Hepatic Failure/GI/Endocrine Emergencies

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Chicago, Illinois
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Learning Objectives

1. Define acute liver failure (ALF), and describe the most common causes for its occurrence.
2. Develop a treatment strategy to help manage and reduce the impact of the complications associated with ALF.
3. Assess the severity of an episode of acute pancreatitis, and understand the efficacy data regarding different treatment modalities.
4. Identify patients at high risk of developing fistulas postoperatively, and assess the need for pharmacologic versus surgical treatment.
5. Recognize cases of postoperative ileus, and develop a treatment strategy for its management.
6. Identify risk factors and treatment options for postoperative nausea and vomiting.
7. Design a treatment plan for patients who present with an acute upper GI bleed.
8. Differentiate between the five major endocrine emergencies in the intensive care unit, and be able to design a therapeutic regimen for each presentation.

Abbreviations in This Chapter

ALF Acute liver failure
AP Acute pancreatitis
DILI Drug-induced liver injury
DKA Diabetic ketoacidosis
ED Emergency department
ERCP Endoscopic retrograde cholangiopancreatography
HHS Hyperosmolar hyperglycemic state
ICP Intracranial pressure
ICU Intensive care unit
NG Nasogastric
NJ Nasojejunal
NSAID Nonsteroidal anti-inflammatory drug
POI Postoperative ileus
PONV Postoperative nausea and vomiting
PPI Proton pump inhibitor
T3 Triiodothyronine
T4 Thyroxine
TSH Thyroid-stimulating hormone

Self-Assessment Questions

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

1. Which option best represents the two signs or symptoms that are currently considered the hallmarks of acute liver failure (ALF)?
   A. Jaundice and encephalopathy.
   B. Thrombocytopenia and encephalopathy.
   C. Coagulopathy and encephalopathy.
   D. Leukocytosis and encephalopathy.

2. A 25-year-old woman presents to the emergency department (ED) 2 hours after an intentional acute overdose of an unknown amount of acetaminophen. According to the Rumack-Matthew nomogram, her acetaminophen level on admission puts her at high risk of hepatoxicity. Which is the most appropriate course of action?
   A. Medication therapy is not indicated, and this patient should recover with supportive care.
   B. Acetylcysteine, which is indicated in acetaminophen overdose, should be administered.
   C. Acetylcysteine is indicated in acetaminophen overdoses; however, this patient is outside the appropriate time window and may not benefit from acetylcysteine therapy.
   D. Acetylcysteine is indicated; it should be given in addition to hemodialysis.

3. A 63-year-old woman with chronic alcohol-induced pancreatitis is admitted to an inpatient unit with new-onset abdominal pain, elevated amylase and lipase levels, and imaging suggestive of necrotizing pancreatitis. Which is the most appropriate course of action in the medical management of this patient’s necrotizing pancreatitis?
   A. Surgical management of necrotic tissue should be undertaken right away.
   B. Antibiotics should be prophylactically administered to preserve the sterility of the necrotized area, and the patient should receive nothing by mouth (i.e., be kept NPO).
C. Antibiotics and surgical management should be deferred, but the patient should be fluid resuscitated, and total parenteral nutrition should be initiated to provide appropriate nutrition.
D. Antibiotics, surgical management, and total parenteral nutrition should be deferred, but the patient should be fluid resuscitated and initiated on enteral feeds, if tolerated.

4. Which class of antibiotics most accurately represents an inappropriate choice for the treatment of an infected necrotizing pancreatitis due to inadequate penetration of the drug to the site of infection?
   A. Carbapenems.
   B. Macrolides.
   C. Cephalosporins.
   D. Fluoroquinolones.

5. A 37-year-old woman presents after a Roux-en-Y gastric bypass for morbid obesity. Her postoperative course was complicated by the formation of an enterocutaneous fistula, fever, and leukocytosis. She was initiated on broad-spectrum antibiotics, and a wound vacuum-assisted closure was placed on her fistula site to help with drainage and healing. Her fistula output was 570 mL/day yesterday, and today, it was recorded as 250 mL/day. Which statement is most accurate regarding her fistula output between the two recordings?
   A. Her output would be defined as low output on both days.
   B. Her output would be defined as high output that has converted to a low output.
   C. Her output would be defined as a high output that has converted to a moderate output.
   D. Her output would be considered moderate on both days.

6. Which therapy has shown the most promising evidence in the treatment of postoperative ileus (POI)?
   A. Metoclopramide.
   B. Erythromycin.
   C. Alvimopan.
   D. Ondansetron.

7. A 69-year-old woman presents to the surgical intensive care unit (ICU) at your institution with an upper gastrointestinal (GI) bleed caused by a gastric ulcer. She has lost a significant amount of blood because of the bleed and currently requires blood transfusions. As part of her diagnostic workup to determine the etiology of her ulcer, she tested positive for a *Helicobacter pylori* infection. Which best reflects an inappropriate treatment option for her?
   A. Octreotide 50-mcg bolus, followed by 50 mg/hour for 72 hours.
   B. Treatment with a proton pump inhibitor (PPI)/antibiotic combination for 14 days.
   C. A therapeutic endoscopy within 24 hours.
   D. Blood transfusions to maintain hemoglobin greater than 7 g/dL.

8. Which set of laboratory abnormalities best reflects those that patients in a thyroid storm typically present with?
   A. High thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) levels.
   B. Low TSH, high T3, and high T4 levels.
   C. Low TSH, high T3, and low T4 levels.
   D. Low TSH, low T3, and low T4 levels.
I. ACUTE LIVER FAILURE

A. Epidemiology
   1. Incidence of less than 10 cases per million persons per year (about 2000 cases a year in the United States), with multiorgan failure and death in as many as 50% of patients (N Engl J Med 2013;369:2525-34; World J Gastroenterol 2013;19:7069-77)
   2. Very difficult to study clinically because of a high mortality rate and low incidence. Methodologies of relevant studies are hindered by the sometimes indeterminate or unique causes of ALF.
   4. Can occur in any age and demographic group, though cases of viral hepatitis are more common in developing countries of Asia and Africa, whereas toxin-related cases, such as those related to acetaminophen toxicity, occur more often in developed countries (World J Gastroenterol 2013;19:7069-77).
   5. ALF accounts for 7% of annual liver transplants in the United States (Hepatology 2012;55:965-7).

B. Definitions
   1. Complex syndrome with several systemic manifestations
   2. Several definitions exist:
      b. U.S. Acute Liver Failure Study Group (US ALFSG) in 2007: Combination of coagulopathy and encephalopathy in patients without a history of liver disease within 26 weeks of jaundice (Stravitz et al., 2007)
      c. American Association for the Study of Liver Disease Position Paper in 2011: An international normalized ratio (INR) of 1.5 or greater with encephalopathy in patients without a history of liver disease and a duration of symptoms of less than 26 weeks (Lee, Stravitz, & Larson, 2012)
   3. Modern definitions try to quantify the time to encephalopathy after the onset of jaundice, which may provide some data regarding the potential cause of ALF (N Engl J Med 2013;369:2525-34; Semin Respir Crit Care Med 2012;33:36-45; Lancet 1993;342:1000).
      a. Hyperacute: Less than 7 days – typically caused by acetaminophen toxicity or viral hepatitis
      b. Acute: 7–21 days
      c. Subacute: More than 21 days and less than 26 weeks – typically drug induced
   4. Hyperacute syndromes tend to have more severe signs and symptoms but tend to have better outcomes than slowly progressing disease.
   5. Hyperacute cases tend to have a significantly higher incidence of cerebral edema, whereas subacute cases tend to have a low incidence (Lancet 1993;342:1000).
Table 1. Causes of Acute Liver Failure in the United States

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>APAP</td>
<td>46%</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>13%</td>
</tr>
<tr>
<td>Non-APAP drug induced</td>
<td>12%</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>7%</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>6%</td>
</tr>
<tr>
<td>Ischemic</td>
<td>5%</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>2%</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>1.2%</td>
</tr>
<tr>
<td>Budd-Chiari</td>
<td>0.94%</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0.94%</td>
</tr>
<tr>
<td>Other</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

APAP = acetaminophen.
(Ann Intern Med 2002;137:947-54)

C. Causes

1. Drug induced:
   a. Acetaminophen
      i. Considered the primary etiology of ALF in the United States (responsible for 46% of cases) and Europe, and was responsible for 70,000 health care encounters and 300 deaths in the United States in 2005 (N Engl J Med 2008;359:285-92; Hepatology 2012;55:965-7; Semin Respir Crit Care Med 2012;33:36-45)
      ii. Rates of ALF caused by acetaminophen have increased during the previous 2 decades.
      iii. ALF can be caused by single administrations of a high dose (either accidentally or with intent) or prolonged and/or frequent administration of therapeutic doses.
         (a) Typical dose needed to cause ALF is greater than 10 g/day; however, liver injury can occur at therapeutic doses (3–4 g/day) (Semin Respir Crit Care Med 2012;33:36-45)
         (b) Other reports indicate a threshold for hepatic toxicity at 150 mg/kg (World J Gastroenterol 2013;19:7069-77).
         (c) Some data suggest that doses of up to 30 g are necessary to cause ALF; thus, the potential to cause liver injury may rely on several factors independent of the dose itself, including a history of alcohol abuse and the use of concomitant drugs that can induce the cytochrome P450 (CYP450) system, specifically CYP2E1 (Ann Gastroenterol 2010;23:257-65).
         (d) Unintentional overdoses – The US ALFSG study from 2002 reported that 38% of patients with acetaminophen-related ALF were concomitantly taking several acetaminophen-containing products and that up to 62% of patients were taking an opioid-/acetaminophen combination (Hepatology 2005;42:1367-72).
      iv. If not treated in the early stages (i.e., before the development of encephalopathy), the mortality rate is around 20%–40% (N Engl J Med 2008;359:285-92).
         (a) Preclinical: No signs or symptoms
         (b) Injury: Elevated alanine aminotransferases
         (c) Failure: Injury plus encephalopathy
         (d) Recovery
vi. Pathophysiology
(a) Typically, glucuronidation or sulfation in the liver converts acetaminophen into benign metabolites; however, about 5% is metabolized by CYP2E1 into electrophile N-acetyl-p-benzoquinone imine (NAPQI), a toxic metabolite that causes hepatotoxicity and necrosis (Chem Res Toxicol 1996;9:580-5; N Engl J Med 2008;359:285-92).
(b) Intrinsic glutathione typically detoxifies NAPQI before any toxicity to the liver can occur by forming a glutathione-acetaminophen product; however, the ingestion of large amounts of acetaminophen can quickly deplete intrinsic glutathione stores (Chem Res Toxicol 1996;9:580-5; N Engl J Med 2008;359:285-92).
(c) Acetylcysteine repletes intrinsic glutathione stores and is a viable antidote for acetaminophen toxicity (to be discussed later in the chapter).

vii. Because of the growing incidence of acetaminophen-related ALF, including unintentional overdoses, the U.S. Food and Drug Administration (FDA) recently provided specific recommendations to manufacturers regarding combination products and required a black box warning on all acetaminophen-containing products, highlighting the risk of hepatotoxicity (www.fda.gov/DRUGS/DRUGSAFETY/ucm381644.htm). The FDA recommends that combination products contain a maximum of 325 mg of acetaminophen because additional amounts of acetaminophen have not been shown beneficial in providing further analgesia, but can increase the risk of hepatotoxicity (www.fda.gov/DRUGS/DRUGSAFETY/ucm381644.htm).

**Patient Case**
1. A 34-year-old man presents with a medical history significant for chronic back pain because of a motor vehicle accident 2 years ago. He consistently takes hydrocodone/acetaminophen 5/500 mg (Vicodin) around the clock and has recently been taking up to 12 tablets a day because his pain has not been controlled with the old dose. Because of the potential for significant hepatotoxicity in these cases, which most accurately depicts the recent recommendation by the FDA?
   A. Acetaminophen should be replaced with ibuprofen in combination products.
   B. To reduce the incidence of incidental liver toxicity, acetaminophen should no longer be combined with opioids.
   C. All acetaminophen/opioid combinations should be classified as schedule II medications.
   D. All combination acetaminophen/opioid products should contain no more than 325 mg of acetaminophen.

viii. The Rumack-Matthew nomogram (Figure 1) is useful in determining which patients are at high risk of hepatotoxicity and should thus be treated with acetylcysteine (Crit Care Clin 2012;28:499-516).
Figure 1. Rumack-Matthew Nomogram

(a) All patients above the possible hepatic toxicity line (150 mcg/mL at 4 hours) are considered at high risk of hepatotoxicity.

(b) Useful only for patients who present with an acute overdose with a known time of ingestion

b. Non-acetaminophen drug-induced liver injury (DILI)
   i. Tends to be idiosyncratic and rare, and most cases occur within 6 months of initiation of a medication (Semin Respir Crit Care Med 2012;33:36-45)
   ii. DILI has an inconsistent presentation, presents randomly among patients, and is not consistently dose related (Am J Gastroenterol 2014;109:950-966).
   iii. Up to 80% of patients with an idiosyncratic drug injury die without a transplant (World J Gastroenterol 2013;19:7069-77).
   iv. No specific treatment modalities exist other than withdrawal of the offending drug; however, acetylcysteine improved transplant-free survival in one study (Gastroenterology 2009;137:856-64).
      (a) Corticosteroids and agents such as ursodeoxycholic acid have little evidence to support their use in the treatment of DILI (Am J Gastroenterol 2014;109:950-966).
   v. A detailed patient medication history should be obtained to identify all potential culprit medications, including herbal medications.
   vi. Typically caused by certain antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), or anticonvulsants (Semin Respir Crit Care Med 2012;33:36-45)
   vii. The RUMAC scoring system may be utilized and differentiates between hepatocellular, cholestatic, and mixed injuries based on certain criteria such time-course since exposure, liver function tests, risk factors, and other data to provide additional information to help diagnose DILI (Am J Gastroenterol 2014;109:950-966)
   viii. See Appendix 1 for a list of medications linked to DILI.
### Patient Case

2. A 17-year-old male teenager with a history of bipolar disorder presents to the ED about 8 hours after an acute overdose of acetaminophen. His acetaminophen level on admission was 237 mcg/mL. According to the Rumack-Matthew nomogram (see Figure 1), which is the best assessment of this patient’s case?

- A. He is not at risk of hepatoxicity according to the Rumack-Matthew nomogram.
- B. He is at possible risk of hepatotoxicity.
- C. He is at probable risk of hepatotoxicity.
- D. Not enough information is provided to assess his risk of hepatotoxicity.

2. Non–drug induced:
   a. Viral
      ii. Hepatitis A: Usually spread by the fecal-oral route and accounts for about 4% of ALF cases in the United States (Lee et al, 2012)
      iii. Hepatitis B
         a) Rates of hepatitis B–induced ALF have fallen significantly in the past few decades and occur mainly in Asian and Mediterranean countries (N Engl J Med 2013;369:2525-34).
         b) Activation of a dormant hepatitis B infection during episodes of immunosuppression is linked to high mortality rates and requires antiviral prophylaxis before periods of planned immunosuppression (e.g., chemotherapy, high-dose steroid therapy) (N Engl J Med 2013;369:2525-34).
      iv. Hepatitis E
         a) Endemic in Russia, Pakistan, Mexico, and India (World J Gastroenterol 2013;19:7069-77)
         b) Can be transmitted to neonates during acute infections in pregnant women
      vi. Herpes simplex virus may rarely cause ALF in immunosuppressed or pregnant patients.
   b. Ischemic injury: May occur in critically ill patients with “cardiac, circulatory, or respiratory failur,” and typically requires supportive care with the intention of providing perfusion to the liver through hemodynamic and respiratory support (N Engl J Med 2013;369:2525-34)
   c. Mushroom ingestion
      i. Typically caused by the *Amanita* genus of mushrooms (World J Gastroenterol 2013;19:7069-77)
      ii. ALF is typically characterized by a history of significant GI symptoms, which can occur within 24 hours of ingestion (World J Gastroenterol 2013;19:7069-77).
   d. Wilson disease
      i. Serious condition with high mortality rates implicated in 2%–3% of ALF cases (Semin Respir Crit Care Med 2012;33:36-45)
      ii. Characterized by “an abrupt onset Coombs negative hemolytic anemia with serum bilirubin greater than 20 mg/dL.” (Semin Respir Crit Care Med 2012;33:36-45)
      iii. Transplant is the only effective option for patients who present with Wilson disease (World J Gastroenterol 2013;19:7069-77).
   e. Autoimmune hepatitis
      i. Extremely rare disorder with an incidence rate of 0.001%–0.002% (Hepat Res Treat 2011:2011:390916)
ii. Defined as a chronic inflammatory disease, typically instigated by an environmental trigger, in which about 20% of cases with stable disease can rapidly deteriorate into ALF (Wang et al, 2013; Hepat Res Treat 2011;2011:390916)

iii. Can be successfully managed with corticosteroids during the early stages of the disease, but patients typically require a liver transplant if the disease progresses to liver failure (Hepat Res Treat 2011;2011:390916)

f. Budd-Chiari syndrome: Caused by an acute thrombus of the hepatic vein and occurs most often in females with a median age of 35 (Nephrol Dial Transplant 2007;22 (suppl 8):viii5-viii8)

g. Pregnancy-related ALF
   i. Acute fatty liver of pregnancy or HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome typically occurs in the third trimester of pregnancy (Semin Respir Crit Care Med 2012;33:36-45).
   ii. Requires emergency delivery of fetus, after which symptoms should dissipate

D. Complications
   a. Neurologic
      i. Encephalopathy (which is a clinical presentation of cerebral edema) can initially be difficult to identify and may present as agitation and confusion; however, encephalopathy can progress rapidly and requires close monitoring by ICUs or units that specialize in the care of patients with liver failure (N Engl J Med 2013;369:2525-34; Hepatology 2012;55:965-7; World J Gastroenterol 2013;19:7069-77).
      ii. The West Haven Coma Scale can be useful in determining the severity of encephalopathy (Hepatology 2002;35:716-21) (see Table 2).

**Table 2. West Haven Coma Scale**

| Grade 1 | Trivial lack of awareness  
|         | Euphoria or anxiety  
|         | Shortened attention span  
|         | Impaired performance of addition  
| Grade 2 | Lethargy or apathy  
|         | Minimal disorientation for time or place  
|         | Subtle personality changes  
|         | Inappropriate behavior  
|         | Impaired performance of subtraction  
| Grade 3 | Somnolence to semi-stupor, but responsive to verbal stimulus  
|         | Confusion  
|         | Gross disorientation  
| Grade 4 | Coma (unresponsive to verbal or noxious stimuli)  

iii. Cerebral edema and elevated intracranial pressures (ICPs) often occur in most patients (75%–80%) with high-grade encephalopathy and constitute the primary etiologies for mortality in patients with ALF (Ann Gastroenterol 2010;23:257-65).
   (a) Elevated ICPs can be caused by several factors but are thought to be primarily caused by osmotic shifts in the brain, inflammation, and neurotoxins (N Engl J Med 2013;369:2525-34; Hepatology 2012;55:965-7; Semin Respir Crit Care Med 2012;33:36-45).
Ammonia is converted to osmotically active glutamine, and levels have been correlated with both encephalopathy and cerebral edema; levels greater than 200 mcg/dL are associated with cerebral herniation (Semin Respir Crit Care Med 2012;33:36-45; World J Gastroenterol 2013;19:7069-77). In ALF, either because of the impaired ability of the hepatocytes or because of the abnormal shunting of venous flow away from the liver caused by portal hypertension, normal mechanisms to detoxify and clear ammonia are no longer effective.

Cerebral edema can lead to tissue hypoxia and long-term neurologic deficits, and severity is directly related to the degree of encephalopathy (Semin Respir Crit Care Med 2012;33:36-45).

Uncontrolled edema and elevated ICPs can lead to uncal herniation and death (Semin Respir Crit Care Med 2012;33:36-45).

Cardiovascular
i. Hemodynamic compromise: Patients will typically have low mean arterial pressure, low systemic vascular resistance, and high cardiac output (World J Gastroenterol 2013;19:7069-77).
ii. Most patients are severely dehydrated before admission because of poor nutritional status and will require fluid resuscitation (Hepatology 2012;55:965-7).

Coagulopathy
i. Decreased synthesis of clotting factors by the liver, as well as increased use of existing factors, may increase the risk of bleeding (Semin Respir Crit Care Med 2012;33:36-45).
ii. Low platelet counts, in addition to altered coagulation laboratory values, suggest an elevated risk of bleeding (Hepatology 2012;55:965-7).
iii. However, studies show that overall hemostasis in patients with ALF is maintained by compensatory mechanisms, even in patients with elevated INR values (Semin Respir Crit Care Med 2012;33:36-45).
iv. There is a balance between a procoagulant state and an anticoagulant state because the lack of hepatic synthesis of clotting factors is offset by the lack of synthesis of natural anticoagulants (N Engl J Med 2013;369:2525-34).

Renal
i. Renal failure is a common complication that occurs in 40%–85% of patients with ALF and in 75% of patients with acetaminophen toxicity (Gastroenterology 2007;13:5552-9).
ii. Causes
   a. Prerenal azotemia: Caused by vasodilatation owing to portal hypertension and worsened by systemic hypoperfusion (Gastroenterology 2007;13:5552-9)
   b. Intrinsic disease: Can occur because of drugs or toxins (Gastroenterology 2007;13:5552-9)

Infection
i. Patients with ALF are at high risk of infection because of the presence of several indwelling catheters and lines in addition to intrinsic monocyte and neutrophil dysfunction (World J Gastroenterol 2013;19:7069-77).
ii. Patients typically present with pneumonias, bloodstream infections, or urinary tract infections (World J Gastroenterol 2013;19:7069-77).

Metabolic abnormalities
i. Lack of effective glycogenolysis and gluconeogenesis caused by impaired hepatocyte function places patients at high risk of hypoglycemia (World J Gastroenterol 2013;19:7069-77).
ii. Profound hypoglycemia can worsen an already altered mental state.

Therapy must be multimodal to support each of the organ systems affected by ALF.
E. Diagnosis

1. An unexplained elevated INR in a patient presenting with encephalopathy requires further evaluation for ALF because the combination of these two symptoms is very specific to ALF (Hepatology 2012;55:965-7).

2. In ALF, certain markers of chronic liver disease (e.g., jaundice, ascites, right upper quadrant pain, portal hypertension) may not be present (Semin Respir Crit Care Med 2012;33:36-45).

Table 3. Diagnostic approach to a patient with suspected ALF

<table>
<thead>
<tr>
<th>History</th>
<th>Assess for exposure history to viruses, drugs, or toxins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assess substance abuse history</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Normal signs of chronic liver disease (ascites, jaundice, right upper quadrant pain) may not be present</td>
</tr>
<tr>
<td></td>
<td>Assess encephalopathy grade</td>
</tr>
<tr>
<td>Laboratory analysis</td>
<td>Basic metabolic panel, CBC, liver function tests, arterial blood gas, acetaminophen levels, ammonia, toxicology screen</td>
</tr>
<tr>
<td></td>
<td>Viral serologies</td>
</tr>
<tr>
<td>Imaging</td>
<td>Liver biopsy useful for determining autoimmune hepatitis or ALF associated with HSV</td>
</tr>
<tr>
<td></td>
<td>Hepatic imaging studies (computed tomography [CT], ultrasonography) may be used to detect a thrombus of the hepatic vein</td>
</tr>
</tbody>
</table>

ALF = acute liver failure; CBC = complete blood cell count; HSV = herpes simplex virus.
Semin Respir Crit Care Med 2012;33:36-45

F. Management of ALF

1. Antidotes
   a. Acetaminophen-induced ALF (See Table 4)
      i. Activated charcoal may be effective if given up to 4 hours after acetaminophen ingestion (Semin Respir Crit Care Med 2012;33:36-45).
      ii. Acetylcysteine: Helps restore depleted glutathione stores
          (a) Several studies have shown promising results when acetylcysteine is promptly administered to a patient with acetaminophen toxicity without exposing the patient to severe adverse events associated with other therapies known to replete glutathione stores, such as methionine and cysteamine (N Engl J Med 2008;359:285-92).
          (b) Can be given by either the oral or the intravenous route; studies have shown similar efficacy rates between the two routes; however, intravenous acetylcysteine is recommended for patients with liver failure (West J Emerg Med 2013;14:218-26; N Engl J Med 2008;359:285-92)
              (1) Benefits of the intravenous route include the time needed to administer the drug as the intravenous route can be completed in 21 hours, whereas the oral route takes 72 hours to complete. The PO route is also associated with significant GI symptoms.
              (2) The US ALFSG suggests intravenous therapy in patients when patients have any of the following (Crit Care Med 2007;35:2498-508):
                  (A) Greater than grade 1 encephalopathy
                  (B) Hypotension
                  (C) If oral therapy cannot be tolerated
(c) Predefined courses for both oral and intravenous therapies may be modified based on patient response, and many poison centers may extend therapy beyond the recommended course if there is a detectable APAP level or if alanine aminotransferase levels continue to remain elevated at the end of therapy, especially if therapy was initiated > 8 hours after ingestion and baseline acetaminophen levels were > 300 mcg/mL (Heard, 2008).

(d) Therapy may continue until the signs and symptoms of encephalopathy or coagulopathy resolve or until the patient receives a liver transplant (N Engl J Med 2008;359:285-92).

Table 4. Acetylcysteine for Acetaminophen-Induced Toxicity

<table>
<thead>
<tr>
<th>Route</th>
<th>Dose</th>
<th>Adverse Effects</th>
</tr>
</thead>
</table>
| Oral  | Loading dose: 140 mg/kg x 1 dose  
Maintenance dose: 70 mg/kg every 4 hours x 17 doses | GI intolerance is extremely common, so the dose may need to repeated if the patient has emesis within 1 hour of administration |
| IV    | 150 mg/kg x 1 (max 15 g) over 60 minutes, followed by 50 mg/kg (max 5 g) over 4 hours, followed by 100 mg/kg (max 10 g) over 16 hours | Anaphylactoid reactions occur in up to 15% of patients |

IV = intravenous.

b. Non–acetaminophen-induced ALF (See Table 5)

i. Acetylcysteine may improve hemodynamics and oxygen delivery to the liver in patients with non–acetaminophen-induced ALF (Gastroenterology 2009;137:856-64).

ii. One study compared acetylcysteine with placebo in the management of non–acetaminophen-induced liver failure and found that survival at 3 weeks was statistically similar between the two groups; however the acetylcysteine group had higher rates of transplant free survival, specifically in patients with coma grades 1 and 2 (52% versus 30%, p=0.010) (Gastroenterology 2009;137:856-64).

(a) Transplantation was used as a rescue modality in about 40% of patients, so true mortality is difficult to assess.

(b) In the subgroup of patients with DILI, transplant-free survival was 58% for the acetylcysteine group and 27% for the placebo group.

Table 5. Acetylcysteine for Non–Acetaminophen-Induced Toxicity

<table>
<thead>
<tr>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
</table>
| Intravenous| 150 mg/kg x 1 over 60 minutes, followed by  
12.5 mg/kg for 4 hours followed by  
6.25 mg/kg for 67 hours |

c. Mushroom poisoning

i. Gastric lavage and activated charcoal may be beneficial for patients still experiencing GI symptoms indicative of a recent ingestion (Int J Hepatol 2012;2012:Article 487480; Semin Respir Crit Care Med 2012;33:36-45).

ii. Although data regarding efficacy are lacking, penicillin G can be used in addition to gastric lavage and activated charcoal (Semin Respir Crit Care Med 2012;33:36-45).

(a) Penicillin G acts an antidote to α-amanitin, a toxin released after mushroom ingestion, and directly competes with and inhibits the ability of the toxin to bind to plasma protein and penetrate the liver (Int J Hepatol 2012;2012:Article 487480).
2. Management of neurologic complications
   a. Encephalopathy
      i. All medications that can cause sedation or confusion should be avoided (i.e. benzodiazepines, anticholinergics, etc.).
      ii. Grade 1 encephalopathy can typically be managed with close monitoring and without medication; grade 2–4 encephalopathy should be treated in an ICU setting, if possible.
      iii. Lactulose can be used to decrease serum ammonia levels in patients with low-grade encephalopathy.
         (a) Dose: 20–30 g three or four times daily to produce 2–3 soft stools a day
         (b) Lactulose has the potential to cause abdominal distension and impair liver transplantation; therefore, its effects may be harmful in the acute setting (Semin Respir Crit Care Med 2012;33:36-45).
   b. Seizures have the potential to increase ICP; therefore, seizures should be quickly controlled with phenytoin and/or benzodiazepines (Semin Respir Crit Care Med 2012;33:36-45). Data are insufficient to suggest the use of prophylactic antiepileptic medications.
   c. Elevated ICPs
      i. ICP should be kept less than 25–30 mm Hg (Semin Respir Crit Care Med 2012;33:36-45).
      ii. Routine ICP monitoring has not been shown beneficial in reducing mortality in patients with ALF, and routine placement of ICP monitors is not recommended in all patients (Crit Care Med 2007;35:2498-508). Clinicians may choose to place an ICP monitor in patients with high-grade encephalopathy (stage III/IV) to provide close monitoring of cerebral edema and prognostic information regarding neurologic recovery if the patient receives a liver transplant (Crit Care Med 2007;35:2498-508).
      iii. Cerebral perfusion pressure should be maintained at 50–60 mm Hg (Semin Respir Crit Care Med 2012;33:36-45).
         (a) Cerebral perfusion pressure = mean arterial pressure – ICP.
      iv. Mannitol may be useful in acutely reducing ICP in patients with ALF.
         (a) Dose: 0.5–1 g/kg intravenously x 1
         (b) Dose may be repeated to effect as long as serum osmolality is less than 320 mOsm/L; however, it is typically ineffective if the baseline ICP is greater than 60 mm Hg (Semin Respir Crit Care Med 2012;33:36-45; World J Gastroenterol 2013;19:7069-77).
         (c) Adverse effects: Fluid overload, hyperosmolarity, and hypernatremia (Semin Respir Crit Care Med 2012;33:36-45).
v. Hyperventilation to a PaCO₂ of 25–30 mm Hg has the potential to temporarily “restore cerebral autoregulation, resulting in vasoconstriction and reduction in ICP” (Semin Respir Crit Care Med 2012;33:36-45). Hyperventilation may be used acutely if mannitol fails to control ICP; however, because of the risks associated with potential cerebral hypoxia, hyperventilation should not be used prophylactically in patients with ALF (Semin Respir Crit Care Med 2012;33:36-45).

vi. In patients with high degrees of encephalopathy, multiorgan failure, or hemodynamic instability, prophylactic hypertonic saline used to maintain a serum sodium of 145–155 mEq/L may be beneficial in reducing the incidence of intracranial hemorrhage (Semin Respir Crit Care Med 2012;33:36-45). Literature suggests using 23.4% saline (30 mL) every 2–3 hours or 3% sodium chloride as a continuous infusion (Crit Care Med 2007;35:2498-508).

vii. Hypothermia (32°C–33°C) “lowers systemic production of ammonia and cerebral uptake and metabolism, in addition to having hemodynamic stabilizing effects and reducing cerebral blood flow”; however, large trials have not shown a positive impact of hypothermia hypertension (N Engl J Med 2013;369:2525-34).

3. Management of hemodynamic instability
   a. Patients should be initially resuscitated with normal saline and then switched to an isotonic saline plus sodium bicarbonate solution if acidotic (Semin Respir Crit Care Med 2012;33:36-45).
   b. Vasopressors should be used if fluid resuscitation fails to maintain a mean arterial pressure greater than 75 mm Hg or a cerebral perfusion pressure of 60–80 mm Hg (Semin Respir Crit Care Med 2012;33:36-45).

4. Management of coagulopathies
   a. Although the INR may be elevated in patients with ALF, overall hemostasis is maintained through compensatory mechanisms.
   b. In patients with an elevated INR without signs and symptoms of an acute bleed, the INR should not be corrected using fresh frozen plasma (Semin Respir Crit Care Med 2012;33:36-45).
      i. Subcutaneous vitamin K (5–10 mg) may be administered because patients with ALF are typically deficient in vitamin K.
      ii. However, subcutaneous administration of vitamin K can lead to erratic absorption; also, vitamin K is typically given intravenously or orally to ensure absorption.
   c. To reduce the risk of spontaneous intracranial hemorrhage, platelets should be provided if the count drops to less than 15–20,000/mm³.
      i. If clinically significant bleeding occurs in patients with platelet counts less than 50,000/mm³, platelet transfusions should be provided.
      ii. Platelet count should be restored to greater than 50,000/mm³ before invasive procedures (Semin Respir Crit Care Med 2012;33:36-45).
   d. Factor VIIa (fVIIa) may be administered in patients with an elevated INR and clinically significant bleeding. Use of fVIIa can lead to an increased risk of thrombosis, and its benefit must be carefully assessed compared with the risk of experiencing devastating thrombotic adverse events.

5. Management of infectious complications
   a. An observational study found that in a cohort of 1551 patients with ALF, prophylactic antibiotic therapy did not reduce the incidence of bloodstream infections (12.8% in the prophylaxis group vs. 15.7% in the non-prophylaxis group, p=0.12) and did not reduce 21-day mortality (Clin Gastroenterol Hepatol 2014;12[11]:1942-1949).
   b. Patients should be monitored closely, and anti-infectives should be promptly initiated if the patient has any signs or symptoms of a systemic infection (Semin Respir Crit Care Med 2012;33:36-45).
c. Some centers preemptively administer antibiotics “in patients who have coagulopathy and organ failure or encephalopathy and those in whom illness progression is considered likely” (N Engl J Med 2013;369:2525-34).

6. Miscellaneous: Corticosteroids
   a. May be used in autoimmune hepatitis
   b. Prednisone 40–60 mg/day while consideration for liver transplantation is under way (Semin Respir Crit Care Med 2012;33:36-45)

7. Transplantation: Considered the definitive treatment for irreversible liver injury

G. Prophylaxis – Antivirals: Lamivudine can be used in patients who are hepatitis B antigen positive during episodes of immunosuppression (i.e., chemotherapy) to reduce the risk of virus activation. Patients with a positive hepatitis B antigen about to undergo chemotherapy or immunosuppression should be given lamivudine prophylaxis during periods of immunosuppression and for up to 6 months after completion of therapy (Gastroenterology 2009;137:856-64).

H. Prognosis
   1. King’s College criteria are widely used to provide prognostic value regarding the decision to perform transplantation versus provide medical therapy. These criteria consider the patient’s age, the cause of ALF, the degree of encephalopathy, bilirubin levels, and the degree of coagulopathy (Bernal and Wendon; NEJM 2013;369(26):2525-34).
   2. The Child-Pugh score is commonly used to provide prognostic information for chronic liver disease but is typically not used for ALF.

II. ACUTE PANCREATITIS

A. Epidemiology
   2. In 2009, acute pancreatitis (AP) was the leading gastroenterology discharge diagnosis in the United States with an annual cost of $2.6 billion (Tenner et al, 2013; Am J Gastroenterol 2013;108(9):1400-15).
   3. AP cases have increased during the previous 3 decades from 40 cases per 100,000 individuals to 70 cases per 100,000 individuals (Tenner et al., 2013; N Engl J Med 2006;354:2142-50).

B. Definitions
   1. Two of the following three criteria must be met for a patient to be given a diagnosis of AP (Gut 2013;62:102-11):
      a. Abdominal pain
      b. Serum lipase (or amylase) levels greater than 3 times the upper limit of normal (UPN)
      c. Imaging (CT, magnetic resonance imaging [MRI], or ultrasonography) consistent with pancreatitis
   2. Grades of severity (Gut 2013;62:102-11; Tenner et al., 2013):
      a. Mild acute AP: Tends to be self-limiting (less than 48 hours) with no organ failure or necrosis
      b. Moderately severe AP: Characterized by local complications and organ failure that lasts less than 48 hours
      c. Severe AP: Characterized by persistent organ failure for more than 48 hours
3. Phases of severe disease (Tenner et al., 2013):
   a. Early: Symptoms of systemic inflammatory response syndrome with or without organ failure during the first week
   b. Late: Complications that occur after 1 week that can last weeks to months (Gut 2013;62:102-11; Tenner et al., 2013)
      i. Peripancreatic fluid collections
      ii. Pancreatic and peripancreatic necrosis (sterile or infected)
      iii. Pseudocysts
      iv. Walled-off necrosis (sterile or infected)

4. A patient is considered to have organ failure when two of the following objective criteria are met (Gut 2013;62:102-11; Tenner et al., 2013):
   a. Shock (systolic blood pressure less than 90 mm Hg)
   b. Pulmonary insufficiency ($P_{aO_2}$ less than 60 mm Hg)
   c. Renal failure (serum creatinine [SCr] of 2 mg/dL after resuscitation)
   d. GI bleeding (greater than a 500-mL blood loss in 24 hours)

5. Pancreatic necrosis: Defined “as diffuse or focal areas of non-viable pancreatic parenchyma > 3 cm in size in > 30% of the pancreas” (Gut 2013;62:102-11)

6. The presence of systemic inflammatory response syndrome during the first 24 hours is predictive of impending organ failure.

C. Pathophysiology
   1. Acute inflammatory condition in which enzymes that are inappropriately released from the pancreas cause pancreatic autodigestion (Med Sci Monit 2009;15:RA147-56)
      a. Edema of the pancreatic lobules
      b. Peripancreatic fat necrosis
      c. Neutrophil infiltration of interstitial spaces

D. Causes
   1. Gallstones (40%–70%) (Tenner et al., 2013)
      a. Occur primarily in older white women and in patients with small stones (less than 5 mm in diameter) (N Engl J Med 2006;354:2142-50)
      b. Usually occur as an acute event that resolves once the gallstone has been removed. Patients typically undergo a cholecystectomy to prevent further episodes in the future.
   2. Alcohol use (25%–35%) (Tenner et al., 2013)
      a. Symptoms can occur as an acute episode or present as a chronic pancreatitis.
      b. Alcohol intake for more than 5 years or greater than 50 g daily increases the risk of pancreatitis; however, only about 5% of patients with a history of heavy alcohol consumption develop the disease (Tenner et al., 2013).
      c. Hypertriglyceridemia (1%–4%) should be suspected if triglyceride levels are greater than 1000 mg/dL.
   3. Certain medications can cause pancreatitis through varied mechanisms, and at least 40 drugs in the top 200 drugs prescribed in 2007 were implicated in AP. Examples include (Baylor Univ Med Cent Proc 2008;21:77-81):
      a. Statins
      b. ACE (angiotensin-converting enzyme) inhibitors
c. Estrogens/hormone replacement therapy
d. HAART (highly active antiretroviral therapy) medications
e. Valproic acid

4. Malignancy – The presence of a pancreatic tumor blocking the main pancreatic duct should be suspected in any patient older than 40 years with signs and symptoms of pancreatitis with no other apparent cause (Tenner et al., 2013).

5. Idiopathic – Pancreatitis without an apparent cause after extensive laboratory testing and/or imaging

E. Diagnosis

1. Signs and symptoms
   a. Abdominal pain, typically epigastric or left upper quadrant (Tenner et al., 2013)
   b. Pain can be severe; however, the location and severity of pain are not indicative of the severity of disease (Tenner et al., 2013). Gallstone pancreatitis–induced pain can be described as “knifelike”; pain radiates to the back (N Engl J Med 2006;354:2142-50).

2. Laboratory abnormalities – Elevations of serum lipase levels are more specific to the diagnosis of AP than are elevations of amylase levels because amylase levels tend to normalize more quickly than lipase levels (N Engl J Med 2006;354:2142-50).
   i. High amylase levels (3 times the UPN), together with abdominal pain, are very indicative of AP (N Engl J Med 2006;354:2142-50).
   ii. Amylase levels may remain normal in alcohol-induced AP and hypertriglyceridemia (Tenner et al., 2013).

3. Imaging
   a. Transabdominal ultrasonography to visualize possible cholelithiasis – better than CT or MRI for identifying “gallstones and sludge and detecting bile duct dilatation” (N Engl J Med 2006;354:2142-50)
   b. Endoscopic ultrasonography: Used to detect biliary causes of AP; however, “endoscopic investigation of an elusive etiology in patients with AP should be limited as the risks and benefits of investigation in these patients are unclear” (Tenner et al., 2013)
   c. CT scans of the abdomen are more than 90% sensitive and specific in diagnosing AP (Tenner et al., 2013; N Engl J Med 2006;354:2142-50).
   d. Magnetic resonance cholangiopancreatography (MRCP) can help detect extremely small gallstones (3 mm in diameter) and provide highly useful images for diagnostic purposes; MRCP is useful in patients who cannot tolerate the contrast dye load necessary to obtain a useful CT scan (Tenner et al., 2013).

Patient Case

3. A 44-year-old woman presents to the ED with a 5-day history of diffuse abdominal pain suggestive of AP. She has been hospitalized in the past with similar episodes that have resolved without medical treatment. Her serum amylase levels on admission, however, are normal. Which would best account for normal amylase levels in a patient with AP?
   A. Amylase levels are not used to diagnose AP.
   B. Amylase levels alone are not enough to diagnose AP; a ratio of amylase to lipase is more important.
   C. Amylase levels have a short half-life and thus may be normal in patients with a late presentation after symptom onset.
   D. Amylase levels will not be elevated during repeat episodes of pancreatitis.
F. Management

1. Hydration
   a. Patients are typically volume depleted for many reasons, including GI intolerance and diaphoresis (Tenner et al., 2013).
   b. Aggressive fluid resuscitation can decrease the risk and incidence of pancreatic necrosis, especially during the first 12–24 hours (Tenner et al., 2013).
   c. Goal is to decrease hematocrit (marker of hemodilution) and decrease blood urea nitrogen (BUN) while maintaining a normal SCr (Tenner et al., 2013).
   d. Lactated Ringer solution has been shown to reduce the incidence of systemic inflammatory response syndrome more effectively than normal saline when administered in either a goal-directed (titrated to lower BUN) or a standard (titrated by hospital staff) manner (Clin Gastroenterol Hepatol 2011;9:710-17). Because trypsinogen is activated at a lower pH, lactated Ringer solution provides the additional benefit of being more pH balanced than normal saline (Tenner et al., 2013).
   e. Because there can be harm in over-resuscitating patients, especially those with cardiac disease or renal disease, aggressive hydration may not be beneficial if there is no response within the first 6–12 hours (Tenner et al., 2013).

2. Endoscopic retrograde cholangiopancreatography (ERCP)
   a. Rationale: Many gallstones are passed through the duodenum and do not cause harm to the patient; however, in some patients, gallstones that are not cleared can cause an obstruction in either the biliary tree or the pancreas (Tenner et al., 2013).
   b. An ERCP, together with a sphincterotomy, may be used to extract gallstones from the pancreatic ducts or biliary tree (N Engl J Med 2006;354:2142-50).
   c. There is considerable risk with ERCP, including bleeding and the potential to worsen AP because of manipulation of the pancreas (N Engl J Med 2006;354:2142-50).
   d. A Cochrane review in 2004 assessed three randomized trials of 511 total patients and found that an early ERCP (within 24–72 hours of admission) with or without a sphincterotomy reduced the risk of complications in patients with severe gallstone-associated AP (odds ratio [OR] 0.27; 95% confidence interval [CI], 0.14–0.53) (Cochrane Database Syst Rev 2004;4:CD003630).
   e. Prevention of post-ERCP pancreatitis:
      i. Rates have decreased significantly during the past few decades, but post-ERCP pancreatitis continues to occur in 2%–4% of patients.
      ii. For patients with a normal bile duct and normal bilirubin levels, endoscopic ultrasonography or MRCP should be used instead of ERCP because the risk of post-ERCP pancreatitis is higher among this group (Tenner et al., 2013).
      iii. Guidewire cannulation: Prevents the incidence of hydrostatic injury caused by contrast agents (Tenner et al., 2013)
      iv. Pancreatic duct stents “decrease the risk of severe post-ERCP pancreatitis in high-risk patients, such as those undergoing ampullctomy, endoscopic sphincter of Oddi manometry, or pancreatic interventions during ERCP”; however, there is a risk of chronic pancreatitis (Tenner et al., 2013).
      v. Rectal NSAIDs (i.e. 100 mg of indomethacin) after an ERCP can be given to patients at high risk of post-ERCP pancreatitis.

3. Infection
   a. Pancreatic and non-pancreatic infections contribute to mortality in patients with AP, and an infected necrotizing pancreatitis has a significantly higher mortality rate than does sterile necrotizing pancreatitis (Tenner et al., 2013).
b. Recent literature suggests that prophylactic antibiotics should not be administered in sterile necrotizing pancreatitis.

c. Data from 11 prospective randomized trials since 1993 suggest that the number needed to treat (NNT) is 1429 for one patient to benefit from the use of prophylactic antibiotics (World J Gastroenterol 2012; 18:279-84; Tenner et al., 2013).

d. For patients who have not improved after 7–10 days of hospitalization, an infection should be suspected, appropriate cultures obtained, and empiric antibiotics initiated; because of penetration issues, only carbapenems, quinolones, metronidazole, or high-dose cephalosporins should be used (Tenner et al., 2013).

e. Use of antibiotics may ameliorate the need for a surgical intervention in many cases.

4. Nutrition

a. Clinical practice has shifted from keeping patients NPO during AP to resting the pancreas to now feeding patients early to decrease the incidence of intestinal atrophy and infectious complications from bacterial translocation (Tenner et al., 2013).

b. Oral feedings with a low-fat solid or liquid diet should be administered to patients with mild pancreatitis if tolerated without GI disturbance or pain (Tenner et al., 2013).

c. In severe AP, enteral nutrition by either the nasogastric (NG) or the nasojejunal (NJ) route should be administered (Tenner et al., 2013).

i. Both routes are safe and effective for patients with AP, though in clinical practice, the NJ route has been preferred.

ii. Enteral nutrition, compared with parenteral nutrition, has been shown to decrease organ failure and reduce infectious complications, mortality, and surgical intervention rate (Crit Care 2013;17:R118).

iii. A recent meta-analysis of three randomized controlled trials of 157 patients showed no significant differences in mortality, tracheal aspiration, diarrhea, exacerbation of pain, or meeting energy balance between NJ and NG groups (Crit Care 2013;17:R118).

iv. NG feeding is easier than NJ feeding because NJ tubes can be difficult to place, expensive, and inconvenient (Crit Care 2013;17:R118).

d. Because of the potential for bacterial translocation caused by the breakdown of a mucosal barrier, parenteral nutrition should be reserved for patients unable to meet their caloric needs through enteral feeds (Crit Care 2013;17:R118).

5. Surgery

a. Cholecystectomy should be performed in patients with gallstones in the gallbladder.

b. Debridement of sterile “necrosis is recommended if associated with gastric outlet obstruction and/or bile duct obstruction”; otherwise, “asymptomatic pancreatic and/or extrapancreatic necrosis does not mandate intervention regardless of size, location, and extension” (Tenner et al., 2013).

c. For stable patients with infected necrotizing pancreatitis, surgical debridement should be delayed for 4 weeks to allow appropriate delineation of necrotic versus non-necrotic tissue, and antibiotics should be tried before surgical intervention (Tenner et al., 2013).

d. Unstable patients with infected necrosis should undergo immediate debridement, and necrosectomy may be required in patients who do not respond to a combination of antibiotics and debridement (Tenner et al., 2013).
Patient Case
4. A 63-year-old man presents to the ED with newly diagnosed sterile necrotizing pancreatitis. He is fluid resuscitated, initiated on enteral feeds, and currently stable. His team is waiting until next month to surgically intervene and debride the necrotic tissue. Because there is a high risk of mortality associated with an infected necrotic pancreas, the team wants to initiate prophylactic antibiotics. Which best depicts the statement that is incorrect regarding antibiotic use in sterile necrotizing pancreatitis?

A. Prophylactic antibiotics have been shown to provide a mortality benefit in patients with necrotizing pancreatitis.
B. Prophylactic antibiotics have not been shown to provide a mortality benefit in patients with necrotizing pancreatitis.
C. If used, high-dose cephalosporins, quinolones, metronidazole, and carbapenems are the drugs of choice because of their penetration of pancreatic tissue.
D. Antibiotics should be delayed about 7–10 days and initiated in patients who have not responded to supportive measures or initiated earlier if frank signs of infection exist.

III. GASTROINTESTINAL FISTULAS

A. Epidemiology
   1. About 40% of patients with Crohn’s disease will develop a spontaneous perianal or external fistula in their lifetime (Gut 2002;49(suppl):iv2-iv10; http://emedicine.medscape.com/article/179444-clinical).
   2. Up to 12% of patients with diverticulitis will develop a fistula (http://emedicine.medscape.com/article/179444-clinical).
   3. During the past 50 years, the mortality rate associated with fistulas has fallen to about 20%; however, the frequency of occurrence and cost of appropriate care have remained stable (http://emedicine.medscape.com/article/179444-clinical).
   4. Complex surgical procedures and an aging population continue to contribute to the incidence of fistula formation in patients.
   5. Lack of fistula output drainage can lead to an internal focus for infection (Gastrointestinal and Liver Disease, 9th ed. 2010).

B. Definition
   1. “An abnormal connection between 2 epithelialized surfaces that usually involves the gut and another hollow organ, such as the bladder, urethra, vagina, or other regions of the gastrointestinal (GI) tract” (http://emedicine.medscape.com/article/179444-clinical)
   2. Fistulas may also connect the intestine to the skin or an abscess, and rarely, a connection may occur between major blood vessels and the intestinal tract, leading to a life-threatening bleed (http://emedicine.medscape.com/article/179444-clinical).
   3. Two main types of classifications (Gut 2002;49(suppl):iv2-iv10; Gastrointestinal and Liver Disease, 9th ed. 2010):
      a. Anatomic: Rely on fistula origin and drainage point (Gastrointestinal and Liver Disease, 9th ed. 2010)
         i. Internal (i.e., ileocolic)
         ii. External (i.e., enterocutaneous)
      b. Physiologic: Classified according to output (Gastrointestinal and Liver Disease, 9th ed. 2010)
         i. High output: Greater than 500 mL/day
         ii. Moderate output: 200–500 mL/day
         iii. Low output: Less than 200 mL/day
4. Lateral fistulas divert off the intestines while maintaining the continuity of the intestinal tract, whereas end fistulas disrupt the continuity of the intestinal tract (Gut 2002;49(suppl):iv2-iv10).

C. Causes
1. About 80% of fistulas are a complication of surgery (i.e. cancer surgery, emergency surgery with inadequate source control, trauma surgery) caused by “ischemia, tension, or distal obstruction,” and about 20% grow spontaneously because of intra-abdominal inflammation (i.e. diverticulitis, inflammatory bowel disease, peptic ulcer disease) or infection because of “abscess formation, perforation, and distal obstruction” (Gut 2002;49(suppl):iv2-iv10; Gastrointestinal and Liver Disease, 9th ed. 2010; Http://emedicine.medscape.com/article/179444-clinical). Spontaneous fistulas can be either external or internal, and surgical fistulas tend to be primarily external.

   a. Inflammatory bowel disease, specifically Crohn’s disease
   b. Cancer
   c. Abdominal trauma
   d. Diverticular disease
   e. Surgical procedures to the abdomen
   f. Previous radiation therapy to the GI tract
   g. Ulcers

3. Use of radiation therapy can lead to fistula formation in 5%–10% of patients (Http://emedicine.medscape.com/article/179444-clinical).

D. Diagnosis
1. In postoperative patients, a fistula should be suspected if the patient presents with abdominal distension, overall lack of recovery since the operation, low-grade fever, abdominal tenderness, or frank wound infection with enteric content leakage (J Gastrointest Surg 2009;13:2068-73).

2. Use of oral charcoal or easily visible dye to determine whether suspicious drainage is related to a fistula that originated in the intestinal tract (Gastrointestinal and Liver Disease, 9th ed. 2010)

3. Radiographic contrast studies using oral, rectal, or retrograde contrast dye to a drainage site can be utilized to diagnose fistulas (Gastrointestinal and Liver Disease, 9th ed. 2010)

E. Treatment
1. Fluid resuscitation and electrolyte management for high-output fistulas (Gastrointestinal and Liver Disease, 9th ed. 2010). Fistula output is iso-osmotic and high in potassium; therefore, replacement fluid should include a maintenance infusion of normal saline with potassium as an additive (Gastrointestinal and Liver Disease, 9th ed. 2010).

2. Drainage to reduce the incidence of infection or abscess formation (Gastrointestinal and Liver Disease, 9th ed. 2010)
   a. Use of percutaneous catheters to help drain fluid collections
   b. Vacuum-assisted closure (VAC) devices to administer negative pressure wound therapy can be used for certain wounds to “increase blood flow, wound drainage, and edema resolution” (SAN 2008;39:47). In enterocutaneous fistulas, a VAC system can help protect skin and decrease fistula output (Gastrointestinal and Liver Disease, 9th ed. 2010).
3. **Nutrition**
   a. Enteral feedings are preferred for patients able to absorb sufficient calories by this route because enteral feedings have “been shown to enhance mucosal proliferation and villous growth through direct and indirect mechanisms. Nutrients in contact with the bowel mucosa also provide direct stimulation to the enterocyte, and feedings high in glutamine may be particularly beneficial because glutamine is the main source of energy of the enterocyte” (Gastrointestinal and Liver Disease, 9th ed. 2010).
   b. In a study of 28 patients with high-output fistulas, patients who received glutamine supplementation (0.3 g/kg/day orally) were 13 times more likely to have spontaneous resolution of their fistulas (Nutr Hosp 2007;22:672-6).
   c. Total parenteral nutrition cannot contain glutamine and does not have the same beneficial effects on gut mucosa as enteral feeds; however, in patients unable to meet their caloric needs through enteral feeds, total parenteral nutrition must be used (Gastrointestinal and Liver Disease, 9th ed. 2010).
   d. In patients with a low-output/distal fistula, enteral feeds should be attempted. In addition, patients with enteral access distal to the fistula should be given enteral feeds (Gastrointestinal and Liver Disease, 9th ed. 2010). Of note, at least 4 feet of intact bowel are necessary to appropriately absorb feedings (J Gastrointest Surg 2009;13:2068-73).

4. **Octreotide**
   a. Mechanism of action (Gastrointestinal and Liver Disease, 9th ed. 2010):
      i. Inhibits the release of gastrin, cholecystokinin, secretin, motilin, and other GI hormones, which decreases the movement of electrolytes, water, and pancreatic enzymes into the intestines
      ii. Relaxes smooth muscle
      iii. Increases water and electrolyte absorption
   b. Efficacy of octreotide has been inconsistent for spontaneous fistula closure rates and mortality; however, data appear to suggest that octreotide consistently decreases high-output fistulas to low-output fistulas and thus may decrease healing time (Gastrointestinal and Liver Disease, 9th ed. 2010).

5. **Assessing the need for surgery**
   a. Many fistulas close spontaneously, with the highest degree of success for the following indicators (Gut 2002;49(suppl):iv2-iv10; Gastrointestinal and Liver Disease, 9th ed. 2010):
      i. Low- to moderate-output fistulas
      ii. Patients younger than 40 years
      iii. Proximal sites
      iv. Patients without malignancy, inflammatory, or infectious disease, or complete anastomotic dehiscence
      v. A long fistulous tract
      vi. Acute duration
      vii. Esophageal, jejunal, pancreaticobiliary, or duodenal stump fistula are more likely to heal spontaneously than are gastric, ileal, and lateral duodenal fistulas.
   b. Patients with complications and in whom the conservative techniques have failed to work may require surgical therapy.

F. **Bowel injury**, which can occur because of trauma or surgical procedures, typically requires emergency surgery to repair the damage.
### Patient Case

5. A 34-year-old morbidly obese woman (body mass index 54 kg/m²) presents after gastric bypass surgery 1 week ago. She comes to the surgical ICU at your institution with an enterocutaneous fistula requiring medical management. Her current output is about 100 mL/day. In the surgical management of fistulas, which best depicts the patient-specific characteristic that is not promising with respect to spontaneous closure of her fistula without a surgical intervention?

A. Her age (younger than 40).
B. Her fistula, which is low output.
C. Her weight.
D. An acute duration.

### IV. POSTOPERATIVE ILEUS

A. Epidemiology
   1. Incidence can vary, depending on the type of procedures and patient-specific factors (US Pharm 2010;35:55-73):
   a. Abdominal hysterectomy: 4.1%
   b. Large bowel resection: 14.9%
   c. Small bowel resection: 19.2%
   2. A post-operative ileus (POI) can lead to a prolonged hospital stay, is uncomfortable for the patient to endure, delays appropriate enteral nutrition, and increases length of stay (Cleve Clin J Med 2009;76:641-8).
   3. Studies have shown that episodes of ileus can double the length of stay after a procedure and add an extra $6,300, on average, per patient to a hospital stay (Cleve Clin J Med 2009;76:641-8).
   4. The total economic impact was close to $1 billion in 2000 (Clin Gasteroenterol Hepatol 2003;1:71-80).

B. Definition
   1. POI is an impairment of appropriate GI motility after a surgical procedure (US Pharm 2010;35:55-73).
   2. Peristalsis is not caused by a mechanical obstruction; peristalsis can affect the stomach, small intestine, or large intestine (Cleve Clin J Med 2009;76:641-8).
   3. Typically lasts 2–3 days after a procedure but may last up to 6 days postoperatively; return to normal bowel function is monitored using objective signs such as passing of flatus, active bowel sounds, or a bowel movement (US Pharm 2010;35:55-73)
   a. Function of the small bowel returns to normal within 24 hours, but it may take up to 3–5 days for the colon to return to normal function (Cleve Clin J Med 2009;76:641-8).
   b. If a POI persists beyond this period, it is called a paralytic ileus (Cleve Clin J Med 2009;76:641-8).

C. Causes
   1. The sympathetic nervous system normally prevents small bowel function, whereas the parasympathetic system does the opposite.
   a. The vagal nerve is important to parasympathetic activity in the stomach; therefore, inadvertent damage to the vagal nerve during abdominal surgery or after a vagotomy can result in impaired emptying of the stomach (Cleve Clin J Med 2009;76:641-8).
   b. During periods of fasting, upper GI tract activity is consistent and controlled by the migrating motor complex (MMC), whereas activity of the large bowel is irregular (US Pharm 2010;35:55-73; Cleve Clin J Med 2009;76:641-8).
c. After eating, the “fed pattern consists of continuous low varying-amplitude, ungrouped contractions whose number, intensity, and duration depend on the food ingested”; therefore, during periods of fasting postoperatively, the contractility of the stomach and small intestines is entirely dependent on the MMC (Arch Surg 2003;138:206-14).

d. The large bowel is more dependent on the autonomic nervous system, which could explain the longer recovery time postoperatively (Cleve Clin J Med 2009;76:641-8).

2. Inflammation of the GI tract after surgery, inhibitory neural reflexes, and the release of inhibitory neurotransmitters such as nitrous oxide, substance P, and vasoactive intestinal peptide are all thought to contribute to the disruption in the MMC (US Pharm 2010;35:55-73).

3. Typically linked to surgical procedures of the abdomen and pelvis, as well as to prolonged surgical procedures, high estimated blood loss, use of high-dose or prolonged opioids, and inhalation anesthesia (US Pharm 2010;35:55-73)

4. Risk factors:
   a. Type of surgery
   b. Previous GI disease
   c. Physical inactivity

5. Exacerbating causes:
   a. Use of opioids can slow motility through antagonism of μ-receptors in the GI tract, and high doses and/or prolonged courses of opioids postoperatively can contribute to sustained ileus (US Pharm 2010;35:55-73).
   b. Because of a lack of intracellular gap junctions, the large intestine is significantly affected by anesthetics such as halothane and enflurane (US Pharm 2010;35:55-73).
   c. Intra-abdominal bleeding
   d. Other medications known to decrease GI motility (e.g., anticholinergics)

D. Diagnosis
   1. POI is typically characterized by “abdominal distension, lack of bowel sounds, and lack of passage of flatus or stool,” and patients typically experience “abdominal pain and bloating, nausea, vomiting, and anorexia” (Clin Gastroenterol Hepatol 2003;1:71-80).
   2. A physical examination for abdominal distension should be done for all patients, followed by plain radiographs to identify air and dilated loops of bowel (Clin Gastroenterol Hepatol 2003;1:71-80).
   3. An abdominal CT scan can be used to rule out a mechanical obstruction (Clin Gastroenterol Hepatol 2003;1:71-80).

E. Management
   1. Use of epidural anesthesia
      a. Thoracic epidural anesthesia “interferes with the afferent and efferent sympathetic reflex arcs” and can significantly reduce the incidence of POI and opioid use (Cleve Clin J Med 2009;76:641-8).
      b. Increases splanchnic blood flow (Arch Surg 2003;138:206-14)
   2. Use of laparoscopic surgery: Laparoscopic surgery leads to a lower inflammatory response and tends to be less painful than open procedures (Cleve Clin J Med 2009;76:641-8).
   3. NG decompression
      a. NG tubes can be used to decrease the incidence of postoperative vomiting and the potential for aspiration, but they are not effective in all patients.
      b. NG tubes should be used selectively as opposed to routinely in postoperative patients because they have been shown to increase the risk of pneumonia, atelectasis, and fever (Clin Gastroenterol Hepatol 2003;1:71-80).

5. Gum chewing
   a. It has been hypothesized that the chewing of gum can lead to “sham feeding,” which “elicits the release of gastrin, pancreatic polypeptide, and neurotensin, all of which affect gastrointestinal motility” (Arch Surg 2003;138:206-14).
   b. Chewing gum three times a day has been shown to reduce time to first flatus (2.1 vs. 3.2 days) and time to first defecation (3.1 vs. 5.8) compared with a control (J Am Coll Surg 2002;195:30-2; Arch Surg 2003;138:206-14).

6. Medication therapy:
   a. NSAID therapy
      i. Adding an NSAID to opioid therapy has been shown to reduce the need for opioids by 20%–30% and can not only reduce the impact of opioids on GI motility but also reduce some of the other adverse events associated with opioids such as nausea and vomiting (Arch Surg 2003;138:206-14).
      ii. Anti-inflammatory effects are beneficial postoperatively.
      iii. Use should be carefully assessed so benefit outweighs the risk of postoperative bleeding caused by platelet inhibition (Arch Surg 2003;138:206-14).
   b. Erythromycin: Motilin receptor agonist/macrolide antibiotic
      i. Has been shown beneficial in accelerating gastric emptying and gastroparesis by around 40% (Cleve Clin J Med 2009;76:641-8)
      ii. Other data are less conclusive regarding its efficacy; in a prospective, double-blind, randomized, placebo-controlled trial of 77 patients who received erythromycin 250 mg intravenously every 8 hours after abdominal surgery, there was no significant difference in first passage of flatus, first liquid meal, first bowel movement, or length of hospital stay (Am J Gastroenterol 1993;88:208-211; US Pharm 2010;35:55-73).
   c. Metoclopramide: Dopamine D₂ receptor antagonist and mixed serotonin-3 antagonist/serotonin-4 agonist
      i. Stimulates gastric, pyloric, and small bowel activity, but studies have been inconclusive regarding its efficacy in POI (Cleve Clin J Med 2009;76:641-8)
      ii. Should not be used in patients with a history of movement disorders and is linked to tardive dyskinesia
      iii. Black box warning: Should not be used for more than 3 weeks in the acute setting
   d. Alvimopan (Entereg): μ-Opioid receptor antagonist
      i. In a pooled analysis of phase III studies, alvimopan 6 mg, 12 mg, or placebo was administered 2 hours or more before surgery and twice daily for up to 7 days after surgery. (a) Alvimopan significantly accelerated GI recovery, accelerated time to hospital discharge orders, and decreased morbidity, hospital stay, and readmission (Ann Surg 2007;245:355-63). (b) The 12-mg dose was especially beneficial in females and patients older than 65 (Ann Surg 2007;245:355-63; Cleve Clin J Med 2009;76:641-8).
      ii. In a randomized, placebo-controlled, double-blind study of 654 patients, alvimopan 12 mg accelerated toleration of solid food and first bowel movement (hazard ratio [HR] 1.5), toleration of solid food and first flatus or bowel movement (HR 1.5), and hospital discharge (HR 1.4) compared with a standardized postoperative care pathway that included early ambulation, oral feeding, and postoperative NG tube removal (Arch Surg 2008;143:1098-105).
      iii. Should be given as a 12-mg dose 30–90 minutes before surgery and then twice daily for up to 7 days (no more than 15 doses) (Cleve Clin J Med 2009;76:641-8). Hospitals that intend to use alvimopan should be enrolled in the EASE (Entereg Access Support and Education) program.
Patient Case

6. A 40-year-old man presents who is about to undergo elective abdominal surgery to remove a malignancy from his liver. Because of the extensiveness of the procedure, the anticipated use of perioperative opioids, and the inhalation anesthesia, the team is putting together a plan to reduce the incidence of POI. Which strategy would be most beneficial for this patient?

A. Use of a hydromorphone patient-controlled analgesia (PCA) postoperatively versus a morphine PCA.
B. Use of alvimopan 12 mg just before surgery and continued twice daily for 7 days.
C. Use of metoclopramide 5 mg intravenously every 6 hours for 7 days postoperatively.
D. Use of octreotide 100 mcg subcutaneously every 8 hours for 7 days postoperatively.

V. POSTOPERATIVE NAUSEA AND VOMITING

A. Epidemiology
   1. Some patients are more concerned about postoperative nausea and vomiting (PONV) than about postoperative pain control (J Obstet Gynaecol Can 2008;30:600-7).
   2. Up to 30% of patients experience vomiting, and up to 50% of patients experience nausea postoperatively (Anesth Analg 2014;118:85-114).

B. Risk Factors
   1. The risk of PONV is 10%, 21%, 39%, and 78% with one, two, three, and four risk factors, respectively (J Obstet Gynaecol Can 2008;30:600-7).
      a. Female sex
      b. History of motion sickness or PONV
      c. Nonsmoker
      d. Use of postoperative opioids
   2. Other risk factors include the use of volatile anesthetics within 0–2 hours, use of nitrous oxide, high doses of neostigmine, and duration of surgery (each 30-minute duration increases the risk of PONV by 60%) (J Obstet Gynaecol Can 2008;30:600-7).
   3. Some data suggest that younger patients with certain types of surgical procedures (cholecystectomy, laparoscopic, or gynecologic) are also at higher risk of PONV (Anesth Analg 2014;118:85-114).

C. Prevention
   1. Regional anesthetics should be used instead of general anesthetics, when possible, because general anesthetics are associated with an 11-fold increase in PONV, with propofol being the best option if general anesthesia has to be administered (J Obstet Gynaecol Can 2008;30:600-7).
   3. High-dose opioid therapy and neostigmine should be minimized or avoided, if possible.
   4. Low-risk patients typically do not require prophylaxis, moderate-risk patients should be provided one or two interventions, and high-risk patients should be provided more than two interventions (Anesth Analg 2014;118:85-114).
      a. Dexamethasone 5–10 mg intravenously should be given at the time of induction (NNT = 4) and not repeated.
      b. A serotonin-3 receptor antagonist (i.e. ondansetron, dolasetron, granisetron, or tropisetron) should be given at the end of surgery (NNT = 7).
      c. Prochlorperazine 5–10 mg intravenously can be given at the end of surgery.
d. A scopolamine patch can be applied the evening before surgery (NNT = 3.8) and should not be repeated.
e. Droperidol 0.625–1.25 mg intravenously can be given at the end of surgery (NNT = 5).
f. Aprepitant 40 mg orally given before the induction of anesthesia is superior to ondansetron.

D. Rescue Therapy
1. Repeat doses of the initial prophylactic drug can be tried if more than 6 hours after surgery; however, if less than 6 hours since surgery, a different drug class should be tried (J Obstet Gynaecal Can 2008;30:600-7).
2. If patients did not receive a prophylactic agent, rescue treatment with a serotonin-3 receptor antagonist should be tried (J Obstet Gynaecal Can 2008;30:600-7).

VI. UPPER GASTROINTESTINAL BLEEDING

A. Epidemiology
1. Upper GI bleeding accounts for about 300,000 hospitalizations per year in the United States at a cost of $2.5 billion (Cleve Clin J Med 2010;77:131-42; PSAP Gastroenterology and Nutrition I 2012:7-26).
2. Peptic ulcers are the most common cause of hospitalization for upper GI bleeds, accounting for 21%–40% of all bleeding episodes (PSAP Gastroenterology and Nutrition I 2012:7-26; Am J Gastroenterol 2012;107:345-60).
3. Upper GI bleeds are 4 times more common than lower GI bleeds, and mortality rates have remained at around 10%–14% despite advances in care, likely because of increased longevity of patients with comorbid conditions (PSAP Gastroenterology and Nutrition I 2012:7-26).

B. Definitions – Bleeding that occurs along the GI tract proximal to the ligament of Treitz (PSAP Gastroenterology and Nutrition I 2012:7-26)

C. Causes
1. Peptic ulcer disease
   a. H. pylori
      i. Considered one of the most common worldwide infections and is closely tied to socioeconomic conditions, with high infection rates in developing countries (Am J Gastroenterol 2007;102:1808-25)
      ii. About 30%–40% of the American population is infected with H. pylori (Am J Gastroenterol 2007;102:1808-25).
      iii. Can cause chronic gastritis, gastric malignancy, and peptic ulcers (causes duodenal ulcers more often than gastric ulcers) (Am J Gastroenterol 2007;102:1808-25; PSAP Gastroenterology and Nutrition I 2012:7-26)
      iv. Incidence of H. pylori–induced peptic ulcer disease has declined during the past 2 decades because of the recognition of the long-term consequences of H. pylori infection.
   b. NSAIDs – Tend to be asymptomatic and typically do not lead to bleeding episodes except in elderly patients with a history of NSAID-induced bleeds (PSAP Gastroenterology and Nutrition I 2012:7-26). Elderly patients, high doses, longer treatment durations, a history of NSAID-related GI bleed, a history of H. pylori infection, and concurrent use of corticosteroids, anticoagulants, or bisphosphonates are factors in the increased risk of bleeding associated with NSAID use (PSAP Gastroenterology and Nutrition I 2012:7-26).
2. Esophageal varices
   a. Considered the second most common cause of upper GI bleeding and are present in 50% of patients with cirrhosis (PSAP Gastroenterology and Nutrition I 2012:7-26)
   b. Mortality rate of a single episode of variceal bleed is about 30%, and about 65% of patients who survive their first episode die of chronic liver disease within 1 year (Cleve Clin J Med 2010;77:131-42).
   c. Portal hypertension caused by the obstruction of venous blood flow through the cirrhotic liver leads to increased pressure in the portal vein and causes the redirection of blood flow to other areas of the body.
   d. Occur most commonly at the gastroesophageal junction because of its thin tissue layer (PSAP Gastroenterology and Nutrition I 2012:7-26)

3. SRMD (stress-related mucosal damage): To be discussed in detail in a different chapter

4. Mallory-Weiss tear: “A longitudinal mucosal laceration in the distal esophagus and proximal stomach” caused by a “sudden increase in intra-abdominal pressure, resulting in a gastric mucosal tear from the forceful distention of the gastroesophageal junction” (PSAP Gastroenterology and Nutrition I 2012:7-26). Risk factors include the following (PSAP Gastroenterology and Nutrition I 2012:7-26):
   a. Anything that can cause an acute rise in intra-abdominal pressure (i.e. coughing, straining at stool, cardiopulmonary resuscitation, trauma, vomiting)
   b. Age 30–50
   c. Alcoholic binges
   d. Diabetic ketoacidosis (DKA)
   e. Hiatal hernias


D. Diagnosis and Evaluation

1. Signs and symptoms:
   b. Coffee ground emesis
   c. Melena
   d. Hematochezia – Present in about 5% of patients with an upper GI bleed but more common in patients with lower GI bleeds. Indicates heavy bleeding if it occurs in patients with an upper GI bleed because about 1000 mL of blood is needed to cause hematochezia, and only 50–100 mL is needed to cause melena (Cleve Clin J Med 2010;77:131-42)
   e. About 50% of patients present with both melena and hematochezia (Cleve Clin J Med 2010;77:131-42; PSAP Gastroenterology and Nutrition I 2012:7-26).
   f. Bleeding ulcers may result in right upper quadrant pain; Mallory-Weiss tears may present as emesis, retching, or coughing before hematemesis; and patients with symptoms associated with chronic liver disease will likely have variceal bleeding (PSAP Gastroenterology and Nutrition I 2012:7-26).
   g. Hemodynamic instability may be present in patients with significant hypovolemia.

2. Laboratory analysis should include an assessment of coagulation, CBC (complete blood cell count), and liver function tests.

3. NG aspirate
   a. Insertion of an NG tube to help assess the aspirate for blood in patients without frank output of blood, though this method is not always sensitive in diagnosing GI bleeds (Cleve Clin J Med 2010;77:131-42)
   b. Can also be useful in removing clotted blood and other debris before endoscopy
4. Diagnostic endoscopy
   a. Should be done within 24 hours of admission in patients at high risk of rebleeding or in patients who are actively bleeding. Helps “identify the source of bleeding, look for predictors of recurrent bleeding, and assess the need for endoscopic intervention” (PSAP Gastroenterology and Nutrition I 2012:7-26)
   b. The risk of rebleeding is highest within the acute period after admission, and 24 hours is considered an appropriate time interval for an endoscopic intervention (World J Gastroenterol 2012;18:1202-7).
   c. Forrest classification (PSAP Gastroenterology and Nutrition I 2012:7-26):
      i. Class I: Frank hemorrhage and oozing
      ii. Class II: Nonbleeding visible vessel, adherent clot, or flat pigmented spot as signs of a recent bleed
      iii. Class III: Clean ulcer base indicative of lesions without an active bleed

5. Indicators of high risk of rebleeding (PSAP Gastroenterology and Nutrition I 2012:7-26):
   a. Endoscopic
      i. Active bleeding
      ii. Nonbleeding visible vessel or adherent clot
      iii. Ulcer size greater than 2 cm
      iv. Ulcers located on posterior lesser gastric curvature or posterior duodenal wall
   b. Clinical
      i. Age older than 65 years
      ii. Shock
      iii. Poor overall health status
      iv. Comorbid illnesses
      v. Low initial hemoglobin concentration
      vi. Melena
      vii. Transfusion requirement
      viii. Presence of frank blood
      ix. Sepsis
      x. Elevated BUN, SCr, or serum aminotransferase
      xi. APACHE (Acute Physiology and Chronic Health Evaluation) score of 11 or greater

E. Risk Stratification
   1. Blatchford score (See Table 6).
      a. Used for identifying low-risk patients who are ready for discharge, but less useful for stratifying the high-risk group
      b. Patients with a score of 0 are considered low risk, whereas all patients with a score greater than 1 are considered high risk, and a score of greater than 6 indicates the need for an active intervention.
   2. Rockall score (See Table 7): Uses both clinical and endoscopic data in its prediction, with higher scores indicating an increased risk of rebleeding
Table 6. Blatchford Score

<table>
<thead>
<tr>
<th>Variables</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>• 100–109 mm Hg</td>
<td>1</td>
</tr>
<tr>
<td>• 90–99 mm Hg</td>
<td>2</td>
</tr>
<tr>
<td>• &lt; 90 mm Hg</td>
<td>3</td>
</tr>
<tr>
<td>BUN</td>
<td></td>
</tr>
<tr>
<td>• 6.5–7.9 mmol/L</td>
<td>2</td>
</tr>
<tr>
<td>• 8.0–9.9 mmol/L</td>
<td>3</td>
</tr>
<tr>
<td>• 10.0–24.9 mmol/L</td>
<td>4</td>
</tr>
<tr>
<td>• ≥ 25 mmol/L</td>
<td>6</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>• 12.0–12.9 g/dL</td>
<td>1</td>
</tr>
<tr>
<td>• 10.0–11.9 g/dL</td>
<td>3</td>
</tr>
<tr>
<td>• &lt; 10 g/dL</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>• Heart rate ≥ 100 beats/minute</td>
<td>1</td>
</tr>
<tr>
<td>• Melena</td>
<td>1</td>
</tr>
<tr>
<td>• Syncope</td>
<td>2</td>
</tr>
<tr>
<td>• Hepatic disease</td>
<td>2</td>
</tr>
<tr>
<td>• Cardiac failure</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 7. Rockall Score

<table>
<thead>
<tr>
<th>Variables</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>• &lt; 60</td>
<td>0</td>
</tr>
<tr>
<td>• 60–79</td>
<td>1</td>
</tr>
<tr>
<td>• ≥ 80</td>
<td>2</td>
</tr>
<tr>
<td>Shock</td>
<td></td>
</tr>
<tr>
<td>• Heart rate &gt; 100 beats/minute</td>
<td>1</td>
</tr>
<tr>
<td>• Systolic blood pressure &lt; 100 mm Hg</td>
<td>2</td>
</tr>
<tr>
<td>Coexisting illness</td>
<td></td>
</tr>
<tr>
<td>• Ischemic heart disease, congestive heart failure, other major illness</td>
<td>2</td>
</tr>
<tr>
<td>• Renal failure, hepatic failure, metastatic cancer</td>
<td>3</td>
</tr>
<tr>
<td>Endoscopic stigmata of recent hemorrhage</td>
<td></td>
</tr>
<tr>
<td>• Clean-base ulcer, flat pigmented spot</td>
<td>0</td>
</tr>
<tr>
<td>• Blood in upper GI tract, active bleeding, visible vessel, clot</td>
<td>2</td>
</tr>
<tr>
<td>Endoscopic diagnosis</td>
<td></td>
</tr>
<tr>
<td>• No lesion, Mallory-Weiss tear</td>
<td>0</td>
</tr>
<tr>
<td>• Peptic ulcer, erosive disease, esophagitis</td>
<td>1</td>
</tr>
<tr>
<td>• Cancer of upper GI tract</td>
<td>2</td>
</tr>
</tbody>
</table>
F. Management

1. Patients should be provided with supplemental oxygenation; hemodynamically unstable patients should be provided with fluid resuscitation; and blood transfusions should be provided for patients with a hemoglobin less than 7.0 g/L (World J Gastroenterol 2012;18:1202-7).

2. If the INR is greater than 1.5, fresh frozen plasma or vitamin K should be administered.

3. Therapeutic endoscopy
   a. Can be used in conjunction with a diagnostic endoscopy to treat the source of bleed once it has been identified
   b. Patients should be sufficiently stable, and excessive amounts of blood and clots in the stomach should be removed (either by the NG tube or through the use of prokinetic agents) before attempting endoscopy (World J Gastroenterol 2012;18:1202-7).
   c. Endoscopic “interventions include application of clips, argon plasma coagulation, injection of epinephrine or sclerosants, bipolar electrocoagulation, band ligation, heater probe coagulation, and laser therapy” (PSAP Gastroenterology and Nutrition I 2012:7-26).
   d. Peptic ulcer disease
      i. Patients with “active bleeding ulcers or a nonbleeding visible vessel in an ulcer bed are the highest risk of rebleeding and therefore need prompt endoscopic hemostatic therapy,” whereas patients with low-risk stigmata do not require endoscopic management (World J Gastroenterol 2012;18:1202-7).
      ii. Data are mixed regarding the use of endoscopic therapy in patients with an adherent clot, but there may be benefit in removing the adherent clot and treating the underlying lesion (Cleve Clin J Med 2010;77:131-42).
   e. Variceal bleeds should be treated with variceal banding or sclerotherapy.

4. Pharmacologic management
   a. Non-variceal bleeding
      i. The mainstay of pharmacologic treatment of acute GI bleeds that are unrelated to varices includes gastric acid suppression with PPIs.
      ii. “Gastric acid inhibits platelet aggregation, impairs clot formation, and promotes fibrinolysis; therefore, inhibiting gastric acid and raising the intragastric pH to 6 or higher may promote clot formation and decrease the risk of rebleeding” (PSAP Gastroenterology and Nutrition I 2012:7-26).
      iii. Histamine-2 blockers are ineffective at achieving a pH greater than 6 (Cleve Clin J Med 2010;77:131-42).
      iv. High-dose PPIs should be used as an adjunct to endoscopic therapy.
         (a) If an endoscopy cannot be performed within 24 hours, or if patients have presumed high-risk stigmata, a PPI infusion with a bolus should be initiated before endoscopy to reduce the incidence of high-risk stigmata and need for an endoscopy (PSAP Gastroenterology and Nutrition I 2012:7-26).
         (b) PPI infusion should be continued for 72 hours after endoscopy to improve the lesion from high-risk to low-risk (PSAP Gastroenterology and Nutrition I 2012:7-26).
         (c) Use of high-dose PPIs after endoscopic therapy has been shown to reduce the risk of rebleeding, need for surgery, and mortality (World J Gastroenterol 2012;18:1202-7).
         (d) Typical doses include an 80-mg bolus, followed by 8 mg/hour for pantoprazole or esomeprazole. Treatment can be de-escalated to once-daily oral PPI therapy after 72 hours.
         (e) High-dose oral PPIs (twice-daily dosing) may be used instead of intravenous therapy in patients with low-risk endoscopic findings such as a clean-based ulcer or flat spot (Cleve Clin J Med 2010;77:131-42).
      v. Octreotide or tranexamic acid should be not used in the management of non-variceal GI bleeds because no benefit has been shown with these treatment options.
b. Variceal bleeds  
   i. All patients who present with variceal bleeds should be given 7 days of prophylactic therapy with norfloxacin, ciprofloxacin, or ceftriaxone because of the high risk of infectious complications and a potential reduction in bleeding complications when antibiotics are used (World J Gastroenterol 2012;18:1202-7).  
   ii. Octreotide “produces selective splanchnic vasoconstriction and decreases portal inflow, thereby indirectly reducing variceal bloodflow” (PSAP Gastroenterology and Nutrition I 2012:7-26).  
      (a) Typically given as a 50-mcg bolus, followed by a 50-mcg/hour continuous infusion; the bolus quickly decreases “the portal venous inflow, portal pressures, azygos flow (collateral bloodflow that drains the main part of the portal venous system), and intravariceal pressures” (PSAP Gastroenterology and Nutrition I 2012:7-26).  
      (b) Shown to induce hemostasis but has no effect on overall mortality (Cleve Clin J Med 2010;77:131-42)  
   iii. Vasopressin may be administered in lieu of octreotide, and although effective in achieving hemostasis in a majority of patients, does not improve mortality rates and can lead to adverse events due to systemic vasoconstriction (PSAP Gastroenterology and Nutrition I 2012:7-26)  

c. Miscellaneous  
   i. Erythromycin or metoclopramide may be used when a large amount of blood in the stomach would hinder an endoscopy. Use has been shown to reduce the need for repeated endoscopy (OR 0.55; 95% CI, 0.32–0.94), but makes no difference in the need for blood products, hospital stay, and need for surgery (Gastrointest Endosc 2010;72:1139-45)  
   ii. H. pylori treatment is outside the scope of this chapter; however, a 14-day treatment should be given to all patients with suspected or diagnosed infection, and eradication should be confirmed 4 weeks after therapy (PSAP Gastroenterology and Nutrition I 2012:7-26).  

5. Surgical management  
   a. For patients whose endoscopic therapy has failed or who are not candidates for endoscopy, angiographic intervention may be required (PSAP Gastroenterology and Nutrition I 2012:7-26).  
   b. Transcatheter embolization may be necessary to treat peptic ulcers that have not responded to PPIs and/or endoscopic therapy.  
   c. For variceal bleeds, balloon tamponade and TIPS (transjugular intrahepatic portosystemic shunt) are effective in controlling bleeding.  

Patient Case  
7. A 27-year-old man with a medical history of Crohn’s disease presents to your ED with frank bloody output from his rectum. The resident on call is in the process of calling the endoscopy team to help diagnose and intervene on an upper GI bleed with an esophagogastroduodenoscopy. Which statement is most accurate regarding the care of this patient?  
   A. An endoscopy is the appropriate course of action and should be completed as soon as possible.  
   B. A PPI continuous infusion should be initiated as soon as possible and continued for 72 hours post-endoscopy.  
   C. The patient, who likely has a lower GI bleed, would benefit from a colonoscopy as opposed to an esophagogastroduodenoscopy.  
   D. An endoscopy and a PPI continuous infusion should be initiated as soon as possible.
VII. ENDOCRINE EMERGENCIES

A. Epidemiology

1. Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the most common diabetic emergencies. DKA specifically accounts for 500,000 hospital days and costs $2.4 billion per year (Postgrad Med J 2007;83:79-86; Diabetes Care 2009;32:1335-43).
   a. Between 1996 and 2006, there was a 35% increase in the incidence of DKA in the United States, with most cases occurring in patients 18–44 years of age (Diabetes Care 2009;32:1335-43).
   b. Most patients who develop DKA have type 1 diabetes mellitus, and DKA is considered the most important contributor to mortality rates in children and adolescents with diabetes (Diabetes Care 2009;32:1335-43).
   c. Mortality rates for DKA are 1%–5%, depending on age and other comorbidities, and can be as high as 5%–20% for HHS (Diabetes Care 2009;32:1335-43).

2. Hypoglycemia is linked to high morbidity and mortality in the ICU, and several changes in the recommendations used to control blood glucose in critically ill patients have occurred during the previous decade (N Engl J Med 2009;360:1283-97).

3. Thyroid storms, also known as critical thyrotoxicosis, are an uncommon manifestation of hyperthyroidism known to occur in less than 10% of patients admitted for thyrotoxicosis (Indian J Endocrinol Metab 2012;16:722-7).
   a. Associated with mortality rates of 20-50% if treated and up to a 100% for untreated cases (Emerg Med Clin N Am 2014;32:277-292).


5. Adrenal insufficiency in the acute setting is a life-threatening disorder caused by mineralocorticoid deficiency.

B. DKA and HHS

1. Clinical presentation of DKA
   a. DKA is a combination of hyperglycemia, ketosis, and acidosis with a blood glucose greater than 250 mg/dL, pH less than 7.30, serum bicarbonate less than 18 mmol/L, anion gap greater than 10, and ketonemia (Postgrad Med J 2007;83:79-86).
   b. Severe DKA cases may present with a pH of less than 7.00, a bicarbonate of less than 10 mmol/L, and an anion gap of greater than 12 (Diabetes Care 2009;32:1335-43).
   c. Lack of insulin leads to a reduced glucose uptake; increased lipolysis, which leads to the formation of ketone bodies; and the development of anion gap metabolic acidosis (Postgrad Med J 2007;83:79-86).
   d. Although symptoms may exist for a few days, ketoacidosis occurs quickly, and patients may deteriorate rapidly.
   e. Typically occurs in young, leaner patients with type 1 diabetes mellitus (Postgrad Med J 2007;83:79-86)
   f. Patients may present with nausea and vomiting (80% of patients), polyuria, polydipsia, weight loss, abdominal pain (30% of patients), and fruity breath from acetone in the blood (Postgrad Med J 2007;83:79-86).
   g. Patients can also present with “polyuria, polydipsia, weight loss, vomiting, dehydration, weakness, and mental status changes” as well as “poor skin turgor, Kussmaul respirations, tachycardia, and hypotension” (Diabetes Care 2009;32:1335-43).
h. Serum potassium levels may be high, given the shift of intracellular potassium to the extracellular space because of the lack of endogenous insulin; however, there is typically a relative deficiency of potassium, which can be worsened with treatment (Diabetes Care 2009;32:1335-43).

2. Clinical presentation of HHS
a. HHS is similar to DKA and is defined as blood glucose greater than 600 mg/dL, pH greater than 7.30, serum bicarbonate greater than 18 mmol/L, and serum osmolality greater than 320 mOsm/L, but patients typically do not present with ketonemia (Diabetes Care 2009;32:1335-43).

b. Presentation is often slower than in DKA, and symptoms evolve over days to weeks; patients also have higher degrees of dehydration owing to osmotic diuresis (Diabetes Care 2009;32:1335-43).

c. Typically occurs in older, obese patients with type 2 diabetes mellitus.

d. Signs and symptoms, including electrolyte abnormalities, are similar to those in DKA; however, confusion is much more apparent in HHS and is directly related to the serum osmolality (Postgrad Med J 2007;83:79-86).

e. Patients with HHS do not develop ketoacidosis because, although there is an overall insulin deficiency in both DKA and HHS, there is enough insulin secretion to prevent ketogenesis in HHS (Diabetes Care 2009;32:1335-43).

f. Lack of access to water, either because of the illness itself or because of an altered thirst response in elderly patients, can worsen the severity of dehydration in the setting of hyperglycemia (Diabetes Care 2009;32:1335-43).

3. Causes of DKA and HHS: Typically caused by an insufficiency of insulin in patients with diabetes combined with another potential trigger such as infection, pancreatitis, and certain drugs (steroids, diuretics, vasopressors, antipsychotics, cocaine).

4. Management
a. Involves fluid resuscitation, electrolyte replacement, and correction of acid-base abnormalities and hyperglycemia.

b. Patients are profoundly hypovolemic; total body water deficits may be as high as 10–12 L and should be replaced within the first 24 hours (Diabetes Care 2009;32:1335-43; Indian J Endocrinol Metab 2012;16:722-7).

i. 0.9% sodium chloride should be administered at a rate of 15–20 mL/kg for the first hour and then titrated to hemodynamic parameters and urine output (Diabetes Care 2009;32:1335-43).

ii. 0.45% sodium chloride infused at a rate of 250–500 mL/hour can be used for patients with normal or high sodium levels.

iii. Maintenance fluids can be switched to a dextrose-containing fluid once blood glucose levels have dropped to less than 200 mg/dL in DKA and less than 300 mg/dL in HHS (Diabetes Care 2009;32:1335-43).

c. Insulin therapy is the main treatment modality of DKA and HHS.

i. Insulin “decreases ketogenesis and inhibits the release of free fatty acids, thereby correcting the acidosis” (Postgrad Med J 2007;83:79-86).

ii. Initiate as a 0.1-unit/kg bolus, followed by a 0.1-unit/kg/hour continuous infusion, to decrease blood glucose levels by 50–75 mg/dL/hour.

(a) DKA: Decrease dose to 0.02–0.05 units/kg/hour once blood glucose levels drop to 200 mg/dL, and maintain a blood glucose of 150–200 mg/dL until resolution of ketoacidosis (Diabetes Care 2009;32:1335-43).

(b) HHS: Decrease dose to 0.02–0.05 units/kg/hour once blood glucose levels drop to 300 mg/dL, and maintain a blood glucose of 200–300 mg/dL until mental status changes have resolved (Diabetes Care 2009;32:1335-43).
iii. Continuous insulin infusions should be continued until resolution of ketoacidosis in DKA and resolution of abnormal serum osmolality and mental status in HHS and then should be switched to subcutaneous insulin.

(a) Doses of 0.5–0.8 units/kg of subcutaneous insulin per day can be used (Diabetes Care 2009;32:1335-43).

(b) Electrolyte replacement: Potassium, phosphate, and bicarbonate should be monitored closely and repleted as needed (replete bicarbonate only if pH is less than 6.9) (Diabetes Care 2009;32:1335-43).

C. Hypoglycemia
   1. Clinical presentation
      a. The NICE-SUGAR study defined a blood glucose level of 41–70 mg/dL (2.3 mmol/L) as moderate hypoglycemia and a level of 40 mg/dL or less (2.2 mmol/L) as severe hypoglycemia (N Engl J Med 2012;367:1108-18; N Engl J Med 2009;360:1283-97).
      b. Patients may have “sweating, trembling, pounding heart, anxiety, and hunger” as well as “visual disturbances, dizziness, confusion, headache, tingling, difficulty speaking, and concentrating” (Indian J Endocrinol Metab 2012;16:722-7).

   2. Causes: Hypoglycemia can be caused by decreased insulin resistance (weight loss, adrenal or pituitary insufficiency), decreased clearance of insulin (renal or hepatic failure), or reduced intake of glucose (Indian J Endocrinol Metab 2012;16:722-7).

   3. Management
      a. For conscious, asymptomatic patients, orange juice or 2–6 dextrose tablets can be provided (Postgrad Med J 2007;83:79-86).
      b. Patients who are hospitalized may be given a 50-mL injection of 50% dextrose.
      c. Glucagon 1 mg can be given subcutaneously in patients who are unconscious and not in a hospital setting (Postgrad Med J 2007;83:79-86).

D. Thyroid Storm
   1. Clinical presentation
      a. Thyroid storms can present as more severe symptoms of thyrotoxicosis, including fever (temperature greater than 38.5°C), significant tachycardia, mental status changes, GI symptoms such as nausea and vomiting, hemodynamic instability, and elevated liver function tests (Postgrad Med J 2007;83:79-86).
      b. Thyroid storms can also cause hyperglycemia due to inhibition of insulin by catecholamines, leukocytosis, and hypercalcemia (Emerg Med Clin N Am 2014;32:277-292).
      c. TSH will be undetectable, and T3 and T4 levels (specifically T3) will be elevated.
      d. In general, “thyrotoxicosis with concomitant alteration in sensorium or cardiopulmonary decompensation is thyroid storm until proved otherwise” (Emerg Med Clin N Am 2014;32:277-292).
      e. The Burch and Wartofsky criteria (See Table 8) has been utilized to help identify a potential storm (Emer Med Clin N Am 2014;32:277-292)
Table 8. Burch and Wartofsky criteria for Thyroid Storm

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td><strong>Temperature (°F)</strong></td>
<td></td>
</tr>
<tr>
<td>• 99-99.9</td>
<td>5</td>
</tr>
<tr>
<td>• 100-100.9</td>
<td>10</td>
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<tr>
<td>• 101-101.9</td>
<td>15</td>
</tr>
<tr>
<td>• 102-102.9</td>
<td>20</td>
</tr>
<tr>
<td>• 103-103.9</td>
<td>25</td>
</tr>
<tr>
<td>• &gt;= 104</td>
<td>30</td>
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<tr>
<td><strong>Tachycardia</strong></td>
<td></td>
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<tr>
<td>• 100-109</td>
<td>5</td>
</tr>
<tr>
<td>• 110-119</td>
<td>10</td>
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<tr>
<td>• 120-129</td>
<td>15</td>
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<tr>
<td>• 130-139</td>
<td>20</td>
</tr>
<tr>
<td>• &gt;= 140</td>
<td>25</td>
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<tr>
<td><strong>Atrial Fibrillation</strong></td>
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<tr>
<td>• Absent</td>
<td>0</td>
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<tr>
<td>• Present</td>
<td>10</td>
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<tr>
<td><strong>Congestive heart failure</strong></td>
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<tr>
<td>• Absent</td>
<td>0</td>
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<tr>
<td>• Mild</td>
<td>5</td>
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<tr>
<td>• Moderate</td>
<td>10</td>
</tr>
<tr>
<td>• Severe</td>
<td>20</td>
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<tr>
<td><strong>Gastro-intestinal-hepatic dysfunction</strong></td>
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<tr>
<td>• Absent</td>
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<tr>
<td>• Moderate (diarrhea, abdominal pain, nausea/vomiting)</td>
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<tr>
<td>• Severe (jaundice)</td>
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<tr>
<td><strong>CNS Disturbance</strong></td>
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<tr>
<td>• Absent</td>
<td>0</td>
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<tr>
<td>• Mild (agitation)</td>
<td>10</td>
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<tr>
<td>• Moderate (delirium, psychosis, extreme lethargy)</td>
<td>20</td>
</tr>
<tr>
<td>• Severe (seizure, coma)</td>
<td>30</td>
</tr>
<tr>
<td><strong>Precipitant history</strong></td>
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<tr>
<td>• Positive</td>
<td>0</td>
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<tr>
<td>• Negative</td>
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<td><strong>Score</strong></td>
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<tr>
<td>➢ &gt;45: Thyroid Storm</td>
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</tr>
<tr>
<td>➢ 25-44: Impending Storm</td>
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</tr>
<tr>
<td>➢ &lt;25: Storm Unlikely</td>
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</table>

2. Causes: Although a history of hyperthyroidism is common, hyperthyroidism by itself typically will not cause a thyroid storm; the illness is typically aggravated by a severe external trigger such as “surgery, burns injury, DKA, cardiovascular accident, parturition, status epilepticus, iodine treatment, or iodinated contrast dyes” (Postgrad Med J 2007;83:79-86).
   a. In some cases, a thyroid storm will be initial presentation for patients with undiagnosed hyperthyroidism
   b. Sepsis and infection are leading exacerbating causes of a thyroid storm (Emerg Med Clin N Am 2014;32:277-292)

3. Management
   a. “Treatment principles are to decrease the production and release of thyroid hormones, to block the effects of circulating T4 and T3, and to deal with the underlying precipitants” (Postgrad Med J 2007;83:79-86).
   b. Patients should be provided with aggressive fluid resuscitation if possible (Emerg Med Clin N Am 2014;32:277-292)
   c. Since cardiovascular collapse leads to systemic decompensation, β-Blockers should be initiated as quickly as possible (e.g., propranolol 80-mg oral loading dose, followed by 60-80 mg PO every 4 hours or 1 mg/minute intravenously titrated to a heart rate less than 100 beats/minute) and high doses may be necessary to attenuate the tachycardia and hypertension and to reduce conversion of T4 to T3. Esmolol infusions may also be utilized to control symptoms. (Postgrad Med J 2007;83:79-86; Emerg Med Clin N Am 2014;32:277-292).
   d. Propylthiouracil (PTU) blocks thyroid hormone synthesis and prevents peripheral conversion of T4 to T3 (Postgrad Med J 2007;83:79-86).
   e. Methimazole (20 mg PO/NG/OG every 6 hours), which may be used instead of PTU, blocks thyroid hormone synthesis but does not block the peripheral conversion of T4 to T3 (Emerg Med Clin N Am 2014;32:277-292)
   f. Intravenous steroids (dexamethasone 2-4 mg IV every 6 hours or hydrocortisone 100 mg IV every 6-8 hours) block the conversion of T4 to T3 and can improve patient outcomes (Postgrad Med J 2007;83:79-86; Emerg Med Clin N Am 2014;32:277-292).
   g. While PTU and Methimazole are useful in decreasing the conversion of new thyroid hormones, iodine and lithium can be utilized to stop the release of preformed hormone; however iodine should be given 1 hour after PTU or methimazole to “reduce the risk of increasing thyroid hormone production by providing more substrate” (Emerg Med Clin N Am 2014;32:277-292).
   h. Salicylates should be avoided in thyroid storm because use can decrease binding of thyroid hormones to proteins and therefore increase the levels of free thyroid hormones (Emerg Med Clin N Am 2014;32:277-292).

E. Myxedema Coma

1. Clinical presentation
   a. Myxedema coma can present as an acute change in mental status and hypothermia; in general, the symptoms are the extreme manifestations of common symptoms associated with hypothyroidism (Postgrad Med J 2007;83:79-86).
   b. Patients have profound depression of metabolic activity, as evidenced by severe hypothermia, mental status changes, hemodynamic compromise, and pericardial effusions (Indian J Endocrinol Metab 2012;16:722-7).
c. Patients may present with shock and arrhythmias, and there is evidence to suggest that there is a prolongation of the QT interval that can lead torsades de pointes (Emerg Med Clin N Am 2014;32:303-317).
d. Patients will typically have elevated TSH levels and markedly decreased or undetectable T3 and T4 levels.
e. More common in older women and occurs frequently during winter months due to altered temperature regulation (Emerg Med Clin N Am 2014;32:303-317).

2. Causes
   a. Myxedema coma may present as the first symptom of new hypothyroidism precipitated by events such as “burns, trauma, surgery, severe infection, hypothermia, cardiovascular event, medications,” and sepsis (Postgrad Med J 2007;83:79-86; Indian J Endocrinol Metab 2012;16:722-7).
   b. Infections are leading precipitators of myxedema coma, and all patients with suspected myxedema coma should have an extensive workup for an underlying infection.
   c. Medications, such as “anesthetics, sedatives, narcotics, amiodarone, lithium, and changes to levothyroxine therapy-replacement therapy” can precipitate myxedema coma (Emerg Med Clin N Am 2014;32:303-317).

3. Management
   a. General treatment measures include rewarming of the patient and the treatment of precipitating illness.
   b. There is controversy regarding the efficacy of using synthetic T4 versus T3, with small case reports suggesting higher mortality with T3 (Emerg Med Clin N Am 2014;32:303-317).
   c. Intravenous or oral levothyroxine (T4) as a bolus of 200–500 mcg, followed by 50–100 mcg/day, can be given to patients, with lower doses used for older and low-weight patients (Postgrad Med J 2007;83:79-86).
   d. Because the conversion of T4 to T3 may be impaired in hypothyroidism, some prefer to give triiodothyronin (T3) 10–20 mcg IV as a loading dose followed by 10 mcg every 4 hours for 24 hours, followed by 10 mcg every 6 hours until the patient can tolerate oral medication (Emerg Med Clin N Am 2014;32:303-317).
   e. Patients may also have an underlying ACTH (adrenocorticotropic hormone) deficiency, and intravenous steroids (hydrocortisone 100 mg IV every 8 hours) should also be administered.

**Patient Case**

8. A 23-year-old man presents to the ED with an acute mental status change and a core body temperature of 94°F. He has a history of hypothyroidism, but according to his family, he had decided to stop taking all of his thyroid medications 1 week earlier. The team has given him a diagnosis of myxedema coma. Which is the most appropriate treatment option for this patient?
   A. T3 10–20 mcg intravenously x 1 followed by 10 mcg every 4–24 hours.
   B. An insulin infusion titrated to a blood glucose of 140–180 mg/dL.
   C. PTU 1000-mg load followed by 200 mg every 4 hours.
   D. Propranolol 1 mg intravenously every 2 hours.
F. Adrenal Insufficiency

1. Clinical presentation
   b. CIRCI (critical illness–related corticosteroid insufficiency) occurs because of decreased circulating cortisol levels combined with corticosteroid tissue resistance (Chest 2009;135:181-93).
   c. Historically, cosyntropin stimulation tests were used in patients with septic shock to measure adrenal response (a 250-mcg dose of cosyntropin with cortisol measures at baseline, 30 minutes, and 60 minutes after the dose, with a change of 9 g/dL or less being indicative of adrenal insufficiency); however, the Surviving Sepsis Campaign guidelines recommend not using stimulation tests because of potential inaccuracies in cortisol immunoassays (Crit Care Med 2013;41:580-637).

2. Causes: Include “autoimmune disorders, infection, sudden withdrawal of adrenal replacement therapy, hemorrhage into adrenal glands, purpura fulminans or sudden failure of adrenal or pituitary functioning due to infection or trauma” (Indian J Endocrinol Metab 2012;16:722-7).

3. Management
   a. For patients with acute adrenal crisis, intravenous fluids in the form of normal saline and steroids should be provided (Postgrad Med J 2007;83:79-86).
   b. Hydrocortisone 50 mg every 6 hours or dexamethasone 4 mg every 6 hours can be given as stress-dose steroid replacement.
      i. CORTICUS: Studied the impact of low-dose hydrocortisone (50 mg intravenously every 6 hours) in patients with septic shock and found that administration of hydrocortisone did not reduce mortality compared with placebo; however, reversal of shock occurred more quickly in the hydrocortisone group (N Engl J Med 2008;358:111-24)
      ii. Steroids should be tapered over 1–3 days and converted to oral hydrocortisone 10 mg orally twice daily (Postgrad Med J 2007;83:79-86).
REFERENCES

Acute Liver Failure
**Acute Pancreatitis**


**Gastrointestinal Fistulas**


**Postoperative Ileus and Nausea/Vomiting**


**Upper Gastrointestinal Bleeding**


Endocrine Emergencies
ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. **Answer: D**
   Because of the risk of incidental hepatotoxicity associated with combination opioid/acetaminophen products, the FDA has recently recommended that health care professionals stop prescribing and dispensing prescription drug products that contain more than 325 mg of acetaminophen per dosage unit (Answer D is correct). The FDA has not recommended discontinuing combination products, substituting APAP with another agent, or rescheduling of all APAP/opioid combinations are Schedule II’s (Answers A, B, and C are incorrect).

2. **Answer: C**
   Based on the time of ingestion and acetaminophen level, enough information is presented for clinicians to make an assessment of PG’s risk of toxicity (Answer D is incorrect). All patients above the “possible hepatic toxicity” line are considered at risk for hepatotoxicity (Answer A is incorrect). According to the nomogram, the patient is at probable risk of developing hepatotoxicity; thus, the patient would benefit from acetylcysteine therapy (Answer C is correct). The patient’s level is high enough to place him higher than the possible risk category (Answer B is incorrect).

3. **Answer: C**
   Individual amylase and lipase levels are both useful in the diagnosis of new onset or repeat pancreatitis (Answers A, B, and D are incorrect). However, amylase levels have a shorter half-life than lipase levels and therefore will not be greatly elevated in patients who present late after symptom onset (Answer C is correct). If checking amylase without lipase levels, there is a potential for missing a diagnosis of pancreatitis in patients who present late after symptom onset.

4. **Answer: A**
   The number needed to treat (NNT) for prophylactic antibiotics is about 1400, and data suggests that prophylactic antibiotics have not shown a mortality benefit in patients with sterile necrotizing pancreatitis (Answer A is correct). Antibiotics should not be routinely administered to patients with necrotizing pancreatitis (Answer B is incorrect). They should be initiated if patients have not responded to supportive measures after 1 week or if patients have clinical signs and symptoms of a systemic infection (Answer D is incorrect). If used, high dose cephalosporins, quinolones, metronidazole, and carbapenems are the drugs of choice due to their penetration of pancreatic tissue (Answer C is incorrect). Appropriate cultures should be drawn before antibiotic therapy is initiated.

5. **Answer: C**
   Factors that suggest the highest degree of success include low- to moderate-output fistulas; patients younger than 40 years; proximal sites; patients without malignancy, inflammatory, or infectious disease; a long fistula tract; an acute duration; and fistulas that are esophageal, jejunal, pancreaticobiliary, or duodenal (Answers A, B, and D are incorrect). Being morbidly obese is a negative prognostic measure in assessing the potential for spontaneous closure of a fistula (Answer C is correct).

6. **Answer: B**
   Of the possible answers, only alvimopan has been shown to reduce the incidence of ileus postoperatively (Answer B is correct). Metoclopramide has shown mixed results, and octreotide is not used in the prevention of POI (Answers C and D are incorrect). All opioids can contribute equally to POI (Answer A is incorrect).

7. **Answer: C**
   Frank bloody output from the rectum is more indicative of a lower GI bleed than an upper GI bleed and patients would benefit from a colonoscopy as opposed to a esophagogastroduodenoscopy (Answer C is correct). Upper GI bleeds typically present as melena from the rectum as opposed to frank bloody output. Because this is not an upper GI bleed, the patient would not benefit from a PPI infusion or an endoscopy (Answers A, B, and D are incorrect).

8. **Answer: A**
   Of the possible answers stated, only triiodothyronine (T3) is appropriate for the treatment of myxedema coma (Answer A is correct). Because the conversion of T4 to T3 is impaired in hypothyroidism, T3 is preferred to T4. Insulin, PTU, and propranolol do not a play in the treatment of myxedema coma (Answers B, C, and D are incorrect).
ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. **Answer: C**
The most recent guidelines from the American Association for the Study of Liver Disease and the U.S. Acute Liver Failure Study Group define ALF as a coagulopathy, usually an INR of 1.5 or greater, with any degree of encephalopathy in patients without preexisting liver disease (Answer C is correct). Although jaundice, thrombocytopenia, and leukocytosis can occur in patients with acute liver failure, they are not currently defined as hallmark signs of the disease that exist in all patients (Answers A, B, and D are incorrect).

2. **Answer: B**
Because her current acetaminophen level correlates to a high risk of hepatotoxicity based on the Rumack-Matthew Nomogram, medication therapy is indicated (Answers A and C are incorrect). All patients above the “possible risk” line in the Rumack-Matthew nomogram should be treated with acetylcysteine as soon as possible (Answer B is correct). In addition, because the ingestion was less than 4 hours ago, activated charcoal may be administered to help decrease the absorption of acetaminophen. Hemodialysis not an appropriate option for an acetaminophen overdose (Answer D is incorrect).

3. **Answer: D**
Patients with acute necrotizing pancreatitis should not have a surgical intervention for at least 4 weeks to allow the appropriate delineation of necrotic versus non-necrotic tissue (Answer A is incorrect). Prophylactic antibiotics have not been shown to improve outcomes, and antibiotics should be withheld until the patient has signs of a systemic infection (Answer B is incorrect). Enteral feeds are always preferred to parenteral nutrition because of the risk of intestinal atrophy and bacterial translocation (Answer C is incorrect). Therapy with surgical interventions, antibiotics, and TPN should be deferred, but enteral feeds should be initiated along with fluid resuscitation (Answer D is correct).

4. **Answer: B**
Only high-dose cephalosporins, quinolones, carbapenems, and metronidazole have the ability to penetrate the pancreatic tissue (Answers A, C, and D are incorrect). Macrolides have not been shown to be beneficial in necrotizing pancreatitis (Answer B is correct).

5. **Answer: C**
Fistula output is defined as high if the output is greater than 500 mL/day, moderate if it is 200–500 mL/day, and low if it is less than 200 mL/day. SK’s fistula output decreased significantly (Answers A and D are incorrect) from 570 mL/day to 250 mL/day, but still not enough to classify her fistula output as low (Answer B is incorrect). Her output decreased from high to a moderate output (Answer C is correct).

6. **Answer: C**
Both erythromycin and metoclopramide have shown mixed results in the treatment of postoperative ileus (Answers A and B are incorrect). Ondansetron has not been studied for this indication (Answer D is incorrect). When used as directed, alvimopan shows a significant benefit in reducing POI in several trials (Answer C is correct).

7. **Answer: A**
*Helicobacter pylori* is a recognized carcinogen and should be eradicated using a 14-day PPI/antibiotic combination (Answer B is incorrect). Patients with an acute upper GI bleed who present with a high-risk bleed should have a diagnostic and therapeutic endoscopy within 24 hours of admission (Answer C is incorrect). Blood transfusions should be administered to keep the hemoglobin greater than 7 g/dL (Answer D is incorrect). Therefore, the only inappropriate treatment option is the use of octreotide (Answer A is correct).

8. **Answer: B**
A thyroid storm is an uncommon but deadly manifestation of hyperthyroidism; therefore, the TSH will be low, whereas T4 and T3 will be high (Answer B is correct). Myxedema coma is a manifestation of hypothyroidism; therefore, patients will typically have a high TSH and low T4/T3 levels. When TSH levels are high, typically both the T3 and T4 levels are low (Answer A is incorrect). Conversely, if the TSH is low, typically both the T3 and T4 levels are high (Answers C and D are incorrect).
### Appendix 1

**Drugs Associated with DILI** (World J Gastroenterol 2013;19:7069-77)

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
<th>Category</th>
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<tbody>
<tr>
<td>Anti-infectives</td>
<td>Amoxicillin/clavulanate</td>
<td>Herbal</td>
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