Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8e >

# Chapter 79: Pancreatitis and Cholecystitis

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# PANCREATITIS

# INTRODUCTION/EPIDEMIOLOGY

Pancreatitis is an inflammatory process of the pancreas that may be limited to just the pancreas, may affect surrounding tissues, or may cause remote organ system dysfunction. Most patients will only have one episode of acute pancreatitis, whereas 15% to 30% will have at least one recurrence.<sup>1,2,3</sup> Between 5% and 25% of patients will ultimately develop chronic pancreatitis.<sup>2,3</sup>

Most cases (~80%) involve only mild inflammation of the pancreas, a disease state with a mortality rate of <1%, which generally resolves with only supportive care.<sup>1,4</sup> A small proportion of patients suffer from more severe disease that may involve pancreatic necrosis, inflammation of surrounding tissues, and organ failure, leading to a 30% mortality rate.<sup>5,6</sup>

The annual incidence of pancreatitis varies among nations and regions. Developed countries have a higher incidence of pancreatitis than developing countries. In general, men and women suffer from acute pancreatitis with equal frequency, although alcohol-associated acute pancreatitis is more common in men, while gallstone-induced pancreatitis is more common in women.<sup>7</sup> Blacks are affected two- to threefold more often than whites but have a mortality rate equal to the general population.<sup>3,8</sup> The incidence of acute pancreatitis varies with age, with a peak in middle age.<sup>9</sup> Other risk factors include smoking, obesity, and diabetes mellitus.<sup>9,10</sup>

Factors associated with acute pancreatitis are listed in **Table 79-1**. Most cases are related to either gallstones or alcohol consumption. About 5% of all patients who undergo endoscopic retrograde cholangiopancreatography for treatment of gallstones develop pancreatitis within 30 days.<sup>11</sup>

#### TABLE 79-1

#### **Causes of Acute Pancreatitis**

Common	Gallstones (35%–75%) <sup>9,12</sup> Alcohol (25%–35%) <sup>9,12</sup> Idiopathic (10%–20%) <sup>13</sup>
Uncommon	Hypertriglyceridemia (triglycerides >1000 milligrams/dL) (1%–4%) <sup>14</sup> Endoscopic retrograde cholangiopancreatography <sup>11</sup> Drugs (1.4%–2%)
More uncommon (total <8% of cases)	Abdominal trauma Postoperative complications Hyperparathyroidism Infection (bacterial, viral, or parasitic) Autoimmune disease Tumor (pancreatic, ampullary) Hypercalcemia Cystic fibrosis
Rare	Ischemia Posterior penetrating ulcer Toxin exposure
Unknown	Congenital abnormalities <sup>15</sup>

The nature of the association between alcohol use and acute pancreatitis is unclear. Some studies suggest that consumption of a large amount of alcohol over a short period of time is a more important factor than chronic alcohol use.<sup>16</sup> However, others suggest that at least 5 years of heavy alcohol use are required before alcohol can reliably be considered the cause.<sup>17</sup>

More than 120 drugs have been linked to acute pancreatitis but together account for fewer than 2% of cases. **Table 79-2** lists the commonly used drugs found by two sets of authors to be most well linked to acute pancreatitis based on number of case reports and recurrence after drug reexposure.<sup>18,19</sup> TABLE 79-2

#### Commonly Used Drugs Associated with Acute Pancreatitis<sup>18,19</sup>

Acetaminophen
Amiodarone
Cannabis
Carbamazepine
Chlorothiazide/hydrochlorothiazide
Codeine (and other opiates)
Dexamethasone (and other steroids)
Enalapril
Estrogens
Erythromycin
Furosemide
Losartan
Methimazole
Metronidazole
Pravastatin/simvastatin
Procainamide
Tetracycline
Trimethoprim-sulfamethoxazole
Tuberculosis antibiotics (dapsone, isoniazid, rifampin)

### PATHOPHYSIOLOGY

The pathophysiology of pancreatitis is not completely understood. Under normal circumstances, trypsinogen is produced in the pancreas and secreted into the duodenum where it is converted into the protease trypsin. In acute pancreatitis, for unclear reasons, trypsin is activated within the pancreatic acinar cells. Activation continues in an unregulated fashion and elimination of activated trypsin is inhibited, resulting in high pancreatic levels of activated trypsin. Activated trypsin in turn activates other digestive enzymes, complements, and kinins, leading to pancreatic autodigestion, injury, and inflammation. Pancreatic injury activates local production of inflammatory mediators, which cause further inflammation.<sup>20,21</sup> Fortunately, most cases never progress beyond local inflammation. However, in a minority of cases, termed necrotizing pancreatitis, pancreatic injury progresses to involve surrounding tissue or possibly remote organ systems.<sup>22</sup> The release of inflammatory mediators from the pancreas, in particular from the acinar cells, and extrapancreatic organs such as the liver leads to remote organ injury and failure, the systemic inflammatory response syndrome, multiorgan failure, and even death.<sup>20,21,22</sup>

### **CLINICAL FEATURES**

HISTORY AND PHYSICAL EXAMINATION

Acute pancreatitis causes acute, severe, and persistent abdominal pain, usually associated with nausea, vomiting, anorexia, and decreased oral intake.<sup>23</sup> The pain is located in the epigastrium or occasionally in the left or right upper quadrants. Pain may radiate to the back, chest, or flanks. Pain may worsen with oral intake or laying supine and may improve with sitting up with the knees flexed.<sup>24,25,26</sup> Other symptoms include abdominal swelling, diaphoresis, hematemesis, and shortness of breath. **Pain described as lower abdominal pain or dull or colicky pain is highly unlikely to be pancreatitis**.<sup>25</sup>

The vital signs may be abnormal, with tachycardia, tachypnea, fever, or hypotension. Pain is confined to the epigastrium or upper abdomen, often with guarding and decreased bowel sounds.<sup>23</sup> Occasionally patients will be jaundiced, pale, or diaphoretic.

Rare physical findings associated with late, severe necrotizing pancreatitis include Cullen's sign (bluish discoloration around the umbilicus signifying hemoperitoneum), Grey-Turner sign (reddish-brown discoloration along the flanks signifying retroperitoneal blood or extravasation of pancreatic exudate), and erythematous skin nodules from focal subcutaneous fat necrosis.<sup>26,27</sup>

# DIAGNOSIS

Formal diagnosis is based on at least two of three criteria: (1) clinical presentation consistent with acute pancreatitis, (2) a serum lipase or amylase value elevated above the upper limit of normal, or (3) imaging findings characteristic of acute pancreatitis (IV contrast-enhanced CT, MRI, or transabdominal US).<sup>25,28</sup> The differential diagnosis is wide and consists of all causes of upper abdominal pain, as detailed in chapter 71, "Acute Abdominal Pain."

### LABORATORY STUDIES

There is no gold standard laboratory diagnosis for acute pancreatitis. Two current guidelines recommend that the amylase or lipase value be at least three times the upper limit of normal;<sup>25,28</sup> some recommend a lipase of two times normal or an amylase of three times normal in a patient with the appropriate clinical presentation;<sup>29</sup> and some recommend that any elevation above normal is consistent with the diagnosis.<sup>23</sup> Normal levels for amylase and lipase are based on values in young, healthy patients, making it difficult to determine applicable levels for older patients or those with multiple comorbidities.<sup>29</sup> Consequently, the combination of an elevated laboratory value with a clinical presentation consistent with pancreatitis is key for diagnosis.<sup>25</sup>

**Amylase** is not a good choice for diagnosis.<sup>25</sup> Amylase rises within a few hours after the onset of symptoms, peaks within 48 hours, and normalizes in 3 to 5 days.<sup>29</sup> About 20% of patients with pancreatitis, most of whom have alcohol- and hypertriglyceridemia-related disease, will have a normal amylase.<sup>30</sup> This fact, along with the rapid decrease in amylase after symptom onset, gives amylase a sensitivity of about 70%, with a positive predictive value ranging from 15% to 72%. <sup>23</sup> Amylase can be elevated in multiple non–pancreas-related diseases, such as renal insufficiency, salivary gland diseases, acute appendicitis, cholecystitis, intestinal obstruction or ischemia, and gynecologic diseases, lowering specificity for pancreatitis.<sup>23,30</sup>

**Lipase** is more specific to pancreatic injury and remains elevated for longer after onset of symptoms than amylase. Lipase may be elevated in diabetics at baseline and in other nonpancreatic diseases such as renal disease, appendicitis, and cholecystitis, but it is less associated with nonpancreatic diseases than amylase.<sup>25,31</sup> Lipase is more sensitive in patients with a delayed presentation and in cases of alcoholic or hypertriglyceridemic pancreatitis.<sup>29</sup>

When an elevation of both **lipase and amylase** is required to diagnose pancreatitis, specificity is increased and sensitivity is decreased compared to using either test alone, but there is no evidence that adding amylase to a nondiagnostic lipase improves diagnostic accuracy over lipase alone.<sup>29</sup>

The urine trypsinogen-2 dipstick test is a rapid, noninvasive test with high sensitivity (82%) and specificity (94%).<sup>32</sup> However, given its current limited availability, it is not included as part of the diagnostic criteria for pancreatitis.<sup>28</sup>

In addition to serum lipase and amylase, obtain blood studies to evaluate renal and liver function, electrolyte status, glucose level, WBC count, and hemoglobin/hematocrit. These lab results help the clinician predict disease severity and outcome (detailed below), optimize the clinical status of the patient, identify complications that need immediate treatment (cholangitis, organ failure), and assess effectiveness of treatment.

An **alanine aminotransferase** of >150 U/L within the first 48 hours of symptoms predicts gallstone pancreatitis with a greater than 85% positive predictive value.<sup>33</sup>

### IMAGING

Imaging can identify the cause of pancreatitis and can identify complications and severity. For patients with acute pancreatitis where gallstones have not been excluded, obtain a transabdominal US in the ED to detect gallstone pancreatitis.<sup>3,28,34</sup> For any patient with respiratory complaints, obtain a chest radiograph to evaluate for pleural effusions and pulmonary infiltrates, both associated with more severe pancreatitis.

In patients who meet the clinical presentation and laboratory criteria, routine early CT, with or without IV or PO contrast, is not recommended for multiple reasons. Most patients have uncomplicated disease and are readily diagnosed by clinical and laboratory criteria. There is no evidence that early CT, with or without contrast, improves clinical outcomes.<sup>28,35,36</sup> Peripancreatic fluid collections or pancreatic necrosis detected by CT of any kind within the first few days of symptoms generally require no treatment, and the complete extent of these local complications is usually not appreciated until at least 3 days after onset of symptoms. The magnitude of morphologic change on imaging studies does not necessarily correlate with disease severity.<sup>37</sup> Finally, IV contrast infusion can cause allergic reactions, nephrotoxicity, and worsening of pancreatitis.<sup>38</sup>

If the clinical diagnosis of acute pancreatitis is in doubt, consider further evaluation with IV contrast **abdominal CT**. Characteristic findings include: (1) pancreatic parenchymal inflammation with or without peripancreatic fat inflammation; (2) pancreatic parenchymal necrosis or peripancreatic necrosis; (3) peripancreatic fluid collection; or (4) pancreatic pseudocyst.<sup>25,39</sup> **Figure 79-1A–D** compares CT image of a normal pancreas to images in various complications. Although noncontrast MRI is not readily available to the ED, this imaging modality can identify the complications of pancreatitis and choledocholithiasis. It can be an alternative for patients with renal failure, patients who are allergic to IV contrast, or pregnant patients.<sup>40</sup>

### FIGURE 79-1.

Abdominal IV contrast-enhanced CT scans showing: A. normal pancreas (*arrow*) with smooth outer contours, clear demarcation between pancreas and surrounding tissues, and without peripancreatic fluid; B. mild pancreatitis with indistinct pancreatic borders (*left arrow*), pancreatic edema, and peripancreatic fluid (*right arrow*); C. edematous pancreas with indistinct borders (*left arrow*) and area of nonenhancing parenchyma pancreatic necrosis with area of acute pancreatic necrosis (low attenuation representing nonenhancing parenchyma; *right arrow*); and D. edematous pancreas with indistinct pancreatic borders (*left arrow*) and a pseudocyst in the pancreatic tail (*right arrow*). [Images contributed by Bart Besinger, MD, FAAEM.]



#### Α

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#### D

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### TREATMENT

**Treatment is supportive and symptomatic therapy (Table 79-3)**. No specific medication effectively treats acute pancreatitis; however, early aggressive hydration decreases morbidity and mortality.<sup>41,42,43</sup> The benefit of fluid resuscitation may result from increased micro- and macrocirculatory support of the pancreas, which prevents complications such as pancreatic necrosis.<sup>44</sup>

#### TABLE 79-3

#### **Treatment of Acute Pancreatitis**

Treatment	Comments
Aggressive crystalloid therapy	Lactated Ringer's preferably 2.5–4 L, at least 250–500 mL/h or 5–10 mL/kg/h
	Use caution in congestive heart failure, renal insufficiency
	Monitor response:
	– Hematocrit 35%–44%
	– Maintain normal creatinine
	– Heart rate <120 beats/min
	– Mean arterial pressure 65–85 mm Hg
	– Urine output 0.5–1 mL/kg/h (if no renal failure)
Vital signs/pulse oximetry	Monitor closely/frequently; initially at least every 2 h, but patients
	may require more frequent monitoring
Electrolyte repletion	Correct low ionized calcium, hypomagnesemia
	Control hyperglycemia
Pain control	Parenteral narcotics
Supplemental oxygen	As needed for respiratory insufficiency
Antiemetics	Control nausea/vomiting
	NPO status
	Nasogastric tube/suction typically not indicated
Antibiotics	If known or strongly suspected infection, give appropriate antibiotics
	based on cause
	Prophylactic antibiotics and antibiotics for mild pancreatitis not indicated
Consultation for endoscopic retrograde	In first 24 h for those with documented biliary obstruction or cholangitis

*Abbreviation:* NPO = nothing by mouth.

Provide fluid resuscitation. Fluid loss results from vomiting, third spacing, increased insensible losses, and decreased oral intake. Patients generally need 2.5 to 4 L of fluid with at least one third delivered in the first 12 to 24 hours.<sup>25,28</sup> The specific rate of fluid delivery depends on the patient's clinical status. In the situation of renal or

heart failure, deliver fluid more slowly to prevent complications such as volume overload, pulmonary edema, and abdominal compartment syndrome. Crystalloids are the resuscitation fluids of choice. Normal saline in large volumes may cause a nongap hyperchloremic acidosis and can worsen pancreatitis, possibly by activating trypsinogen and making acinar cells more susceptible to injury.<sup>25,45</sup> A single randomized study showed a decreased incidence of systemic inflammatory response syndrome in patients who received lactated Ringer's instead of 0.9% normal saline.<sup>45</sup> Regardless of which fluid is selected, monitor vital signs and urine output as responses to hydration.

Control pain and nausea. Pain control is best achieved with IV opioid analgesics. Initially, place patients on NPO (nothing by mouth) status and administer antiemetics. There is no benefit to nasogastric intubation.

Prolonged bowel and pancreas rest increases gut atrophy and bacterial translocation, leading to infection and increasing morbidity and mortality.<sup>46</sup> In the ED, if nausea and vomiting have resolved and pain has decreased, transition the patient to oral pain medications and small amounts of food.<sup>47</sup> A low-fat solid foods diet provides more calories than a clear liquid diet and is safe.<sup>48</sup>

Acute pancreatitis by itself is not a source of infection, and prophylactic use of antibiotics and antifungals is not recommended.<sup>49</sup> Administer antibiotics if a source of infection is demonstrated, such as cholangitis, urinary tract infection, pneumonia, or infected pancreatic necrosis.<sup>49</sup>

# SEVERITY CLASSIFICATIONS OF ACUTE PANCREATITIS

Although most patients with acute pancreatitis have mild uncomplicated disease, a small percentage of patients have more severe disease. In the ED, it is difficult to distinguish disease severity, because most patients present so early in the disease course that complications that define moderately severe or severe disease are not evident. Moderately severe acute pancreatitis is characterized by transient organ failure (<48 hours), local complications, or systemic complications. Severe disease includes one or more local or systemic complications and persistent organ failure (>48 hours). Critical acute pancreatitis is persistent organ failure and infected pancreatic necrosis.<sup>50</sup>

Local complications involve the pancreas and surrounding tissues and include acute peripancreatic fluid collections, pancreatic pseudocyst, acute pancreatic or peripancreatic necrosis, walled off necrosis, gastric outlet dysfunction, splenic and portal vein thrombosis, and colonic inflammation/necrosis.<sup>22</sup> These are not usually well demonstrated on CT scan until at least 72 hours after the onset of symptoms. Suspect local complications in patients who have persistent or recurrent abdominal pain, an increase in pancreatic enzyme levels after an initial decrease, new or worsening organ dysfunction, or sepsis (fever, increased WBC count).

Organ failure can be seen in any system, but three organ systems are particularly susceptible: cardiovascular, respiratory, and renal. Because of the susceptibility of these three organ systems, pay special attention during the patient's initial evaluation.

Other possible complications of acute pancreatitis are listed in Table 79-4.

#### TABLE 79-4

#### **Complications of Acute Pancreatitis**

Pancreatic	Peripancreatic	Extrapancreatic	
Fluid	Fluid collection	Cardiovascular	GI
collection	Necrosis	Hypotension	Peptic ulcer
Necrosis	Intra-abdominal or retroperitoneal	Hypovolemia	disease/erosive gastritis
Sterile or	hemorrhage	Myocardial depression	GI perforation
infected	Pseudoaneurysm (of contiguous visceral	Myocardial infarction	GI bleeding
Acute or	arteries, e.g., the splenic)	Pericardial effusion	Duodenal or stomach
walled off	Bowel inflammation, infarction, or	Pulmonary	obstruction
Abscess	necrosis	Hypoxemia	Splenic infarction
Ascites	Biliary obstruction with jaundice	Atelectasis	Renal
	Splenic or portal vein thrombosis	Pleural effusion (with or	Oliguria
		without fistula)	Azotemia
		Pulmonary infiltrates	Acute renal failure
		Acute respiratory	Thrombosis of renal
		distress syndrome	artery or vein
		Respiratory failure	Metabolic
		Hematologic	Hyperglycemia
		Disseminated	Hypocalcemia
		intravascular coagulation	Hypertriglyceridemia

#### PREDICTION OF DISEASE SEVERITY

A number of different scoring systems exist, including the Ranson criteria, Acute Physiology and Chronic Health Examination-II, modified Glasgow score, Bedside Index for Severity in Acute Pancreatitis, and Balthazar CT Severity Index. These scoring systems include many data points, some of which are not collected until at least 48 hours after presentation, limiting their utility in the ED.<sup>51</sup> None of these scoring systems is superior to another.<sup>52</sup> **Systemic inflammatory response syndrome at admission and persistent at 48 hours predicts severe acute pancreatitis more simply and as accurately as the various scoring systems.**<sup>6,52,53</sup> **Besides systemic inflammatory response syndrome, a number of other clinical findings at initial assessment are associated with severe disease. These findings include patient characteristics (age >55 years, obesity, altered mental status, comorbidities), laboratory findings (BUN >20 milligrams/dL or rising; hematocrit >44% or rising; increased creatinine), and radiologic findings (many or large extrapancreatic fluid collections, pleural effusions, pulmonary infiltrates).**<sup>22,41,54</sup>

Overall, acute pancreatitis has a mortality rate of approximately 1%.<sup>4</sup> Moderately severe and severe disease mortality rates are 5% and 30%, respectively.<sup>6,55</sup> Most patients who die do so from multiorgan failure. The sensitivity of systemic inflammatory response syndrome on admission for mortality is 100% with a specificity of

31%, whereas the sensitivity and specificity of systemic inflammatory response syndrome at 48 hours (persistent systemic inflammatory response syndrome) are 77% to 89% and 79% to 86%, respectively.<sup>6,53</sup> Systemic inflammatory response syndrome at admission and 48 hours, combined with patient characteristics (age, comorbidities, and obesity) and response to treatment, helps predict outcome.

# **DISPOSITION AND FOLLOW-UP**

Patients with nonbiliary pancreatitis whose pain can be controlled in the ED and who can tolerate oral feeding can be discharged. Patients who are discharged from the ED should be referred for appropriate follow-up to help prevent recurrence.

Consider admission for a first bout of acute pancreatitis, for any case of biliary pancreatitis, and for patients needing frequent IV pain medication, not tolerating oral intake because of vomiting or increasing pain, with persistent abnormal vital signs, or with any signs of organ insufficiency (e.g., increased creatinine).

Admit to the intensive care unit a patient with severe pancreatitis or anyone who meets local criteria for an intensive care unit admission. Any patient who has any signs, symptoms, laboratory values, or imaging results suggesting the need for intensive care should also receive consideration for intensive care unit admission or at least an intermediate care unit admission.

Biliary pancreatitis requires either admission by surgeon or early surgical consultation for consideration of early cholecystectomy.<sup>56</sup> Cholecystectomies in patients not suffering from documented gallstone pancreatitis are associated with increased recurrence of acute pancreatitis.<sup>57</sup>

Patients with cholangitis or known biliary obstruction on admission may benefit from early endoscopic retrograde cholangiopancreatography.<sup>58</sup> Early routine endoscopic retrograde cholangiopancreatography in patients without one of these two complications does not improve mortality or modify or prevent local complications.<sup>58</sup>

# SPECIAL CONSIDERATIONS

# MEDICATIONS

Medications associated with acute pancreatitis can be categorized into three groups: antiretrovirals, chemotherapy, and immunosuppressants. Patients taking these medications are at particular risk of severe disease because of the underlying disease combined with the medication side effects. 2',3'-Dideoxyinosine can cause potentially fatal pancreatitis, whereas patients receiving the antiretrovirals lamivudine and nelfinavir are at lower risk.<sup>18,19</sup>

Cancer patients undergoing chemotherapy with one or more of seven medications have a risk of pancreatitis complicating the disease course. These medications are L-asparaginase, cisplatin, cytarabine, ifosfamide, mercaptopurine, pegaspargase, and tamoxifen.<sup>18,19</sup> These agents are used to treat leukemias, lymphomas, sarcomas, and breast, cervical, lung, ovarian, and testicular cancers.

Patients receiving azathioprine for posttransplantation immunosuppression or treatment of inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease are also at risk of developing pancreatitis.<sup>18,19</sup>

# CHRONIC PANCREATITIS

Chronic pancreatitis is a continuum of acute pancreatitis. From 5% to 25% of patients can progress to chronic pancreatitis.<sup>2,3</sup> Progression is most common in alcohol-induced disease, but may happen in any situation.<sup>2,3</sup>

Attacks are similar to acute pancreatitis. The goal of treatment is hydration and pain and nausea control. The mortality risk of chronic pancreatitis recurrences is generally lower than that of acute pancreatitis<sup>.2,3</sup>

# CHOLECYSTITIS

# INTRODUCTION AND EPIDEMIOLOGY

Cholecystitis is inflammation of the gallbladder that is usually caused by an obstructing gallstone.

**Gallstones** produce disease states, including acute calculous cholecystitis, that vary considerably in their severity, clinical presentation, and management strategies. In the United States, the prevalence of gallstones is 8% among men and 17% among women.<sup>59</sup> Prevalence increases with age and with increasing body mass index. Bariatric surgery is also a risk factor for the development of gallstones.<sup>60</sup> The vast majority of gallstones are asymptomatic. *Asymptomatic gallstones* may be discovered incidentally on diagnostic imaging performed for another purpose. The risk of developing symptoms or complications is 1% to 4% per year.<sup>61</sup>

**Biliary colic** is the most common complication of gallstone disease. Patients experience recurrent attacks of steady upper abdominal pain that typically last no more than a few hours and resolve spontaneously when the gallstone moves from its obstructing position. If the obstructing stone remains in place, acute cholecystitis may develop over time as the gallbladder becomes distended, inflamed, and in some cases infected. As acute cholecystitis evolves, it may result in necrosis and gangrene of the gallbladder wall (**gangrenous cholecystitis**). **Emphysematous cholecystitis** occurs when the inflamed gallbladder becomes infected with gas-producing organisms. **Gallbladder perforation** is an uncommon but life-threatening complication of cholecystitis. Gangrenous cholecystitis, emphysematous cholecystitis, and gallbladder perforation may occur with or without the presence of gallstones.

**Choledocholithiasis**, gallstones within the common bile duct, may be either primary (arising from within the bile ducts) or, more commonly, secondary (forming in the gallbladder and then migrating to the common bile duct). Choledocholithiasis or other causes of common bile duct obstruction, such as stricture or tumor, may be complicated by *cholangitis*, an infection of the biliary tree. **Chronic cholecystitis** is a state of prolonged gallbladder inflammation typically caused by recurrent episodes of cystic duct obstruction by gallstones. Fibrotic thickening of the gallbladder wall develops. **Biliary sludge** is microlithiasis composed of cholesterol crystals, calcium bilirubinate pigment, and other calcium salts. It may be seen on CT or US. The clinical course of biliary sludge is variable. It may resolve spontaneously or progress to cause complications including biliary colic, cholecystitis, cholangitis, or pancreatitis. **Acute acalculous cholecystitis** occurs in the absence of gallstones. It occurs much less commonly than calculous cholecystitis but is more likely to result in complications. It tends to occur in the setting

of critical illness such as septic shock, burns, and major trauma or surgery. Old age, diabetes, and immunosuppression are also risk factors.

# PATHOPHYSIOLOGY

Bile is produced by hepatocytes and transported via the biliary system to the small intestine where bile acids are necessary for the digestion and absorption of lipids. Bile is also the vehicle for eliminating a number of substances from the body including bile pigments (e.g., bilirubin), cholesterol, and some drugs. Bile is stored and concentrated in the gallbladder. When a meal is eaten, the gallbladder is provoked to contract by cholecystokinin and neural stimulation, resulting in the expulsion of bile into the cystic duct and then to the common bile duct, where it reaches the duodenum at the sphincter of Oddi.

Gallstone formation is a multifactorial process that involves supersaturation of bile components, crystal nucleation, and gallbladder dysmotility.<sup>62</sup> Gallstones are classified based on their composition into two categories: pigment stones and cholesterol stones. Pigment stones may be further divided into brown and black stones (**Table 79-5**).

TABLE 79-5

### **Gallstone Types**

	Cholesterol Stones	Pigment Stones
Composition	Cholesterol monohydrate crystals	Black: Calcium bilirubinate Brown: Mixed composition; usually occur in setting of bacterial or helminthic infection of bile
Relative frequency	80%	20%
Radiographic appearance	Radiolucent	Radiopaque
Typical patients	Obese, female, elderly, rapid weight loss	Black: Chronic liver disease or hemolytic disease Brown: Bile duct stasis (sclerosing cholangitis, strictures); more common in Asia

Nonobstructing gallstones typically do not cause symptoms. As gallstones migrate through the biliary tree, they can obstruct the gallbladder neck, cystic duct, or common bile duct. The resultant distention and increased intraluminal pressure cause pain, nausea, and vomiting. Symptoms are relieved if the gallstone returns to a nonobstructing position within the gallbladder lumen or if it passes through the biliary tree into the duodenum. If the obstruction does not resolve, inflammation results from a complex process that involves mechanical

distention, ischemia, and inflammatory mediators including prostaglandins. Interestingly, this long-held notion that gallbladder outlet obstruction is the inciting event in acute cholecystitis has been recently challenged.<sup>63</sup>

Bile cultures are positive in about half of patients with acute cholecystitis.<sup>64,65,66</sup> Gram-negative organisms predominate (*Escherichia coli*, 39%; *Klebsiella*, 35%), although gram-positive (*Streptococcus*, 18%; *Enterococcus*, 17%) and anaerobic (*Clostridia*, 14%; *Bacteroides*. 3%) infections occur as well.<sup>65</sup> Polymicrobial infections are common.

# **CLINICAL FEATURES**

# HISTORY

Biliary colic presents with pain in the epigastrium or right upper quadrant of the abdomen that occasionally radiates to the back. Despite its name, the pain of biliary colic is more often described as steady than colicky. The pain is often accompanied by nausea and vomiting. Its association with food intake is variable. Fatty food intolerance is not a reliable predictor of gallstone presence.<sup>67,68</sup> Biliary colic demonstrates significant circadian periodicity, with a peak in symptom occurrence around midnight.<sup>69</sup>

Symptoms of biliary colic typically last a few hours or less. If pain persists longer, gallstone complications of greater severity, such as acute cholecystitis or cholangitis, must be considered. In acute cholecystitis, pain becomes more localized to the right upper quadrant and increases in severity as peritoneal irritation occurs.<sup>70</sup>

# PHYSICAL EXAMINATION

Patients with biliary colic typically have mild right upper quadrant tenderness without peritoneal signs. In acute cholecystitis, tenderness is more severe and may occasionally be accompanied by rigidity or rebound tenderness. Murphy's sign (the sudden cessation of deep inspiration due to pain when examining fingers reach the inflamed gallbladder upon palpation of the right subcostal region) is 65% sensitive and 87% specific for acute cholecystitis.<sup>71</sup> Patients with biliary colic are afebrile. Fever is classically described in acute cholecystitis but is in fact present in only about one third of cases.<sup>71</sup> Jaundice is rarely seen in acute cholecystitis. Jaundice in the setting of biliary tract stone disease implies an obstruction of the common bile duct from choledocholithiasis or extrinsic compression of the bile duct by an impacted cystic duct or gallbladder stone or adjacent inflammation (Mirizzi's syndrome).

# DIAGNOSIS

The diagnosis of gallstones can be readily established with radiographic studies. However, it is incumbent upon the emergency physician to distinguish the patient with simple biliary colic from the patient with a more serious gallstone complication such as acute cholecystitis, choledocholithiasis, cholangitis, or gallstone pancreatitis.

Establishing the diagnosis of acute cholecystitis requires the integration of data from the history and physical examination with the results of laboratory and radiographic studies. There is no single clinical or laboratory finding

that can be relied upon to rule in or rule out the diagnosis.<sup>71</sup> Diagnostic criteria for acute cholecystitis have been proposed (**Table 79-6**).<sup>72</sup>

### TABLE 79-6

### Diagnostic Criteria for Acute Cholecystitis<sup>\*</sup>

Local signs	Murphy's sign
	Right upper quadrant mass, pain, or tenderness
Systemic	Fever
signs	Elevated C-reactive protein
	Elevated WBC count
Imaging	Imaging findings characteristic of acute cholecystitis (see Table 79-7)
Diagnosis	Suspected: One local sign and one systemic sign Definite: One local sign, one systemic sign, and imaging findings of acute cholecystitis
Accuracy	Sensitivity 91.2%, specificity 96.9% for definite diagnosis criteria compared with surgical pathology gold standard

<sup>\*</sup>Acute hepatitis, chronic cholecystitis, and other acute abdominal disorders should be excluded.

The classic presentation of cholangitis is *Charcot's triad*: fever, right upper quadrant abdominal pain, and jaundice. It is present in slightly more than half of the cases.<sup>73</sup> Most patients will have a fever and right upper quadrant pain; the presence of jaundice is less common, occurring in about two thirds of patients. *Reynolds' pentad* adds altered mental status and shock to Charcot's triad.<sup>74</sup> It is seen in less than 10% of patients with cholangitis.<sup>73</sup>

The differential diagnosis of acute cholecystitis includes other diseases of the biliary tract such as biliary colic, choledocholithiasis, and cholangitis and other conditions of the GI tract such as pancreatitis, hepatitis, peptic ulcer disease, gastritis, and functional dyspepsia. Appendicitis may occasionally present with right upper quadrant pain. Chest disease such as pneumonia, pleurisy, or pulmonary embolism may present with pain of the upper abdomen.

### LABORATORY TESTING

Laboratory tests are typically normal in biliary colic. A leukocytosis may be seen in acute cholecystitis, but its absence does not exclude the diagnosis. A leukocyte count of >10,000/mm<sup>3</sup> has a 63% sensitivity, 57% specificity, positive likelihood ratio of 1.5, and negative likelihood ratio of 0.6.<sup>71</sup> The mean leukocyte count in cholecystitis is 12,600/mm<sup>3</sup>.<sup>75</sup> Elevation of C-reactive protein is associated with acute cholecystitis but is nonspecific.<sup>76</sup>

Liver function tests, including bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and γ-glutamyl transpeptidase, are often normal in acute cholecystitis. They are more likely to be elevated in the setting of choledocholithiasis or other cause of bile duct obstruction.<sup>77,78</sup> Abnormal γ-glutamyl transpeptidase is the most sensitive and specific serum marker of choledocholithiasis.<sup>79</sup> Marked elevations (>1000 IU/L) of alanine aminotransferase or aspartate aminotransferase can occur in the setting of choledocholithiasis but are more suggestive of a hepatocellular necrotic process.<sup>80</sup>

### IMAGING

Plain radiography of the abdomen is of minimal value in assessing for biliary tract stone disease. Most gallstones do not contain sufficient amounts of calcium to be visible on plain x-rays. Plain radiography may demonstrate biliary tree air reflective of emphysematous cholecystitis or biliary-enteric fistula, but these are better and more reliably demonstrated with other imaging modalities.

#### Ultrasound

Abdominal US (Figure 79-2) is the imaging modality of choice for acute cholecystitis.<sup>81</sup> Its sensitivity and specificity for acute cholecystitis are 81% and 83%, respectively.<sup>82</sup> Advantages of US include its availability, lack of ionizing radiation, short study time, excellent sensitivity for gallstones, and ability to elicit tenderness with placement of the US probe. Sonographic Murphy's sign, maximal tenderness over a sonographically identified gallbladder, is particularly important in the US diagnosis of cholecystitis. The presence of gallstones and a sonographic Murphy's sign has a positive predictive value of 92% for acute cholecystitis. The absence of both gallstones and the sonographic Murphy's sign has a negative predictive value of 95%.<sup>83</sup> Gallbladder wall thickening and pericholecystic fluid are relatively nonspecific for cholecystitis and may result instead from conditions such as ascites, heart failure, liver disease, or pancreatitis.

#### FIGURE 79-2.

Abdominal US demonstrating acute cholecystitis with a gallstone (*arrowhead*), gallbladder sludge (*asterisk*), and pericholecystic fluid (*arrow*). [Image contributed by Bart Besinger, MD, FAAEM.]



Source: J.E. Tintinalli, J.S. Stapczynski, O.J. Ma, D.M. Yealy, G.D. Meckler, D.M. Cline: Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8th Edition www.accessmedicine.com Copyright © McGraw-Hill Education. All rights reserved. Bedside US of the right upper quadrant performed by emergency physicians is a useful modality for the diagnosis of cholelithiasis.<sup>84</sup> Its accuracy for diagnosing acute cholecystitis has been questioned.<sup>85,86</sup> However, in the hands of emergency physicians who are highly trained in its use, point-of-care US for cholecystitis is comparable to that performed by US technicians and interpreted by radiologists.<sup>87</sup>

#### CT, MRI, and Hepatobiliary Iminodiacetic Acid Scanning

Acute cholecystitis may be demonstrated on IV contrast-enhanced **abdominal CT**, although the sensitivity and specificity of CT for cholecystitis are ill-defined (**Figure 79-3**). Limitations of CT include its relative insensitivity (~75%) for gallstones and its inability to detect a Murphy's sign.<sup>88</sup> IV contrast-enhanced CT may reveal complications of cholecystitis, such as gangrenous cholecystitis, emphysematous cholecystitis, gallstone ileus, and gallbladder perforation, that are not as reliably demonstrated on US.<sup>89</sup>

### FIGURE 79-3.

Enhanced abdominal CT showing acute cholecystitis with a radiodense gallstone at the gallbladder neck (*arrow*) and a thickened gallbladder wall (*arrowheads*). [Image contributed by Bart Besinger, MD, FAAEM.]



Source: J.E. Tintinalli, J.S. Stapczynski, O.J. Ma, D.M. Yealy, G.D. Meckler, D.M. Cline: Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8th Edition www.accessmedicine.com Copyright © McGraw-Hill Education. All rights reserved.

**Technetium-99m hepatobiliary iminodiacetic acid cholescintigraphy** is 96% sensitive and 90% specific for acute cholecystitis.<sup>82</sup> An injected radiotracer is excreted by the liver into bile, allowing visualization of the bile ducts and

gallbladder. In acute cholecystitis, the obstructed cystic duct results in nonvisualization of the gallbladder. Cholescintigraphy may also reveal delayed gallbladder emptying (*biliary dyskinesia*). Cholescintigraphy requires hours to perform, limiting its use in the ED.

**MRI, including magnetic resonance cholangiopancreatography**, may be used to evaluate the gallbladder and biliary tree. The sensitivity and specificity of IV gadolinium-enhanced MRI for cholecystitis are similar to those of US.<sup>82</sup> MRI, however, demonstrates more consistent visualization of the biliary tree, has less interpreter variability, and is a useful alternative to those patients who are difficult to examine with US.<sup>81</sup>

#### Imaging for Choledocholithiasis

Choledocholithiasis is difficult to exclude with US or CT. US fails to visualize the entire extrahepatic biliary tree in many patients and has a sensitivity for choledocholithiasis of about 60%.<sup>90</sup> CT, although limited by its inability to detect poorly calcified stones, performs somewhat better than US.<sup>91,92</sup> On either US or CT, the combined findings of gallbladder stones and common bile duct dilation provide indirect evidence of choledocholithiasis. Normal common bile duct diameter is <5 mm, although diameter is increased in patients with prior cholecystectomy and in the elderly. More definitive evaluation for choledocholithiasis can be accomplished by magnetic resonance cholangiopancreatography, endoscopic US, or endoscopic retrograde cholangiopancreatography.

Imaging findings in acute cholecystitis are summarized in Table 79-7.

#### TABLE 79-7

# Imaging for Acute Cholecystitis

Modality	Findings	Comment
US	Sonographic Murphy's sign Gallbladder wall thickening >3 mm Pericholecystic fluid Gallbladder distention: short axis >40 mm	Preferred initial imaging test.
СТ	Gallbladder wall thickening >3 mm Pericholecystic fluid Pericholecystic fat stranding Hyperdense gallbladder wall Gallbladder distention	Demonstrates complications such as gangrene, gas formation, and perforation. Insensitive for gallstones. Useful in evaluating alternative diagnoses.
HIDA	Nonvisualization of gallbladder	Excellent sensitivity and specificity. Time consuming, limited availability, ionizing radiation.
MRI/MRCP	Gallbladder wall thickening >3 mm Pericholecystic fluid Pericholecystic fat signal changes Gallbladder distention: short axis >40 mm	Specificity and sensitivity similar to US. Excellent visualization of biliary tree. Time consuming, limited availability.

*Abbreviations:* HIDA = hepatobiliary iminodiacetic acid cholescintigraphy; MRCP = magnetic resonance cholangiopancreatography.

### TREATMENT

**Asymptomatic gallstones** generally require no treatment. Elective cholecystectomy is occasionally recommended for those at high risk for gallstone complications such as patients with sickle cell disease, patients with planned organ transplantation, or those belonging to ethnic groups at high risk for gallbladder cancer.

ED management of **biliary colic** includes symptom control and referral to a general surgeon for outpatient laparoscopic cholecystectomy. Symptom management in the ED includes antiemetics and analgesics. Nonsteroidal anti-inflammatory drugs are first-line therapy. The analgesic efficacy of parenteral nonsteroidal anti-inflammatory drugs is comparable to that of opioids in biliary colic. Additionally, nonsteroidal anti-inflammatory drugs decrease the frequency of short-term gallstone complications such as cholecystitis.<sup>93</sup> Opioid analgesics are often required for pain control. All opioids cause some degree of sphincter of Oddi spasm and increase in biliary pressure.<sup>94</sup> The clinical significance of this is unclear, and there is no evidence that any particular opioid drug is superior in treating the pain of biliary colic. Anticholinergic agents such as atropine and glycopyrrolate do not improve biliary colic pain.<sup>95,96</sup>

**Acute cholecystitis** and its complications are managed in the hospital with surgical consultation. Early laparoscopic cholecystectomy is often the treatment of choice. ED treatment includes the provision of analgesia, administration of antiemetics for nausea and vomiting, cessation of oral intake, volume and electrolyte replacement, and administration of antibiotics. Appropriate antibiotic regimens include second- and third-generation cephalosporins, carbapenems, β-lactam/β-lactamase inhibitor combinations, or the combination of metronidazole and a fluoroquinolone.<sup>97,98,99</sup> The value of antibiotics in mild acute cholecystitis has recently been guestioned.<sup>100</sup>

**Cholangitis** can be a life-threatening disease that demands aggressive care including generous fluid resuscitation, the timely administration of antibiotics, and early biliary decompression. Endoscopic retrograde cholangiopancreatography is the decompression procedure of choice in most instances, and when cholangitis is suspected, emergency consultation with a GI surgeon or gastroenterologist is needed. Percutaneous or surgical drainage is an alternative when endoscopic retrograde cholangiopancreatography is not feasible or is unsuccessful.

# DISPOSITION AND FOLLOW-UP

Once symptoms are adequately controlled, patients with biliary colic are typically discharged from the ED to follow up with a general surgeon. They should be instructed to return to the ED if symptoms of gallstone complications (e.g., prolonged pain, fever, jaundice) arise. Patients who present to the ED with acute cholecystitis or cholangitis require hospital admission. For suspected cholangitis, emergency consultation or transfer to an institution with treatment capabilities for endoscopic retrograde cholangiopancreatography is necessary. Patients with severe illness, including many with cholangitis, should be admitted to a critical care unit.

# SPECIAL CONSIDERATIONS

**Emphysematous cholecystitis** is characterized by gas in the gallbladder wall or lumen resulting from infection with gas-producing organisms such as *Clostridium* species, *E. coli*, and *Klebsiella* species (**Figure 79-4**). It is associated with underlying diabetes and is more common in older patients. Its association with gallstones is variable. Gas

occupying the gallbladder may be seen on plain x-rays, US, or, more reliably, IV contrast-enhanced CT. Emphysematous cholecystitis is noTable for a 15% mortality, which is much higher than the mortality rate in uncomplicated cholecystitis.<sup>101</sup> In addition to broad-spectrum antibiotics, patients with emphysematous cholecystitis require prompt surgical consultation and consideration for urgent cholecystectomy. Percutaneous cholecystostomy is an alternative therapy for severely ill patients.

# FIGURE 79-4.

Contrast-enhanced abdominal CT showing emphysematous cholecystitis with gallstones (*arrowhead*), intraluminal gallbladder gas (*arrow*), and pericholecystic inflammatory changes (*plus sign*). [Images contributed by Bart Besinger, MD, FAAEM.]



Source: J.E. Tintinalli, J.S. Stapczynski, O.J. Ma, D.M. Yealy, G.D. Meckler, D.M. Cline: Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8th Edition www.accessmedicine.com Copyright © McGraw-Hill Education. All rights reserved.

**Gallstone ileus** is a mechanical small bowel obstruction caused by an ectopic gallstone that has reached the intestinal lumen via a biliary-enteric fistula. Such a fistula may occur in the setting of inflammation secondary to cholecystitis. Gallstone ileus may be diagnosed on plain films of the abdomen or, more dependably, with CT. The classic radiographic appearance is Rigler's triad: a small bowel obstruction, pneumobilia, and an ectopic gallstone.<sup>102</sup> Operative therapy is typically indicated.

Acalculous cholecystitis represents a small minority of cholecystitis cases and most often occurs in the inpatient setting among patients with critical illness. Nevertheless, it may be occasionally encountered in the ED, particularly in immunocompromised patients. Diagnosis is challenging because the clinical presentation is variable and no test result is pathognomonic. US, IV contrast-enhanced CT, and cholescintigraphy are helpful in establishing the diagnosis, but sensitivity and specificity are less than for calculous cholecystitis. Acalculous cholecystitis runs a more fulminant course than cholecystitis associated with gallstones. Complications such as gangrene and perforation are common, and mortality is high.<sup>103</sup>

**Chronic cholecystitis** is gallbladder inflammation and scarring that occurs over time, usually secondary to intermittent cystic duct obstruction. It presents in a manner similar to biliary colic or acute cholecystitis, although symptoms and examination findings may be more subtle. Patients may report recurrent episodes of pain.

**Postcholecystectomy syndrome** refers to a heterogeneous group of disorders that present with persistent abdominal symptoms after removal of the gallbladder. In the early postcholecystectomy period, bile leak is the principal concern. Choledocholithiasis is a common cause of postcholecystectomy pain. Symptom-producing common bile duct stones may be "retained" (present at the time of surgery) or may develop postoperatively, formed primarily in the bile ducts often in the setting of bile stasis.<sup>104</sup> Postcholecystectomy syndrome may result from nonbiliary pain that was erroneously attributed to a biliary cause and therefore not remedied by cholecystectomy.

# **PRACTICE GUIDELINES**

Tenner S, Baillie J, DeWitt J, et al: American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 108: 1400, 2013.

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