancer</td>
</tr>
<tr>
<td>• Erythema nodosum, pyoderma gangrenosum</td>
</tr>
<tr>
<td>• Spondyloarthritis</td>
</tr>
</tbody>
</table>

**Colon cancer screening in patients at increased risk**

<table>
<thead>
<tr>
<th><strong>Indication</strong></th>
<th><strong>Colonoscopy recommendations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family history of adenomatous polyps or CRC</strong></td>
<td></td>
</tr>
<tr>
<td>• 1 first-degree relative age &lt;60</td>
<td></td>
</tr>
<tr>
<td>• ≥2 first-degree relatives at any age</td>
<td>• Age 40 or 10 years before the age of diagnosis in affected relative*</td>
</tr>
<tr>
<td></td>
<td>• Repeat every 5 years</td>
</tr>
<tr>
<td><strong>Inflammatory bowel disease</strong></td>
<td></td>
</tr>
<tr>
<td>• UC</td>
<td></td>
</tr>
<tr>
<td>• CD with colonic involvement</td>
<td>• 8-10 years postdiagnosis (12-15 years if disease only in left colon)</td>
</tr>
<tr>
<td></td>
<td>• Repeat every 1-3 years</td>
</tr>
<tr>
<td><strong>Classic FAP</strong></td>
<td>• Age 10-12</td>
</tr>
<tr>
<td></td>
<td>• Repeat annually</td>
</tr>
<tr>
<td><strong>HNPPCC (Lynch syndrome)</strong></td>
<td>• Age 20-25</td>
</tr>
<tr>
<td></td>
<td>• Repeat every 1-2 years</td>
</tr>
</tbody>
</table>
Patients with **ulcerative colitis** have an increased risk of **colorectal cancer** (CRC), and the risk is proportionate to the duration and extent of disease. CRC risk is also likely elevated in patients with Crohn disease involving the colon (Crohn colitis).

CRC screening with **colonoscopy** and mucosal sampling should be offered to patients with ulcerative colitis, beginning **8 years after the initial diagnosis** (patients with disease limited to the rectum and left colon may begin 12-15 years post diagnosis). Repeat colonoscopy should be performed **every 1-2 years** thereafter. Colonic dysplasia is associated with progression to adenocarcinoma, and prophylactic colectomy is advised if dysplasia is identified.

A screening colonoscopy interval of 5 years is appropriate for patients without inflammatory bowel disease who are found to have 1 or 2 small adenomatous polyps. Five years is also an appropriate interval for patients with a first-degree family history of CRC or adenomatous polyps.

### CELIAC DISEASE

The diagnosis of celiac disease is highly correlated with positive results on serological studies, primarily **IgA anti-tissue transglutaminase** and **IgA anti-endomysial antibodies**. However, many patients with biopsy-confirmed celiac disease (as in this case) will have negative results on IgA antibody testing due to an associated **selective IgA deficiency**, which is **common in celiac disease**. If IgA serology is negative but the suspicion for celiac disease is high, total IgA should be measured (or IgG-based serologic testing should be done).

Collagenous colitis is an uncommon disorder producing chronic watery diarrhea. The colon is frequently involved, but colonoscopy shows normal mucosa. Biopsy shows mucosal subepithelial collagen deposition. Celiac dz is MC in patients of Northern European descent, and prevalence increases with age.

**D-xylose** is a monosaccharide that can be absorbed in the proximal small intestine without degradation by pancreatic or brush border enzymes. It is subsequently excreted in the urine. In the D-xylose test, the patient is given an oral dose of D-xylose, with subsequent assay of urine and venous blood. Patients with proximal small intestinal mucosal disease (eg, celiac disease) cannot absorb the D-xylose in the intestine, and urinary and venous D-xylose levels will be **low**, as seen in this patient. By contrast, patients with malabsorption due to enzyme deficiencies (eg, chronic pancreatitis) will have normal absorption of D-xylose.
A false-positive D-xylose test (ie, low urinary D-xylose level despite normal mucosal absorption) can be seen in the following:

- Delayed gastric emptying
- Impaired glomerular filtration
- **Small intestinal bacterial overgrowth** (SIBO), characterized by alterations in small intestinal flora (due to abnormal intestinal anatomy or motility), leading to bacterial fermentation of the D-xylose before it can be absorbed. SIBO is treated with *rifaximin*; therefore, it is unlikely in this patient whose D-xylose test results did not change following treatment with rifaximin.

**D-xylose test of proximal small intestinal absorption**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Bulky, foul-smelling, floating stools</td>
</tr>
<tr>
<td>Fat &amp; protein</td>
<td>Loss of muscle mass, loss of subcutaneous fat, fatigue</td>
</tr>
<tr>
<td>Iron</td>
<td>Pallor (anemia), fatigue</td>
</tr>
<tr>
<td>Calcium &amp; vitamin D</td>
<td>Bone pain (ostomalacia), fracture (osteoporosis)</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Easy bruising</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Hyperkeratosis</td>
</tr>
</tbody>
</table>
Differential diagnoses

Tropical sprue

- **Definition**: A disease characterized by chronic diarrhea with subsequent malabsorption in association with a stay in the tropics or subtropics.
- **Epidemiology**: occurs in residents of the tropics and subtropics or in travelers returning from these areas (after trips lasting several weeks)
- **Etiology**: exact cause not known; most likely due to bacterial infection that leads to structural damage of the intestinal mucosa
- **Clinical findings**
  - Chronic diarrhea with steatorrhea
  - Abdominal cramps
  - Progressive weight loss
  - Fatigue
- **Diagnostics**
  - Blood tests: megaloblastic anemia (due to deficiency of folate and vitamin B₁₂), hypoalbuminemia, hypocalcemia, vitamin D deficiency
  - Serology for antibodies to rule out celiac disease
  - Stool analysis
    - Fecal fat 10–40 g/d
    - Rule out infection with pathogens (e.g., *Giardia lamblia, Entamoeba histolytica*)
  - Endoscopy of the small bowel and biopsy
    - Villous atrophy, elongated crypts, presence of inflammatory cells (plasma cells, lymphocytes, eosinophils)
    - Mainly affects duodenum and jejunum but may progress to ileum
- **Treatment**: tetracycline in combination with folic acid for 3–6 months
*Celiac disease and tropical sprue have similar features (e.g., steatorrhea, abdominal pain, weight loss), but only tropical sprue responds to antibiotics.

**Whipple disease**

- **Definition**: an infectious disease caused by *Tropheryma whippelii*, an intracellular GP bacteria

- **Epidemiology**
  - Very rare
  - Most commonly occurs in males older than 40 years \[14\]

- **Clinical features**
  - Intestinal manifestations
    - Abdominal pain
    - Malabsorption syndrome (including diarrhea and/or steatorrhea): commonly occurs later in the disease progression
  - Extraintestinal manifestations
    - **Enteropathic arthritis** (60% of cases)
    - Arthralgias and arthritis, especially sacroiliitis (40% of cases)
    - Fever
    - Polyserositis
    - LAD
    - **Cardiac symptoms** (e.g., valve insufficiencies)
    - **Neurological symptoms** (e.g., myoclonia, ataxia, impairment of oculomotor function)

- **Diagnostics**
  - Small intestine biopsies: detection of PAS-positive foamy macrophages in the lamina propria
    - If gastrointestinal symptoms are absent, biopsies may also be taken from other sites with disease activity
- PCR testing and immunohistochemistry staining
- Imaging may show enlarged mesenteric nodes.
- If neurological complaints occur: Perform a lumbar puncture and CSF analysis and neuroimaging (MRI).

**Treatment**
- *IV ceftriaxone* for 2 weeks
- Maintenance treatment with oral *TMP-SMZ* for 1 year

*Anyone who CANT appreciate the foamy, PAS-toral rivers of England gets Whipped: the most important features of Whipple disease are Cardiac symptoms, Arthralgias, Neurologic symptoms, Trots (diarrhea), and foamy, PAS-positive macrophages on biopsy.

*Whipple disease is lethal if left untreated!*

**Treatment**

- **Lifelong gluten-free diet**
  - Abstain from products containing: *wheat, rye, barley, spelt*
  - Recommended foods: rice, maize, potatoes, soy beans, millet, potentially oats
  - In ~ 70% of cases, clinical improvement occurs within two weeks after initiating the diet.
  - Histological improvement occurs within weeks to months after beginning the diet.

- In case of secondary lactase deficiency: avoid milk products
- Iron and vitamin substitution
- Supplementation of calcium and vitamin D to prevent bone loss

*Managing celiac disease mainly consists of maintaining a lifelong gluten-free diet!*
### Complications
- See clinical features of malabsorption
- Secondary lactase deficiency
- Moderately increased risk of malignancies
  - Enteropathy-associated T-cell lymphoma (EATL):
    - Origin: intraepithelial T cells
    - Localization: often proximal jejunum
    - Clinical presentation: initially often asymptomatic, but B symptoms and gastrointestinal symptoms may be present
  - Adenocarcinoma of the small bowel

### Prevention
- There is no proven measure to prevent celiac disease.
- With infants, introducing small amounts of wheat (into the supplementary diet) between 4–6 months of age does not increase the risk of developing celiac disease

### SIBO
A patient with uncontrolled diabetes and opiate use has bloating, abdominal pain, loose stools, and a positive glucose breath test; this presentation suggests small intestinal bacterial overgrowth (SIBO). SIBO results when bacteria originating from the colon grow in excess in the small bowel. It can develop in patients with altered small bowel motility (eg, uncontrolled diabetes mellitus, chronic opiate use, scleroderma) or in those who have had surgery involving the ileocecal valve. Other predisposing conditions include small intestinal diverticula, chronic pancreatitis, and gastric hypochlorhydria (eg, chronic proton pump inhibitor use).

Patients typically have mild abdominal pain, bloating, flatulence, and watery diarrhea. Vitamin B₁₂ deficiency is common due to bacterial consumption; however, folate levels may be elevated due to bacterial production of the nutrient. The gold standard for diagnosis is a jejunal aspiration demonstrating a high bacterial concentration (eg, >10⁵ colony-forming units/mL); however, this test is invasive and not easily performed. SIBO is more commonly diagnosed by a carbohydrate breath test using either glucose or lactulose. Patients with SIBO have an earlier peak in breath hydrogen/methane (due to carbohydrate metabolism by bacteria in the small intestine) compared to those without SIBO (in whom carbohydrate metabolism primarily occurs in the colon). Treatment is with oral antibiotics (eg, rifaximin, neomycin) to reduce bacterial load.
A gluten-free diet is used to manage celiac disease, which can present with bloating and diarrhea; however, a confirmatory test is required before instituting dietary changes (eg, tissue transglutaminase, duodenal biopsy).

Mesalamine is used for mild ulcerative colitis, which presents with diarrhea and abdominal pain. However, bloody stools are common and a fecal occult blood test is often positive. A positive carbohydrate breath test is unexpected.

Omeprazole is used for gastroesophageal reflux and functional dyspepsia, neither of which result in loose stools or a positive carbohydrate breath test.

Oral vancomycin is used to treat *Clostridioides* (formerly *Clostridium*) *difficile*, which presents with severe, watery diarrhea in a patient recently exposed to antibiotics or after a recent hospitalization. However, infection with *C. difficile* would not result in a positive carbohydrate breath test.

Pancreatic enzyme replacement is used in chronic pancreatitis, which can cause abdominal pain and uncontrolled diabetes. However, the pain is typically epigastric and worse post-prandially. Additionally, steatorrhea (greasy, bulky stool that is difficult to flush) would be expected.

**LACTOSE INTOLERANCE (LI)**

| Lactase concentration declines steadily as one ages into adulthood, especially in people of non-European ancestry. MClly seen in Asian-americans (90%), African, Latin, or Native americans. Present in adults age 20-40. Symptoms occur as the osmotic load of undigested lactose passes through the intestines, drawing water into the lumen and decreasing transit time. In addition, colonic bacteria ferment lactose, creating short-chain fatty acids and hydrogen gas (bloating).
| LI can be established in patients who have a history of consuming several servings of lactose products and whose symptoms resolve after initiating a lactose-free diet. If the diagnosis is inconclusive (eg, atypical age or ethnicity), a lactose breath hydrogen test can be performed. Treatment consists of diet change or supplementation with lactase. The lactose tolerance test is cumbersome and time consuming. Currently, the **lactose hydrogen breath test** has largely replaced the lactose tolerance test.

Urine test for reducing substances is positive in patients with glucosuria, galactosuria, etc. The diarrhea secondary to lactase deficiency has a high osmotic gap, due to the unmetabolized lactose and organic acids. The osmotic gap is
calculated as 290 - [2 (stool Na + stool K)] and is greater than 50 mOsm/kg in all forms of osmotic diarrhea. Acid steatocrit is a test for fat malabsorption. Insufficient bile salt absorption by the terminal ileum can result in diarrhea in the immediate postoperative period after cholecystectomy, but symptoms typically resolve within a few weeks to months. The use of PPI has been associated with *Clostridium difficile* infections. However, *C difficile* infections are typically associated with acute onset of watery diarrhea and low-grade fever. Fecal occult blood testing is frequently positive. SIBO occurs when bacteria from the colon are inappropriately present in the small intestine. The diarrhea is frequently greasy. SIBO is usually associated with underlying motility disorders (eg, diabetes mellitus) or anatomical abnormalities (eg, jejunocolic fistula).

**Differential diagnoses**

- Food protein intolerance
  - Common antigens: cow milk proteins (lactalbumin or casein, among others); soy protein; egg protein
  - Reactions are either IgE-mediated (eg, cow’s milk allergy) or non-IgE-mediated
  - Clinical findings
    - Abdominal pain, nausea, vomiting, and diarrhea
    - Food protein-induced proctocolitis (eg, caused by milk or soy protein)
      - Affects primarily young infants; typically manifests at 2–8 weeks of age
      - Stools tinged with blood and mucus in otherwise healthy children
      - A clinical diagnosis
      - Management: continue breastfeeding and advise the mother to avoid dairy and soy products
      - Resolution of symptoms once causative antigen is removed
- IBS
- IBD
- GI infections (eg, giardiasis, bacterial, viral)
- SIBO
- CF
- Bowel malignancy

**Treatment**
Avoid or reduce intake of milk products: lactose-free or lactose-reduced products have become more readily available
- Many patients tolerate small amounts of milk (∼240 mL per day).
- Use of alternative foods, such as soy-based products
- Awareness of lactose in processed foods or foods other than dairy products (e.g., bread, salad dressings)

Oral lactase supplements
- Recommended when traveling or before consuming food or milk products containing lactose
- A wide variety of non-standardized over-the-counter lactase supplements are available

**ANOREXIA NERVOSA**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Anorexia nervosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>• BMI &lt;18.5 kg/m²</td>
<td>• Fear of weight gain, distorted body image</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Osteoporosis</td>
</tr>
<tr>
<td>• Amenorrhea</td>
</tr>
<tr>
<td>• Lanugo, hair loss, dry skin</td>
</tr>
<tr>
<td>• Gastroparesis, constipation</td>
</tr>
<tr>
<td>• Enlarged parotid glands (if binge/purge type)</td>
</tr>
<tr>
<td>• HoTN, hypothermia, bradycardia</td>
</tr>
<tr>
<td>• Cardiac atrophy, arrhythmias</td>
</tr>
</tbody>
</table>

A young woman with constipation has bradycardia, borderline HoTN, and cold intolerance (e.g., wearing multiple layers despite warm weather). Along with her **low body weight** (BMI <18.5 kg/m²) and **distorted body image** (e.g., saying her stomach is "puffing up" when it is scaphoid on examination), this presentation is suggestive of **anorexia nervosa** (AN). GI complications of AN are extremely common; decreased food intake and/or electrolyte abnormalities often results in **slowed colonic transit** time and **constipation**. Other typical gastrointestinal complications include **gastroparesis** (e.g., postprandial N, early satiety), **GER**, and elevated **LFTs**.

Because individuals with AN often try to keep their disorder hidden from others, it is also important to be aware of the possible physical signs of AN, which include abnormal vital signs, emaciation, lanugo, **dry skin, hair loss, arrhythmias**, and **parotid gland enlargement** (when purging is present). In medically stable patients, **first-line treatment includes nutritional rehabilitation and psychotherapy**.

********
Autonomic neuropathies are most common in patients with uncontrolled DM. Gastrointestinal manifestations include **gastroparesis** (eg, postprandial nausea, early satiety), and **diarrhea**; constipation is unexpected. In addition, autonomic neuropathy typically causes **tachycardia**, not bradycardia.

Functional constipation does not explain low body weight, distorted body image, or abnormal vital signs.

Hypothyroidism can also present with constipation, cold intolerance, and bradycardia. However, **HTN** and weight gain are typical; a patient w/ low blood pressure and body weight are more suggestive of AN.

Although IBS can cause alterations in bowel habits (eg, constipation, diarrhea), it is characterized by the presence of **abdominal pain**. In addition, irritable bowel syndrome would not be expected to cause abnormal vital signs, cold intolerance, or low body weight.

Partial SBO can cause intermittent constipation but typically presents with abdominal pain, distension, N, and tympanic bowel sounds. It usually occurs in the setting of prior abdominal surgery or Crohn disease.