

GASTROINTESTINAL DISORDERS

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Learning Objectives

1. Review and apply national guideline treatment strategies to the following gastrointestinal (GI) disorders: gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), ulcerative colitis (UC), Crohn disease (CD), viral hepatitis, chronic liver disease, constipation, diarrhea, irritable bowel syndrome (IBS), nausea, vomiting, pancreatitis, and upper GI bleeding, including prevention of stress-related mucosal disease (SRMD).
2. Recommend appropriate pharmacologic and non-pharmacologic interventions for the management of GERD.
3. Differentiate between clinical signs, symptoms, risk factors, and treatment of PUD associated with both *Helicobacter pylori* and nonsteroidal anti-inflammatory drugs.
4. Discuss the role of pharmacologic intervention in the treatment of nonvariceal upper GI bleeding and the prevention of SRMD.
5. Review the clinical differences in signs, symptoms, and treatment of CD and UC.
6. Identify the common manifestations of chronic liver disease and their treatment.
7. Review the treatment and prevention of both acute and chronic viral hepatitis.
8. Recognize pertinent information for educating patients and prescribers about the appropriate use of pharmacologic agents for various GI disorders.
9. Recommend appropriate pharmacologic and non-pharmacologic interventions for diarrhea and constipation.
10. Review recommendations for the treatment and prevention of nausea and vomiting.
11. Discuss the clinical and treatment differences between acute and chronic pancreatitis.
12. Discuss the role of pharmacologic intervention in the treatment of IBS.
13. Discuss commonly encountered statistical tests and concepts, using GI disorders as examples.

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of the chapter.

1. A 58-year-old African American man presents with a 2-month history of burning epigastric pain and intermittent difficulty swallowing. The pain is unrelieved by positional changes or by eating, and he has tried over-the-counter (OTC) antacids with minimal relief. He takes amlodipine 5 mg/day for hypertension and ibuprofen for occasional back pain. Which is best for this patient?
 - A. Initiate famotidine 20 mg/day.
 - B. Refer for possible endoscopic evaluation.
 - C. Initiate omeprazole 20 mg twice daily.
 - D. Change amlodipine to hydrochlorothiazide.
2. A 50-year-old woman is seen today in the clinic for severe pain related to the swelling of three of her metacarpophalangeal joints on each hand and swelling of her right wrist. She is unable to write or perform her usual household activities. Radiographs of these joints reveal bony decalcifications and erosions. A serum rheumatoid factor is obtained, which is elevated. Her medical history includes type 2 diabetes mellitus, hypertension, and dyslipidemia. Her medications include metformin 1000 mg twice daily, glyburide 10 mg/day, metoprolol 100 mg twice daily, aspirin 81 mg/day, and rosuvastatin 5 mg/day. The primary care provider would like to initiate systemic anti-inflammatory therapy for this patient's rheumatoid arthritis with high-dose nonsteroidal anti-inflammatory drug (NSAID) therapy; however, the primary care provider is worried about potential gastrointestinal (GI) toxicity. Which regimen is best for treating this patient's pain while minimizing the risk of GI toxicity?
 - A. Celecoxib 400 mg twice daily.
 - B. Indomethacin 75 mg/day plus ranitidine 150 mg/day.
 - C. Naproxen 500 mg twice daily plus omeprazole 20 mg/day.
 - D. Piroxicam 20 mg/day plus misoprostol 600 mcg three times/day.

3. A 68-year-old Hispanic man is assessed in the emergency department for a 36-hour history of black, tarry stools; dizziness; confusion; and vomiting a substance resembling coffee grounds. He has a medical history of osteoarthritis, hypertension, myocardial infarction (MI) in 1996 and 1998, and seasonal allergies. He has been taking naproxen 500 mg twice daily for 4 years, metoprolol 100 mg twice daily, aspirin 325 mg/day, and loratadine 10 mg/day. Nasogastric (NG) aspiration is positive for blood, and subsequent endoscopy reveals a 3-cm antral ulcer with a visible vessel. The vessel is obliterated using an epinephrine solution, and a rapid urease test is negative for *Helicobacter pylori*. Which recommendation is best for this patient?
- Intravenous ranitidine 50 mg/hour for 5 days.
 - Sucralfate 1 g four times/day by NG tube.
 - Oral lansoprazole 15 mg/day by NG tube.
 - Pantoprazole 80 mg intravenous bolus, followed by an 8-mg/hour infusion.
4. A 38-year-old white woman presents with an 8-week history of new-onset cramping abdominal pain together with two to four bloody stools per day. She has a medical history of urinary tract infection and reports an allergy to “sulfa”-containing medications (shortness of breath). Colonoscopy reveals diffuse superficial colonic inflammation consistent with ulcerative colitis (UC). The inflammation is continuous and extends to the hepatic flexure. Which drug therapy is best?
- Sulfasalazine 4 g/day.
 - Hydrocortisone enema 100 mg every night.
 - 6-mercaptopurine (6-MP) 75 mg/day.
 - Mesalamine (Delzicol) 1.6 g orally three times/day.
5. A 45-year-old African American man with a history of alcoholic cirrhosis (Child-Pugh class B) was seen in the clinic today for a follow-up. He was recently referred for screening endoscopy, which revealed several large esophageal varices. He has no history of bleeding; 1 month ago, propranolol 10 mg orally three times/day was initiated. At that time, his vital signs included temperature 98.7°F, heart rate (HR) 85 beats/minute, respiratory rate (RR) 15 breaths/minute, and blood pressure (BP) 130/80 mm Hg. At his evaluation today, he seems to be tolerating the propranolol dose and has no new concerns. His vital signs now include temperature 98.6°F, HR 79 beats/minute, RR 14 breaths/minute, and BP 128/78 mm Hg. Which is the best course of action?
- Continue current therapy, with a close follow-up in 4 weeks.
 - Increase propranolol to 20 mg orally three times/day.
 - Add isosorbide dinitrate 10 mg orally three times/day.
 - Change propranolol to atenolol 25 mg orally once daily.
6. A new stool antigen test to detect *H. pylori* was tested in 1000 patients with suspected peptic ulcer disease (PUD), and 865 had a positive result. All patients had also undergone a concomitant endoscopy with biopsy and culture as the gold standard comparative test, and 900 had a positive result. Of these 900 patients with confirmed disease, only 850 also had a positive result with the new stool antigen test. From these results, which best represents the sensitivity and specificity of the new stool antigen test?
- Sensitivity 82%, specificity 86%.
 - Sensitivity 85%, specificity 97%.
 - Sensitivity 94%, specificity 85%.
 - Sensitivity 96%, specificity 90%.
7. A 50-year-old Asian woman is seeking advice about a recent possible exposure to hepatitis A virus (HAV). She saw on the local news report that a chef at a local restaurant where she had eaten about 3 weeks earlier had active HAV. Having heard that HAV could be transmitted through food, she would like to know her options. She has not previously received the HAV vaccine. Which is the best recommendation for this patient?
- Initiate HAV vaccine.
 - Administer HAV immune globulin.
 - Continue to observe the patient for symptoms.
 - Initiate HAV vaccine and immune globulin.

8. A 48-year-old woman is admitted to the general medicine floor with abdominal pain, severe nausea and vomiting, and abdominal distension secondary to alcoholic hepatitis. She has a history of alcohol abuse for 20 years and takes no current medications. Her serum creatinine (SCr) is 0.5 mg/dL, aspartate aminotransferase (AST) 250 IU/L, alanine aminotransferase (ALT) 60 IU/L, total bilirubin 10.3 mg/dL, prothrombin time 19 seconds (control 12 seconds), and albumin 2.1 g/L. An abdominal paracentesis shows no evidence of spontaneous bacterial peritonitis. She reports no known drug allergies. What treatment is best for this patient's alcoholic hepatitis?
- A. Naproxen 220 mg orally twice daily.
 - B. Octreotide 50 mcg/hour intravenously.
 - C. Prednisolone 40 mg/day.
 - D. Midodrine 7.5 mg three times daily.
9. A 50-year-old, 80-kg man with a history of intravenous drug abuse and chronic hepatitis C virus (HCV) (genotype 2) was initiated on pegylated interferon (PEG-IFN) 180 mcg subcutaneously and ribavirin 400 mg orally twice daily 2 weeks ago. He returns to the clinic today with fatigue, scleral icterus, and pallor. There is no clinical evidence of bleeding. Laboratory values reveal the following: hematocrit 31% (baseline 39%), total bilirubin 3.2 mg/dL (indirect 2.7 mg/dL, direct 0.5 mg/dL), AST 150 IU/mL (baseline 300 IU/mL), ALT 180 IU/mL (baseline 400 IU/mL), SCr 0.7 mg/dL, HCV RNA 1×10^6 IU/mL (baseline 2.3×10^6 copies/mL), white blood cell count (WBC) 7.8×10^3 cells/mm³, and platelet count 160,000/mm³. Which is the most likely cause of this patient's current symptoms?
- A. Worsening of his liver disease secondary to inadequate treatment.
 - B. An adverse effect secondary to treatment with PEG-IFN.
 - C. Systemic manifestations of chronic HCV disease.
 - D. An adverse effect secondary to treatment with ribavirin.
10. A 35-year-old man with a history of Crohn disease (CD) is in the clinic today with a chief concern of mucopurulent drainage from an erythematous region on his abdomen. Examination reveals a moderate-size enterocutaneous fistula in the left upper abdominal area. He takes mesalamine (Pentasa) 250 mg 4 capsules three times/day and azathioprine 150 mg/day. His physician wants to prescribe infliximab. Which recommendation is best when initiating infliximab therapy?
- A. Rule out tuberculosis by purified protein derivative or QuantiFERON-TB test.
 - B. Administer a test dose before the initial infusion.
 - C. Admit to the hospital for the administration of all doses.
 - D. Obtain an echocardiogram to assess cardiac function.
11. A 41-year-old woman with a history of bipolar disorder and recurrent urinary tract infections is admitted to the general medicine service with severe nausea, vomiting, fever, and back pain. On examination, she has fever, dry mucous membranes, and right-sided costovertebral tenderness. A urinalysis, which reveals many bacteria, is positive for leukocyte esterase. Her SCr is 1.3 mg/dL and blood urea nitrogen (BUN) is 29 mg/dL, and she is 65 inches tall and weighs 70 kg. She takes risperidone 6 mg twice daily and sertraline 150 mg/day. She reports an allergy to trimethoprim/sulfamethoxazole that causes a rash. Which drug would be best for treating this patient's nausea?
- A. Prochlorperazine 10-mg tablet orally twice daily.
 - B. Metoclopramide orally disintegrating tablets (ODTs) 5 mg three times/day.
 - C. Ondansetron 4 mg intravenously three or four times/day.
 - D. Diphenhydramine 50 mg intravenously three or four times/day.

12. A 75-year-old man with a history of hypertension, type 2 diabetes mellitus, and chronic low back pain is admitted to the hospital for abdominal pain lasting 2 days. He denies fever, chills, or sick contacts. His last bowel movement was 3–4 days ago. On examination, he is afebrile and has moderate left upper and lower quadrant tenderness. An abdominal radiograph reveals large amounts of stool in the colon with no signs of obstruction. He currently takes lisinopril 20 mg/day, verapamil 240 mg once daily, acetaminophen 500 mg four times/day, oxycodone sustained release 20 mg twice daily, and oxycodone/acetaminophen 5/325 mg as needed for pain. His SCr is 1.8 mg/dL (baseline 1.7 mg/dL); he is 58 inches tall and weighs 68 kg. Which therapy would be best to manage this patient's constipation?
- A. Sodium phosphate oral solution.
 - B. Bisacodyl suppository.
 - C. Methylcellulose tablets.
 - D. Methylnaltrexone injection.
13. A 65-year-old man with a history of hypothyroidism, heart failure, and MI is admitted to the intensive care unit with severe community-acquired pneumonia. Six hours after admission, he develops acute respiratory failure, hypotension, and acute kidney injury from presumed sepsis; he is placed on mechanical ventilation. An NG tube is placed. He currently takes ramipril 10 mg/day, metoprolol 100 mg twice daily, levothyroxine 125 mcg/day, and aspirin 81 mg/day. His WBC is 25×10^3 cells/mm³, platelet count 170,000/mm³, SCr 3.8 mg/dL (baseline 1.1 mg/dL), potassium 4.9 mEq/L, BUN 65 mg/dL, international normalized ratio (INR) 1.1, AST 30 IU/mL, and ALT 45 IU/mL. He is 68 inches tall and weighs 79 kg. Which approach is most appropriate for preventing stress-related mucosal disease (SRMD) in this patient?
- A. Sucralfate 1 g four times/day by NG tube.
 - B. Magnesium hydroxide 30 mL four times/day by NG tube.
 - C. Cimetidine 8-mg/hour intravenous infusion.
 - D. Pantoprazole 40 mg intravenously once daily.
14. A newly available NSAID was designed to reduce the incidence of adverse GI events compared with traditional NSAIDs. A large retrospective cohort study compares the incidence of ulceration and bleeding associated with the use of this new NSAID with that of ibuprofen and naproxen. The results indicate that the new agent is associated with no statistically or clinically significant reduction in ulceration or bleeding with long-term use compared with ibuprofen and naproxen. The investigators of the study argue that the lack of difference in safety is because the drug is being promoted as safer; therefore, most patients receiving it are at a much higher baseline risk of NSAID-induced ulceration and bleeding. If this phenomenon did indeed affect the study results, which potential source of bias would probably be present?
- A. Recall bias.
 - B. Misclassification bias.
 - C. Interviewer bias.
 - D. Channeling bias.
15. A new enzyme immunoassay for HCV RNA has a reported sensitivity of 95% and a specificity of 92%. If the prevalence of HCV in a cohort of 500 patients is 40%, which best represents the positive predictive value of this new test?
- A. 75%.
 - B. 89%.
 - C. 92%.
 - D. 96%.

I. GASTROESOPHAGEAL REFLUX DISEASE (GERD)

A. Definition

1. “GERD is defined by consensus and as such is a disease comprising symptoms, end-organ effects and complications related to the reflux of gastric contents into the esophagus, oral cavity, and/or the lung”
Strength of guideline evidence is rated by the GRADE system (Level of Evidence and Strength).

Table 1. Level of Evidence and Strength

Level of Evidence	Definition
High	Further research was unlikely to change the authors’ confidence in the estimate of the effect
Moderate	Further research would probably affect confidence in the estimate of effect
Low	Further research would be expected to have an important impact on the confidence in the estimate of the effect and would be likely to change the estimate
Strength of Evidence	
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects
Conditional	There is uncertainty about the trade-offs

2. Definition subdivides GERD into the following categories:
 - a. Symptoms without erosions on endoscopy (nonerosive reflux disease)
 - b. Symptoms with erosions on endoscopy (erosive reflux disease)
3. Symptoms
 - a. Typical symptoms: heartburn (pyrosis), regurgitation, acidic taste in the mouth
 - b. Extraesophageal or atypical symptoms: Chronic cough, asthma-like symptoms, recurrent sore throat, laryngitis or hoarseness, dental enamel loss, and noncardiac chest pain; sinusitis, pneumonia, bronchitis, and otitis media are less common atypical symptoms.
 - c. Alarm symptoms: dysphagia, odynophagia, bleeding, weight loss, choking, chest pain, and epigastric mass. These symptoms warrant immediate referral for more invasive testing.
 - d. Aggravating factors: recumbency (gravity), elevated intra-abdominal pressure, reduced gastric motility, decreased lower esophageal sphincter (LES) tone, and direct mucosal irritation
 - e. Long-term complications: esophageal erosion, strictures or obstruction, Barrett esophagus, and reduction in patient’s quality of life

B. Diagnosis

1. Symptoms
 - a. A presumptive diagnosis of GERD can be established in the setting of typical symptoms of heartburn and regurgitation. Empiric therapy with a proton pump inhibitor (PPI) is recommended if patient has typical symptoms of heartburn or regurgitation. (Strong recommendation/Moderate level of evidence)
 - b. Screening for *H. pylori* is *not* recommended. (Strong/Low)
 - c. Patients with noncardiac chest pain that is suspected of having been caused by GERD should have a diagnostic evaluation before institution of therapy. (Strong/Low)
2. Endoscopy: Upper endoscopy is not necessary in the presence of typical GERD symptoms. Endoscopy is recommended in the presence of alarm symptoms and in the screening of patients at high risk of complications. Repeat endoscopy is not indicated in patients without Barrett esophagus in the absence of new symptoms. (Strong/Moderate)

3. Manometry: Recommended for preoperative evaluation but has no role in the diagnosis of GERD (Strong/Low)
4. Ambulatory pH testing
 - a. Ambulatory esophageal reflux monitoring is indicated before considering endoscopic or surgical therapy in patients with nonerosive reflux disease as part of the evaluation of patients who are refractory to PPI therapy and in situations when the diagnosis of GERD is in question. (Strong/Low)
 - b. Ambulatory reflux monitoring is the only test that can assess reflux symptom association. (Strong/Low)
 - c. Ambulatory reflux monitoring is not necessary in the presence of short- or long-segment Barrett esophagus to establish a diagnosis of GERD. (Strong/Moderate)

C. Treatment Strategies for GERD

1. Nonpharmacologic interventions and lifestyle modifications are unlikely to control symptoms in most patients. The American Gastroenterological Association (AGA) guidelines cite insufficient evidence to advocate lifestyle modifications for all patients; rather, they advocate use in targeted populations. Thus, the following lifestyle modifications should be implemented only in the patient populations specified.
 - a. Dietary modifications in patients whose symptoms are associated with certain foods or drinks. Routine global elimination of food triggers *not* recommended according to the 2013 guidelines. (Conditional/Low)
 - i. Avoid aggravating foods and beverages; some may reduce LES pressure (alcohol, caffeine, chocolate, citrus juices, garlic, onions, peppermint or spearmint) or cause direct irritation (spicy foods, tomato juice, coffee).
 - ii. Reduce fat intake (high-fat meals slow gastric emptying) and portion size.
 - iii. Avoid eating 2–3 hours before bedtime.
 - iv. Remain upright after meals.
 - b. Weight loss if overweight or recent weight gain (Conditional/Mod)
 - c. Reduce or discontinue nicotine use in patients who use tobacco products (affects LES).
 - d. Elevate head of bed and avoid meals 2–3 hours before bedtime if nocturnal symptoms. (Conditional/Low)
 - e. Avoid tight-fitting clothing (decreases intra-abdominal pressure).
 - f. Avoid medications that may reduce LES pressure, delay gastric emptying, or cause direct irritation: α -adrenergic antagonists, anticholinergics, benzodiazepines, calcium channel blockers, estrogen, nitrates, opiates, tricyclic antidepressants, theophylline, NSAIDs, and aspirin.
2. Pharmacologic therapies
 - a. Initial treatment depends on the severity, frequency, and duration of symptoms.
 - i. “Step-down” treatment: Starting with maximal therapy, such as therapeutic doses of PPIs, is always appropriate as a first-line strategy in patients with documented esophageal erosion. Advantages: Rapid symptom relief, avoidance of overinvestigation. Disadvantages: Potential overtreatment, higher drug cost, increased potential for adverse effects
 - ii. “Step-up” treatment: Start with lower-dose over-the-counter (OTC) products. Advantages: Avoids overtreatment, has lower initial drug cost. Disadvantages: Potential undertreatment (partial symptom relief; may take longer for symptom control; may lead to overinvestigation)
 - b. The AGA treatment guideline recommendation summary follows.

Table 2. AGA Treatment Guideline Recommendation

Area	Recommendation (Level/Strength)
Treatment	<ul style="list-style-type: none"> Erosive esophagitis should be treated with an 8-week course of PPIs; no major differences in products (Strong/High) Use maintenance PPIs if return of symptoms or complications (Strong/Moderate) Bedtime histamine-2 receptor antagonists can be used if a.m. PPI and nighttime symptoms, but tachyphylaxis develops (Conditional/Low) Further testing needed before use of metoclopramide or baclofen (Conditional/Mod)
Dosing	<ul style="list-style-type: none"> Traditional PPIs should be given 30–60 minutes before meals (Strong/Moderate) Newer PPIs offer dosing flexibility in relation to meals (Conditional/Moderate) Initiate PPIs once daily before a.m. meal (Strong/Moderate) Twice-daily PPIs if partial response to once-daily PPIs or nighttime symptoms (Strong/Low) Twice daily if partial response to once daily or can switch to another PPI (Conditional/Low)

PPI = proton pump inhibitor.

c. Pharmacologic agents

i. Antacids

- Calcium-, aluminum-, and magnesium-based products are available OTC in a wide variety of formulations (capsules, tablets, chewable tablets, and suspensions).
- Neutralizing acid and raising intragastric pH results in decreased activation of pepsinogen and increased LES pressure; rapid onset of action but short duration, necessitating frequent dosing
- Some products (Gaviscon) contain the antirefluxant alginic acid, which forms a viscous layer on top of gastric contents to act as a barrier to reflux (variable added efficacy).
- Used as first-line therapy for intermittent (less than twice weekly) symptoms or as breakthrough therapy for those on PPI/histamine-2 receptor antagonist (H2RA) therapy; not appropriate for healing established esophageal erosions
- Adverse reactions: Constipation (aluminum), diarrhea (magnesium), accumulation of aluminum and magnesium in renal disease with repeated dosing
- Drug interactions: Chelation (fluoroquinolones, tetracyclines); reduced absorption because of increases in pH (ketoconazole, itraconazole, iron, atazanavir, delavirdine, indinavir, nelfinavir) or increases in absorption, leading to potential toxicity (raltegravir, saquinavir)

ii. Histamine-2 receptor antagonists

- Reversibly inhibit histamine-2 receptors on the parietal cell
- All agents available as prescription and OTC products; a variety of formulations available; generics exist for all prescription products

Table 3. Histamine-2 Receptor Antagonists

Agent	Oral OTC Formulations	Oral Prescription Formulations
Ranitidine (Zantac)	75-mg tablet (Zantac 75) 150-mg tablet (Zantac 150)	150-mg tablets/EFFERdose tablets/granules 300-mg tablet 15 mg/mL of syrup
Cimetidine (Tagamet)	200-mg tablet (Tagamet-HB)	300-, 400-, 800-mg tablets 300 mg/5 mL of solution
Nizatidine (Axid)	75-mg tablet (Axid AR)	150-mg/300-mg capsules 15 mg/mL of solution
Famotidine (Pepcid) Pepcid Complete	10-mg tablets, gelatin capsules, chewable tablets (Pepcid AC) 20-mg tablets 10 mg + 800 mg of calcium carbonate + 165 mg of magnesium hydroxide chewable tablets	20-mg/40-mg tablets 20-mg/40-mg rapidly disintegrating tablet 40-mg/5-mL suspension

OTC = over the counter.

- (c) OTC H2RA products may be used for on-demand therapy for intermittent mild–moderate GERD symptoms; preventive dosing before meals or exercise is also possible for all agents. Higher prescription doses are often necessary for more severe symptoms or for maintenance dosing. Prolonged use is associated with the development of tolerance and reduced efficacy (tachyphylaxis).
 - (d) Therapy with H2RAs is less efficacious than therapy with PPIs in healing erosive esophagitis.
 - (e) Adverse effects: Most are well tolerated. Central nervous system (CNS) effects such as headache, dizziness, fatigue, somnolence, and confusion are the most common. Older adults and patients with reduced renal function are more at risk. Prolonged cimetidine use is associated with rare development of gynecomastia.
 - (f) Drug interactions: May affect the absorption of drugs dependent on lower gastric pH (e.g., ketoconazole, itraconazole, iron, atazanavir, delavirdine, indinavir, nelfinavir) or increases in absorption leading to potential toxicity (raltegravir, saquinavir). Cimetidine also inhibits cytochrome P450 (CYP) enzymes 1A2, 2C9, 2D6, and 3A4. Warfarin, theophylline, and other agents metabolized by these enzymes may be affected. Cimetidine may also compete with medications and creatinine for tubular secretion in the kidney.
- iii. Proton pump inhibitors
- (a) Irreversibly inhibit the final step in gastric acid secretion; greater degree of acid suppression achieved and typically longer duration of action than H2RAs
 - (b) Most effective agents for short- and long-term management of GERD and for management of erosive disease
 - (c) Most costly agents: Omeprazole and lansoprazole now available as generic prescription-strength products and OTC. The OTC products are considered safe and effective for intermittent short-term (2 weeks) use in patients with typical heartburn symptoms. Long-term use of OTC products should be discussed with prescriber to prevent loss of follow-up or to assess for potential undertreatment.
 - (d) Most effective when taken orally before meals; for divided dosing, give evening dose before evening meal instead of at bedtime.

Table 4. Proton Pump Inhibitors

Product	Dosage Forms
Esomeprazole (Nexium)	Delayed-release capsule (20 mg/40 mg) IV solution (20- and 40-mg vials) Delayed-release oral suspension (2.5-, 10-, 20-, 40-mg packets)
Omeprazole (Prilosec) Prilosec OTC Zegerid OTC	Delayed-release capsule (10 mg/20 mg/40 mg); delayed-release 20-mg tablet (magnesium salt) Immediate-release powder for oral suspension (20- and 40-mg packets); sodium bicarbonate buffer = 460 mg of Na ⁺ /dose (2 20-mg packets are not equivalent to 1 40-mg packet) Zegerid OTC 20-mg immediate-release capsules with sodium bicarbonate (1100 mg/capsule)
Lansoprazole (Prevacid) Lansoprazole (Prevacid 24HR)	Prevacid 24HR 15-mg delayed-release capsule Delayed-release capsule (15 mg/30 mg) Delayed-release oral suspension (15 mg/30 mg) Delayed-release orally disintegrating tablet (15 mg/30 mg)
Rabeprazole (AcipHex)	Delayed-release enteric-coated tablet (20 mg)
Pantoprazole (Protonix)	Delayed-release tablet (20 mg/40 mg) IV solution (40 mg/vial) Pantoprazole granules 40 mg/packet
Dexlansoprazole (Dexilant)	Delayed-release capsule (30 mg/60 mg)
Esomeprazole strontium	Delayed-release capsule (20 mg/40 mg base)
Product	Alternative Administration Technique
Omeprazole (Prilosec) Esomeprazole (Nexium) Zegerid	Open capsules; mix with applesauce or juice Simplified omeprazole suspension; contents dissolved in bicarbonate (NG/OG) Open esomeprazole capsules and mix with 60 mL of water by NG tube, or dissolve oral suspension in 15 mL of water and administer by NG tube; IV bolus, or continuous infusion Zegerid mix packet with 20 mL water in syringe (NG)
Lansoprazole (Prevacid)	Open capsules; mix with applesauce, ENSURE, cottage cheese, pudding, yogurt, or strained pears, or 60 mL of tomato, orange, or apple juice Open capsules + 40 mL of apple juice (NG/OG) Simplified lansoprazole suspension; contents dissolved in bicarbonate (NG/OG) <i>DO NOT</i> use oral suspension for NG/OG; mix packet with 30 mL of water and swallow Orally disintegrating tablet by oral syringe: Use 4 mL for 15 mg or 10 mL for 30 mg Orally disintegrating tablet by NG tube (>8 French): Same preparation as for oral syringe
Rabeprazole (AcipHex)	<i>DO NOT CRUSH</i>
Pantoprazole (Protonix)	<i>DO NOT CRUSH</i> IV (bolus or continuous infusion) Pantoprazole suspension (compounded with bicarbonate)
Dexlansoprazole (Dexilant)	Open capsules and sprinkle on applesauce

IV = intravenous; NG = nasogastric; OG = orogastric.

(e) Adverse reactions

- (1) Overall, well tolerated; possible adverse effects include headache, dizziness, nausea, diarrhea, and constipation. Long-term use is not associated with significant increases in endocrine neoplasia or symptomatic vitamin B₁₂ deficiency. As an option, the 2013 AGA guidelines list the switching of PPIs in patients experiencing adverse effects. (Conditional/Low)
- (2) Summary of major adverse effects of PPIs and prevention and management strategies

Table 5. Summary of Major Adverse Effects of PPIs and Prevention and Management Strategies

Adverse Effect	Prevention and Management
Risk of fracture (hip, wrist, spine)	<ul style="list-style-type: none"> • Concern about fractures should not affect decision to use PPIs, except in patients with other known risk factors for hip fracture (Conditional/Moderate) • Patients with osteoporosis can remain on PPIs • Limit dose and duration • Ensure adequate calcium and vitamin D • BMD screening if at risk of low bone mass • Weight-bearing exercise
Hypomagnesemia	<ul style="list-style-type: none"> • Reevaluate need • Limit dose and duration • Consider baseline testing (presence of diuretics, digoxin) • Supplementation
<i>Clostridium difficile</i> –associated diarrhea	<ul style="list-style-type: none"> • Reevaluate need • Limit dose and duration • Evaluate for <i>C. difficile</i> if patient receiving PPI has diarrhea that is not improving • Have patients report diarrhea
Community-acquired pneumonia	<ul style="list-style-type: none"> • Short-term use may increase risk; long-term risk is not elevated (Conditional/Moderate) • Assess for vaccine status

BMD = bone mineral density; PPI = proton pump inhibitor.

(f) Drug interactions

- (1) Inhibition of CYP450: Omeprazole inhibits the metabolism of substrates such as diazepam through CYP2C19 inhibition.
 - (A) Recent data suggest a reduced effectiveness of clopidogrel through CYP2C19-mediated inhibition of conversion to active metabolite by omeprazole. Recommendations according to the U.S. Food and Drug Administration (FDA) are to avoid omeprazole and to use pantoprazole as an alternative. The 2013 AGA guidelines consider the PPI/clopidogrel interaction NOT clinically significant. (Strong/High)
 - (B) Interaction with high-dose intravenous methotrexate. The labeling for both intravenous methotrexate and the PPIs has been updated to include this interaction, which places patients at higher risk of methotrexate toxicity. Proposed mechanisms include reduced methotrexate excretion by PPI inhibition of BCRP or reduced renal excretion by inhibition of renal H⁺/K⁺-ATPase. Patients receiving high-dose intravenous methotrexate should avoid PPI use, with a switch to ranitidine if needed. There is some thought that holding the PPI dose for 2 days before and after methotrexate administration may prevent the interaction.

- (2) Drugs with pH-dependent absorption (e.g., ketoconazole, itraconazole, protease inhibitors)
- iv. Proton pump inhibitors
 - (a) The 2013 guidelines state that therapy for GERD other than acid suppression, including prokinetic therapy or baclofen, should not be used in patients with GERD without diagnostic evaluation. (Conditional/Mod)
 - (b) Work through cholinergic mechanisms to facilitate increased gastric emptying.
 - (c) Metoclopramide: Dopamine antagonist; must be dosed several times a day; associated with many adverse effects such as dizziness, fatigue, somnolence, drowsiness, extrapyramidal symptoms (EPS), and hyperprolactinemia. New 5- and 10-mg ODT formulations (metoclopramide [Metozolv ODT]) are now available. Indications for GERD and diabetic gastroparesis
 - (d) Bethanechol: Cholinergic agonist; poorly tolerated because of adverse effects such as diarrhea, blurred vision, and abdominal cramping; may also increase gastric acid production
 - (e) Cisapride: Available only on a restricted basis for patients whose other therapies have failed; cisapride was withdrawn from the market initially because of cardiac arrhythmia (torsades de pointes) when used in combination with drugs inhibiting CYP3A4.
- v. Surgical therapy
 - (a) Surgical therapy is a treatment option for long-term therapy in patients with GERD. (Strong/High)
 - (b) Surgical therapy is generally not recommended in patients who do not respond to PPI therapy. (Strong/High)
 - (c) Surgical therapy is as effective as medical therapy for carefully selected patients with chronic GERD when performed by an experienced surgeon. (Strong/High)
 - (d) Obese patients contemplating surgical therapy for GERD should be considered for bariatric surgery. Gastric bypass would be the preferred operation in these patients. (Conditional/Moderate)

Patient Case

1. A 55-year-old man with an 8-month history of GERD symptoms 4 or 5 days/week has been receiving lansoprazole 15 mg daily by mouth, with the use of magnesium hydroxide for breakthrough symptoms. His symptoms are still present 3–4 days/week and are disruptive to his daily life. He has implemented lifestyle modifications and has been adherent to the lansoprazole. His medical history is significant for hypothyroidism. He takes levothyroxine 100 mcg once daily. An endoscopy performed last week revealed no ulcers or erosions. Which treatment approach is best for this patient?
 - A. Add metoclopramide 10 mg 4 times/day.
 - B. Increase lansoprazole to 15 mg twice daily
 - C. Switch to omeprazole 20 mg daily.
 - D. Add sucralfate 1000 mg 4 times/day.

II. PEPTIC ULCER DISEASE

A. Classification of peptic ulcer disease (PUD)

1. Duodenal ulcer
 - a. Common causes: *H. pylori* infection (95%), NSAIDs, low-dose aspirin
 - b. Uncommon causes: Zollinger-Ellison syndrome, hypercalcemia, granulomatous diseases, neoplasia, infections (cytomegalovirus, herpes simplex, tuberculosis), ectopic pancreatic tissue
 - c. Clinical signs and symptoms: Epigastric pain, possibly worse at night; often, pain occurs 1–3 hours after a meal and may be relieved by eating. Pain may also be episodic. Associated symptoms may include heartburn, belching, a bloated feeling, nausea, and anorexia.
2. Gastric ulcer
 - a. Common causes: NSAIDs, *H. pylori* infection
 - b. Uncommon causes: Crohn disease (CD), infections (cytomegalovirus, herpes simplex)
 - c. Clinical signs and symptoms: Epigastric pain, which is often made worse by eating; associated symptoms may include heartburn, belching, a bloated feeling, nausea, and anorexia.
3. Complications of PUD
 - a. Bleeding
 - b. Gastric outlet obstruction
 - c. Perforation
4. Patients at risk of NSAID-induced GI toxicity

Table 6. Risk Factors for NSAID-Induced GI Complications

Category	Risk Factors
High risk	1. History of complicated ulcer 2. Several (>2) risk factors 3. Concomitant use of corticosteroids, anticoagulants, or antiplatelet drugs
Moderate risk (1 or 2 risk factors)	1. Age >65 years 2. High-dose NSAID therapy 3. History of uncomplicated ulcer 4. Concurrent use of aspirin (including low dose), corticosteroids, or anticoagulants
Low risk	No risk factors

GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

- a. Some NSAIDs such as ibuprofen, diclofenac, and nabumetone are intrinsically less toxic to the GI tract than naproxen, which is considered moderate risk. Other agents such as piroxicam, indomethacin, and ketorolac are considered high-risk drugs.
- b. Duration of NSAID use (higher risk in first 3 months). Presence of chronic debilitating disorders such as rheumatoid arthritis or cardiovascular (CV) disease may also contribute to the increased GI toxicity of NSAIDs, but these are not generally considered independent risk factors.
- c. *H. pylori* infection is thought to confer additive risk of GI toxicity in NSAID users.
5. Diagnosis
 - a. Symptom presentation
 - b. Testing for *H. pylori* infection: Practitioners must be willing to treat if testing is positive because *H. pylori* is a known carcinogen.
 - i. Testing is indicated for patients with active ulcer disease, history of PUD, or gastric mucosa-associated lymphoid tissue lymphoma.
 - ii. The test-and-treat strategy for identifying *H. pylori*-positive patients is also acceptable for patients with unevaluated dyspepsia who have no alarm symptoms and are younger than 55 years

c. Diagnostic tests for *H. pylori* infection

i. Invasive (endoscopic)

- (a) Histology: 90%–95% sensitive, 98%–99% specific, subject to sampling error
- (b) Rapid urease tests (*Campylobacter*-like organism [CLO] test, Hp-fast, and PyloriTek): Detect the presence of ammonia (NH₃) in a sample generated by *H. pylori* urease activity; 80%–95% sensitive, 95%–100% specific. False negatives may result from a partly treated infection, GI bleeding, achlorhydria, or use of PPIs, H₂RAs, or bismuth. Patients should discontinue antisecretory agents for at least 1 week before test is performed.
- (c) Culture: Costly, time-consuming, and technically difficult, although 100% specific

ii. Noninvasive

- (a) Serologic tests (QuickVue *H. pylori* gII, FlexSure HP): Detect immunoglobulin G (IgG) to *H. pylori* in the serum by enzyme-linked immunosorbent assay (ELISA); 85% sensitive, 79% specific. Cannot distinguish between active infection and past exposure. Because antibodies persist for long periods after eradication, cannot use to test for eradication after treatment. Newly available tests will detect the presence of CagA or VacA antibodies.
- (b) Urea breath test (BreathTek UBT, PYtest): Detects the exhalation of radiolabeled CO₂ after the ingestion of ¹³C- or ¹⁴C-radiolabeled urea. *H. pylori* hydrolysis of the radiolabeled urea results in CO₂ production; 97% sensitive, 95% specific. Used to make a diagnosis and to test for eradication. Recent use of antibiotics or PPIs may result in false negatives in up to 40% of patients. Patients should discontinue antisecretory agents or antibiotics at least 2 weeks before UBT testing or wait 4 weeks after treatment has ended before having the UBT performed.
- (c) Stool antigen tests (Premier Platinum HpSA, ImmunoCard STAT! HpSA): Polyclonal or monoclonal antibody tests that detect the presence of *H. pylori* in the stool; 88%–92% sensitive, 87% specific. Can be used to make a diagnosis and confirm eradication. Recent use of bismuth, antibiotics, or PPIs may also result in false negatives. Patients should discontinue antisecretory agents or antibiotics at least 2 weeks before stool antigen testing or wait 4 weeks after treatment has ended before having the stool antigen test performed.

B. Treatment of *H. pylori*–Associated Ulcers

1. General recommendations, based on the American College of Gastroenterology (ACG) guidelines, are to include an antisecretory agent (preferably a PPI) plus at least two antibiotics (clarithromycin and amoxicillin or metronidazole) in the eradication regimen.
2. Therapy duration is 7–14 days, depending on the regimen chosen. The ACG guidelines state that 14 days is preferred. Most regimens last for 10 days.
3. Follow-up testing for eradication should be performed in patients with a history of ulcer complication, gastric mucosa–associated lymphoid tissue lymphoma, early gastric cancer, or recurrence of symptoms.
4. UBTs or stool antigen tests are preferred for confirming eradication (should wait at least 4 weeks after treatment for both).
5. Quadruple-based therapy with bismuth subsalicylate, metronidazole, tetracycline, and a PPI is considered a first-line treatment and can also be used for 14 days if triple-based therapy fails or if the patient has an intolerance of or allergy to components of the triple-drug therapy. Pylera, a quadruple-based therapy formulated with tetracycline, bismuth, and metronidazole in 1 capsule, contains the bismuth subcitrate salt rather than the subsalicylate salt.
6. Sequential therapy involved administration of a PPI and amoxicillin given first for the first 5 days, followed by a PPI, clarithromycin, and tinidazole for an additional 5 days. This therapy requires further validation before widespread use will be accepted.
7. A bismuth-based quadruple therapy for 14 days or a levofloxacin-based triple therapy for 10 days can be used in patients who have not responded to initial regimens as salvage therapy.

Table 7. *H. pylori* Treatment Regimens

Regimen ^{a,b}	Duration (days)	Efficacy (%) ^c
Lansoprazole 30 mg BID + amoxicillin 1000 mg BID + clarithromycin 500 mg BID	10–14	81–86
Esomeprazole 40 mg once daily + amoxicillin 1000 mg BID + clarithromycin 500 mg BID	10–14	70–85
Omeprazole 20 mg BID + amoxicillin 1000 mg BID + clarithromycin 500 mg BID	10–14	70–85
Rabeprazole 20 mg PO BID + amoxicillin 1000 mg BID + clarithromycin 500 mg BID	7	70–85
Bismuth subsalicylate 525 mg QID + metronidazole 500 mg TID + tetracycline 500 mg QID + PPI BID	14	75–90
Bismuth subcitrate 420 mg + tetracycline 375 mg + metronidazole 375 mg 3 capsules QID + PPI BID ^d	10	85–92
Sequential therapy: PPI + amoxicillin 1 g BID for 5 days; then PPI, clarithromycin 500 mg BID + tinidazole 500 mg BID for 5 days	10 (5 each treatment)	>90

^aPantoprazole 40 mg BID or dexlansoprazole does not have an FDA-approved indication for *H. pylori* eradication; however, it could be substituted in any of the 10- to 14-day regimens.

^bMetronidazole 500 mg BID can be substituted for amoxicillin or clarithromycin in patients with penicillin or macrolide allergy for the triple-drug regimens. Treat for 14 days in this instance.

^cRates are based on intention to treat.

^dTriple-capsule formulation.

BID = twice daily; PO = orally; PPI = proton pump inhibitor; QID = 4 times/day; TID = 3 times/day.

C. Primary Prevention of NSAID-Induced Ulcers

1. Implement risk factor modification.
2. Test and treat for *H. pylori* if patient is beginning long-term NSAID therapy.
3. Determine level of GI-related risk (low, medium, high) using Table 6.
4. Because of the association of increased risk of CV events with NSAID use, patient's CV risk should be determined as well. The ACG guidelines define those at *high CV risk* as patients who require low-dose aspirin for prevention of cardiac events. Naproxen is the only NSAID that has been touted as not appearing to increase the risk of CV events; therefore, its use is preferred in patients with CV risk factors per the ACG guidelines. However, in February 2014 an FDA panel voted against label changes that would indicate a lower cardiovascular thrombotic risk (<http://www.fda.gov/AdvisoryCommittees/Calendar/ucm380871.htm>).

Table 8. Preventive Strategies Based on Risk of NSAID-Related GI Complications and CV Risk

<p>If low CV risk and:</p> <p>Low GI risk^a → NSAID (lowest dose of least ulcerogenic agent)</p> <p>Moderate GI risk^b → NSAID + PPI or misoprostol</p> <p>High GI risk^c → COX-2 inhibitor + PPI or misoprostol</p>
<p>If high CV risk (requirement for low-dose aspirin) and:</p> <p>Low GI risk^a → Naproxen + PPI or misoprostol</p> <p>Moderate GI risk^b → Naproxen + PPI or misoprostol</p> <p>High GI risk^c → Avoid NSAIDs or COX-2 inhibitors</p>

^aNo risk factors.

^bOne or two risk factors present.

^cPositive history of ulcer complication or several (more than 2) risk factors or use of steroids and anticoagulants.

COX-2 = cyclooxygenase-2; CV = cardiovascular; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

5. Misoprostol (Cytotec) should be given at full doses (800 mcg/day in divided doses); however, this therapy is poorly tolerated because of excessive nausea, vomiting, diarrhea, and abdominal cramping.
6. Concomitant use of antiplatelet agents and NSAIDs
 - a. Need for antiplatelet therapy should first be evaluated.
 - b. If antiplatelet therapy is deemed necessary, assess for the presence of GI risk factors (see Table 6). These guidelines also cite dyspepsia or GERD symptoms as risk factors.
 - c. Test and treat for *H. pylori* in patients with a history of a nonbleeding ulcer and in those with a history of an ulcer-related complication. Eradicating *H. pylori* before beginning long-term antiplatelet therapy is optimal.
 - d. PPIs are the preferred gastroprotective agents for both treatment and prevention of aspirin- and NSAID-associated GI injury.
 - e. Gastroprotective therapy should be prescribed for patients with GI risk factors who require the use of any NSAID (including OTC and cyclooxygenase-2 [COX-2] inhibitors) in conjunction with cardiac-dose aspirin.
 - f. Gastroprotective therapy should be prescribed for patients with GI risk factors who require preventive doses of aspirin. Aspirin doses greater than 81 mg/day should not be used in patients with GI risk factors during the long-term phase of aspirin therapy.
 - g. PPIs should be prescribed for patients receiving concomitant aspirin and anticoagulant therapy (unfractionated heparin, low-molecular-weight heparin, warfarin, dabigatran, rivaroxaban, apixaban, and fondaparinux).
 - h. A target international normalized ratio (INR) of 2–2.5 should be used in patients for whom warfarin is added to concomitant aspirin and clopidogrel therapy. The combination of both aspirin and clopidogrel with warfarin should be used only when benefit outweighs risk.
 - i. Clopidogrel is not recommended as a substitute for patients with recurrent ulcer bleeding. Aspirin plus a PPI is superior to clopidogrel.
 - j. The health care provider (HCP) who decides to discontinue aspirin therapy in patients with short-term bleeding episodes should weigh the risks of subsequent GI or cardiac events.
 - k. For patients receiving dual antiplatelet therapy (aspirin plus clopidogrel) who require elective endoscopy (particularly colonoscopy and polypectomy), consider deferring if patient is at high risk of cardiac events. Elective endoscopy should be deferred for 1 year after the placement of drug-eluting stents.

D. Treatment and Secondary Prevention of NSAID-Induced Ulcers

1. Risk factor modification
2. Discontinue or lower NSAID dose, if possible. Ulcers will heal with appropriate treatment, but healing may take longer with continued NSAID use.
3. Test for *H. pylori* and treat, if present.
4. Drug therapy
 - a. PPIs: Drugs of choice for healing and secondary prevention of NSAID-induced ulcers. Combination product Vimovo contains esomeprazole with naproxen in the same tablet (375 mg/20 mg or 500 mg/20 mg).
 - b. Misoprostol: Appears to be as effective as PPIs for healing and secondary prevention however, it necessitates several doses per day and is poorly tolerated because of the high incidence of diarrhea and abdominal pain.
 - c. Cyclooxygenase inhibitors: Celecoxib was shown to have rates of ulcer recurrence and bleeding comparable to those of a diclofenac plus omeprazole combination; use of celecoxib may be limited by its recent association with CV effects. Use of celecoxib is uncertain in combination with low-dose aspirin for secondary prevention of GI events.
 - d. Combination of a COX-2 inhibitor and a PPI is not well studied but may be considered in high-risk patients such as older adults, especially if they are receiving aspirin plus steroids or warfarin or have a history of a recent complicated GI event and require continued NSAID or aspirin use.
 - e. The H₂RAs: Inferior to misoprostol and PPIs in healing and preventing recurrence
 - f. Clopidogrel is not recommended as a substitute in patients with recurrent ulcer bleeding. Aspirin plus a PPI is superior to clopidogrel.
3. CV safety of COX-2 inhibitors and NSAIDs
 - a. The main theory underlying the development of excess thrombotic events with COX-2 inhibitor use is that when COX-2–mediated prostacyclin production is reduced, the prothrombotic prostaglandin thromboxane A continues to be produced by COX-1, leading to the development of a prothrombotic state. The degree of development of these events does not appear to be equal across the class of COX-2 inhibitors.
 - b. Guidelines for appropriate use and safety of NSAIDs, aspirin, and COX-2 inhibitors have been published by both the AHA and a multidisciplinary clinical group.
 - c. Celecoxib was not associated with increases in CV events until the Adenoma Prevention with Celecoxib trial for cancer prevention was terminated in December 2004. Daily doses of 400 and 800 mg of celecoxib conferred a 2.5- and 3.4-fold higher risk of fatal and nonfatal MI, which suggests a dose-related response for this toxicity.
 - d. A stepped approach is recommended for patients with CV disease or risk factors for ischemic heart disease who require analgesic treatment of musculoskeletal symptoms based on recommendations from the AHA.
 - i. Consider using acetaminophen, aspirin, tramadol, or short-term narcotics first.
 - ii. Nonacetylated salicylates can be considered next.
 - iii. Non–COX-2-selective NSAIDs can be used next, followed by NSAIDs with some COX-2 activity. Use the lowest dose possible to control symptoms.
 - iv. The COX-2 inhibitors should be reserved as last line. In patients at increased risk of thromboembolic events, coadministration with aspirin and a PPI may be considered.
 - v. Routinely monitor BP, renal function, and signs of edema or GI bleeding.

- e. Methods to reduce CV risk such as tobacco cessation, BP reductions, lipid control, and glucose control are recommended for NSAID users but have not been proved to reduce NSAID-associated CV risk. In patients for whom the risk of GI bleeding outweighs the CV risk, lower-risk NSAIDs such as ibuprofen, etodolac, diclofenac, or celecoxib should be used. In patients for whom the CV risk outweighs the risk of GI bleeding, COX-2 inhibitors should be avoided. Limit the dose and therapy duration if possible.
- f. An FDA article also reviews the effects of ibuprofen on the attenuation of aspirin's antiplatelet effects. The AHA recommends that ibuprofen be taken at least 30 minutes after or 8 hours before the ingestion of immediate-release low-dose aspirin to prevent this interaction.
- g. In February 2014 an FDA panel voted against label changes that would indicate a lower cardiovascular thrombotic risk with naproxen compared with other NSAIDs. (<http://www.fda.gov/AdvisoryCommittees/Calendar/ucm380871.htm>). This was despite a 2013 meta-analysis that demonstrated that naproxen had lower CV risk compared with high-dose diclofenac and ibuprofen (Lancet 2013;382:769–79).

Patient Cases

2. A 68-year-old woman referred to a gastroenterologist has intermittent upper abdominal pain with anemia and heme-positive stools. She has a history of type 2 diabetes mellitus with peripheral neuropathy and hypertension. She reports no known drug allergies and takes metformin 1000 mg twice daily, aspirin 325 mg/day, lisinopril 20 mg once daily, and gabapentin 1000 mg three times/day. In addition, she reports using OTC ketoprofen daily for the past 2 months secondary to uncontrolled pain. Her colonoscopy is negative, but her endoscopy reveals a 1-cm gastric ulcer with an intact clot. A rapid urease test (CLO) performed on the ulcer biopsy specimen is negative. Which treatment is best for this patient's ulcer?
 - A. Ranitidine 150 mg twice daily for 4 weeks.
 - B. Lansoprazole 30 mg twice daily plus amoxicillin 1000 mg twice daily plus clarithromycin 500 mg twice daily for 10 days.
 - C. Lansoprazole 30 mg/day for 8 weeks.
 - D. Misoprostol 200 mcg two times/day for 8 weeks.
3. A 42-year-old man is in the clinic with the chief concern of sharp epigastric pain for the past 6 weeks. He states that the pain is often worse with eating and that it is present at least 5 days/week. He states that although he initially tried OTC antacids with some relief, the pain returns about 3 hours after each dose. He does not currently take any other medications. He reports an allergy to sulfa-containing medications (rash). His practitioner is concerned about a potential peptic ulcer and tests him for *H. pylori* using a UBT, the result of which is positive. Which treatment for *H. pylori* is best?
 - A. Amoxicillin 1 g twice daily plus clarithromycin 500 mg twice daily plus omeprazole 20 mg twice daily for 5 days.
 - B. Cephalexin 1 g twice daily plus clarithromycin 500 mg twice daily plus omeprazole 20 mg twice daily for 10 days.
 - C. Bismuth subsalicylate 525 mg four times/day plus tetracycline 500 mg four times/day plus metronidazole 500 mg three times/day plus omeprazole 20 mg twice daily for 14 days.
 - D. Levofloxacin 500 mg once daily plus metronidazole 500 mg twice daily plus omeprazole 20 mg twice daily for 21 days.

III. UPPER GI BLEEDING

- A. Background: Prevalence is 170 cases/100,000 adults; associated annual costs are about \$750 million, and mortality is 6%–10%.
- B. Causes of Upper GI Bleeding
 1. Peptic ulcer disease (40%–70%)
 - a. NSAIDs and low-dose aspirin use
 - b. *H. pylori*
 2. Esophagitis
 3. Erosive disease
 4. Esophageal varices
 5. Mallory-Weiss tear
 6. Neoplasm
 7. Stress ulcers (critically ill patients)
- C. Clinical Symptoms and Presentation
 1. Hematemesis or “coffee-ground” emesis
 2. Hematochezia
 3. Nausea, vomiting
 4. Melena
 5. Shock (tachycardia, clammy skin)
 6. Hypotension
 7. Associated organ dysfunction (renal, hepatic, cardiac, cerebral hypoperfusion)

Table 9. Clinical Predictors of Death Associated with Nonvariceal Upper GI Bleeding

Advanced age (>75 years at highest risk)	Red blood on rectal examination
Shock or hypotension	Elevated serum urea
>1 comorbid condition	Serum creatinine >150 $\mu\text{mol/L}$ (1.7 mg/dL)
Continued bleeding or rebleeding	Elevated aminotransferases
Blood in gastric aspirate	Sepsis
Hematemesis	Onset of bleeding during hospitalization for other causes

Table 10. Predictors of Persistent or Recurrent Upper GI Bleeding

Age >65 years	Initial hemoglobin <10 g/dL or hematocrit <30%
Shock (systolic blood pressure <100 mm Hg)	Coagulopathy
Comorbid illness	Endoscopic findings:
Erratic mental status	Active bleeding on endoscopy
Ongoing bleeding	Presence of high-risk stigmata
Red blood on rectal examination	Adherent clot
Melena	Ulcer size ≥ 2 cm
Blood in gastric aspirate	Gastric or duodenal ulcer
Hematemesis	Location of ulcer on superior or posterior wall

D. Management of Ulcer-Related GI Bleeding

1. Volume resuscitation and hemodynamic stabilization
 - a. Placement of one or two large-bore intravenous catheters
 - b. Replacement with crystalloid such as 0.9% normal saline is preferred; colloids such as blood can be given after initial resuscitation in patients with hemoglobin of less than 7 g/dL to maintain a hemoglobin concentration of 8–10 g/dL.
2. Risk stratification
 - a. Clinical signs and symptoms
 - b. Use of clinical scoring scales such as Blatchford or Rockall scores to determine the risk of early rebleeding and the need for urgent versus nonemergency intervention. Patients with low risk of rebleeding may be discharged after endoscopy.
 - c. Placing an NG tube for aspiration can be considered but is not required.
 - d. Endoscopy (within 24 hours if possible or within 12 hours with high-risk clinical features)
 - e. Assessment of comorbid illnesses (liver disease, coagulopathies, cardiac status)
3. Endoscopic therapy
 - a. Endoscopic therapy associated with reductions in rebleeding, need for surgery, and mortality. Perform within 12–24 hours of presentation.
 - b. Observation of low-risk stigmata (a clean-based ulcer or a nonprotuberant pigmented dot in an ulcer bed) is not an indication for hemostatic therapy.
 - c. Clots visible in an ulcer bed should be irrigated, with treatment of underlying lesions.
 - d. The presence of high-risk stigmata warrants immediate hemostatic therapy.
4. Endoscopic strategies
 - a. The combination of injection and coaptive therapy is the most efficacious approach.
 - b. The use of either technique plus pharmacotherapy is superior to monotherapy.
 - c. Sclerotherapy: No single solution for injection is superior to another.
 - i. Epinephrine with or without ethanolamine is inferior by itself. Combine with another endoscopic therapy.
 - ii. Cyanoacrylate
 - iii. Thrombin
 - iv. Sodium tetradecyl sulfate
 - v. Polidocanol
 - d. Thermal coaptive therapy: No single method is superior to another.
 - i. Heater probe thermocoagulation
 - ii. Multipolar electrocoagulation
 - iii. Laser coagulation (not often used because of cost)
 - iv. Argon plasma coagulation
 - e. Placement of hemostatic clips
5. Pharmacotherapeutic management of nonvariceal upper GI bleeding
 - a. Treatment guidelines apply to bleeding NSAID-induced ulcers as well.
 - b. Remove medications that are contributing to bleeding (e.g., NSAIDs).
 - c. Pre-endoscopic erythromycin, 250 mg intravenously, can be considered to improve diagnostic yield, but this has not been shown to improve outcomes (conditional recommendation).
 - d. PPI therapy
 - i. Use of a pre-endoscopic dose (80-mg intravenous bolus, followed by an 8-mg/hour intravenous infusion) of PPI may be considered. This does not result in reduced mortality, surgery, or rate of rebleeding, but it may reduce the lesion size, the possibility of finding a high-risk lesion, and the need for endoscopic therapy. PPIs may be given if endoscopy will be delayed or cannot be performed.

- ii. Bolus 80 mg plus a continuous infusion of 8 mg/hour for 72 hours after endoscopic therapy for patients with active bleeding or nonbleeding visible vessel or with adherent clot. Intravenous pantoprazole or esomeprazole can be used; most data are with intravenous omeprazole (used in Europe).
 - iii. Associated with decreases in rebleeding, mortality, and need for surgery in patients with active bleeding who have undergone successful endoscopic intervention.
 - iv. Oral once-daily PPI therapy can be used for patients with a flat spot or clean-based ulcer.
 - e. Use of H2RAs or somatostatin-octreotide is *not* recommended.
 - f. Test for *H. pylori* and treat if results are positive. If negative, retest. No need for a PPI after eradication
 - g. Assess the need for continued secondary prevention with PPI therapy. If needed, a single daily oral dose of a PPI is recommended.
 - h. Assess the need for NSAID or aspirin use. If NSAID therapy is needed, then use of a COX-2 inhibitor plus a PPI is recommended, barring any significant CV risk. Otherwise, a PPI should be used.
 - i. If use of low-dose aspirin is required, reinstitute when CV risk is thought to outweigh GI risk. Use a PPI and reinstitute within 1–3 days, if not within 1 week. Clopidogrel has a higher rate of rebleeding than aspirin.
 - j. Long-term PPI therapy is recommended for ulcers not associated with NSAIDs or *H. pylori*.
- E. Prophylaxis of Stress-Related Mucosal Disease (SRMD) in Critically Ill Patients
- 1. Stress-related injury: Superficial diffuse upper GI ulceration
 - 2. Stress ulcer: Deeper mucosal ulceration; may lead to bleeding and hemodynamic compromise
 - 3. Contributing factors to SRMD development
 - a. Hypoperfusion of the GI tract
 - b. Altered susceptibility to gastric acid
 - c. Loss of defense mechanisms: Mucous/bicarbonate layer, prostaglandins, cellular renewal
 - d. Alterations in gastric motility; may affect absorption of drugs
 - 4. Pharmacologic prevention
 - a. Not routinely recommended in non-intensive care unit settings
 - b. Recommended in patients in an intensive care unit setting with the risk factors listed in Table 11.

Table 11. Risk Factors for Initiation of Prophylaxis for SRMD

Mechanical ventilation >48 hours ^a	Two or more of the following:
Coagulopathy (platelet count <50,000/mm ³ , INR >1.5) ^a	Sepsis syndrome
Thermal injury (>35% BSA)	ICU stay >1 week
Severe head or spinal cord injury	Occult bleeding
GI bleeding or ulceration within past year	High-dose corticosteroids
Multiple trauma (injury severity score >16)	(250 mg of hydrocortisone equivalent)
Perioperative transplant period	Hepatic failure
Low intragastric pH	Acute renal insufficiency
Major surgery (lasting >4 hours)	Hypotension
Acute lung injury	Anticoagulation

^aIndependent risk factors for SRMD.

BSA = body surface area; GI = gastrointestinal; ICU = intensive care unit; INR = international normalized ratio; SRMD = stress-related mucosal disease.

5. Preventive treatment options
 - a. Antacids: Effectively raise pH and prevent bleeding; require several oral doses per day or administration by NG tube; possibility of diarrhea, constipation, and electrolyte abnormalities
 - b. Sucralfate
 - i. Works by providing a direct mucosal barrier; also modulates pepsin, mucus activity, bicarbonate secretion, and tissue growth repair
 - ii. Use has fallen out of favor. Requires many oral doses or administration by NG tube. May lead to aluminum accumulation and constipation. No effect on platelet count and is associated with lower rates of pneumonia development. Possibility of binding to other drugs in GI tract
 - iii. General efficacy regarding bleeding considered similar to that of H2RAs
 - c. Histamine-2 receptor antagonists
 - i. Reduce gastric acid secretion by inhibition of histamine stimulation of the parietal cell; may be associated with the development of tolerance or tachyphylaxis with continued use
 - ii. Considered efficacious in the prevention of clinically significant bleeding; oral, intravenous intermittent dosing, and continuous infusion are all possible options; high-dose intravenous (ranitidine, cimetidine, or famotidine) use can be considered first-line therapy. Cimetidine is the only H2RA that is FDA approved for SRMD prevention.
 - iii. Associated with CNS adverse effects and the rare development of thrombocytopenia; require adjustment for renal dysfunction
 - d. Proton pump inhibitors
 - i. The American Society of Health-System Pharmacists guidelines include minimal recommendations for PPI use because of the lack of data at that time; however, PPIs are commonly used for SRMD prevention.
 - ii. PPIs are similar to H2RAs in safety and efficacy.
 - iii. Oral or intravenous routes may be used. Alternative formulations exist for patients with difficulty swallowing or with feeding tubes (see section on GERD).
 - iv. Oral PPIs are also as efficacious as intravenous PPI therapy for maintaining equivalent pH
 - v. Intravenous PPI therapy is generally considered equivalent to high-dose intravenous H2RA therapy.
 - vi. Recent associations with *C. difficile* infections in hospitalized patients

IV. INFLAMMATORY BOWEL DISEASE

- A. Background
 1. Inflammatory bowel disease (IBD) includes both UC and CD. In some instances, UC may be indistinguishable from CD. This is referred to as indeterminate or intermediate colitis.
 2. Pathophysiology: Continuing inflammation of the GI mucosa; exact cause is unknown, but it is thought that the inflammation is secondary to an antigen-driven response
 3. Contributing factors
 - a. Defects in the intestinal epithelial barrier and immune system
 - b. Genetic: Definite genetic association; first-degree relatives of affected patients have a 4–20 times higher risk of developing IBD
 - c. Environmental
 - i. NSAIDs: Worsen IBD, probably secondary to alteration of epithelial barrier
 - ii. Smoking: Worsens CD; however, is associated with improvement in UC symptoms

- iii. Luminal bacteria: Endogenous intestinal bacteria thought to be highly involved in stimulating the intestinal inflammatory response observed in IBD
- iv. Dietary: Dietary antigens may also contribute to ongoing inflammation.
- d. Various proinflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor (TNF), release and contribute to the ongoing inflammatory process.

B. Clinical Features

1. Presenting symptoms common to both diseases include fever, abdominal pain, diarrhea (may be bloody, watery, or mucopurulent), rectal bleeding, and weight loss. Symptoms may vary depending on disease location.

Table 12. Clinical Features of Inflammatory Bowel Disease

Clinical Findings	Ulcerative Colitis	Crohn Disease
Bowel involvement	Confined to rectum and colon Terminal ileal involvement (backwash ileitis) occurs in a minority of patients	May be anywhere from mouth to anus (66% of cases located in ileum)
Perianal involvement	Unlikely	Yes
Depth of ulceration	Superficial	May extend to submucosa or deeper
Continuous inflammation	Very common	Rarely, a patchy, “cobblestone” appearance
Histology	Nontransmural, crypt abscesses	Transmural lesions Granulomas
Fistula, perforation, or strictures	No	Yes
Development of toxic megacolon	Yes	No
Malabsorption or malnutrition	Rare	Yes, often vitamin deficiencies; possible growth retardation in children
Risk factor for colorectal cancer	Yes	Uncommon
Pseudopolyps	Common	Fairly uncommon

2. Systemic manifestations
 - a. Both UC and CD may present with concurrent systemic manifestations.
 - b. Hepatobiliary: primary sclerosing cholangitis, cholangiocarcinoma, hepatitis or cirrhosis, cholelithiasis, steatosis
 - c. Rheumatologic arthritis, sacroiliitis, ankylosing spondylitis
 - d. Dermatologic: erythema nodosum, aphthous ulcers, pyoderma gangrenosum
 - e. Ocular: iritis or uveitis, episcleritis
3. Gauging clinical severity
 - a. Ulcerative colitis (based on Truelove and Witt criteria)

Table 13. Clinical Severity of Ulcerative Colitis

Mild	Moderate	Severe	Fulminant
<4 stools/day (\pm blood) No fever, anemia, or tachycardia Normal ESR	>4 stools/day (\pm blood) Minimal signs of systemic toxicity	>6 stools/day with blood Temp >99.5°F HR >90 beats/minute ESR >30 mm/hour Hb <75% of normal Abdominal tenderness Bowel wall edema	>10 stools/day with continuous blood Temp >99.5°F HR >90 beats/minute ESR >30 mm/hour Transfusions required Abdominal pain Dilated colon

ESR = erythrocyte sedimentation rate; Hb = hemoglobin; HR = heart rate; Temp = temperature.

- b. Crohn disease
 - i. Mild–moderate: Tolerates oral administration; absence of fever, dehydration, and abdominal tenderness; less than 10% weight loss
 - ii. Moderate–severe: Failed treatment of mild–moderate; these symptoms usually present; possibly anemia, nausea and vomiting, considerable weight loss
 - iii. Severe–fulminant: No response to outpatient steroids; high temperature, abdominal pain, persistent vomiting; possible obstruction, abscess, cachexia, rebound tenderness
 4. General management considerations
 - a. Rule out possible infectious causes of bloody diarrhea in patients with acute symptoms.
 - b. Most patients will receive a colonoscopy to confirm the diagnosis and extent of disease.
 - c. Surgery is a viable option when complications (abscess, fistula, perforation) occur or when fulminant disease is unresponsive to medical treatment.
 - d. Distribution and severity of disease will dictate the initial choice of therapeutic agents.
 - e. Most patients will require maintenance therapy because of the high incidence of relapse after induction therapy; the relapse rate is 35%–80% at 2 years for CD and 50%–70% at 1 year for UC.
- C. Medical Management of IBD
 1. Adjunctive therapies: Use with caution in active disease because reduction in motility may precipitate toxic megacolon.
 2. Loperamide (Imodium): May be useful for proctitis or diarrhea; 2 mg after each loose stool (16 mg/day maximum)
 3. Antispasmodics
 - a. Dicyclomine (Bentyl), 10–40 mg orally four times/day
 - b. Propantheline (Pro-Banthine), 7.5–15 mg orally three times/day
 - c. Hyoscyamine (Levsin), 0.125–0.25 mg orally/slow release every 4 hours as needed
 4. Cholestyramine (Questran): Possibly for bile salt–induced diarrhea after ileal resection
- D. Medications Used to Treat IBD
 1. Treatment is selected on the basis of disease location and severity.
 2. Aminosalicylates
 - a. Used for both induction and maintenance of remission
 - b. Sulfasalazine: Prototype agent (Azulfidine, Azulfidine-EN)
 - i. The drug is cleaved by colonic bacteria to the active portion (5-aminosalicylate) and the inactive carrier molecule sulfapyridine.

- ii. Efficacy is best in colonic disease because of the colonic activation of the drug. Toxicity may be dose related and related to the sulfapyridine portion.
- iii. Dose-related adverse effects: GI disturbance, headache, arthralgia, folate malabsorption
- iv. Idiosyncratic adverse effects: rash, fever, pneumonitis, hepatotoxicity, bone marrow suppression, hemolytic anemia, pancreatitis, decreased sperm production in men
- v. Avoid in patients with a sulfa allergy.
- vi. Doses are 4–6 g/day for induction and 2–4 g/day for maintenance; available as immediate-release and enteric-coated products. Doses should be titrated beginning at 500–1000 mg once or twice daily to avoid adverse effects.
- c. 5-Aminosalicylates (non-sulfa containing)
 - i. In general, better tolerated than sulfasalazine; considered first line in mild–moderate UC and CD
 - ii. Product selection depends on location of disease.
 - iii. Olsalazine is associated with secretory diarrhea in up to 25% of patients.
 - iv. Rare instances of nephrotoxicity with use of 5-aminosalicylates

Table 14. Aminosalicylate Formulations

Drug	Trade Name	Formulation	Strength	Daily Dosage Range (g)	Site of Action
Mesalamine	Rowasa ^a	Enema	4 g/60 mL	4	Rectum Terminal colon
	Delzicol	Delayed-release capsule	400 mg	1.6–4.8	Distal ileum
	Asacol HD	Delayed-release resin	800 mg		Colon
	Canasa	Suppository	1000 mg	1	Rectum
	Pentasa	Microgranular-coated tablet	250 mg 500 mg	2–4	Small bowel Colon
	Lialda	MMX delayed-release tablet	1.2 g	2.4–4.8 (once daily)	Colon
	Apriso	INTELLICOR delayed- and extended-release capsule	0.375 g	0.375–1.5 (once daily)	Colon
Olsalazine	Dipentum	Dimer of mesalamine (capsule)	250 mg	1–3	Colon
Balsalazide	Colazal	Capsule	750 mg	2–6.75	Colon
	Giazo	Tablet	1100 mg		

^aGeneric mesalamine enema now available.

3. Corticosteroids
 - a. Work quickly to suppress inflammation during acute flares
 - b. No role in maintenance therapy; however, more than 50% of patients with severe disease may become steroid-dependent
 - c. Budesonide is about 15 times more potent than prednisone; because of its high first-pass metabolism, allow a 2-week overlap when changing from prednisone to budesonide to prevent adrenal insufficiency. Formulated to release in the terminal ileum and treats only terminal ileal and ascending colonic disease
 - d. Adverse effects (systemic therapy) are adrenal suppression, glucose intolerance, hypertension, sodium/water retention, osteoporosis, cataracts, and impaired wound healing.

Table 15. Corticosteroid Preparations

Route	Agents	Dose	Comments
Oral	Prednisone Prednisolone	20–60 mg/day	Taper ASAP
	Budesonide capsule (Entocort EC)	9 mg/day PO, then 6 mg/day Can be continued for up to 3 months	Minimal absorption; indicated for mild–moderate active CD involving terminal ileum or ascending colon
	Budesonide tablet (Uceris)	9 mg/day in the a.m. for 8 weeks	Minimal absorption; indicated for mild–moderate active UC
IV	Hydrocortisone Methylprednisolone	100 mg every 8 hours 15–48 mg/day	7- to 10-day course; change to PO when gut is functional
Topical (rectal)	Cortenema (100 mg/60 mL)	100 mg HS	Hydrocortisone-based products
	Cortifoam (90 mg/applicator)	90 mg/day BID	Used for patients with distal disease
	Anucort-HC 25 mg Proctocort 30 mg	25–50 PR BID	Suppositories; use for proctitis

ASAP = as soon as possible; BID = twice daily; CD = Crohn disease; HS = at bedtime; IV = intravenous; PO = by mouth; PR = rectally; UC = ulcerative colitis.

4. Immunomodulators

- 6-MP (or Purinethol), azathioprine (Imuran, Azasan; prodrug of 6-MP), or methotrexate
- Doses: Azathioprine 2–2.5 mg/kg/day orally, 6-MP 1–1.5 mg/kg/day orally, methotrexate 15–25 mg/week intramuscularly (CD only)
- Indicated only for maintenance because of its long onset of action (3–15 months)
- Use may result in a steroid-sparing effect.
- Azathioprine and 6-MP are metabolized by the enzyme thiopurine methyltransferase (TPMT); reduced expression of TPMT may result in slower metabolism and increased toxicity. TPMT activity or *TPMT* genotype or phenotype should be determined before initiating therapy.
- Adverse reactions
 - Azathioprine and 6-MP: Pancreatitis (3%–15%), bone marrow suppression, nausea, diarrhea, rash, possible hepatotoxicity. Risk of hepatosplenic T-cell lymphoma, especially in younger male patients. Risk is great if combined with a TNF α antagonist.
 - Methotrexate: Bone marrow suppression, nausea, diarrhea, rash, pulmonary toxicity, hepatotoxicity

5. Infliximab (Remicade)

- Chimeric monoclonal antibody versus TNF
- Indicated for both CD and UC
 - Moderate–severe active disease
 - Fistulizing CD
 - Maintenance of moderate–severe disease
- Available as intravenous infusion only; very expensive
- Studies of patients whose conventional therapy failed; response is about 40%–80%
- Dosing: Moderate–severe active disease or fistulizing disease: 5 mg/kg as single dose, followed by 5 mg/kg at 2 and 6 weeks, then every 8 weeks as maintenance. Patients losing response with time may be treated with a 10-mg/kg dose.

- f. Adverse reactions
 - i. Infusion related: Hypotension, fever, chills, urticaria, pruritus; infuse over at least 2 hours (may pretreat with acetaminophen or antihistamine)
 - ii. Delayed hypersensitivity: May be associated with fever, rash, myalgia, headache, or sore throat 3–10 days after administration
 - iii. Infection: Use is associated with the reactivation of latent infections (bacterial, including disseminated tuberculosis, fungal, and sepsis); do not give to patients with active infections. Tuberculosis should be ruled out in patients before any biologic agents are initiated.
 - iv. Heart failure exacerbations: Contraindicated in New York Heart Association class III/IV heart failure; do not exceed 5-mg/kg dose in other patients with chronic heart failure.
 - v. Antibody induction: Up to 50% of patients may develop antinuclear antibodies; 19% may develop anti–double-stranded DNA antibodies.
 - vi. Bone marrow suppression (pancytopenia)
 - vii. Black box warning. Applies to all tumor necrosis factor alpha (TNF α) antagonists: Unusual cancers have been reported in children and teenage patients taking TNF blockers. Hepatosplenic T-cell lymphoma has occurred mostly in teenaged or young adult males with CD or UC who were taking infliximab and azathioprine or 6-MP.
 - viii. Hepatitis (reactivation of hepatitis B virus [HBV], autoimmune hepatitis); discontinue use if liver function tests rise to more than 5 times the upper limit of normal (ULN)
 - ix. Vasculitis with CNS involvement
- 6. Adalimumab (Humira)
 - a. Fully humanized antibody to TNF α ; therefore, theoretically, no development of antibodies
 - b. Indicated for both induction and maintenance therapy for moderate–severe active CD and UC in patients unresponsive to conventional therapy; also indicated for patients who no longer respond to infliximab
 - c. Dosing: Induction, 160 mg subcutaneously on day 1 (given as four separate 40-mg injections) or two 40-mg/day injections for 2 consecutive days, followed by 80 mg subcutaneously 2 weeks later (day 15). Then, can decrease dose to 40 mg subcutaneously every 2 weeks starting on day 29 of therapy
 - d. Efficacy
 - i. Complete remission rates at week 4 ranges from 21% to 54%
 - ii. Efficacy rates for maintenance therapy range from 56% to 79% at week 4 to 36% to 46% at week 56.
 - iii. The adverse effect profile of adalimumab is similar to that of infliximab, except for the development of antibodies to adalimumab.
- 7. Certolizumab (Cimzia)
 - a. Humanized monoclonal antibody fragment linked to polyethylene glycol (PEG), with murine-complimentary determining regions
 - b. Indicated for maintenance therapy for moderate–severe active CD in patients unresponsive to conventional therapy
 - c. Dosing: Induction, 400 mg subcutaneously, then 400 mg subcutaneously at weeks 2 and 4; maintenance dose is 400 mg subcutaneously every 4 weeks
 - d. Efficacy
 - i. Patients with a C-reactive protein concentration greater than 10 mg/L have the best response. Up to 37% response at 6 weeks versus 26% for placebo.
 - ii. Up to 62% of patients with an initial response and a C-reactive protein concentration greater than 10 mg/L may be maintained in remission at 26 weeks.
 - iii. Certolizumab adverse effect profile is similar to that of other TNF α antagonists.

8. Golimumab (Simponi)
 - a. Human IgG1k monoclonal antibody
 - b. Indicated for moderate to severe UC in patients intolerant of previous therapies or requiring continuous steroid therapy
 - c. Dosing: 200 mg subcutaneously at week 0, then 100 mg at week 2, then 100 mg every 4 weeks
 - d. Similar efficacy and toxicity profile compared with other TNF α antagonists.
9. Natalizumab (Tysabri)
 - a. Humanized monoclonal antibody that antagonizes integrin heterodimers and inhibits α 4 integrin-mediated leukocyte adhesion
 - b. Indicated for inducing and maintaining clinical response and remission in adult patients with moderate–severe active CD who have had an inadequate response to, or are unable to tolerate, conventional therapies and inhibitors of TNF α
 - c. Dosing
 - i. All patients must be enrolled in the TOUCH program before the drug is dispensed because of its association with progressive multifocal leukoencephalopathy.
 - ii. Induction and maintenance doses are both 300 mg intravenously every 4 weeks. If no effect after 12 weeks or inability to discontinue steroids within 6 months of beginning therapy, treatment should be discontinued
 - d. Efficacy
 - i. The ENACT 1 and 2 trials showed similar results for natalizumab and placebo at 10 weeks (56% vs. 49%; $p=0.05$). However, those who initially responded had rates of sustained response (61% vs. 28%; $p=0.001$) at week 36.
 - ii. Discontinue if no response is observed by week 12 of treatment.
 - iii. May also improve quality of life in patients who initially respond after 48 weeks of treatment.
 - e. Safety
 - i. Natalizumab is associated with the development of progressive multifocal leukoencephalopathy. Monitor for mental status changes while on treatment. Consider magnetic resonance imaging and lumbar puncture if mental status changes or weakness is observed.
 - ii. Potential for hepatotoxicity; monitor for jaundice or other signs of liver disease
 - iii. Increased risk of infection
 - iv. Infusion-related reactions: Observe patient for 1 hour after infusion.
 - v. The drug should not be used in combination with inhibitors of TNF α or immunosuppressants.
10. Vedolizumab (Entyvio)
 - a. Humanized monoclonal antibody that targets α 4 β 7-integrin-mediated leukocyte adhesion
 - b. Indicated use as induction and maintenance therapy for patients with UC and CD for whom other therapies, including TNF- α antagonists, have failed
 - c. Induction and maintenance doses are both 300 mg intravenously given at 0, 2, and 6 weeks, then given every 4 weeks. Discontinue if no evidence of improvement at 14 weeks.
 - d. The GEMINI I study demonstrated efficacy in induction and maintenance for moderate–severe UC with a clinical response rate of 47% vs. 25% versus placebo at 6 weeks ($p<0.001$). The GEMINI II Study of induction and maintenance of moderate to severe CD demonstrated rates of remission of 14.5% vs. 6.8% for placebo at 6 weeks ($p=0.02$).
 - e. Safety profile is similar to that of natalizumab, with the exception of a lower risk of progressive multifocal leukoencephalopathy because vedolizumab's mechanism is more specific for leukocyte homing in the gut. There is not a required prescribing program for this agent.
11. Medical management of UC: Treatment is selected according to disease location and severity
 - a. Guideline definitions of UC distribution
 - i. Distal disease: Distal to splenic flexure (may use oral/systemic or topical [rectal] therapy)
 - ii. Extensive disease: Proximal to splenic flexure (requires systemic/oral therapy)

- b. Mild–moderate distal disease
 - i. First-line therapy: Topical (enema/suppository) aminosalicylates are preferred and are superior to oral aminosalicylates and topical corticosteroids (grade A evidence). Oral budesonide (Uceris) can be considered an alternative first-line therapy.
 - ii. Patients refractory to oral aminosalicylates or topical corticosteroids may respond to mesalamine enemas or suppositories.
 - iii. Oral mesalamine plus topical mesalamine can be considered, and this combination may be more effective than either agent alone (grade A evidence).
 - iv. Patients refractory to the above agents may require 40–60 mg of oral prednisone or infliximab given as 5 mg/kg intravenously at weeks 0, 2, and 6.
 - v. Maintenance
 - (a) Mesalamine suppositories (1 g rectally every day or 1 g three times/week) are effective for maintaining remission in patients with proctitis.
 - (b) Mesalamine enemas (2–4 g/day) are effective for maintaining remission in patients with distal disease extending to the splenic flexure and may also be given three times/week.
 - (c) Oral treatment with sulfasalazine (2–4 g/day), mesalamine (1.5–4.8 g/day), or balsalazide (6.75 g/day) is also effective.
 - (d) Combining oral and topical mesalamine is more effective than using either regimen alone.
 - (e) Topical steroids have no role in maintenance therapy.
 - (f) Nicotine replacement (15–25 mg/day transdermally) may improve symptoms as an adjunctive therapy. Effects seem to be most beneficial in ex-smokers.
 - (g) Azathioprine, 6-MP, infliximab, or adalimumab may be necessary if patients do not respond to aminosalicylate therapy.
- c. Mild–moderate active extensive disease
 - i. First-line therapy: Oral sulfasalazine (4–6 g/day) or an alternative aminosalicylate at a dose equivalent to mesalamine 4.8 g/day or oral budesonide (Uceris) can be considered an alternative first-line therapy.
 - ii. Patients refractory to the combination of oral and topical aminosalicylate agents may require oral corticosteroids (40–60 mg of prednisone).
 - iii. Azathioprine or 6-MP may be used for patients who are unresponsive to oral steroids but not acutely ill enough to require intravenous treatment with infliximab or adalimumab.
 - iv. Infliximab, adalimumab, golimumab, or certolizumab may be used for moderate active disease in patients who are steroid-refractory or steroid-dependent or are intolerant of, or unresponsive to, azathioprine or 6-MP.
 - v. Maintenance
 - (a) Aminosalicylates are the preferred agents for maintenance of remission.
 - (b) Patients should not be treated with long-term steroids for maintenance therapy.
 - (c) Azathioprine or 6-MP is an effective steroid-sparing agent for maintenance of remission; can be used in combination with aminosalicylates
 - (d) Infliximab may be given for maintenance of moderate disease at a dose of 5 mg/kg every 8 weeks if patients are initially responsive. Adalimumab may also be used at a dose of 40 mg subcutaneously every 2 weeks. Certolizumab can be used at a dose of 100 mg subcutaneously every 4 weeks.
- d. Severe disease
 - i. Patients with severe symptoms refractory to oral/topical aminosalicylates or corticosteroids should be treated with a 7- to 10-day course of intravenous corticosteroids (hydrocortisone 300 mg or methylprednisolone equivalent 60 mg/day).

- ii. Alternatively, infliximab, adalimumab, or certolizumab should be used for severe disease as a next step in therapy.
 - iii. Antibiotics, particularly metronidazole, have mixed results in the treatment of active UC. In the absence of infection, their use provides little clinical benefit. Antibiotics may be used in severe colonic disease or for patients with pouchitis.
 - iv. Patients refractory to 3–5 days of intravenous corticosteroids are candidates for intravenous cyclosporine (4 mg/kg/day; target concentration of 350–500 ng/mL), followed by oral therapy at 8 mg/kg/day with a target concentration of 200–350 ng/mL if initial response to intravenous cyclosporine is obtained. Adding azathioprine or 6-MP to oral cyclosporine has shown better long-term success in maintaining remission, and this should be implemented.
 - v. Patients refractory to the above are candidates for colectomy.
 - vi. Patients with toxic megacolon should undergo bowel decompression, treatment with broad-spectrum antibiotics, and possibly colectomy.
 - e. Management of pouchitis
 - i. Patients with ileoanal anastomosis who develop symptoms of pouchitis may be treated with metronidazole (250 mg or 20 mg/kg three times/day), ciprofloxacin 500 mg twice daily, or the combination of both antibiotics.
 - ii. Use of oral probiotics (VSL #3) may be beneficial in preventing recurrent pouchitis.
12. Medical management of CD
- a. Treatment is selected according to disease location and severity.
 - b. Mild–moderate active disease: First line for ileal, ileocolonic, or colonic disease
 - i. Oral aminosalicylate (mesalamine 3.2–4 g/day or sulfasalazine 6 g/day). Commonly used but considered minimally effective
 - ii. Budesonide 9 mg/day is preferred for terminal ileal or ascending colonic disease.
 - iii. Metronidazole 10–20 mg/kg/day may be used in patients not responding to oral aminosalicylates, but it is generally more effective in patients with perianal or colonic disease.
 - iv. Ciprofloxacin 1 g/day is considered as effective as mesalamine (generally, second line) but is usually more effective in perianal or colonic disease and is typically used in combination with metronidazole.
 - c. Moderate–severe disease
 - i. Corticosteroids (prednisone 40–60 mg/day or budesonide 9 mg/day if terminal ileal involvement) until resolution of symptoms and resumption of weight gain
 - ii. Anti-TNF α agents in combination with thiopurines are the preferred therapies for induction of remission for moderate to severe CD. Thiopurine monotherapy or methotrexate is not recommended to induce remission in moderate to severe active CD according to the 2013 guideline update.
 - (a) Infliximab 5 mg/kg is an alternative first-line treatment (improvement in up to 80% of patients). Infliximab may be combined with azathioprine in patients whose therapy with aminosalicylates and corticosteroids has failed and who are naive to biologic agents. This combination is superior to each drug given alone; however, there is a risk of hepatosplenic T-cell lymphoma.
 - (b) Certolizumab 400 mg subcutaneously and then 400 mg subcutaneously at weeks 2 and 4, or adalimumab 160 mg subcutaneously initially followed by 80 mg subcutaneously 2 weeks later, may also be considered for use as an alternative therapy for moderate to severe disease, particularly in patients with C-reactive protein values greater than 10 mg/L.
 - (c) Adalimumab may be used as initial therapy or for patients who no longer respond to infliximab therapy because they developed antibodies to infliximab.

- iii. Natalizumab or vedolizumab 300 mg intravenously every 4 weeks may be considered for patients who did not respond to any other conventional medical therapy.
- iv. Methotrexate maintenance therapy (15–25 mg/week intramuscularly or subcutaneously) is effective in patients whose active disease has responded to intramuscular methotrexate and who have steroid-dependent or steroid-refractory disease.
- d. Severe–fulminant disease
 - i. Severe symptoms despite oral corticosteroids or infliximab therapy
 - ii. Assess need for surgical intervention (mass, obstruction, and abscess).
 - iii. Administer intravenous corticosteroids (40–60 mg of prednisone equivalent).
 - iv. Parenteral nutrition may be needed after 5–7 days.
 - v. Possibly use intravenous cyclosporine if steroids fail.
- e. Maintenance therapy
 - i. No role for long-term corticosteroid use, but budesonide may be used for up to 3 months in patients with mild–moderate disease having ileal involvement
 - ii. Azathioprine/6-MP or infliximab, or the combination, can be used after induction with corticosteroids.
 - iii. Azathioprine/6-MP or mesalamine (more than 3 g/day) may also be used after surgical resection to prevent recurrence.
 - iv. Infliximab 5 mg/kg at 0, 2, and 6 weeks and then every 8 weeks or adalimumab 40 mg subcutaneously every other week (starting on day 29 of therapy)
 - v. Natalizumab or vedolizumab 300 mg intravenously every 4 weeks may be considered for patients who did not respond to any other conventional medical therapy.
 - vi. Methotrexate intramuscularly 25 mg for up to 16 weeks, followed by 15 mg/week intramuscularly, is effective for patients with chronic active disease.
- f. Perianal disease
 - i. Simple perianal fistulas
 - (a) Antibiotics: Metronidazole or ciprofloxacin
 - (b) Azathioprine/6-MP
 - (c) Infliximab, adalimumab, certolizumab
 - ii. Complex perianal fistulas
 - (a) Infliximab, adalimumab, or certolizumab
 - (b) Antibiotics: Metronidazole or ciprofloxacin (mainly as adjunctive therapy in this case)
 - (c) Azathioprine/6-MP or methotrexate
 - (d) Cyclosporine or tacrolimus

Patient Cases

4. A 35-year-old man presents with newly diagnosed mild–moderately active UC affecting his descending colon and rectum (left-sided disease). He takes loratadine 10 mg/day for seasonal allergies. He has no known drug allergies. Which drug regimen is best?
- A. Balsalazide 750 mg twice daily.
 - B. Methotrexate 25 mg intramuscularly once weekly.
 - C. Infliximab 5 mg/kg intravenously.
 - D. Mesalamine enema 1000 mg rectally once daily.

Patient Cases (*continued*)

5. A 25-year-old woman presents to the clinic with a 12-week history of cramping abdominal pain, fever, fatigue, and 3–4 bloody stools a day. A colonoscopy reveals patchy inflammation in the colon and terminal ileum consistent with moderately active Crohn disease. She has an allergy to penicillin (rash). Vital signs include temperature 98°F, HR 100 beats/minute, RR 18 breaths/minute, and BP 118/68 mm Hg. She is 65 inches tall and weighs 120 lb. Which therapeutic choice is best?
- Mesalamine (Pentasa) 1000 mg 4 times/day.
 - Infliximab 275 mg intravenously and azathioprine 110 mg daily.
 - Budesonide (Entocort) 9 mg orally once daily.
 - Adalimumab 40 mg subcutaneously every 2 weeks.

V. COMPLICATIONS OF LIVER DISEASE

Scoring Systems for Severity of Liver Disease

Table 16. Child-Pugh Classification of the Severity of Cirrhosis

Variable	Score		
	1 Point	2 Points	3 Points
Encephalopathy	Absent	Mild–moderate	Severe to coma
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/L)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds above normal)	1–4	4–6	>6

*Class A = total score of 5 or 6; class B = total score of 7–9; class C = total score of 10 or more.

Table 17. Model for End-Stage Liver Disease (MELD)

Version	Calculation	Comments
Original	$9.57 \times \ln(\text{creatinine}) + 3.78 \times \ln(\text{total bilirubin}) + 11.2 \times \ln(\text{INR}) + 6.43$	<ul style="list-style-type: none"> Score ranges from 6 to 40 Higher number indicates more severe disease Used to predict mortality and prioritize patients for liver transplantation
MELD-Na	$\text{MELD} - \text{Na} - [0.025 \times \text{MELD} \times (140 - \text{Na})] + 140$	<ul style="list-style-type: none"> Incorporates sodium May better discriminate risk of death
UNOS modification	Original MELD equation with limits set on laboratory values that are entered	<ul style="list-style-type: none"> Lower end of laboratory values for SCr, bilirubin, and INR are set at 1 with a maximum of 4 If 2 or more dialysis treatments within the prior week or within 24 hours of CVVHD within the prior week, SCr concentration automatically set to 4.0 mg/dL

MELD Score Calculators available at www.mayoclinic.org/meld/mayomodel5.html.

CVVHD = continuous venovenous hemodialysis; INR = international normalized ratio; Na = sodium, SCr = serum creatinine; UNOS = United Network for Organ Sharing.

A. Ascites

1. Definition: Free fluid in the abdominal cavity secondary to increased resistance within the liver (forces lymphatic drainage into the abdominal cavity) and reduced osmotic pressure within the bloodstream (hypoalbuminemia); develops at a 5-year cumulative rate of 30% in compensated liver disease
2. Clinical features: Protuberant abdomen, shifting dullness, fluid wave, bulging flanks, abdominal pain
3. Diagnosis
 - a. Clinical features
 - b. Abdominal ultrasonography
 - c. Paracentesis. Can use serum-ascites albumin gradient, calculated by subtracting the ascites albumin concentration from the serum albumin concentration; a value greater than 1.1 indicates ascites secondary to portal hypertension
4. Treatment
 - a. Alcohol cessation if alcohol induced
 - b. Attainment of negative sodium balance
 - i. Dietary sodium restriction (less than 2000 mg/day), fluid restriction to less than 1.5 L/day if serum sodium is less than 120–125 mmol/L
 - ii. Goal is excretion greater than 78 mmol/day of sodium. A random spot urine sodium concentration greater than the potassium concentration (ratio greater than 1) correlates with a 24-hour sodium excretion of greater than 78 mmol/day with 90% accuracy.
 - iii. Diuretics
 - (a) A combination of furosemide and spironolactone is preferable as initial therapy in most patients. When used in combination, a ratio of 40 mg of furosemide to every 100 mg of spironolactone is an appropriate starting regimen. Amiloride 10–40 mg/day may be substituted for spironolactone in patients who develop tender gynecomastia.
 - (b) If tense ascites is present, may use large-volume paracentesis. Administer albumin at a dose of 6–8 g/L of ascitic fluid removed (if more than 5 L is removed at one time).
 - (c) If refractory ascites is present, may consider midodrine 7.5 mg three times daily as add-on therapy to diuretics.
 - iv. No upper limit of weight loss if massive edema is present, 0.5 kg/day in patients without edema
 - v. Monitor for electrolyte imbalances, renal impairment, and gynecomastia (spironolactone).
 - c. Discontinue drugs associated with sodium/water retention such as NSAIDs. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be avoided also to prevent renal failure.

B. Hepatic Encephalopathy

1. Definition: Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.
 - a. Thought to be secondary to the accumulation of nitrogenous substances (mainly NH_3) arising from the gut; overall, NH_3 serum concentrations do not correlate well with mental status
 - b. Other theories are related to the activation of GABA (γ -aminobutyric acid receptors) by endogenous benzodiazepine-like substances, possible zinc deficiency, or altered cerebral metabolism.
2. Clinical features and criteria
 - a. May result in acute encephalopathy with altered mental status and progress to coma if untreated; asterixis (“hand flap”) is a classic physical finding.
 - b. May be precipitated by various factors including constipation, GI bleeding, infection, hypokalemia, dehydration, hypotension, and CNS-active drugs (benzodiazepines and narcotics)
 - c. The West Haven Criteria and the Glasgow Coma Scale can be used to classify and grade.

Table 18. Common Criteria and Clinical Symptoms for Hepatic Encephalopathy

West Haven Criteria	ISHEN ^a	Clinical Description
Unimpaired		No current or history of encephalopathy
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed and executive functions or neurophysiological alterations without clinical evidence of mental change
Grade I		Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction Altered sleep rhythm
Grade II	Overt	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behavior Dyspraxia Asterixis
Grade III		Somnolence to semistupor Responsive to stimuli Confused Gross disorientation Bizarre behavior
Grade IV		Coma

^aInternational Society for Hepatic Encephalopathy and Nitrogen Metabolism.

3. Classifications

- a. Subtypes according to underlying disease
 - i. Type A: Due to acute liver failure
 - ii. Type B: Due to portosystemic bypass or shunting
 - iii. Type C: Due to cirrhosis
- b. Duration
 - i. Episodic
 - ii. Recurrent (occurs within a time frame of 6 months or less)
 - iii. Persistent: Denotes a pattern of behavioral alteration that is always present and interspersed with relapses of overt hepatic encephalopathy (HE)
- c. Presence or absence of precipitating factors
 - i. Precipitated
 - ii. Nonprecipitated

4. Treatment

- a. Assess need for airway support and remove possible precipitating factors.
- b. Main treatments targeted at reducing the nitrogen load in the gut
- c. Treatment recommendations are based on type C

Table 19. Treatment of Hepatic Encephalopathy due to Cirrhosis (Type C)

Type	Recommendations
Episodic overt HE type C	<p>Treat episodic overt HE and then use secondary prophylaxis</p> <p>Primary prophylaxis is not indicated unless cirrhosis and high risk for HE</p> <p>Lactulose is first-line treatment for overt HE</p> <p>Rifaximin can be used as add-on therapy with lactulose to prevent recurrence after the second episode of overt HE</p> <p>Oral BCAA or IV LOLA can be used as alternative or additional therapy in patients unresponsive to traditional therapies</p> <p>Neomycin or metronidazole can be used as alternative treatment</p>

BCAA = branched chain amino acids; HE = hepatic encephalopathy; IV = intravenous; LOLA = L-ornithine L-aspartate.

- d. Lactulose
 - i. Nonabsorbable disaccharide: Metabolized by colonic bacteria to acetic and lactic acid; NH_3 present in the GI lumen is reduced to ammonium ion (NH_4^+) through the reduction in pH (“ammonia trapping”) and is therefore unable to diffuse back into the bloodstream. Lactulose may also alter bacterial metabolism, resulting in increased uptake of NH_3 .
 - ii. Dose: 45 mL orally every 1–2 hours until the patient has a loose bowel movement, then titrate to two or three loose bowel movements a day (typically, a 15- to 45-mL dose two or three times daily); may also administer as an enema (300 mL plus 700 mL of water retained for 1 hour). Powder formulation (KRISTALOSE) is available in 10- and 20-g packets that may be dissolved in 4 oz water (10 g = 15 mL traditional lactulose). This formulation is more palatable than the traditional syrup.
 - iii. May be continued over the long term to prevent recurrent encephalopathy
 - iv. Flatulence, diarrhea, and abdominal cramping are common adverse effects.
- e. Antibiotics
 - i. Targeted at reducing the number of intraluminal urease-producing bacteria that may be associated with excess NH_3 production
 - ii. Neomycin (3–6 g/day in three or four divided doses \times 1–2 weeks, then 1–2 g/day maintenance) or metronidazole (250 mg orally twice daily) may be used; neomycin is considered as effective as lactulose.
 - iii. From 1% to 3% of neomycin is absorbed, so use caution with long-term use in patients with renal insufficiency; long-term metronidazole use may result in peripheral neuropathy.
 - iv. Rifaximin is as effective as lactulose and other nonabsorbable antibiotics and may be better tolerated. Approved dose for reduction in overt encephalopathy in patients 18 years and older is 550 mg twice daily. Drug cost may be greater, but this may be offset by fewer hospitalizations and shorter lengths of stay. Previous studies in the short-term setting have used 400 mg three times/day.
- f. Other possible treatments
 - i. A recent trial demonstrated that PEG 3350 4 liters given orally or via nasogastric tube over 4 hours resulted in faster improvement in encephalopathy compared with lactulose (Rahimi RS, Singal AG, Cuthbert JA, et al. JAMA 2014;174(11):1727-33)
 - ii. Benzodiazepine antagonists such as flumazenil may be used in cases of suspected benzodiazepine overdose.
 - iii. Zinc supplementation should be used in patients with documented zinc deficiency.

- iv. Branched chain amino acids and IV L-ornithine L-aspartate are alternative or additional therapies in patients unresponsive to traditional therapies
- v. Nutritional interventions include 35–40 kcal/kg/day based on IBW and 1.2–1.5 g/kg/day protein intake

C. Gastroesophageal Varices

1. Background

- a. Resistance to blood flow within the liver secondary to cirrhosis results in the development of portal hypertension. Collateral blood vessels (e.g., esophageal varices) are formed because of this increased resistance to blood flow.
- b. Variceal hemorrhage may occur in around 25%–35% of patients with cirrhosis and varices; mortality rates are as high as 30%–50% per bleed; recurrence rates are as high as 70% within the first 6 months after an initial bleed.

2. Management of acute variceal bleeding

- a. Fluid resuscitation and hemodynamic stabilization. Maintain hemoglobin concentration of about 8 g/dL. Administration of fresh frozen plasma or platelet may be considered for patients with considerable coagulopathy.
- b. Endoscopy to assess the extent of disease with potential intervention
 - i. Sclerotherapy: Effective in discontinuing bleeding in 80%–90% of patients; may be associated with complications such as perforation, ulceration, stricture, and bacteremia; possible sclerosing agents include ethanolamine and sodium tetradecyl sulfate
 - ii. Endoscopic variceal band ligation may be used as an alternative to sclerotherapy; fewer complications
- c. Medical management of acute variceal bleeding
 - i. Should be instituted after fluid resuscitation (before endoscopy, if possible)
 - ii. Most therapies are targeted at reducing splanchnic blood flow and portal pressure; combination of endoscopic and vasoactive therapies most effective
 - iii. Vasopressin: 0.2–0.4 unit/minute plus nitroglycerin 40–400 mcg/minute for 3–5 days
 - (a) Vasopressin use results in splanchnic vasoconstriction; used less often secondary to the need for both drugs and coronary vasoconstriction/hypertension with vasopressin (nitroglycerin attenuates these effects to some extent)
 - (b) More adverse effects than octreotide, so overall, less preferable
 - iv. Octreotide or somatostatin
 - (a) Works possibly by preventing postprandial hyperemia, by reducing portal pressure (by reduced splanchnic blood flow) through inhibitory effects on vasoactive peptides such as glucagon, or by a local vasoconstrictor effect
 - (b) Preferred agent in combination with endoscopic interventions because of more favorable adverse effect profiles; main adverse effects include hyperglycemia and abdominal cramping
 - (c) Dosing
 - (1) Octreotide: 50-mcg intravenous bolus, then 50 mcg/hour intravenously for 3–5 days
 - (2) Somatostatin: 250-mcg intravenous bolus, then 250–500 mcg/hour intravenously for 3–5 days
- v. Nondrug measures to control bleeding
 - (a) Typically used for medically unresponsive bleeding
 - (b) Minnesota or Blakemore tube: Balloon compression applied directly to bleeding varices

- (c) Transjugular intrahepatic portosystemic shunt: Results in shunting of blood from the portal circulation; however, may be associated with complications such as bleeding and infection
 - (d) Surgery
- vi. Antibiotic therapy
 - (a) Use of oral or intravenous prophylactic antibiotics in patients with cirrhosis with variceal bleeding reduces short-term mortality; these agents should be prescribed.
 - (b) Typical regimens include a fluoroquinolone (norfloxacin or ciprofloxacin) orally for 7 days. Intravenous therapy (ciprofloxacin) can be used if the oral route of administration is not an option. Ceftriaxone 1 g/day intravenously may be used if high rates of fluoroquinolone resistance are present.
- d. Prevention of variceal bleeding
 - i. Primary prophylaxis
 - (a) A screening esophagogastroduodenoscopy is recommended to evaluate for esophageal and gastric varices when the diagnosis of cirrhosis is made.
 - (b) Pharmacologic therapy is not recommended to prevent the development of varices in patients with cirrhosis who have not yet developed varices.
 - (c) Patients who have small varices and no history of bleeding but meet the criteria for increased risk of bleeding (Child-Pugh class B or C, red wale marks on varices) should receive preventive drug therapy with nonselective β -blockers.
 - (d) Nonselective β -blockers can be considered; however, the long-term benefit is unclear in patients who have small varices and no history of bleeding but who do *not* meet the criteria for increased risk of bleeding.
 - (e) Nonselective β -blockers are indicated in all patients with medium or large varices and no history of bleeding. An endoscopic variceal ligation (EVL) can be used if nonselective β -blockers are contraindicated.
 - (f) Mechanism of nonselective β -blockers: Blockade of β_1 -receptors reduces cardiac output, whereas blockade of β_2 -receptors prevents splanchnic vasodilation; unopposed α_1 -mediated constriction of the splanchnic circulation also leads to reductions in portal pressure.
 - (g) Therapy should aim for an HR of 55–60 beats/minute or a 25% reduction from baseline.
 - (h) Nonselective β -blockers are associated with a significant reduction in the incidence of first bleed.
 - (i) Long-acting nitrates (isosorbide mononitrate or dinitrate) should not be used for primary prophylaxis. These agents are believed to decrease intrahepatic resistance and are considered as effective as propranolol; however, there is an increased incidence of mortality in some studies when they are used as monotherapy.
 - (j) Shunt surgery or endoscopic sclerotherapy should not be used for primary prophylaxis.
 - ii. Secondary prophylaxis
 - (a) All patients with a history of variceal bleeding should receive secondary prophylaxis to prevent recurrent bleeding.
 - (b) A combination of endoscopic variceal band ligation and nonselective β -blockers is considered the most effective regimen.
 - (c) Nonselective β -blockers are associated with approximately a 20% reduction in the incidence of variceal rebleeding; reductions in mortality are minimal and inconsistent between trials most studies are of patients with Child-Pugh class A or B cirrhosis; class C patients may be unable to tolerate β -blockers.

- (d) Combining nonselective β -blockers with nitrates leads to slightly higher reductions in rebleeding rates; however, no added mortality benefit is observed, and there is a higher incidence of adverse effects with the combination.
- (e) Sclerotherapy is no longer recommended for secondary prophylaxis because EVL has been shown to be better, with fewer complications.
- (f) The transjugular intrahepatic portosystemic shunt is very effective at preventing recurrent bleeding; however, it is associated with a 30%–40% incidence of encephalopathy; reserve for medically unresponsive patients
- (g) Contraindications to nonselective β -blockers: asthma, insulin-dependent diabetes with frequent hypoglycemia, peripheral vascular disease
- (h) Adverse effects of nonselective β -blockers: light-headedness, fatigue, shortness of breath, sexual dysfunction, bradycardia
- (i) Adverse effects of EVL: transient dysphagia, chest discomfort

D. Spontaneous Bacterial Peritonitis (SBP)

1. Background

- a. Definition: Infection of previously sterile ascitic fluid without an apparent intra-abdominal source. SBP is considered a primary, as opposed to secondary, peritonitis.
- b. May be present in 10%–30% of hospitalized patients with cirrhosis and ascites
- c. Associated with 20%–40% of in-hospital mortality; poor prognosis after recovery, with 2-year survival after initial episode reported as about 30%

2. Pathophysiology

- a. Principal theory is seeding of the ascitic fluid from an episode of bacteremia.
- b. The bacteria present are usually enteric pathogens; thus, they may enter the blood because of increases in gut permeability secondary to portal hypertension, suppression of hepatic reticulo-endothelial cells, or translocation of the gut wall and dissemination through the mesenteric lymph system.
- c. Reduced opsonic activity of the ascitic fluid and alterations in neutrophil function may also be contributing factors.
- d. Enteric gram-negative pathogens are most commonly involved, and more than 90% of cases involve a single bacterial species.

Table 20. Most Commonly Isolated Bacteria Responsible for Spontaneous Bacterial Peritonitis

Gram-negative Bacilli (50%)	Gram-positive Bacilli (17%)
<i>Escherichia coli</i> , 37%	<i>Streptococcus pneumoniae</i> , 10%
<i>Klebsiella</i> spp., 6%	Other streptococci, 6%
Other, 7%	<i>Staphylococcus aureus</i> , 1%

3. Clinical and laboratory features

- a. Clinical presentation may be variable, but common symptoms include fever, abdominal pain, nausea, vomiting, diarrhea, rebound tenderness, and exacerbation of encephalopathy; about 33% of patients may present with renal failure, which is associated with significant increases in mortality. Although GI bleeding and septic shock or hypotension occur, they are rare.
- b. Laboratory
 - i. May see systemic leucocytosis or increases in serum creatinine (SCr)
 - ii. Abdominal paracentesis must be performed
 - (a) The presence of more than 250 polymorphonuclear cells/mm³ is diagnostic for SBP.

- (b) Lactate dehydrogenase, glucose, and protein values may help distinguish it from secondary peritonitis.
 - iii. Blood cultures positive in 50%–70% of cases; ascitic fluid cultures positive in 67% of cases
 - iv. Gram stain of ascitic fluid is typically low yield.
- 4. Treatment of acute SBP
 - a. Because of the high associated mortality, treatment should be initiated promptly in patients with clinical and laboratory features consistent with SBP. If ascitic fluid polymorphonuclear cells are less than 250 cells/mm³, empiric antibiotic therapy can be initiated if other signs of infection are present.
 - b. Up to 86% of ascitic fluid cultures may be negative if one dose of an antibiotic is given before cultures are drawn.
 - c. Predictors of poor outcomes include bilirubin more than 8 mg/dL, albumin less than 2.5 g/dL, creatinine more than 2.1 mg/dL, hepatic encephalopathy, hepatorenal syndrome (HRS), and upper GI bleeding.
 - d. Antibiotic therapy plus albumin if patient meets criteria for use (see below)
 - i. Empiric therapy targeting enteric gram-negative organisms should be instituted.
 - ii. Third-generation cephalosporins have been studied the most and are considered first line: cefotaxime (2 g every 8–12 hours) or ceftriaxone (2 g/day intravenously).
 - iii. Other agents such as fluoroquinolones may be used. Ofloxacin 400 mg orally twice daily can be considered in patients without prior exposure to fluoroquinolones and no evidence of shock, vomiting, grade II or higher encephalopathy, or SCr greater than 3 mg/dL.
 - iv. Avoid aminoglycosides because of the high risk of renal failure in patients with cirrhosis and SBP.
 - v. Treatment duration: 5–10 days; most studies suggest that a 5-day treatment period is as effective as a 10-day period
 - e. Albumin
 - i. Rationale: The hemodynamics of patients with cirrhosis reflect a state of intravascular hypovolemia and organ hypoperfusion; SBP is thought to exacerbate this effect, resulting in progressive renal hypoperfusion and precipitation of renal failure or HRS.
 - ii. The regimen most commonly used is based on one study (N Engl J Med 1999;341:403-9).
 - (a) Albumin dosing: 1.5 g/kg on admission; 1 g/kg on hospital day 3
 - (b) In addition, should give antibiotic treatment; cefotaxime was used in this study
 - (c) The incidence of renal failure was 10%, compared with 33% for placebo (p=0.002).
 - (d) In-hospital mortality was 10% for albumin, 29% for placebo (p=0.01).
 - (e) Thirty-day mortality was reduced to 21% with albumin, compared with 41% for placebo (p=0.03).
 - (f) Guidelines suggest using this albumin regimen with antibiotics if SCr is more than 1 mg/dL, BUN more than 30 mg/dL, or total bilirubin more than 4 mg/dL.
- 5. Prevention
 - a. Prophylactic oral antibiotics are used to prevent SBP in high-risk patients to reduce the number of enteric organisms in the GI tract (GI decontamination), with the hope of reducing the chance of bacterial translocation.
 - b. Antibiotic regimens are similar for both primary and secondary prevention:
 - i. Fluoroquinolones: Norfloxacin or ciprofloxacin
 - ii. Trimethoprim/sulfamethoxazole 1 double-strength tablet five times/week (Monday through Friday)

- c. Primary prevention
 - i. For acute upper GI bleeding (7-day course during hospitalization only), give ceftriaxone or norfloxacin 400 mg twice daily.
 - ii. May also consider for indefinite use in patients without GI bleeding if ascitic fluid protein concentration is less than 1.5 g/dL and at least one of the following is present: SCr more than 1.2 mg/dL, BUN more than 25 mg/dL, sodium less than 130 mg/dL, or Child-Pugh score more than 9 with bilirubin more than 3 mg/dL
 - iii. Use norfloxacin 400 mg once daily or trimethoprim/sulfamethoxazole.
 - d. Secondary prevention
 - i. All patients recovering from an initial episode of SBP should be treated with oral prophylactic antibiotics (norfloxacin or trimethoprim/sulfamethoxazole) indefinitely.
 - ii. Consider patient for liver transplantation because 2-year survival is 25%–30% after recovery.
- E. Hepatorenal Syndrome (HRS)
- 1. Criteria in patients with cirrhosis and ascites: SCr greater than 1.5 mg/dL, no improvement in SCr to less than 1.5 mg/dL after withdrawal of diuretics and administration of albumin, absence of shock, no current nephrotoxins, absence of parenchymal kidney disease and microhematuria, and a normal renal ultrasound
 - 2. Subtypes
 - a. Type 1: Doubling of SCr to greater than 2.5 mg/dL or a 50% reduction in CrCl to less than 20 mL/minute in less than 2 weeks
 - b. Type 2: Nonrapid progression of worsening of renal function. Associated with high mortality
 - 3. Treatment: Albumin in combination with octreotide (200 mcg subcutaneously three times daily) or midodrine (12.5 mg three times daily maximum) may be considered for type 1 HRS. Albumin plus norepinephrine may also be tried if the patient is in the ICU.
- F. Alcoholic Liver Disease
- 1. Subset of chronic liver disease. Patients may develop steatosis and eventually progress to cirrhosis. About 10%–35% of patients may develop severe alcoholic hepatitis.
 - 2. Prognosis of alcoholic hepatitis may be initially evaluated by the Maddrey discriminant function (MDF) score, calculated as $4.6 \times (\text{patient's PT} - \text{control PT}) + \text{total bilirubin (mg/dL)}$, where PT is prothrombin time. Patients whose score is greater than 32 are believed to have a poor prognosis. Patients with a model for end-stage liver disease (MELD) score greater than 18 can also be considered for drug therapy.
 - a. Patients with an MDF greater than 32, with or without encephalopathy, or a MELD score greater than 18 should be considered for a 4-week course of prednisolone 40 mg/day, followed by a 2-week taper. This may lead to a 30% decrease in the risk ratio of short-term death.
 - b. Patients with an MDF greater than 32 can be considered for treatment with pentoxifylline 400 mg three times/day, especially if there are contraindications to corticosteroids. This has shown to lower hospital mortality by 14% compared with placebo.
 - 3. Long-term treatment of alcoholic liver disease with propylthiouracil or colchicine is not recommended.

Patient Cases

6. A 47-year-old woman with a history of alcoholic cirrhosis (Child-Pugh class C) is admitted to the hospital with nausea, abdominal pain, and fever. Physical examination reveals a distended abdomen with shifting dullness, a positive fluid wave, and the presence of diffuse rebound tenderness. She also has 1+ lower extremity edema. Current medications include furosemide 80 mg twice daily and spironolactone 200 mg once daily. A diagnostic paracentesis reveals turbid ascitic fluid, which was sent for culture. Laboratory analysis of the fluid revealed an albumin concentration of 0.9 g/dL and the presence of 1×10^3 white blood cells (45% polymorphonuclear neutrophils). Serum laboratory studies reveal an SCr of 1.2 mg/dL, BUN 37 mg/dL, aspartate aminotransferase AST 60 IU/mL, alanine aminotransferase (ALT) 20 IU/mL, serum albumin 2.5 g/dL, and total bilirubin 3.2 mg/dL. Which is the best course of action?
 - A. Initiate intravenous albumin and await culture results.
 - B. Initiate intravenous vancomycin plus tobramycin.
 - C. Initiate intravenous cefotaxime plus albumin therapy.
 - D. Initiate oral trimethoprim/sulfamethoxazole double strength.
7. A 56-year-old man with a history of Child-Pugh class B cirrhosis secondary to alcohol abuse is admitted with a 2-day history of confusion, disorientation, somnolence, and reduced oral intake. On examination, he is afebrile, with abdominal tenderness, reduced reflexes, dry mucous membranes, and asterixis. Paracentesis is negative for infection. He takes propranolol 40 mg three times/day. Which recommendation is best for treating this patient's hepatic encephalopathy?
 - A. Initiate rifaximin 550 mg orally twice daily.
 - B. Initiate lactulose 30 mL orally every 2 hours.
 - C. Initiate PEG-3350 17 g orally twice daily.
 - D. Initiate ceftriaxone 1 g intravenously daily.

VI. VIRAL HEPATITIS

- A. Definitions: For all hepatitis virus infections, acute hepatitis is defined as infection for less than 6 months, whereas chronic infection is infection for more than 6 months.
- B. Hepatitis A Virus (HAV)
 1. Background
 - a. An RNA virus that is associated with the development of self-limited hepatitis
 - b. Transmission occurs mainly through the fecal-oral route.
 - i. Areas of poor sanitation; also associated flooding leading to increased spread
 - ii. Foodborne: shellfish, water, milk, vegetables
 - iii. Person-to-person contact: sexual, day care, intravenous drug use, household, restaurant workers
 - c. After exposure, incubation for 14–50 days takes place; patients may have general, nonspecific symptoms such as nausea, vomiting, diarrhea, myalgia, fever, abdominal pain, and jaundice.
 - d. Most patients have self-limited disease lasting less than 2 months; death of the hepatocyte results in elimination of the virus.
 - e. HAV is associated with very low mortality (less than 1%) and is not associated with the development of chronic hepatitis. Fulminant hepatitis may occur in some instances.

2. Diagnosis
 - a. Clinical signs and symptoms such as nausea, abdominal pain, jaundice, fever, malaise, or anorexia. Some patients may have mild asymptomatic disease.
 - b. Recent possible exposures
 - c. Laboratory data
 - i. Immunoglobulin M (IgM) antibody to HAV (anti-HAV): Detectable in the serum 5–10 days before the onset of symptoms; once the infection clears, the IgM antibody is replaced by IgG antibodies during a 2- to 6-month period; these antibodies confer lifelong protective immunity against subsequent infection.
 - ii. Elevation of aminotransferases
 - d. Management of acute HAV infection is mainly supportive; avoid hepatotoxic medications such as acetaminophen.
3. Preexposure prophylaxis
 - a. Active (vaccination) or passive (immune globulin) prophylaxis can be used.
 - b. Havrix (GlaxoSmithKline) and Vaqta (Merck) are the two available HAV vaccines; Twinrix is a combination HAV and HBV product (GlaxoSmithKline).
 - c. Populations requiring preexposure prophylaxis with HAV vaccine
 - i. All children older than 1 year
 - ii. Children living in areas where rates of hepatitis are above twice the national average
 - iii. People working in or traveling to countries with high or intermediate endemicity (may take up to 4 weeks for full protection)
 - iv. Men who have sex with men
 - v. Illegal drug users
 - vi. Those with occupational risk of exposure (exposure to sewage)
 - vii. Patients with chronic liver disease
 - viii. Patients with clotting factor disorders
 - ix. Optional: Food handlers, workers in institutions
 - d. Populations requiring preexposure prophylaxis with HAV immune globulin
 - i. Travelers to endemic countries
 - ii. Children younger than 1 year (vaccine not approved for this age group)
 - iii. Doses: 0.02 mL/kg intramuscularly (3 months' coverage or more); 0.06 mL/kg intramuscularly (3–5 months' coverage); repeat every 5 months if travel or exposure is prolonged
4. Postexposure prophylaxis
 - a. Immune globulin can be given at a dose of 0.02 mL/kg intramuscularly within 2 weeks of exposure. HAV vaccine may also be used. Efficacy approaches that of immune globulin, but it is recommended only in patients 12 months to 40 years of age.
 - b. Offer to those not previously vaccinated in the following situations:
 - i. Close personal contact with a documented infected person
 - ii. Staff or attendees of day care centers if one or more cases are recognized in children or employees or if cases are recognized in two or more households of attendees
 - iii. Common source of exposures
 - (a) If a food handler receives a diagnosis of HAV, vaccine or immune globulin should be administered to other food handlers at the same establishment. Administration of HAV vaccine or immune globulin to patrons typically is not indicated but may be considered if:
 - (1) Although the food handler was probably infectious, he or she both directly handled uncooked or cooked food and had diarrhea or poor hygienic practices.
 - (2) Patrons can be identified and treated in 2 weeks or less after exposure.

- (b) In settings where repeated exposures to HAV may have occurred, stronger consideration of HAV vaccine or immune globulin use could be warranted. In a common-source outbreak, postexposure prophylaxis should not be provided to exposed individuals after cases have begun to occur because the 2-week period after exposure during which immune globulin or HAV vaccine is known to be effective will have been exceeded.

C. Hepatitis B Virus

1. Background

- a. HBV is a DNA virus; there are more than 350 million infected patients worldwide.
- b. Transmission routes
 - i. Parenteral: intravenous drug abuse, needlestick, transfusion, ear or body piercing
 - ii. Bodily fluids: saliva, semen, vaginal fluid
 - iii. Sexual contact: heterosexual and homosexual; prostitution
 - iv. Perinatal: mother to child at birth
- c. Associated with both acute and chronic disease. Natural history of HBV is age-dependent. Risk of developing chronic infection after an acute infection is 90% in neonates, 25%–30% in children younger than 5 years, and 10% in adults.
- d. Chronic infection with HBV increases the risk of developing hepatocellular carcinoma.
- e. Diagnosis
 - i. Clinical signs and symptoms: nausea, vomiting, diarrhea, myalgia, fever, abdominal pain, jaundice (30% may have no symptoms)
 - ii. Serologic diagnosis
 - iii. Combinations of serologic markers must be reviewed to distinguish acute from chronic infections.
 - iv. Eight different HBV genotypes (A–H) exist. Routine genotype testing is not endorsed by the guidelines.

Table 21. HBV Serologies

Serologic Marker	Abbreviation	Comment
Surface antigen	HBsAg	First detectable serum antigen during acute infection; also present in chronic infection
Core antigen	HBcAg	Present early after cell damage during acute infection; typically unable to measure this in the serum
E antigen	HBeAg	Denotes ongoing active viral replication
Anti-surface antigen antibody	Anti-HBs	Confers protective immunity; present after recovery from acute infection or after vaccination
Anticore antigen antibody (IgG)	Anti-HBc	Appears at onset of symptoms Denotes prior exposure to HBV Cannot use to distinguish acute from chronic infection
Anti-E antibody	Anti-HBe	May indicate peak replication has passed
HBV DNA	HBV DNA	Marker of active HBV replication

HBcAg = hepatitis B core antigen; HBeAg = hepatitis B early antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IgG = immunoglobulin G.

- (a) Most patients have hepatitis B early antigen (HBeAg)-positive disease.
- (b) HBeAg-negative disease: Mutation in the precore or core promoter regions. These variants are known as precore mutants; these mutations do not allow monitoring of loss of E antigen as a clinical marker of suppressed replication. Monitor reduction in HBV DNA in these patients; patients infected with these variants also tend to have lower serum HBV DNA and more fluctuating liver function tests.
- (c) Centers for Disease Control and Prevention guidelines for screening for HBV infection indicate that the serologic assay for HBV surface antigen (HBsAg) should be the serologic screening test used for the following populations. Additional HBVs are needed in combination with the HBsAg for select populations as listed below.
 - (1) People born in geographic regions with HBsAg prevalence greater than 2% regardless of vaccination history
 - (2) Men who have sex with men; also test for anti-HBc or anti-HBs
 - (3) Past or current intravenous drug users; also test for anti-HBc or anti-HBs
 - (4) Patients receiving cytotoxic chemotherapy or immunosuppressive therapy related to organ transplantation or rheumatologic or GI disorders. In addition, test for anti-HBc or anti-HBs.
 - (5) U.S.-born people not vaccinated as infants whose parents were born in regions with HBV endemicity greater than 8%
 - (6) People with elevated ALT and AST of unknown etiology
 - (7) Donors of blood, plasma, organs, tissues, or semen. In addition, test for anti-HBc and HBV DNA.
 - (8) Pregnant women (during each pregnancy, preferably in the first trimester)
 - (9) Infants born to HBsAg-positive mothers
 - (10) Household, needle sharing, or sex contacts of people known to be HBsAg positive. In addition, test for anti-HBc or anti-HBs.
 - (11) People who are the sources of blood or bodily fluid for exposures that might require postexposure prophylaxis
 - (12) People who are human immunodeficiency virus (HIV) positive. In addition, test for anti-HBc or anti-HBs.

v. Clinical definitions

Table 22. Clinical Definitions of HBV

Chronic HBV Infection	Inactive HBV Carrier State
<ul style="list-style-type: none"> HBsAg positive >6 months Serum HBV DNA 20,000 IU/mL (105 copies/mL), lower values 2000–20,000 IU/mL (104–105 copies/mL) are often observed in HBeAg-negative chronic HBV Persistent/intermittent elevation of AST and ALT Chronic hepatitis and moderate–severe necroinflammation on biopsy 	<ul style="list-style-type: none"> HBsAg positive >6 months HBeAg negative, anti-HBeAg positive Serum HBV DNA <2000 IU/mL (104 copies/mL) Persistently normal AST and ALT; absence of significant hepatitis on biopsy

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBcAg = hepatitis B core antigen; HBeAg = hepatitis B early antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; LFT = liver function test.

2. Treatment of chronic infection

a. Treatment recommendations

- i. Patients who are HBeAg positive with elevated ALT concentrations and compensated liver disease should be observed for 3–6 months for spontaneous conversion from HBeAg positive to anti-HBeAg negative before initiating treatment. Antiviral treatment should be considered in patients whose ALT remains greater than two times the ULN and whose HBV DNA is more than 20,000 IU/mL.
 - ii. Patients who are HBeAg negative with positive anti-HBe as well as normal ALT and HBV less than 2000 IU/mL should be monitored every 3 months for 1 year and then every 6–12 months if they remain in the inactive carrier state.
- b. Patients who meet the criteria for chronic infection as outlined previously should be treated. Choice of initial therapy is based on patient profile, prior treatments, contraindications to drug therapy, and medication and monitoring costs.
- c. Monitoring for efficacy should be based on the following responses:
- i. Biochemical: ↓ Liver function tests to within the normal range
 - ii. Virologic: ↓ HBV DNA to undetectable concentrations and loss of HBeAg if HBeAg positive
 - (a) A primary nonresponse is considered a decrease in HBV DNA of less than 2 log/mL after at least 24 weeks of therapy. Patients *NOT* meeting these criteria should receive an alternative treatment.
 - (b) Response should be assessed by reductions in HBV DNA for HBeAg-negative patients.

3. Drug therapies

a. Interferon alfa (IFN α)/PEG-IFN

- i. Cytokine with antiviral, antiproliferative, and immunomodulatory effects
- ii. Best predictors of response to treatment are high pretreatment ALT, low-serum HBV DNA, presence of active inflammation on biopsy, and acquisition of infection because an adult HBeAg-negative disease responds less favorably to interferon (IFN).
- iii. Dosing
 - (a) Traditional agents: HBeAg positive: Typical dose is 5 million units/day subcutaneously \times 16–24 weeks or 10 million units subcutaneously three times/week \times 16–24 weeks; patients with HBeAg-negative disease should be treated for 12 months.
 - (b) PEG- α -2a (Pegasys): 180 mcg subcutaneously once weekly \times 48 weeks (duration is the same for HBeAg-negative and HBeAg-positive disease)
- iv. In general, response to traditional IFN is poor; 37% loss of HBsAg, 33% loss of HBeAg with 12–24 weeks of treatment; this equates to about 20% better than placebo. Some trials suggest that PEG-IFN has only slightly better efficacy in HBeAg-positive disease, with 25% loss of HBV DNA and 30% loss of HBeAg at 48 weeks. Adherence may be better because of less-frequent dosing.
- v. If a response is obtained, it is usually long lasting (more than 4 years).
- vi. Treatment with IFN typically results in an increase in ALT 4–8 weeks into treatment. This is an expected response; it should not be viewed as an adverse effect of therapy.

Table 23. Available IFN α Products

Product	IFN Subtype	Route of Administration	Dosage Forms
Roferon-A ^a	α -2a	SC or IM	Single-dose vial (36 MU/mL) Multidose vial (18 MU/vial) Prefilled syringe (3, 6, 9 MU/0.5 mL)
Infergen	Acon-1	SC	Single-dose vials 9 mcg (0.3 mL), 15 (0.5 mL)
Intron ^a	α -2b	SC or IM	Powder, solution, multidose pen
PEG-Intron	PEG- α -2b	SC	Single-dose vials (2 mL) + diluent 50, 80, 120, 150 mcg/0.5 mL Single-use Redipen 50, 80, 120, 150 mcg/0.5 mL
Pegasys ^{a,b}	PEG- α -2a	SC	Single-dose vial (1 mL) 180 mcg/mL Prefilled 180 mcg syringes (4/pack) Autoinjector 180 mcg

^aPreferred for HBV.^bFDA approved for HBV.HBV = hepatitis B virus; IFN α = interferon alfa; IM = intramuscular; PEG = pegylated; SC = subcutaneous.

vii. Adverse effects

- (a) IFN is associated with many serious adverse effects, including bone marrow suppression.
 - (1) Leukopenia: May use filgrastim (granulocyte colony-stimulating factor) for support
 - (2) Thrombocytopenia: Minimal data with oprelvekin (interleukin-11). Not used because of many adverse effects including pulmonary hypertension
 - (b) Predisposition to infections
 - (c) CNS: Depression, psychosis, anxiety, insomnia, seizures. Adverse CNS effects occur in 22%–31% of patients.
 - (d) Flulike symptoms (tolerance usually develops after a few weeks)
 - (e) Anorexia, alopecia, thyroid dysfunction, neuropathy
 - (f) Exacerbation of underlying autoimmune disorders (i.e., thyroid)
 - (g) Ischemic or hemorrhagic cerebrovascular disorders
 - (h) Serious hypersensitivity and rash formation
 - (i) Manufacturers give recommendations for dose reductions in patients who develop bone marrow suppression and depression while on therapy.
 - (j) Contraindicated in patients with current psychosis, a history of severe depression, neutropenia, thrombocytopenia, symptomatic heart disease, decompensated liver disease, and uncontrolled seizures; also, use caution in patients with autoimmune disorders
- b. Reverse transcriptase inhibitors
- i. In general, lamivudine and telbivudine are not preferred as first-line therapies because of high rates of resistance.
 - ii. All reverse transcriptase inhibitors carry a black box warning for the development of lactic acidosis and severe hepatomegaly with steatosis. Monitor for worsening liver function tests, and periodically assess renal function. Female and obese patients are at higher risk. Reductions in bone mineral density (BMD) have been associated with long-term use. Assess baseline BMD in patients older than 12 years with a history of pathologic fracture or osteoporosis.

- iii. Lamivudine (Epivir-HBV)
 - (a) Reduces HBV DNA by 3–4 log
 - (b) Dose: 100 mg/day orally (tablets or solution) for at least 1 year (HBeAg negative and positive); dose is 150 mg orally twice daily for patients with HIV coinfection; doses require adjustment for reduced renal function
 - (c) Efficacy: 17%–32% loss of HBeAg and 41%–72% normalization of ALT at 52 weeks; may be used for IFN failures and in patients with decompensated liver disease
 - (d) Toxicity: Well tolerated (headache, nausea, vomiting, fatigue), rare lactic acidosis
 - (e) Resistance: Prolonged use is associated with the development of mutations in the YMDD sequence of the HBV polymerase (20% at 1 year, 70% at 4 years). Risk factors for lamivudine resistance include elevated pretherapy HBV DNA or ALT, male sex, increased body mass index, previous exposure to lamivudine or famciclovir, and inadequate suppression on HBV DNA after 6 months of treatment.
 - (f) Therapy discontinuation is often accompanied by rebound liver function test elevations; viral breakthrough may also be evident during treatment.
- iv. Adefovir (Hepsera)
 - (a) Reduces HBV DNA by 24 log
 - (b) Indicated in HBeAg-positive and HBeAg-negative disease, as well as in decompensated liver disease; also effective in lamivudine-resistant YMDD mutants and IFN failures
 - (c) Dose: 10 mg orally every day for at least 1 year in HBeAg-negative and HBeAg-positive disease
 - (d) Efficacy: Up to 72% normalization of ALT and 12% loss of HBeAg at 48 weeks
 - (e) Toxicity: Renal dysfunction (3%), headache, nausea, vomiting, fatigue, rare lactic acidosis
 - (f) Therapy discontinuation is often accompanied by rebound liver function test elevations; viral breakthrough may also be evident during treatment. Resistance reported as 29% at 5 years
- v. Entecavir (Baraclude)
 - (a) Indicated for HBeAg-negative and HBeAg-positive patients with persistently elevated AST or ALT or histologically active disease. Effective in lamivudine-resistant YMDD mutants
 - (b) Reduces HBV DNA by up to 6.86 log in HBeAg-positive, naive patients and by 5.2 log in HBeAg-negative patients or those with lamivudine resistance
 - (c) Dose: 0.5 mg orally once daily for patients older than 16 years and nucleoside naive; 1 mg orally once daily for patients older than 16 years with HBV viremia while receiving lamivudine or in lamivudine-resistant HBV
 - (d) Dose adjustments required for renal impairment
 - (e) Toxicity: Similar to lamivudine with headache, cough, upper respiratory infection, abdominal pain; possibly fewer ALT flares. Rare lactic acidosis. Resistance reported as similar to 1% at 5 years.
- vi. Telbivudine (Tyzeka)
 - (a) Indicated for HBeAg-negative and HBeAg-positive patients with persistently elevated AST or ALT or histologically active disease
 - (b) Not effective in lamivudine-resistant YMDD mutants
 - (c) A direct comparison with lamivudine (GLOBE trial) showed greater efficacy in both HBeAg-negative and HBeAg-positive patients. Reduces HBV DNA by up to 6.45 log in HBeAg-positive, naive patients and by 5.2 log in HBeAg-negative patients. Dose: 600 mg orally once daily. Dose adjustments required for renal impairment

- (d) Toxicity: Similar to lamivudine; small incidence of myopathy. Creatine kinase elevations greater than 7 times the ULN; for telbivudine, 9% versus 3% with lamivudine in the GLOBE study. Rare lactic acidosis. Resistance reported as 25% at 2 years
- vii. Tenofovir (Viread)
 - (a) Nucleotide analog, formulated as tenofovir disoproxil fumarate, indicated for chronic HBV infection
 - (b) Effective for lamivudine-resistant HBV
 - (c) Dose adjustments required for renal impairment
 - (d) Toxicity: Overall, well tolerated. Headache, nausea, and nasopharyngitis most commonly reported. Potential renal toxicity, so periodic monitoring of SCr recommended. Potential ALT flares on withdrawal. Rare lactic acidosis

Table 24. Summary of Treatment Recommendations for Chronic HBV Infection in Adults

HBV Population	Preferred Treatment Options	Duration	Comments
HBeAg positive	Entecavir and tenofovir are preferred oral agents Use of the other oral reverse transcriptase inhibitors is possible but not preferred	Minimum of 1 year	Preferred if contraindications or nonresponse to IFN α
	IFN α PEG-IFN α	16 weeks 48 weeks	If contraindication or no response, use entecavir and tenofovir
HBeAg negative	Entecavir and tenofovir are preferred oral agents Use of the other oral reverse transcriptase inhibitors is possible but not preferred	>1 year	Preferred if contraindications or no response to IFN α
	IFN α PEG-IFN α	\geq 1 year	If contraindication or nonresponse, use entecavir and tenofovir
Development of resistant HBV	Lamivudine or telbivudine resistance: Add adefovir or tenofovir or change to entecavir Adefovir resistance: Add lamivudine Entecavir resistance: Change to tenofovir	N/A	Confirm resistance with genotypic testing Reinforce adherence to therapy

HBeAg = hepatitis B early antigen; HBV = hepatitis B virus; IFN α = interferon alfa; N/A = not applicable; PEG = pegylated.

4. Preventive strategies

- a. Vaccination (preexposure); indicated in the following groups:
 - i. All infants born to HBsAg-negative mothers
 - ii. Adolescents with high-risk behavior (intravenous drug abuse, multiple sex partners)
 - iii. Workers with possible occupational risk of exposure
 - iv. Staff and clients at institutions for the developmentally disabled
 - v. Hemodialysis patients
 - vi. Patients receiving clotting factor concentrates
 - vii. Household contacts and sex partners of infected patients
 - viii. Adoptees from countries where HBV infection is endemic
 - ix. International travelers (more than 6 months' travel in an endemic area, short-term travel if contact with blood in a medical setting is expected, or sexual contact with residents in areas of intermediate to high endemic disease); series of vaccinations started 6 months before travel

- x. Injection drug users
- xi. Sexually active homosexual or bisexual men, as well as heterosexual men and women
- xii. Patients seeking treatment for a sexually transmitted disease
- xiii. Inmates of long-term correctional facilities
- xiv. Patients with chronic HIV infection or chronic liver disease
- xv. All HCPs whose work-, training-, and volunteer-related activities involving reasonably anticipated risk of exposure to blood or bodily fluids. Recently vaccinated HCPs should, if possible, undergo testing for anti-HBs 1–2 months after finishing the HBV series. If anti-HBs is greater than 10 mIU/mL, no further testing is necessary. If anti-HBs is less than 10 mIU/mL, an additional dose of HBV vaccine should be administered, with repeat testing at 1–2 months.
- xvi. All other people seeking protection from HBV infection
- b. Available HBV vaccines (dose schedules vary by age)
 - i. Dose schedules

Table 25. Dose Schedules for Hepatitis B Vaccinations

Patient and Age Groups		Recombivax HB		Engerix-B		Schedule
		Dose (mcg)	Volume (mL)	Dose (mcg)	Volume (mL)	Most common schedule is 3 IM doses at 0, 1, and 6 months Variations in schedule may occur, depending on age and medical history
Infants (<1 year)		5	0.5	10	0.5	
Children (1–10 years)		5	0.5	10	0.5	
Adolescents	11–15 years	10	1	N/A	N/A	
	11–19 years	5	0.5	10	0.5	
Adults	≥20 years	10	1	20	1	
Hemodialysis patients and other immunocompromised people	<20 years	5	0.5	10	0.5	
	>20 years	40	1	40	2	

IM = intramuscular; N/A = not applicable.

- ii. Obtain titers 1–2 months after the third dose of the series for HCPs.
- iii. HBV vaccines are available as combination products with HAV (Twinrix), DTP/IPV (Pediarix), and Hib (Comvax).
- c. Postexposure prophylaxis
 - i. Exposure may result in the need for HBV vaccine or immune globulin.
 - ii. Doses of HBV immune globulin are 0.06 mL/kg intramuscularly and must be given within 7 days of exposure.
 - iii. Patient populations requiring postexposure prophylaxis
 - (a) Perinatal transmission
 - (1) Children born to HBsAg-positive mothers should receive vaccine plus HBV immune globulin within 12 hours of birth.
 - (2) Children born to mothers with unknown HBsAg status (but suspected) should receive vaccine within 12 hours of birth; testing should be performed on child, and if positive, HBV immune globulin should be administered within 1 week.
 - (3) Infants weighing less than 2 kg at birth whose mothers are documented as HBsAg negative should receive the first dose of vaccine 1 month after birth or at hospital discharge, whichever comes first.

- (b) Sexual contact or household contact with an infected person: Should receive HBV immune globulin plus vaccine series if exposed person is previously unvaccinated
- (c) Sexual contact or household contact with an HBV carrier: Should receive vaccine series if exposed person was previously unvaccinated
- (d) Postexposure recommendations for HCPs

Table 26. Centers for Disease Control and Prevention Recommendations for Management of HBV Postexposure for HCPs

HBV Status of HCP	Postexposure Testing		Postexposure Prophylaxis		Postvaccination Serologic Testing ^a
	Source Patient (HBsAg)	HCP Testing (anti-HBs)	HBIG	Vaccination	
Documented responder ^b	No action needed				
Documented nonresponder after 6 doses ^c	Positive or unknown	— ^d	HBIG × 2 separated by 1 month	—	No
	Negative	No action needed			
Response unknown after 3 doses	Positive or unknown	<10 mIU/mL ^d	HBIG × 1	Initiate revaccination	Yes
	Negative	<10 mIU	None		
	Any result	≥10 mIU	No action needed		
Unvaccinated or incompletely vaccinated or vaccine refusers	Positive or unknown	— ^d	HBIG × 1	Complete vaccination	Yes
	Negative	—	None	Complete vaccination	Yes

^a1–2 months after last dose of HBV vaccine series.

^bAnti-Hbs >10 mIU/mL after >3 doses of HBV vaccine.

^cAnti-Hbs <10 mIU/mL after >6 doses of HBV vaccine.

^dHCPs who have anti-HBs <10 mIU/mL, or who are unvaccinated or incompletely vaccinated, and sustain an exposure to a source patient who is HBsAg positive or has unknown HBsAg status should undergo baseline testing for HBV infection as soon as possible after exposure and follow-up testing about 6 months later.

HBIG = hepatitis B immune globulin; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCP = health care provider.

D. Hepatitis C Virus

1. Background

- a. RNA virus: Six genotypes (50 subtypes)
 - i. Genotype 1 (subtypes 1a, 1b, and 1c) accounts for 70%–75% of infections in the United States.
 - ii. Genotypes 2 (subtypes 2a, 2b, and 2c) and 3 (3a and 3b) are common in the United States.
 - iii. Genotype helps determine therapy duration and likelihood of responding to therapy.
- b. Leading cause of liver disease and liver transplantation in the United States; also a common cause of hepatocellular carcinoma
- c. Viral replication occurs in the hepatocyte (virus is not directly cytopathic).
- d. Transmission: Mainly bloodborne (transfusion, intravenous drug abuse)
 - i. High risk: Transfusion, intravenous drug abuse, men who have unprotected sex with men, hemodialysis, incarceration
 - ii. Low risk
 - (a) Snorting cocaine or other drugs
 - (b) Occupational exposure

- (c) Body piercing and acupuncture with unsterilized needle
 - (d) Tattooing
 - (e) From pregnant mother to child
 - (f) Nonsexual household contacts (rare)
 - (g) Sharing razors or toothbrushes
 - (h) Sexual transmission
 - e. Associated with acute and chronic infection; after acute infection, most patients (60%–85%) develop chronic infection
2. Clinical features: About 30% of patients are asymptomatic.
- a. Acute infection: Symptoms present 4–12 weeks after exposure; most patients are asymptomatic and seldom progress to fulminant disease; those who develop symptoms have nonspecific findings such as malaise, weakness, anorexia, and jaundice.
 - b. Chronic infection: Defined as the presence of viral RNA in the serum for 6 months or more
 - i. May be associated with the long-term development of end-stage liver disease, cirrhosis, hepatocellular carcinoma
 - ii. Progression to complications and end-stage liver disease may be accelerated by concurrent alcohol use and coinfection with HIV; younger female patients have slower progression.
 - c. Extrahepatic manifestations: rheumatoid symptoms, glomerulonephritis, cryoglobulinemia
3. Diagnosis and monitoring
- a. Clinical signs and symptoms such as nausea, abdominal pain, jaundice, fever, malaise, or anorexia. Many patients have asymptomatic disease.
 - b. Populations to test
 - i. Suspected exposure
 - ii. HIV infection
 - iii. Intravenous or intranasal drug abuse
 - iv. Receipt of clotting factors before 1987 or blood before 1992
 - v. Hemodialysis
 - vi. Abnormal ALT
 - vii. Those receiving an organ transplant before 1992, including those who were ever incarcerated
 - viii. Adults born between 1945 and 1965
 - ix. Getting a tattoo in an unregulated setting
 - x. Health care, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood
 - xi. Unexplained chronic liver disease and chronic hepatitis, including elevated ALT
 - xii. Annual testing for injection drug users and HIV-positive men who have unprotected sex with men
 - c. Laboratory
 - i. Serum anti-HCV antibodies: 99% sensitivity and specificity (enzyme immunoassays). Used as an initial screening for HCV; presence of anti-HCV antibody does not confer protective immunity from subsequent infection
 - ii. Serum HCV RNA
 - (a) Obtain in patients who test positive for anti-HCV antibodies, in patients with negative anti-HCV antibodies who are suspected to have liver disease and have had an HCV exposure in the past 6 months, and in immunocompromised patients.
 - (b) Quantitative: Viral load is typically polymerase chain reaction reported in international units per milliliter; obtain for patients who will receive treatment; for use in monitoring treatment response. Preferred assays for diagnosis and monitoring of drug therapy

- (c) Qualitative: Typically polymerase chain reaction; lower limit of detection of 50 IU/mL (equivalent to 100 copies/mL) is preferred (specificity is about 98%); typically used to confirm diagnosis in patients who are HCV antibody positive. The American Association for the Study of Liver Diseases (AASLD) guidelines state that there is no longer a need for qualitative assays. Quantitative assays are preferred.
- (d) Important 2013 update from the FDA regarding HCV assays
 - (1) An HCV assay with a lower limit of quantification of 25 IU/mL or less and a limit of HCV RNA detection of around 10–15 IU/mL should be used for monitoring response to therapy and decision-making during triple therapy (Class 2a, Level A).
 - (2) Response-guided therapy should be considered only when no virus is detected by a sensitive assay 4 weeks after initiation of the HCV protease inhibitor (Class 1, Level A).

Table 27. Definitions and Monitoring of Long-term HCV Treatment Based on HCV RNA

Parameter	Definition
Rapid virologic response	Undetectable HCV RNA at week 4 of treatment
Sustained virologic response	Undetectable HCV RNA 12 weeks after finishing treatment

HCV = hepatitis C virus.

- iii. Liver biopsy: Consider if patient and HCP want to obtain information about fibrosis stage or prognosis or to make a decision about treatment. ALT: Nonspecific; may fluctuate with chronic disease (should decrease with treatment)
 - iv. Genotyping: Genotype 1 is the most common genotype in the United States; it is also the least responsive to treatment. Genotypes 2 and 3 are the other two most common genotypes in the United States.
 - v. Treatment response depends on other factors such as race, age, or coinfection. *IL28B* genotyping can also be considered for genotype 1 infection to help predict response to therapy.
4. Treatment
- a. Acute HCV infection
 - i. Preexposure or postexposure prophylaxis is not recommended.
 - ii. Monitor HCV RNA every 4–6 weeks for 6–12 months to detect spontaneous clearance. If the decision is to treat, monitor for at least 12 weeks to detect spontaneous clearance.
 - iii. The same regimens used for chronic HCV are recommended for treatment. An alternative regimen is PEG ± ribavirin (RIBA) for 16 weeks in genotype 2 or 3 if a rapid virologic response (RVR) is obtained or for 24 weeks if genotype 1.
 - b. Chronic infection
 - i. Therapy goal is to attain a sustained virologic response (SVR), defined as the absence of detectable HCV RNA 12 weeks after treatment and is considered a clinical cure if obtained.
 - ii. Prioritization for treatment should be given to the following patient populations.
 - (a) Highest priority
 - (1) Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)
 - (2) Organ transplant
 - (3) Type 2 or 3 mixed cryoglobulinemia with end-organ manifestations such as vasculitis
 - (4) Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
 - (b) Next highest priority
 - (1) Fibrosis (Metavir F2)
 - (2) HIV-1 coinfection
 - (3) Hepatitis B virus coinfection

- (4) Other coexistent liver disease such as nonalcoholic steatohepatitis
 - (5) Debilitating fatigue
 - (6) Type 2 diabetes (insulin resistant)
 - (7) Porphyria cutanea tarda
- (c) Patients who may be at high risk for transmission and may benefit from prioritized treatment to reduce risk of transmission
 - (1) Men who have sex with men
 - (2) Active injected drug users
 - (3) Incarcerated people
 - (4) People on long-term hemodialysis
- c. RIBA in the treatment of HCV infection
 - i. Oral nucleoside analog
 - ii. Available as 200-mg tablets (Copegus) or capsules (Rebetol) (generic now available)
 - iii. Significant adverse effect profile
 - (a) Hemolytic anemia: May occur in up to 10% of patients (usually within 1–2 weeks of initiating therapy); may worsen underlying cardiac disease; monitor complete blood cell count (CBC) at baseline, 2 weeks, 4 weeks, and periodically thereafter. In patients with no cardiac history, decrease dose to 600 mg/day when hemoglobin drops to 10 g/dL or less, and discontinue when hemoglobin drops to 8.5 g/dL or less. In patients with a cardiac history, decrease dose to 600 mg/day if hemoglobin drops more than 2 g/dL in any 4-week period during treatment. Discontinue if hemoglobin drops to less than 12 g/dL 4 weeks after dose reduction. May use epoetin or darbepoetin to stimulate red blood cell production, improve anemia and sustain initial starting dose. Also need to confirm iron studies are normal and within range during treatment
 - (b) Teratogenicity: Category X drug; requires a negative pregnancy test at baseline and every month up to 6 months after treatment, as well as the use of two forms of barrier contraception during treatment and for 6 months after treatment. Applies to women taking the drug and female partners of male patients taking ribavirin
 - (c) Other possible adverse events include pancreatitis, pulmonary dysfunction (dyspnea, pulmonary infiltrate, and pneumonitis), insomnia, irritability or depression (often referred to as “riba rage”), and pruritus.
- d. Protease inhibitors for chronic HCV infection. Telaprevir and boceprevir agents are no longer recommended as first-line therapies for HCV infection.

Table 28. Protease Inhibitors Used to Treat Chronic HCV Infection

	Telaprevir (Incivek)	Boceprevir (Victrelis)	Simeprevir (Olysio)
FDA-approved indication	Long-term HCV therapy (genotype 1) in combination with PEG-IFN α and ribavirin in patients with compensated liver disease Not studied in Child-Pugh class B or C	Chronic HCV genotype 1 infection, in combination with PEG-IFN α and ribavirin, in adult patients (≥ 18 years) with compensated liver disease, including cirrhosis, who were previously untreated or who have not responded to previous interferon and ribavirin therapy	Chronic HCV genotype 1 infection in combination with PEG/RIBA or sofosbuvir
Dose and formulation	750 mg orally 3 times/day for at least 12 weeks, followed by PEG-IFN and ribavirin for 12 weeks if undetectable HCV RNA at weeks 4 and 12 Give doses 7–9 hours apart; give with meal that has at least 20 g of fat, ingested 20 minutes previously 375-mg tablets Take missed doses if within 4 hours	800 mg orally three times/day Give doses 7–9 hours apart; give with meal or light snack 200-mg capsules Take missed doses if within 2 hours	150 mg once daily with food for 12 weeks, combined with PEG-IFN and ribavirin Dose recommendations cannot be made for patients of East Asian ancestry or those with moderate to severe hepatic impairment
Contraindications	Pregnant women or male partners of pregnant women (category B, but must be used with ribavirin, which is category X) CYP3A4 substrates or inducers Alfuzosin, rifampin, DHE, St. John's wort, atorvastatin, lovastatin, simvastatin, pimozide, sildenafil, tadalafil, oral triazolam, or midazolam Several other drug-drug interactions that may require dose adjustment of interacting drug (see package insert)	Pregnant women or male partners of pregnant women (category B, but must be used with ribavirin, which is category X) CYP3A4 substrates or inducers Alfuzosin, rifampin, DHE, St. John's wort, atorvastatin, lovastatin, simvastatin, pimozide, sildenafil, tadalafil, oral triazolam, or midazolam Several other drug-drug interactions that may require dose adjustment of interacting drug (see package insert)	Pregnant women or male partners of pregnant women (category C, but must be used with ribavirin, which is category X) Screening for the NS3Q80K polymorphism Alternative therapies should be considered in patients with genotype 1a and this polymorphism Administration with substances that are moderate or strong inducers or inhibitors of CYP3A is not recommended Also inhibits OATP1B1/3 and P-glycoprotein Several drug-drug interactions that may require dose adjustment of interacting drug (see package insert)
Adverse effects	Rash (56%), DRESS syndrome, or Stevens-Johnson syndrome Anemia, pruritus, nausea	Anemia, neutropenia, fatigue, dysgeusia	Photosensitivity, rash; contains a sulfonamide moiety but no reports of problems with sulfa allergy

CYP = cytochrome P450; DHE = dihydroergotamine; DRESS = drug reaction/rash with eosinophilia and systemic symptoms; FDA = U.S. Food and Drug Administration; HCV = hepatitis C virus; PEG-IFN = pegylated interferon.

- e. NS5B/A polymerase inhibitors sofosbuvir (Sovaldi) and sofosbuvir/ledipasvir (Harvoni)
 - i. Indications
 - (a) Sofosbuvir: HCV genotypes 1, 2, 3, and 4, including those with hepatocellular carcinoma meeting Milan criteria and those with HCV/HIV coinfections in combination with PEG/RIBA
 - (b) Sofosbuvir/ledipasvir: genotype 1 infection in combination with simeprevir
 - ii. Dosing: 400-mg tablet once daily with or without food
 - (a) Sofosbuvir renal dosing: No dosing recommendations for glomerular filtration rate (GFR) less than 30 mL/minute
 - (b) Dose reductions for ribavirin
 - (1) When used with sofosbuvir according to U.S. prescribing information, 600 mg daily is recommended in patients with no cardiac disease if hemoglobin is less than 10 g/dL, and recommendations are to discontinue if hemoglobin is less than 8.5 g/dL. In patients with stable cardiac disease, reduce the ribavirin dose if there is a greater than 2-g/dL decrease in hemoglobin during any 4-week period, and discontinue if hemoglobin is less than 12 g/dL, despite 4 weeks at reduced dose.
 - (2) When used with sofosbuvir according to the 2014 AASLD/Infectious Diseases Society of America (IDSA) guidelines: For GFR 30–50 mL/minute, use alternating doses of 200 and 400 mg daily; for GFR less than 30 mL/minute or with end-stage renal disease or hemodialysis, reduce to 200 mg/day
 - iii. Adverse effects: fatigue, headache
 - iv. Drug interactions
 - (a) Avoid use with potent P-glycoprotein inducers.
 - (b) Concentrations are significantly affected by anticonvulsants (carbamazepine, phenytoin, phenobarbital, and oxcarbazepine), rifabutin, rifampin, St. John's wort, and tipranavir/ritonavir.
- f. NS5A/B inhibitor combination (ombitasvir/dasabuvir) plus boosted protease inhibitor (paritaprevir/ritonavir); Viekira Pak
 - i. Indication: Genotype 1 infection with or without compensated cirrhosis
 - ii. Dosing: Two paritaprevir 75 mg/ritonavir 50 mg/ombitasvir 12.5 mg combination tablets once daily in the morning plus one dasabuvir 250 mg tablet twice daily in combination with ribavirin for genotypes 1a and 1b (with cirrhosis); no ribavirin needed for genotype 1b without cirrhosis
 - iii. Duration: 12 weeks except for genotype 1a with cirrhosis or patients with liver transplant, who should receive 24 weeks.
 - iv. Interactions with CYP3A4 substrates and inducers and CYP2C8 substrates and inhibitors. Contraindicated with ethinyl estradiol-containing products
 - v. Adverse effects: fatigue, nausea, pruritus, and those associated with ribavirin. Avoid in Child-Pugh class C liver disease.
- g. Treatment recommendations for chronic HCV infection

Table 29. Treatment Recommendations for Chronic HCV Genotype 1 Infection in Treatment-Naïve Patients or Those Who Have Experienced Relapse After Prior PEG-IFN/RBV Therapy

Genotype	Recommended Therapies	Alternative	Not Recommended
1a	LDV (90mg)/SOF (400mg) × 12 weeks SOF (400mg)+ SMV (150mg) ^c ± RBV ^a × 12 weeks ^d PVR/RITON/OMBI/ DAS + RBV ^a × 12 weeks ^d	None	SOF + RBV
1b	LDV (90mg)/SOF (400mg) × 12 weeks SOF (400mg)+ SMV (150mg) ^c × 12 weeks ^d PVR/RITON/OMBI/ DAS (+/- RBV) ^c × 12 weeks ^d	None	PEG/RBV +/- SOF, SMV, TVR, BOC PEG, RBV, or DAA Monotherapy
2	SOF + RBV × 12 weeks; extend to 16 weeks if cirrhosis	None	PEG/RBV × 24 weeks PEG, RBV, DAA monotherapy Any regimen with TVR, BOC, LDV
3	SOF + RBV × 24 weeks	SOF + RBV + PEG × 12 weeks	PEG/RBV × 24–48 weeks PEG, RBV, DAA monotherapy Any regimen with TVR, BOC, SMV
4	LDV (90mg)/SOF (400mg) × 12 weeks SOF (400mg)+ RBV ^a × 24 weeks PVR/RITON/OMBI/ DAS + RBV ^a × 12 weeks ^d	SOF + SMV + RBV ^a + PEG × 12 weeks SOF + SMV +/- RBV ^a × 24–48 weeks	PEG/RBV +/- SMV × 24–48 weeks PEG, RBV, DAA monotherapy Any regimen with TVR or BOC
5	SOF + RBV + PEG × 12 weeks	PEG/RBV × 48 weeks	PEG, RBV, DAA monotherapy Any regimen with TVR or BOC
6	LDV (90mg)/SOF (400mg) × 12 weeks	SOF + RBV ^a + PEG × 12 weeks	

^aRBV dosing is weight based (1000 mg/day for <75 kg and 1200 mg/day for >75 kg).

^bSofosbuvir and simeprevir are FDA approved for use without RBV for genotype 1 infection ^cFor genotype 1a, testing for the Q80K polymorphism should be performed and other treatments considered, if present.

^d12 weeks without cirrhosis; 24 weeks with cirrhosis

^eRBV only recommended if presence of cirrhosis

BOC = boceprevir; DAA = directly acting agent; DAS = dasabuvir; IFN = interferon; LDV = ledipasvir; PEG = pegylated interferon alfa; PVR = paritaprevir RBV = ribavirin; RIT = ritonavir SMV = simeprevir; SOF = sofosbuvir; TVR = telaprevir.

- h. Monitoring
 - i. Baseline HCV RNA, genotype, CBC, liver function tests (LFTs), thyroid-stimulating hormone (TSH), and GFR. Pregnancy test for women receiving RIBA
 - ii. On therapy: Obtain HCV at 4 weeks to assess for RVR and then again at the end of treatment. Every 4 weeks check CBC, SCr, LFTs; every 12 weeks check TSH.
 - iii. After treatment: Check HCV RNA at 12 weeks to assess for SVR
- i. Prevention of HCV
 - i. No vaccine or immune globulin available
 - ii. Risk factor modification
 - (a) Intravenous drug abuse: methadone maintenance, syringe exchange
 - (b) Sexual contact: appropriate barrier contraception
 - (c) Avoid blood exposure: Occupational (universal precautions) or other contact (e.g., sharing toothbrushes or razors or receiving a tattoo)
 - (d) The HAV and HBV vaccine to prevent further progression of liver disease

Patient Cases

8. A 45-year-old woman with a history of intravenous drug abuse is seen in the clinic for an evaluation of chronic HBV infection. Although she received the HBV diagnosis 8 months ago, she has not yet been treated for it. Laboratory values reported today include HBsAg positive, HBeAg positive, AST 650 IU/mL, ALT 850 IU/mL, HBV DNA 107,000 IU/mL, SCr 0.9 mg/dL, INR 1.3, and albumin 3.9 g/dL. She has no evidence of ascites or encephalopathy. A liver biopsy has revealed severe necroinflammation and bridging fibrosis. Resistance testing reveals the presence of the YMDD mutation. Which is the best course of action?
- A. Withhold drug therapy and recheck HBV DNA in 6 months.
 - B. Initiate PEG-IFN α -2a plus ribavirin.
 - C. Initiate lamivudine 100 mg/day.
 - D. Initiate tenofovir 300 mg/day.
9. A 38-year-old white man is seen today for a new diagnosis of chronic HCV, genotype 1a. Pretreatment laboratory values include AST 350 IU/mL, ALT 420 IU/mL, HCV RNA 950,000 IU/mL, SCr 1 mg/dL, hemoglobin 12 g/dL, and white blood cell count (WBC) 12×10^3 cells/mm³. A liver biopsy reveals a Metavir score of F3/A2, and overall he has compensated liver disease. Further testing reveals presence of the NS3 80 QK polymorphism. He weighs 75 kg and is 72 inches tall. He reports no known drug allergies. Which option is best for treating this patient's chronic HCV infection?
- A. Withhold therapy and reassess in 12 months.
 - B. Initiate sofosbuvir and simeprevir.
 - C. Initiate sofosbuvir and ledipasvir.
 - D. Initiate ribavirin and sofosbuvir.

VII. NAUSEA AND VOMITING

A. Definitions and Pathophysiology

1. Definitions

- a. Nausea: Unpleasant sensation of the imminent need to vomit; may or may not lead to the act of vomiting
- b. Vomiting: Forceful expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature

2. Pathophysiology

- a. Stimuli for nausea are processed through several major anatomic areas, each of which has various receptors associated with input to the medullary vomiting center.
 - i. Visceral stimuli: Mediated through dopamine and serotonin receptors. Major stimuli include:
 - (a) Gastric irritants
 - (b) Nongastric stimuli (peritonitis, intestinal or biliary distension, pancreatitis, gastroparesis)
 - (c) Abdominal radiation
 - (d) Chemotherapeutic agents
 - (e) Pharyngeal stimulation
 - ii. Chemoreceptor trigger zone (located in the area postrema): Mediated by dopamine (D_2), serotonin, and some histamine (H_1) and muscarinic (M_1) and substance P/neurokinin 1; major stimuli include:
 - (a) Medications: Opiates, dopamine agonists, digoxin, chemotherapeutic agents, macrolides, general anesthetics
 - (b) Metabolic disturbances (uremia, diabetic ketoacidosis, hypercalcemia, hypoxemia)
 - (c) Bacterial toxins
 - (d) Radiation therapy
 - iii. Vestibular labyrinths: Mediated through H_1 and M_1 . Major stimuli include:
 - (a) Motion sickness
 - (b) Labyrinth infection
 - iv. Cerebral cortex: Receptor involvement not well characterized; noxious odors, visions, and tastes

Table 30. Common Clinical Conditions Associated with Nausea and Vomiting

Category	Conditions
Infectious	Viral or bacterial gastritis or gastroenteritis, pyelonephritis
Gastrointestinal	Pancreatitis, gastroparesis, hepatitis
CNS	Migraine, stroke, pain, seizures, motion sickness, meningitis
Endocrine or metabolic	Pregnancy, uremia, DKA, hypercalcemia
Cardiovascular	Myocardial infarction, heart failure
Other	Postoperative, cerebral mass

CNS = central nervous system; DKA = diabetic ketoacidosis.

- b. Clinical consequences of nausea and vomiting include dehydration, electrolyte disturbances, aspiration, and Mallory-Weiss syndrome.

B. Treatment and Prevention Strategies

1. Removal or treatment of the underlying cause
2. Correction of dehydration and electrolyte disturbances. Oral rehydration preferred, if possible, with oral rehydration solutions (e.g., Pedialyte, diluted Gatorade)
3. Drug treatment: Use drugs that target receptors involved with stimuli. May need combination of drugs with different mechanisms. Also may need alternative dose forms (intravenous, subcutaneous, suppository)
 - a. Major drug classes of antiemetics: All are antagonists at the respective receptors.
 - b. Drugs of choice for different situations include:
 - i. General medical use: phenothiazines, serotonin antagonists
 - ii. Chemotherapy induced: Serotonin antagonists, phenothiazines, aprepitant, and dronabinol. (See “Oncology Supportive Care” chapter for treatment and prevention.)
 - iii. Postoperative: serotonin antagonists, scopolamine
 - iv. Motion sickness: antihistamines, scopolamine
 - v. Pregnancy: phosphorylated carbohydrate solution, pyridoxine, antihistamines
 - vi. Gastroparesis: Metoclopramide

Table 31. Select Antiemetics

Drug	Formulations	Comments
Phenothiazines		
Promethazine (Phenergan)	Tablets Suppositories Injection	Antidopaminergic, anticholinergic, and antihistaminergic activity May cause EPS, injection site irritation (do not use subcutaneously), sedation, anticholinergic effects IV formulation should be diluted because of risk of tissue necrosis
Prochlorperazine (Compazine)	Tablets Syrup Suppositories Injection	Mainly antidopaminergic activity May cause EPS, injection site irritation (do not use subcutaneously)
Serotonin antagonists		
Ondansetron (Zofran)	Tablets ODT Oral solution Injection Oral-soluble film (Zuplenz)	Overall, well tolerated No liquid required for ODT or soluble film Contraindicated with apomorphine Associated with QTc prolongation; correct hypomagnesemia and hypokalemia
Granisetron (Kytril)	Injection Tablet Oral solution Patch	Overall, well tolerated Twice-daily dosing Associated with QTc prolongation
Palonosetron (Aloxi)	Injection	Long duration of action: 24 hours to 5 days Only one dose required
Dolasetron (Anzemet)	Injection Tablets	Typically, a one-time dose Contraindicated with apomorphine Associated with QTc prolongation; correct hypomagnesemia and hypokalemia

Table 31. Select Antiemetics (*continued*)

Drug	Formulations	Comments
Antihistamines		
Dimenhydrinate (Dramamine) Cyclizine (Marezine) Meclizine (Bonine) Doxylamine (Unisom)	Tablets	Take 30–60 minutes before travel Risk of sedation and anticholinergic adverse effects
Butyrophenones		
Haloperidol Droperidol	Injection, tablets Injection	Risk of extrapyramidal adverse effects; risk of QTc prolongation; requirement for baseline ECG and 2- to 3-hour postdose cardiac monitoring
Miscellaneous agents		
Scopolamine (Transderm Scop)	Patch	Apply behind ear 4 hours before travel May wear for up to 72 hours Do not cut patch Risk of anticholinergic adverse effects
Aprepitant Fosaprepitant (Emend) Netupitant/palonosetron (Akynzeo)	Capsules Injection Capsule	Targets substance P/neurokinin 1 (NK1) receptors Reduces efficacy of warfarin and oral contraceptives Dose-dependent inhibitor of CYP3A4 Targets substance P/neurokinin 1 (NK1) receptors and 5-HT ₃ Avoid in severe renal or hepatic disease
Dronabinol (Marinol)	Tablets	Delta-9 tetrahydrocannabinol Targets central endogenous cannabinoid receptors Used most often for chemotherapy-induced N/V May cause appetite stimulation, euphoria, cognitive impairment
Phosphorylated carbohydrate solution (Emetrol)	Oral solution	Use undiluted for best effect Do not use for >1 hour (or maximum of 5 doses) Safe in pregnancy Avoid in diabetes and fructose intolerance
Doxylamine/pyridoxine (Diclegis)	Delayed-release tablet (10 mg/10 mg)	Approved for NVP in women who do not respond to conservative management 2–4 tablets daily Pregnancy category A

CYP = cytochrome P450; ECG = electrocardiogram; EPS = extrapyramidal symptoms; IV = intravenous; N/V = nausea and vomiting; NVP = nausea and vomiting of pregnancy; ODT = orally disintegrating tablet; SR = sustained release.

- c. Nondrug therapy for nausea and vomiting: Acupressure wristbands (Sea-Band); work by stimulating the pericardium 6 (P6) point. May be used for preventing all types of nausea

VIII. PANCREATITIS

A. Classification and Pathophysiology

1. Acute

- a. Characterized by inflammation in the pancreas ranging from mild to severe
- b. An initial insult leads to the release of trypsin in the pancreas, leading to the activation of pancreatic enzymes and intrapancreatic inflammation and complications. May then progress to extrapancreatic complications. Usually reversible once underlying cause is removed
- c. Two distinct phases
 - i. Early (within 1 week): Associated with systemic inflammatory response syndrome (SIRS) or organ damage
 - ii. Late (more than 1 week): Associated with local complications
- d. Typical signs and symptoms include abdominal pain and distension, nausea, vomiting, jaundice, and fever.
 - i. Local complication: necrosis, hemorrhage, pseudocyst, abscess, infection
 - ii. Systemic complications: SIRS, acute respiratory distress syndrome, shock, organ failure
- e. Main causes of acute pancreatitis
 - i. Long-term alcohol abuse
 - ii. Gallstones
 - iii. Drugs

Table 32. Common Causes of Drug-Induced Pancreatitis

Didanosine	Pentamidine
Asparaginase	Mesalamine/sulfasalazine
Azathioprine/mercaptopurine	Estrogens
Valproic acid	Tetracycline
Diuretics (furosemide, HCTZ)	Trimethoprim/sulfamethoxazole
Exenatide	Sitagliptin

HCTZ = hydrochlorothiazide.

- iv. Post–endoscopic retrograde cholangiopancreatography
 - v. Hypertriglyceridemia (generally greater than 1000 mg/dL)
 - vi. Idiopathic
 - vii. Structural abnormalities
 - viii. Toxins (scorpion venom)
 - ix. Trauma
 - x. Ischemia
- #### 2. Chronic
- a. Characterized by irreversible structural and functional loss of pancreatic function caused by long-standing inflammation and repeated injury
 - b. Repeated injury results in loss of both exocrine and endocrine function.
 - c. Typical signs and symptoms include chronic abdominal pain, steatorrhea, weight loss or cachexia, jaundice, and hyperglycemia. Complications: diabetes, pseudocysts, calcification, ascites, biliary stricture

d. Risk factors for chronic pancreatitis are based on the M-ANNHEIM Classification

M = Multiple risk factors

A = Alcohol consumption

N = Nicotine

N = Nutritional factors (high fat and protein, hyperlipidemia)

H = Hereditary factors

E = Efferent duct factors

I = Immunologic factors

M = Miscellaneous and rare factors (includes drugs)

B. Diagnosis

1. Acute pancreatitis

a. Diagnosis is typically made on the basis of two of the three following:

i. Presence of abdominal pain

ii. Laboratory diagnosis: Serum lipase (more than 3 times the ULN) is the most sensitive test. Patients may also have hyperglycemia and other electrolyte abnormalities related to vomiting. Patients often have a leukocytosis and a fever.

iii. Imaging: Abdominal ultrasonography and computed tomography (CT) scan to evaluate pancreas, biliary system, and presence of local complications

b. Severity and prognosis

Table 33. Common Scoring Systems to Classify Severity and Prognosis of Acute Pancreatitis

Atlanta Symposium Criteria for Acute Pancreatitis	Ranson Criteria for Prognosis ^a	
Mild: Absence of organ failure or local complications Moderately severe: Local complications or transient organ failure (<48 hours) Severe: Persistent organ failure >48 hours	At admission: Age >55 years (older than 70 years) WBC >16,000/L (18,000/L) Blood glucose >200 mg/dL (220 mg/dL) Serum lactate dehydrogenase >350 IU/L (>400 IU/L) Serum AST >250 IU/L (same)	Within next 48 hours: Decrease in hematocrit by >10% (same) Estimated fluid sequestration of >6 L (4 L) Serum calcium <8 mg/dL (same) Pao ₂ <60 mm Hg (omitted) BUN level increase >5 mg/dL after intravenous fluid hydration (>2 mg/dL) Base deficit of >4 mmol/L (6 mmol/L)

^aValues in parentheses are for gallstone induced; >3 criteria indicate severe disease.

AST = aspartate transaminase; BUN = blood urea nitrogen; WBC = white blood cell count.

2. Chronic pancreatitis: Diagnosis is typically made on the basis of clinical signs and symptoms plus laboratory and imaging.

a. Laboratory diagnosis: Serum lipase may be normal; hyperglycemia and low albumin or prealbumin may also be present.

b. Imaging: CT scan may reveal pancreatic calcification or pseudocyst.

C. Treatment Strategies

1. Acute pancreatitis: Treatment is largely supportive; should include removal or treatment of underlying cause if possible
 - a. Temporarily withhold oral intake and provide rehydration with intravenous fluids, typically 250–500 mL/hour of lactated Ringer's. Treat electrolyte disturbances (hypokalemia, hypocalcemia, hyperglycemia).
 - b. Pain management: Use of intravenous narcotics (avoid meperidine); patient-controlled analgesia is often used
 - c. Antiemetics: intravenous ondansetron, prochlorperazine, or promethazine
 - d. Nutrition: If mild pancreatitis, then oral feeding can be resumed if no vomiting is present. If severe pancreatitis is present, use enteral nutrition to prevent infectious complications. Avoid total parenteral nutrition (higher rates of infection, mortality, and length of stay).
 - e. Antibiotics: In general, not recommended for routine prophylaxis in severe pancreatitis. Antibiotics may be used if extrapancreatic infection is present. If infected necrosis is present, then carbapenems, fluoroquinolones, or metronidazole may be useful in delaying the need for intervention.
 - f. Endoscopic retrograde cholangiopancreatography may be needed for cholangitis or gallstone pancreatitis. This is often followed by cholecystectomy to prevent future episodes.
2. Chronic pancreatitis: Treatment is largely symptomatic.
 - a. Abstinence from alcohol is essential. May need pharmacologic intervention and supportive care (e.g., Alcoholics Anonymous)
 - b. Pain management: Often requires combination of nonnarcotic and narcotic analgesics (long-acting morphine, oxycodone, or transdermal fentanyl) in combination with pancreatic enzyme replacement. Avoid acetaminophen if long-term alcohol use.
 - c. Antiemetics: oral ondansetron, prochlorperazine, or promethazine as needed
 - d. Nutrition: Goal is to maximize caloric intake and weight gain and reduce steatorrhea. May need more frequent, lower-fat meals and fat-soluble vitamin supplementation. Long-term enteral or parenteral nutrition may be required.
 - e. Use of pancreatic enzyme replacement therapy
3. Pancreatic enzyme replacement therapy
 - a. Goal is to simulate the digestion of food that normally occurs with normal pancreatic enzyme release to reduce maldigestion and malabsorption.
 - b. Products are enteric-coated microspheres or microtablets that contain lipase, amylase, and protease. Meant to mix with food, they release enzymes at intestinal pH values greater than 5.5. Products should not be crushed or chewed.
 - c. Enzyme products were historically considered nutritional supplements. The FDA has now mandated FDA approval of all enzyme products.

Table 34. Pancreatic Enzyme Replacement Products

Brand Name	Lipase (units)	Amylase (units)	Protease (units)	Formulation
Viokace	10,440 20,880	39,150 78,300	39,150 78,300	Immediate-release tablet
Creon	3000 6000 12,000 24,000 36,000	15,000 30,000 60,000 120,000 180,000	9500 19,000 36,000 76,000 114,000	Capsules with enteric-coated microspheres (0.17–1.6 mm)
Ultresa	13,800 20,700 23,000	27,600 41,400 46,000	27,600 41,400 46,000	Capsules with enteric-coated minitables (2 mm in diameter × 2–4 mm in thickness)
Zenpep	3000 5000 10,000 15,000 20,000 25,000 40,000	16,000 27,000 55,000 82,000 109,000 136,000 218,000	10,000 17,000 34,000 51,000 68,000 85,000 136,000	Capsules with enteric-coated beads (1.8–1.9 mm for 3000/5000 units) (2.2–2.5 mm for all other strengths)
Pancreaze	2600 4200 10,500 16,800 21,000	10,850 17,500 43,750 70,000 61,000	6200 10,000 25,000 40,000 37,000	Capsules with enteric-coated microtablets (2 mm)
Pertzye	8000 16,000	30,250 28,750	28,750 57,500	Capsules with bicarbonate-buffered enteric-coated microspheres (0.8–2 mm)

- d. Dosing is based on the lipase content (units) of the product.
 - i. Starting adult doses are generally 30,000–40,000 units per meal, with one-half dose for snacks. May also use weight-based dosing of 500–1000 units/kg per meal for those older than 4 years or 1000–2500 units/kg per meal for ages 1–4
 - ii. Maximal dose is 2500 units/kg per dose or 10,000 units/kg/day.
 - iii. Give enzymes immediately before or during meal.
 - iv. Titrate according to weight gain and reduction in steatorrhea.
 - v. May need to add PPI if maximal response is not seen
- e. Adverse effects of pancreatic enzyme therapy
 - i. Nausea or abdominal cramping
 - ii. Enzymes are derived from porcine pancreas, so patients with pork allergy cannot use them.
 - iii. Hyperuricosuria, hyperuricemia
 - iv. Fibrosing colonopathy (generally seen with doses greater than 10,000 units/kg/day)
 - v. Pregnancy category C

IX. DIARRHEA

A. Classification and Pathophysiology

1. Clinical definition: Alteration in a normal bowel movement characterized by an increase in the water content, volume, or frequency (more than three per day) of stool
 - a. Acute is generally considered less than 72 hours to 14 days.
 - b. Chronic is generally considered more than 14–30 days.
2. May be classified into several major categories related to underlying cause
 - a. Secretory
 - i. Secondary to enhanced secretion by intestinal mucosa. Often, large, watery volume with loss of electrolytes
 - ii. Common causes: bacterial or viral or bacterial enteritis, gastric hypersecretion, carcinoid, stimulant laxatives, bile acid malabsorption, celiac disease, IBD (mucosal)
 - b. Osmotic
 - i. Secondary to the presence of hyperosmolar gradient in the intestinal lumen
 - ii. Common causes: osmotic laxatives, carbohydrate malabsorption (lactase deficiency), fat malabsorption (pancreatic insufficiency), short bowel syndrome
 - c. Exudative or inflammatory
 - i. Secondary to inflammation or infiltration or invasion of the intestinal mucosa
 - ii. Common causes: IBD, invasive infection (*C. difficile* toxin, enterotoxigenic *Escherichia coli*, cytomegalovirus, *Shigella*), ischemic colitis, radiation enterocolitis, neoplasm
 - d. Altered motility or motor
 - i. Secondary to autonomic nerve dysfunction
 - ii. Common causes: diabetic neuropathy, postvagotomy, hyperthyroidism, irritable bowel syndrome (IBS), Addison disease
3. Drug-induced diarrhea. May occur by a variety of mechanisms

Table 35. Common Causes of Drug-Induced Diarrhea

Antibiotics	NSAIDs
Antineoplastics	Digoxin
Laxatives	Prostaglandins (misoprostol)
Levothyroxine (over-replacement)	Colchicine
Metoclopramide	Orlistat
Acarbose or miglitol	Sorbitol (sugar-free products)

NSAID = nonsteroidal anti-inflammatory drug.

B. Diagnosis

1. Need to evaluate patient history thoroughly
 - a. Evaluate for disease- and drug-induced causes (laxative, recent antibiotic use), recent travel history, and temporal relation to food intake.
 - b. Assess fluid and electrolyte status.
 - c. Assess CBC and stool culture, and evaluate for ova and parasites if infectious cause is suspected. *C. difficile* toxin and culture if recent antibiotic use or hospitalization
 - d. Evaluate stool pH, electrolytes, osmolarity, or fat content, if indicated.
 - e. Imaging (abdominal CT scan) or endoscopy with biopsy may be indicated, particularly for inflammatory diarrhea or suggestion of neoplasm or celiac disease.
2. Referral to higher level of care or further evaluation may be necessary for some patients.
 - a. Immunocompromised
 - b. Infants and children
 - c. Pregnant women
 - d. Presence of fever
 - e. Blood in the stool
 - f. Weight loss (greater than 5%)
 - g. Suspected invasive infection

C. Treatment Strategies

1. Removal or treatment of underlying causes, if possible
2. Rehydration
 - a. Intravenous fluids appropriate for hospitalized patients
 - b. Oral rehydration appropriate for all patients if no vomiting is present
 - i. Sodium and glucose are key ingredients of oral rehydration solutions because they have active uptake into the intestinal mucosa even during active diarrhea. This results in water being pulled back into circulation. Other formulations (popsicles) are also available.
 - ii. Gatorade may need to be diluted because it has a large amount of carbohydrates.
3. Dietary modifications
 - a. Avoid dairy products because transient lactase deficiency may occur.
 - b. “BRAT” diet for adults
 - c. May need to interrupt feedings for pediatric patients
4. Drug therapy for diarrhea (see “Infectious Diseases” chapter for management of infectious causes)
 - a. Several different agents available for management of diarrhea
 - b. Avoid antimotility agents if invasive infection is suspected.

Table 36. Select Therapies for the Management of Diarrhea

Drugs	Mechanism	Role	Adverse Effects and Precautions
Loperamide	μ -Receptor agonist	Mild to moderate noninvasive diarrhea Adjunctive to other nonopiate therapies	Minimal CNS effects Avoid if suspected invasive infection Pregnancy category B
Opiates Tincture of opium Diphenoxylate + atropine	μ -Receptor agonist	Moderate to severe noninvasive diarrhea Suboptimal response to loperamide or bismuth Refractory diarrhea	CNS effects, respiratory depression Constipation, possible anticholinergic effects with atropine Avoid if suspected invasive infection
Bismuth subsalicylate	Antisecretory Binds toxins	Mild–moderate diarrhea Prevention of traveler’s diarrhea	Stool discoloration Avoid in salicylate allergy, age <12 years, pregnancy, nursing Caution with anticoagulants May bind other drugs May interfere with some radiographic procedures
Lactase	Enzyme	Lactase deficiency or intolerance	Well tolerated
Probiotics (<i>Lactobacillus</i> , <i>Saccharomyces</i>)	Competition with pathogenic organisms, production of anti-microbial substances, enhancement of immune response	Prevention of antibiotic-associated diarrhea Adjunctive therapy for treatment of <i>C. difficile</i> Small intestinal bacterial overgrowth	Well tolerated Caution if severely immunocompromised
Octreotide	Antisecretory suppression of hormone release	Treatment of tumor-associated diarrhea (VIPoma [Verner-Morrison syndrome], carcinoid) HIV-associated diarrhea	Hyperglycemia Gallstone formation
Teduglutide (Gattex)	GLP-2 analog	Approved for adult patients with short bowel syndrome who are dependent on parenteral support	Colonic neoplasms; colonoscopy recommended every 5 years Intestinal obstruction Biliary/pancreatic disease (bilirubin, amylase, lipase, alkaline phosphatase, every 6 months)

CNS = central nervous system; GLP-2 = glucagon-like peptide-2; HIV = human immunodeficiency virus.

X. CONSTIPATION

A. Definition and Pathophysiology

1. Bowel symptoms (difficult or infrequent passage of stool, hardness of stool, or a feeling of incomplete evacuation) that may occur in isolation or secondary to another underlying disorder. The 2013 guidelines distinguish between normal-transit constipation and slow-transit constipation. Another definition is “a symptom based disorder defined as unsatisfactory defecation and is characterized by infrequent stools, difficult stool passage, or both”
2. May also be characterized by difficulty with or incomplete evacuation, straining, or presence of hard, dry stools. Abdominal pain and distension may occur, as well as low back pain and anorexia.
3. Pathophysiology is related to many different factors. Common causes include:
 - a. Altered motility (e.g., ileus)
 - b. Neurogenic causes (autonomic neuropathies, Parkinson disease)
 - c. Endocrine or metabolic disorders (e.g., hypothyroidism, diabetes, hypokalemia, hypercalcemia, uremia)
 - d. Pregnancy
 - e. Psychogenic causes
 - f. Structural abnormalities or obstruction
 - g. Nutritional (e.g., reduced fiber and water intake)
 - h. Medications
4. Constipation that is not due to an underlying organic cause is referred to as chronic idiopathic constipation (CIC) or functional constipation.

Table 37. Common Causes of Drug-Induced Constipation

Opioids	Calcium channel blockers
Antihistamines	Calcium supplements and antacids
Tricyclic antidepressants	Aluminum-containing drugs (antacids, sucralfate)
Scopolamine, benztropine	Iron supplements
Diuretics	Phenothiazines
Bile acid sequestrants	Benzodiazepines

B. Diagnosis

1. Need to evaluate patient history thoroughly
 - a. Need to establish patient baseline and evaluate for disease- and drug-induced causes
 - b. Assessment of fluid and electrolyte status, thyroid function
 - c. Imaging (abdominal CT scan or radiograph) may be necessary to assess for ileus, obstruction, or dilatation.
2. Referral for further evaluation may be necessary for some patient populations.
 - a. Symptoms for more than 1–2 weeks despite treatment
 - b. Considerable pain or cramping
 - c. Pregnancy
 - d. Presence of fever
 - e. Blood in the stool
 - f. Reduction in stool caliber
 - g. Weight loss
 - h. Paraplegia, quadriplegia
3. Diagnosis of CIC (functional constipation) is based on the ROME III Criteria, which is presence of two or more of the following:
 - a. Straining during at least 25% of defecations

- b. Lumpy or hard stools in at least 25% of defecations
 - c. Sensation of incomplete evacuation for at least 25% of defecations
 - d. Sensation of anorectal obstruction or blockage for at least 25% of defecations
 - e. Manual maneuvers to facilitate at least 25 % of defecations (e.g., digital evacuation, support of the pelvic floor)
 - f. Fewer than three defecations per week
- C. Treatment Strategies
1. Removal or treatment of underlying causes, if possible
 2. Nonpharmacologic interventions
 - a. Increase fluid intake to 6–8 glasses of water per day, although minimal evidence to support efficacy if dehydration is not present
 - b. Increase dietary fiber to 20–30 g/day.
 - c. Incorporate or increase exercise to 3–5 days/week.
 3. Drug therapy for prevention and treatment of constipation
 - a. Choose drug therapy on the basis of desired onset of action, patient preference, presence of potential contraindications, and use in special populations.
 - b. Provide patient education on alternative dose forms (enema, suppository).

Table 38. Drug Therapy Options for Treatment and Prevention of Constipation

Drugs	Role	Comments
Saline osmotic laxatives		
Magnesium citrate Magnesium hydroxide Sodium phosphate	Acute or intermittent constipation Preoperative or preprocedure bowel preparation	Fast onset (15 minutes to 3 hours) Avoid in renal impairment, HF, cirrhosis FDA warning regarding oral sodium phosphate and development of acute phosphate nephropathy (avoid use for bowel preparations)
Osmotic laxatives		
Glycerin	Management of acute or intermittent constipation Used in pediatric patients	Suppository Fast onset (within 1 hour)
Lactulose	Management of acute, intermittent, or chronic constipation, including CIC; preferred in chronic liver disease	Onset 1–2 days (may require multiple doses) Associated with gas and bloating Syrup or powder for solution
Polyethylene glycol	Acute or chronic constipation Effective for CIC Preoperative/colon preparation	Onset 1–3 days Safe in renal and hepatic disease and pregnancy Overall, well tolerated; may be used long term
Stimulant laxatives		
Bisacodyl	Short-term relief of acute or intermittent constipation or as part of preoperative or colonoscopy bowel preparation	Oral onset 6–12 hours, suppository within 1 hour Oral tablets are enteric coated
Senna	Short-term relief of acute or intermittent constipation Often used long term for prevention of opioid-induced constipation	Tablets and liquid Onset 6–12 hours May cause abdominal cramping, electrolyte disturbances, melanosis coli

Table 38. Drug Therapy Options for Treatment and Prevention of Constipation (*continued*)

Drugs	Role	Comments
Bulk-forming laxatives		
Psyllium Inulin Wheat dextrin Calcium polycarbophil Methylcellulose	Intermittent or chronic constipation	Onset 12–72 hours; less effective in drug-induced constipation and STC Requires adequate water intake to be effective Several formulations; soluble forms can be incorporated into foods, liquids, and recipes Safe in renal and hepatic disease, pregnancy, geriatrics May cause gas and bloating
Miscellaneous agents		
Docusate sodium Docusate potassium	Prevention of opioid-induced constipation in combination with senna or prevention of straining in post-MI, postsurgical, and pregnant patients	Onset 1–6 days Requires adequate water intake to be effective
Methylnaltrexone (Relistor)	FDA approved for opioid-induced constipation in palliative care patients and for opioid-induced constipation in adult patients with noncancer pain	Peripheral opiate antagonist; will not reverse central analgesia Subcutaneous injection given every other day Based on weight Onset within 4 hours in ~50% of patients
Naloxegol (Movantik)	FDA approved for opioid-induced constipation in adult patients with noncancer pain	Peripheral μ -receptor opioid antagonist 12.5-mg and 25-mg capsules Adjust dose for CrCl <60 mL/minute Contraindicated with use of strong CYP3A4 inhibitors or in patients with obstruction
Lubiprostone (Amitiza)	FDA approved for CIC in adults and for IBS-C in women >18 years	Chloride channel (ClC-2) activator; results in intestinal fluid secretion May reduce bloating and abdominal pain Main adverse effect: Nausea Dose is 24 mcg twice daily for constipation and 8 mcg twice daily for IBS-C Need negative pregnancy test before use
Linaclotide (Linzess)	FDA approved for IBS-C and CIC	Guanylate cyclase-C agonist: Increases fluid secretion and transit time 145- and 290-mcg capsules IBS-C: 290 mcg orally once daily; for CIC: 145 mcg orally once daily Take on empty stomach 30 minutes before meal Common adverse effects: diarrhea, abdominal pain, flatulence, and abdominal distension Contraindicated in pediatric patients <6 years and in mechanical obstruction Avoid in patients 6–17 years of age Pregnancy category C

CIC = chronic idiopathic constipation; CrCl = creatinine clearance; CYP = cytochrome P450; FDA = U.S. Food and Drug Administration; HF = heart failure; IBS-C = constipation-predominant irritable bowel syndrome; MI = myocardial infarction; STC = slow-transit constipation.

XI. IRRITABLE BOWEL SYNDROME

A. Definition and Pathophysiology

1. IBS is considered a functional GI disorder.
2. Definition divides IBS into the following subtypes:
 - a. Diarrhea predominant (IBS-D)
 - b. Constipation predominant (IBS-C)
 - c. Mixed IBS (IBS-M): features of both IBS-D and IBS-C
 - d. Unclassified (IBS-U)
3. The pathophysiology is thought to involve alterations in both CNS and intestinal pain perception, alterations in GI motility and secretion, and contributions from current or past psychosocial factors, gas retention, and possibly previous GI infection or bacterial overgrowth.
 - a. IBS is more common in women, people in lower socioeconomic groups, and patients younger than 50 years.
 - b. Patients experience significant reductions in quality of life and use more health care resources.
 - c. Comorbid psychiatric illnesses such as depression and anxiety may be present in a significant percentage of patients.
4. Symptoms: In addition to diarrhea or constipation, pain is often a component of all subtypes. Other symptoms (e.g., bloating, distension, spasm, urgency) may be present as well.

B. Diagnosis

1. Typically a diagnosis of exclusion. Need to rule out other GI causes with a thorough workup. Evaluation of a patient's pattern of symptoms may provide insight into subtype, although patients may alternate between forms.
2. Several diagnostic criteria and scoring systems have been developed, including the Kruis, Manning, and Rome criteria.
 - a. Generally the ROME III criteria are used mostly commonly and are as follows: Recurrent abdominal pain or discomfort at least 3 days per month in the past 3 months, associated with one of the following: improvement with defecation, onset with change in frequency of stool, onset in change in form or appearance of stool. Symptoms should have started at least 6 months before diagnosis.
 - b. Guidelines recommend that if other GI diseases are excluded and no alarm features (e.g., weight loss, bleeding, anemia) are present, diagnosis of IBS can be made with confidence.
 - c. The ACG guidelines also recommend:
 - i. Screening for celiac disease in patients with IBS-D and IBS-M
 - ii. No endoscopy if younger than 50 years and no alarm symptoms
 - iii. No routine food allergy testing
 - iv. No routine checking for small intestinal bacterial overgrowth unless lactose intolerance is a concern, despite dietary intervention

C. Treatment Strategies

1. Treatment involves a mix of drug, diet, and psychosocial interventions. Cognitive behavioral therapy, dynamic psychotherapy, and hypnotherapy have all shown effectiveness in IBS.
2. Dietary intervention involves avoidance of foods that trigger symptoms.
3. Drug therapy should target main symptoms and possible psychiatric comorbidities. Combinations of drugs may be necessary for maximal effectiveness.
 - a. Antispasmodics: Used mostly for short-term relief of abdominal pain but may also treat diarrhea in patients with IBS-D. May be used on an as-needed or scheduled basis
 - i. Dicyclomine (Bentyl): Anticholinergic adverse effects

- ii. Hyoscyamine (Levsin, Levsin SL), anticholinergic adverse effects
- iii. Peppermint oil: Use enteric-coated products; may worsen GERD but may improve symptoms in IBS and is superior to placebo
- b. Tricyclic antidepressants: Treat pain, improve global symptoms, and slow motility in patient with IBS-D. Can be used in IBS-C but may worsen constipation.
 - i. Amitriptyline, nortriptyline, and imipramine are the most studied.
 - ii. Doses cannot be raised high enough to treat comorbid depression.
 - iii. Potential for anticholinergic effects, sedation, CV effects, and drug interactions
- c. Selective serotonin reuptake inhibitors (SSRIs): Treat pain and improve global symptoms similar to tricyclic antidepressants. Used for both IBS-D and IBS-C
 - i. Fluoxetine, sertraline, citalopram, and paroxetine are all viable options.
 - ii. Tend to have a prokinetic effect, so may also improve constipation in IBS-C; however, can also use in IBS-D, especially if comorbid depression or anxiety exists
 - iii. Adverse effects include insomnia, sexual dysfunction, and withdrawal.
- d. Laxatives: Used for IBS-C
 - i. Psyllium has best evidence; however, it may cause bloating and gas formation. Calcium polycarbophil may be used as an alternative bulk-forming agent; wheat or corn bran should not be used.
 - ii. PEG-based laxatives (MiraLAX) may increase stool frequency, but they have no effects on reductions in abdominal pain and overall symptoms in IBS. Minimal to no bloating.
 - iii. Avoid stimulant laxatives because they may worsen abdominal pain.
- e. Lubiprostone: FDA approved for IBS-C in women older than 18 years
 - i. Chloride channel activator; improves motility and possibly pain
 - ii. Dose is 8 mcg twice daily with meals for IBS-C.
 - iii. Nausea and diarrhea are main adverse effects; it is costly as well.
- f. Tegaserod (Zelnorm): Serotonin-4 partial agonist that is FDA approved for IBS-C
 - i. Improves pain, global symptoms, and motility
 - ii. Available on an emergency-use basis only because of its association with the development of CV events in women
- g. Alosetron (Lotronex): Serotonin-3 antagonist that is FDA approved for IBS-D
 - i. Improves global symptoms and reduces motility
 - ii. Associated with the development of colonic ischemia, so available only through manufacturer prescribing program
- h. Loperamide: No effects on global symptoms or pain but reduces motility and increases stool consistency. May be used as an adjunct to other therapies in IBS-D
- i. Probiotics: Some evidence to support improvement in global symptoms, bloating, and flatulence. Not enough evidence exists to recommend specific strains.
- j. Antibiotics: A short course (10–14 days) of nonabsorbable antibiotic may improve global symptoms of IBS, especially bloating in IBS-D.
 - i. Rifaximin 400 mg two or three times daily for 10–14 days has shown some efficacy. This agent is expensive and does not have an FDA-approved indication for IBS.
 - ii. Limited data with neomycin and metronidazole
- k. Linaclotide (Linzess)
 - i. Approved for IBS-C
 - ii. Guanylate cyclase-C agonist: Increases fluid secretion and decreases transit time
 - iii. 290 mcg orally once daily taken on an empty stomach 30 minutes before meals
 - iv. Common adverse effects: diarrhea, abdominal pain, flatulence, and abdominal distension

Patient Cases

10. A 55-year-old man with a history of chronic alcohol abuse for 25 years is seen in the clinic for an evaluation of chronic pancreatitis. For the past 2 months, he has noticed an increase in the frequency of bowel movements to four or five times daily. He describes his stools as foul smelling and slimy. During this time, he has experienced 14 kg of unintentional weight loss and has intermittent abdominal pain. Quantification of fecal fat indicates an excretion of 20 g every 24 hours. His albumin is 2.1 g/dL, and he weighs 61 kg. He currently takes morphine controlled release 45 mg twice daily and oxycodone 5–10 mg every 4–6 hours as needed. Which is the best course of action for this patient?
- A. Increase MS-Contin to 60 mg twice daily.
 - B. Initiate dronabinol to improve appetite.
 - C. Initiate pancrelipase 30,000 units per meal.
 - D. Add a multivitamin to his regimen.
11. A 32-year-old woman has experienced intermittent crampy abdominal pain 3–5 days/week, bloating, and reduced frequency of bowel movements for the past 6 months. Before this, she had a bowel movement on a daily basis; now, she reports a bowel movement every 2–3 days. She often needs to strain to evacuate her bowels. She reports that her symptoms do not appear related to specific foods. An extensive diagnostic workup is negative, and she is given a diagnosis of IBS-C. She is otherwise healthy and reports no known drug allergies. Which therapeutic intervention is best for this patient?
- A. Amitriptyline 50 mg/day.
 - B. VSL #3 three capsules daily.
 - C. Tegaserod 6 mg twice daily.
 - D. Lubiprostone 8 mcg twice daily.
12. A 30-year-old woman who is 14 weeks pregnant presents with mild myalgias; a low-grade fever (temperature 99.8°F); four or five loose, watery bowel movements; and one episode of vomiting during the past 18 hours. She reports her 3-year-old daughter and several children in her day care class had the same symptoms 3 days ago. A rapid influenza test is negative, her WBC is 8×10^3 cells/mm³, and her SCr is 0.9 mg/dL. She takes a prenatal vitamin and reports no known drug allergies. She is given a diagnosis of a presumed viral gastroenteritis. Which is the best treatment for this patient's diarrhea?
- A. Loperamide.
 - B. Bismuth subsalicylate.
 - C. Lactase.
 - D. Pyridoxine.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Patients receiving PPI therapy for GERD should be reassessed for evaluation of efficacy. This patient has had some improvement in frequency of symptoms but is still not optimally controlled despite implementing lifestyle modifications and being adherent. There is no evidence that upper GI dysmotility is the cause of his GERD symptoms, so adding metoclopramide would not be preferred (Answer A). Switching to an alternative PPI such as omeprazole (Answer C) could be attempted, but typically this would be considered in the case of intolerance to another agent. Sucralfate (Answer D) has no role in GERD treatment. The GERD guidelines do endorse increasing the PPI frequency to twice daily in patients with continued symptoms, making Answer B correct.

2. Answer: C

The two most common causes of PUD are *H. pylori* and NSAID use. This patient has a gastric ulcer with evidence of a clot (indicating recent bleeding) in the setting of multiple NSAID use (aspirin plus ketoprofen). In addition, she is older than 60 years, which is another risk factor for an NSAID-induced ulcer. This is probably contributing to her upper GI problems and anemia. The rapid urease test performed on the biopsy specimen is negative, indicating the absence of *H. pylori*. First, the patient should discontinue NSAID use. NSAID use can markedly delay healing; therefore, it should be continued only if necessary. Healing of the ulcer should be facilitated by appropriate acid-suppressive therapy. Histamine-2 receptor antagonists, although effective in some instances, are less efficacious in the healing of gastric ulcers than are the PPIs, making Answer A incorrect. Because the patient has tested negative for *H. pylori*, use of an *H. pylori* eradication regimen is not necessary; therefore, Answer B is incorrect. Misoprostol, which is effective in preventing and healing ulcers, is not preferred because of the need for several daily doses, and it is very poorly tolerated because of a high incidence of abdominal pain, cramping, and diarrhea. The dose should also be at least 600 mcg/day. PPIs are the preferred drugs for healing NSAID-induced ulcers because of their excellent efficacy and favorable adverse effect profile, and they are better tolerated, making Answer C correct.

3. Answer: C

The test-and-treat approach is appropriate in dyspeptic patients thought to have *H. pylori* infections. Patients older than 45–55 years, or those with alarm features, should be referred for endoscopic evaluation to rule out the possibility of a more complicated disease. Ambulatory patients can be tested for *H. pylori* using various diagnostic approaches (e.g., UBT). The eradication of *H. pylori* leads to high rates of ulcer healing and minimizes ulcer recurrence. According to treatment guidelines, eradication regimens for *H. pylori* infection should include at least two antibiotics plus an antisecretory agent given for 10–14 days. This can be accomplished with triple-drug therapies containing amoxicillin (or metronidazole) plus clarithromycin in addition to a PPI. Likewise, quadruple therapy with bismuth, tetracycline, metronidazole, and a PPI can be used first line in penicillin-allergic patients or as a second-line treatment of initial failures of triple-drug therapy. This patient requires treatment secondary to a positive test. Answer A would be appropriate if the duration were at least 10 days. Answer B is not correct because cephalosporins are not recommended in *H. pylori* treatment regimens. Answer D is incorrect because fluoroquinolone-based regimens should be reserved as salvage therapy for patients whose triple and quadruple therapy has failed and the duration of 21 days is too long, making Answer C correct; quadruple therapy offers similar efficacy and is a viable first line. Patient adherence should be reinforced to maximize efficacy.

4. Answer: D

Treatment with topical aminosalicylate therapy (e.g., a suppository or enema) (Answer D) is a more effective option for patients with mild–moderate UC with distal disease compared with oral therapies such as balsalazide (Answer A). Methotrexate (Answer B) has a limited role in maintaining corticosteroid-induced remission in patients with CD. Infliximab would be indicated for moderate–severe UC when aminosalicylate therapy or budesonide has failed.

5. Answer: B

This patient is experiencing moderate to severe to CD involving the terminal ileum and colon. Mesalamine

(Answer A), though well tolerated, is minimally effective in CD and would not be indicated for moderate to severe disease. Budesonide (Answer C) is effective in mild–moderate CD affecting the terminal ileum and proximal colon, so the disease severity and location of the disease would not fit this regimen. Adalimumab would be appropriate, but the dose is for maintenance and would need to be 160 mg initially for induction. Combining infliximab and azathioprine (Answer B) has been shown to result in the highest rates of remission in moderate to severe CD compared with use of either agent alone.

6. Answer: C

Patients with cirrhosis and ascites are at risk of developing SBP, an infection of the ascitic fluid usually caused by an enteric gram-negative organism. Typical signs of infection include fever, abdominal pain, nausea, and rebound tenderness. Diagnosis is made on the basis of clinical symptoms plus laboratory evidence. The laboratory diagnosis is by paracentesis, with identification of more than $250/\text{mm}^3$ neutrophils (polymorphonuclear neutrophils) in the ascitic fluid. This patient's value is $450/\text{mm}^3$. Should clinical and laboratory signs and symptoms be present, antibiotic therapy directed against enteric gram-negative bacteria should be initiated. Third-generation cephalosporins such as cefotaxime and ceftriaxone are preferred. Aminoglycosides should be avoided because of their potential to cause nephrotoxicity. Vancomycin should be reserved for resistant gram-positive organisms. In addition to antibiotic therapy, use of intravenous albumin reduces the incidence of renal failure and improves in-hospital and 30-day mortality; it is indicated given that the patient's SCr is greater than 1.0 mg/dL and her BUN is greater than 30 mg/dL. Use of oral antibiotics to treat acute SBP is not well studied; however, an oral regimen (e.g., norfloxacin or trimethoprim/sulfamethoxazole daily) should be instituted and continued indefinitely after recovery to reduce the incidence of subsequent infections.

7. Answer: B

Management of overt hepatic encephalopathy should initially involve removal and treatment of precipitating factors and use of therapies aimed at reducing ammonia concentration. Recent guidelines recommend use of lactulose (Answer B) to rapidly reduce ammonia

concentrations in the short term. Therapy can also be continued as prophylaxis against subsequent episodes if needed. Nonabsorbable antibiotics such as rifaximin can be used, but rifaximin 550 mg twice daily (Answer A) is indicated for use in prevention of recurrent hepatic encephalopathy and is effective when combined with lactulose. Ceftriaxone (Answer D) would not as effective as rifaximin and is indicated in patients with cirrhosis who present with upper GI bleeding. Although PEG-3350 (Answer C) has been shown to have some efficacy in treatment of hepatic encephalopathy, the dose used in recent trials was 4 L administered over 4 hours.

8. Answer: D

This patient has evidence of a chronic HBV infection on the basis of elevations in ALT and AST, the presence of HBsAg, and high concentrations of circulating HBV DNA, as well as evidence of severe necroinflammation on biopsy. The patient has HBeAg positivity, and a YMDD mutation is present. She appears to have compensated liver disease on the basis of her albumin, INR, and lack of ascites or encephalopathy. Given her persistently elevated liver function tests, biopsy results, and high viral load, she should receive treatment. Treatment with an oral reverse transcriptase inhibitor is preferred first-line therapy. Interferon and ribavirin are preferred for chronic HCV infection (Answer B). Given that the patient has a lamivudine-resistant organism, as evidenced by the presence of the YMDD mutation, a drug therapy that treats lamivudine-resistant pathogens (e.g., tenofovir) is recommended as initial therapy (Answer D).

9. Answer: C

This patient has newly diagnosed chronic HCV infection. Withholding therapy (Answer A) at this time would not be optimal because the patient is considered high priority for treatment because of advanced fibrosis and has no contraindications to treatment. Sofosbuvir and simeprevir (Answer B) could be used for genotype 1a, but the NS3 80 QK polymorphism significantly reduces the effectiveness of simeprevir, making this the less preferred choice. The combination of sofosbuvir and ledipasvir (Answer C) is another first line option and would be preferred. Sofosbuvir and ribavirin (Answer D) is the recommended regimen for genotypes 2 and 3.

10. Answer: C

This patient has signs and symptoms of maldigestion and malabsorption secondary to the loss of pancreatic exocrine function. This is manifested by the presence of steatorrhea, weight loss, and an elevated fecal fat concentration. Management should include replacement of exogenous pancreatic enzymes to facilitate nutrient digestion and absorption. Oral pancrelipase products are pork derived and contain lipase, amylase, and protease. A typical starting dose for an adult patient should deliver 30,000–40,000 lipase units per meal, with titration based on reduction in steatorrhea and evidence of weight gain. Although chronic abdominal pain is a typical symptom of chronic pancreatitis, increasing the patient's morphine dose will not help with the symptoms related to the lack of enzymes. Likewise, using appetite stimulants such as dronabinol will not be beneficial if enzyme therapy is not initiated. Finally, this patient is malnourished, and use of a multivitamin would be beneficial; however, patients with chronic pancreatitis may need extra supplementation of fat-soluble vitamins after enzyme therapy is initiated and increased caloric intake to facilitate weight gain.

11. Answer: D

This patient meets the criteria for IBS-C on the basis of a negative diagnostic workup and the presence of abdominal pain, bloating, and constipation for more than 3 months. Drug therapy should target the predominant symptoms. The agents most beneficial in IBS-C are bulk-forming laxatives, which improve the frequency of bowel movements and may reduce bloating, and SSRIs, which provide relief from abdominal pain, improve global symptoms of IBS, and improve motility in most patients. The tricyclic antidepressants have effects similar to those of the SSRIs but are associated with anticholinergic effects, which may worsen constipation. Thus, amitriptyline would not be preferred in this case. Lubiprostone is approved for IBS-C in women older than 18 years and improves motility and possibly abdominal pain. It is the best choice presented, given the patient's symptoms. Probiotics such as VSL #3 may improve global symptoms of IBS, but they would not improve bowel frequency, so use would be best with another therapy that would increase stool frequency. Though effective for IBS-C when it was available, tegaserod is available only on an emergency basis because of its association with the development of CV events.

12. Answer: A

Diarrhea is caused by a variety of conditions, with viral pathogens being one of the most common causes. This patient probably developed diarrhea through contact with her daughter, who is in day care and had similar symptoms a few days earlier. In addition, her low-grade fever, myalgias, watery diarrhea, and vomiting point to a potential viral cause. Although most episodes of viral gastroenteritis are self-limited, symptomatic relief may be necessary to prevent dehydration. Selection of antidiarrheal therapy should be based on patient preference and the presence of any precautions or contraindications. If this patient desires therapy, a therapy should be chosen that minimizes risk to the patient and the fetus given that she is pregnant. Loperamide is an effective agent for short-term relief of diarrhea and carries an FDA pregnancy category B rating, so it would be the best choice in this case. Use of bismuth, although effective, should be avoided in pregnant and nursing patients because of the risk of potential toxicity. Lactase would be indicated only if the patient's diarrhea were secondary to lactose intolerance. Pyridoxine is used for the treatment and prevention of nausea and vomiting in pregnancy, but it has no effect on the treatment of diarrhea related to viral gastroenteritis.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B

This patient has signs of dysphagia, an alarm symptom that may be associated with a more complicated case of GERD. The patient has tried antacids with minimal relief and has a history of NSAID use. The patient is older than 45 years, which increases his risk of developing gastric cancer. Therefore, he should be referred for endoscopic evaluation to rule out a more complicated disease. Using either H2RAs or a PPI as initial therapy would be appropriate if the patient did not respond to antacids; however, a twice-daily dosing of PPIs is not necessary as initial dosing. Changing medications that reduce LES tone (e.g., calcium channel antagonists) is an appropriate recommendation for reducing GERD symptoms; this should be considered after invasive testing is performed.

2. Answer: C

For patients beginning long-term NSAID therapy, a thorough assessment of patient- or drug-related factors that may predispose them to the development of GI toxicity is necessary. Likewise, an evaluation of the patient's level of CV risk is necessary. Based on the use of low-dose aspirin for preventing CV events, this patient would be considered at high risk of CV events. Efforts to avoid GI toxicity should include the use of the least GI-toxic agent at the lowest effective therapeutic dose. A GI-protective agent should be considered to minimize NSAID-induced erosions and ulcers. Indomethacin and piroxicam are more likely to cause GI complications than naproxen. Use of COX-2 inhibitors is acceptable in patients with rheumatoid arthritis because these agents reduce GI complications and effectively treat pain. However, this patient has CV risk factors including diabetes, hypertension, and dyslipidemia. Recent findings of increased CV events, especially with high doses of COX-2 inhibitors, would preclude their use. Therapy with an acid-suppressive agent is also an acceptable choice for GI prevention in users of nonselective NSAIDs. Proton pump inhibitors are effective for this indication. The H2RAs are ineffective in preventing serious NSAID-induced GI complications. Misoprostol, although effective, is associated with a high incidence of diarrhea and abdominal pain, as well as the need for multiple daily dosing. Given that this patient is considered at moderate risk of

GI complications because of the patient's use of aspirin and need for high-dose NSAIDs, the use of naproxen plus a PPI would be preferred, according to the recent ACG guidelines.

3. Answer: D

This patient presents with signs and symptoms consistent with an NSAID-induced upper GI bleed. He has several risk factors for NSAID-induced GI bleeding, including age older than 60 years, use of aspirin, and long duration of NSAID use. The presence of underlying CV disease, although not a direct risk factor, may also contribute to increases in NSAID GI toxicity. He also has many criteria that place him at high risk of rebleeding. On the basis of the consensus recommendations for nonvariceal bleeding, he should receive an intravenous PPI by bolus and subsequent continuous infusion for 72 hours. Note that in the guidelines provided, it states that this therapeutic approach can be extrapolated to patients with NSAID-induced ulcers and bleeding, even though most of the data included in the guidelines pertain to non-NSAID-induced causes of upper GI bleeding. He will then require treatment with an appropriate dose of an oral PPI for at least 8 weeks; after that, he should be assessed for possible continued prophylactic use. Histamine-2 receptor antagonists are less efficacious for the treatment and prevention of rebleeding for NSAID-induced ulcers. Sucralfate has minimal efficacy in the setting of acute GI bleeding; more often, it is used in preventing SRMD in critically ill patients. Oral PPIs are effective in preventing and healing NSAID-induced ulcers; however, in this case, the dose of lansoprazole is inadequate for treatment. Oral PPIs should be used at an appropriate dose after intravenous therapy.

4. Answer: D

On the basis of this patient's presenting symptoms, she would probably be classified in the mild to moderate active disease category. First-line therapy for active extensive disease would consist of an oral aminosalicylate at a dose equivalent to mesalamine 4.8 g/day. A product such as Asacol is formulated to release mesalamine in the colon, which would be appropriate in this case. Sulfasalazine has reported efficacy for this indication and is activated in the colon; however, this patient

reports a life-threatening allergy to sulfonamide-containing medications. Topical therapy with hydrocortisone enema would be appropriate if the patient had disease distal to the splenic flexure. Immune modulators such as 6-MP have a long onset of action (3–15 months) and are not appropriate for acute active disease.

5. Answer: B

Primary prophylaxis of bleeding should be instituted in patients with large varices and cirrhosis. Nonselective β -blockers are appropriate as first-line therapy. Therapy should be targeted to achieve an HR of 55 beats/minute or a 25% reduction from baseline. The patient has taken propranolol for 1 month and has not met these goals. Because he is tolerating propranolol, the dose should be increased, and he should be observed to reassess the need for further dosage adjustments. Adding a nitrate would increase the reduction in portal pressures; however, nitrates have not been shown to improve mortality. Most patients experience an increased risk of adverse effects with this combination. Nonselective β -blockers are preferred to β -selective agents because antagonism of the β -receptor prevents splanchnic vasodilation.

6. Answer: C

The sensitivity of a test can be thought of as the proportion of patients with a disease who have a positive test, whereas specificity deals with the proportion of patients without the disease who have a negative test. Calculating these values is accomplished by establishing a 2×2 table representing the results of the test. The sensitivity can be calculated by dividing the number of patients having the disease using the new test who were also positive using a gold standard test (true positives), which in this case is 850, by the number of patients receiving a diagnosis of having the disease using the gold standard, which in this case is 900. The 900 represents the true positives as well as the 50 patients with the disease but without the diagnosis of it, according to the new test (false negatives). Specificity can be calculated by taking the number of patients not having the disease using the gold standard who tested negative with the new test (true negatives = 85). Then, divide this by the number of patients who truly had no disease using the gold standard, 100, which incorporates the 15 patients who tested positive with the new test but truly had no disease (i.e., false positives). Sensitivity = $850 / (850 + 50) = 94\%$; specificity = $85 / (85 + 15) = 85\%$.

Result	Infection	No Infection	Total
Positive	850	15	865
Negative	50	85	135
Total	900	100	1000

7. Answer: C

Postexposure therapy for HAV may be offered to restaurant patrons if a food handler at a restaurant is documented to have HAV and is considered infectious while handling food. The most effective therapies for postexposure prophylaxis are administration of HAV immune globulin or vaccine. The efficacy of the vaccine approaches that of immune globulin but only in patients younger than 40, according to the Centers for Disease Control and Prevention guidelines. The period for administration should be within 14 days of exposure; therefore, this patient does not meet the criteria for receiving HAV immune globulin or vaccine. She should be observed for signs and symptoms of active disease. Hepatitis A vaccine should be offered to patients as pre-exposure therapy if they are considered at risk of exposure to HAV. The combination of vaccine and immune globulin for postexposure therapy is unnecessary.

8. Answer: C

This patient is presenting with elevated aminotransferases, consistent with alcoholic hepatitis. Prognosis of alcoholic hepatitis may be initially evaluated by the Maddrey discriminant function (MDF) score, calculated as $4.6 \times (\text{patient's PT} - \text{control PT}) + \text{total bilirubin (mg/dL)}$, where PT is prothrombin time. Patients whose score is greater than 32 are believed to have a poor prognosis. This patient's MDF score is 42.5, so she would qualify for treatment with a 4-week course of prednisolone 40 mg/day, followed by a 2-week taper (Answer C). This may lead to a 30% decrease in the risk ratio of short-term death. Naproxen (Answer A), though having anti-inflammatory activity, has no role in the treatment of alcoholic hepatitis and may precipitate acute kidney injury in patients with liver disease and therefore should be avoided. Octreotide (Answer B) would be indicated in the setting of acute variceal bleeding, and midodrine (Answer D) is indicated for hepatorenal syndrome. This patient has no evidence of either condition.

9. Answer: D

The treatment of chronic HCV is PEG-IFN in combination with ribavirin. Genotypes 2 and 3 respond well to therapy. Although this patient appears to be responding to treatment, as evidenced by reductions in aminotransferases and HCV RNA, the earliest that HCV RNA should be evaluated is 4 weeks, not 2 weeks. Interferon therapy is associated with many adverse effects (e.g., flulike symptoms, CNS effects, leukopenia, thrombocytopenia). This patient does not appear to be experiencing these types of symptoms or those consistent with extrahepatic manifestations of HCV (e.g., glomerulonephritis or rheumatologic disorders). The patient does have evidence of hemolysis, including scleral icterus, rapid decline in hematocrit, fatigue, and elevated indirect bilirubin, probably representing hemolytic anemia secondary to ribavirin, which commonly occurs within the first 2 weeks of therapy. Furthermore, there is no evidence that the decrease in hematocrit is secondary to bleeding.

10. Answer: A

Infliximab is an appropriate agent for the treatment of fistulizing CD. Because of its effects on TNF, latent infections such as tuberculosis may become reactivated during therapy. Therefore, patients should have a purified protein derivative or QuantiFERON-TB test to rule out underlying tubercular disease before treatment is initiated. Although infliximab therapy is associated with infusion-related reactions, administering a test dose is not routinely recommended. Infliximab may be administered in a clinic setting; it does not require admission to the hospital for monitoring. Infliximab therapy is associated with exacerbations of underlying heart failure and is contraindicated in patients with New York Heart Association class III or IV disease. This patient is young, with no history of heart failure, and has no clinical signs of heart failure. Therefore, a baseline echocardiogram is not necessary to assess cardiac function.

11. Answer: C

Treatment of nausea and vomiting in medical inpatients may be accomplished by administering a variety of antiemetics. Nausea and vomiting are common symptoms associated with pyelonephritis and will subside once appropriate antibiotic therapy adequately treats the infection. However, patients will need symptomatic

relief until the antibiotics take effect. Agents typically used for medical inpatients include phenothiazines and serotonin antagonists. Use of intravenous or rectal formulations is usually preferred for patients with severe nausea, such as this patient. Ondansetron is a serotonin antagonist that can be administered as needed intravenously and is effective in treating nausea caused by a variety of medical conditions. Despite its effects on serotonin, it should not cause any significant interaction with the patient's sertraline dose. Prochlorperazine, a commonly used antiemetic, would be a viable option; however, using the oral product in this case would not be preferred, given that the patient has severe vomiting. In addition, prochlorperazine is a dopamine antagonist, and the patient is receiving a high dose of risperidone. This combination may lead to the development of EPS and, in severe cases, QTc prolongation. Metoclopramide is typically used as an antiemetic when gastroparesis is present or as an adjunctive therapy for patients whose other therapies have failed. Metoclopramide also has dopamine antagonist effects and may lead to the development of EPS. Diphenhydramine is more effective for nausea related to motion sickness, but it would not effectively treat severe short-term nausea or the other options.

12. Answer: B

This patient presents with acute constipation given his symptoms of abdominal pain, both by complaints and on examination; reduced frequency of bowel movements; and radiographic evidence of a large quantity of stool in the colon. Contributing factors include the use of verapamil and oxycodone without the use of a drug regimen to prevent constipation. Therapy should be instituted to provide a quick onset to initiate a bowel movement and provide symptom relief. Saline laxatives such as sodium phosphate provide quick results, especially when given by enema. The oral formulation of sodium phosphate results in phosphate absorption and is problematic in patients with chronic kidney disease caused by the development of hyperphosphatemia and phosphate nephropathy. This patient's CrCl is about 34 mL/minute, so saline laxatives should be avoided. Bisacodyl suppositories provide rapid stimulation of the lower intestinal tract without the risk of electrolyte absorption, so they would be preferred in this case. Methylcellulose is a bulk-forming laxative that would not treat the patient's acute constipation, but it would

be an option for preventing constipation on a long-term basis in this patient once the short-term episode is resolved. Although methylnaltrexone is indicated for opioid-induced constipation, it would generally not be used as first-line agent given the need for injection and the added cost compared with traditional laxatives.

13. Answer: D

Stress-related mucosal disease develops in critically ill patients and may lead to significant upper GI bleeding. Therapy initiation to prevent SRMD is based on the presence of risk factors. Independent risk factors include mechanical ventilation and coagulopathy. This patient is currently on a ventilator and has other risk factors such as sepsis, hypotension, and acute renal insufficiency, so he would meet criteria for initiating pharmacologic prophylaxis. Both H2RAs and PPIs are viable first-line options. Cimetidine carries an FDA-approved indication for the prevention of SRMD; however, the dosing provided is incorrect because 50 mg/hour is the approved dose. Likewise, cimetidine would need to be dose adjusted for the patient's CrCl, which can be assumed less than 10 mL/minute. Pantoprazole would be a better choice in this case, and it does not require adjustment for the CrCl. Sucralfate has been historically used to prevent SRMD, but it has fallen out of favor because of the need for multiple daily dosing and the risk of aluminum accumulation in patients with kidney disease. Antacids are not as effective as H2RAs, require multiple daily dosing, and are associated with electrolyte accumulation in patients with kidney injury.

14. Answer: D

Several different forms of bias exist that may adversely affect the validity or results of a trial. Errors in sampling or measurement, incorrect patient enrollment methods, or differences in patient populations studied in a trial are examples of areas of study design and conduction that may introduce bias. When evaluating drug literature, an important aspect of deciding whether the reported results are valid is to recognize important causes of bias. A retrospective cohort design typically uses medical records to evaluate events that occurred in the past after exposure to a drug. Recall bias pertains to study outcomes or events that patients are asked to recall, with results differing depending on the ability of patients to remember an event. For this study, objective documentation of ulceration or bleeding was performed to make

comparisons between groups, eliminating patient recall as a potential bias. Misclassification bias is typically problematic in case-control studies, in which patients may be entered in the case study group but have not actually been exposed to the drug in question, which would not be applicable in this case. Interviewer bias, also known as observer bias, is typically problematic in direct patient survey studies and pertains to variation in the way different investigators collect data within a trial. To eliminate this bias, everyone involved in data collection in a study should be appropriately trained in the same manner of data collection to maintain consistency. Again, because an objective measure of GI toxicity was recorded by endoscopy, the possibility of interviewer bias is minimized. Channeling bias is a form of allocation bias in which medications with similar therapeutic indications are administered to patients with differing prognoses or risk levels. Should claims be made that a new drug introduced to a therapeutic class has particular advantages—in this case, a safer GI toxicity profile—then the chance that use will be channeled to high-risk patients is much greater. Given that the drug may be studied in higher-risk patients rather than the comparator group, the development of more events in this newer drug group may mask potential differences in safety and cause these events to be attributed to drug-induced toxicity.

Result	Infection	No Infection	Total
Positive	190	24	214
Negative	10	276	286
Total	200	100	500

15. Answer: B

Positive predictive value tells you the proportion of patients with a disease when the presence of the disease is indicated by a diagnostic test. It is affected by disease prevalence; thus, as disease prevalence falls, so does the positive predictive value of the test. Using the sensitivity, specificity, and prevalence, a 2×2 table can be constructed. The positive predictive value is calculated by dividing the true positives by the sum of the true and false positives. In this case, that would be $190 / (190 + 24) \times 100 = 89\%$.