The Management of Acute Cholangitis

Theodore N. Pappas, MD, and Morgan L. Cox, MD

Acute cholangitis is characterized by infection and inflammation of the biliary tract resulting from biliary obstruction. The spectrum of clinical severity can range from mild to potentially life-threatening disease accompanied by septic shock and multiorgan dysfunction. It is a morbid condition with a natural history of rapid deterioration, which makes expeditious diagnosis critical.

EPIDEMIOLOGY

Cholangitis occurs at median age of 50 to 60 years. Risk factors include smoking, increasing age, and biliary instrumentation. The risk factors for cholelithiasis apply to cholangitis, given gallstones are the most common cause. It affects males and females equally.

Acute cholangitis occurs in the setting of biliary obstruction, which leads to the stasis of bile. Up to 70% of cases are due to secondary choledocholithiasis (stones originating in the gallbladder). Other sources of obstruction include malignant and benign strictures, primary sclerosing cholangitis (PSC), and primary choledocholithiasis known as *recurrent pyogenic cholangitis.* Obstruction also can stem from iatrogenic manipulation, including anastomotic or ischemic strictures and obstructed biliary stents. Acute cholangitis is a common complication of previously placed internalized biliary drains. These drains can become kinked or clogged, leading to obstruction and subsequent infection. A complete list of acute cholangitis causes is listed in Box 1.

Given the incidence of secondary choledocholithiasis, the most common location of obstruction is "low" or distal in the common bile duct (CBD). Proximal obstruction most likely is due to malignancy or recurrent pyogenic cholangitis. The location of the obstruction is critical in determining the most appropriate therapy.

PATHOGENESIS

The body's mechanism for preventing biliary infection includes the continuous flow of bile, bile salts that are inherently bacteriostatic, and IgA. Bile is sterile at baseline. Bacteria can enter the biliary system via duodenal ascent typically prevented by the sphincter of Oddi. Hematogenous spread from the portal vein rarely occurs. Iatrogenic manipulation has the potential to introduce bacteria into the biliary tree, and stents are foreign bodies allowing bacterial colonization. Endoscopic retrograde cholangiopancreatography (ERCP) has been implicated in 0.5% to 1.7% of cases of cholangitis.

Once bacteria has entered the biliary system, it has the ability to proliferate, causing increased intrabiliary pressure. This in turn increases the permeability of the epithelium, allowing translocation of bacteria from bile to systemic circulation through lymphatic and venous channels, leading to sepsis.

Acute cholangitis is typically polymicrobial with the most common isolates being bowel flora, gram-negative in particular. The most frequently identified gram-negative bacteria are *Escherichia coli* (25% to 50% of cases), *Klebsiella* species (15% to 20% of cases), *Enterobacter* species (5% to 10% of cases), and *Pseudomonas* species. The most commonly isolated gram-positive bacteria are *Enterococcus* species (10% to 20% of cases). The contribution of anaerobes, such as *Bacteroides* and *Clostridium* species, to the pathogenesis of acute cholangitis is controversial. However, anaerobes are not uncommonly cultured in specimens obtained from elderly patients and those who have undergone biliary instrumentation.

Other rare pathogens include helminths, fungi, and viruses, including CMV and EBV. These atypical pathogens should be considered in endemic areas for parasitic infection and the immunocompromised.

PRESENTATION

In 1877 a French neurologist and professor in anatomic pathology, Jean-Martin Charcot, described the Charcot's triad of symptoms consisting of fever, right upper quadrant abdominal pain, and jaundice found in acute cholangitis. The triad is reported in up to 75% of cases but likely present in only 15% to 20%. The most common component is fever occurring in more than 80% of cases. The presentation was extended by B.M. Reynolds and E.L. Dargan in 1959 to include hypotension and altered mental status known as *Reynolds' pentad,* which is found in less than 5% of cases. The pentad suggests systemic disease and sepsis.

When a patient experiences the set of symptoms previously mentioned, an adequate differential diagnosis includes cholecystitis, Mirizzi's syndrome, liver abscess, infected choledochal cysts, and right lower lobe pneumonia or empyema. Remember to consider cholangitis in elderly and immunocompromised patients because they may not have these common symptoms. This can lead to a delay in diagnosis and poor outcome.

DECISION-MAKING ALGORITHM

In 2013 the Tokyo guidelines were updated to outline the management of acute cholangitis and cholecystitis, which has brought an evidence-based approach to the definition, diagnosis, and management of these conditions. The guidelines include clinical, laboratory, and imaging criteria. Criteria for suspected and definite diagnosis are seen in Box 2.

The workup of acute cholangitis begins with laboratory testing. Complete blood count (CBC) exhibits leukocytosis, neutrophilia, and likely a left shift. Elevated alkaline phosphatase, transaminitis, and conjugated hyperbilirubinemia will be revealed on comprehensive metabolic panel. Elevated amylase and lipase is a rare finding with cholangitis, unless the obstructing stone is located at the ampulla or has passed causing a gallstone pancreatitis. Along with basic labs,

BOX 1: Causes of Acute Cholangitis

Noniatrogenic

Benign Conditions

Choledocholithiasis
- Primary
- Secondary

Pancreatitis (chronic/acute), including pancreatic pseudocyst
Papillary stenosis
Mirizzi's syndrome
Choledochal cysts and Caroli's disease
Biliary strictures
- Ischemia
- Primary sclerosing cholangitis
- Recurrent choledocholithiasis
- Recurrent cholangitis
- Other inflammatory conditions

Malignancies

Pancreatic cancer
Cholangiocarcinoma
Duodenal/ampullary cancer
Primary tumor or metastasis to liver, gallbladder, or porta hepatis

Iatrogenic

Obstructed biliary endoprosthesis
Iatrogenic biliary stricture
- Direct surgical trauma
- Ischemia-induced stricture
- Anastomotic stricture (bilibiliary/bilioenteric anastomosis)

BOX 2: Diagnostic Criteria for Acute Cholangitis: Tokyo Guidelines

A. Clinical context and clinical manifestations
   1. History of biliary disease
   2. Fever or chills
   3. Jaundice
   4. Abdominal pain (right upper quadrant or upper abdominal)
B. Laboratory data
   1. Evidence of inflammatory response*
   2. Abnormal liver function tests†
C. Imaging findings
   1. Biliary dilation or evidence of an etiology (stricture, stone, stent, etc.)
D. Suspected diagnosis
   1. Two or more items in A
E. Definite diagnosis
   1. Charcot's triad (2 + 3 + 4)
   2. Two or more items in A + both items in B + item C

From Hirota M, Tadahiro T, Kawarada Y, et al: Tokyo guidelines for the management of acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Surg.* 2007;14:1-126, 2007.

*Abnormal white blood cell count, increased serum C-reactive protein level, and other changes indicating inflammation.

†Increased serum alkaline phosphatase, γ-glutamyl transpeptidase, aspartate aminotransferase, and alanine aminotransferase levels.

cultures should be sent from blood, bile, and removed biliary stents to allow for subsequent tapering of antibiotics.

After labs and cultures are sent, imaging studies are necessary to confirm dilated bile ducts, reveal the specific cause for obstruction, exclude differential diagnoses, and guide therapeutic interventions. A transabdominal ultrasound should be ordered as the first study in most cases with suspected biliary tree pathology, including acute cholangitis. An ultrasound is readily available, noninvasive, rapidly performed, and cost effective. Performing an ultrasound is feasible even in severe cases. It has low sensitivity for choledocholithiasis but a very high sensitivity for CBD dilation. It is possible ductal dilation will not be apparent in an early presentation.

There are several other primary imaging studies available to evaluate the biliary tree, but they do not have a role in the diagnosis of cholangitis. This includes HIDA scan, which is indicated only to identify cystic duct obstruction. Also infection in cholangitis reduces the secretion of the radiotracer used for HIDA. Endoscopic ultrasonography (EUS) has excellent sensitivity for choledocholithiasis but should not be used in the acute setting. It is helpful for further characterization of a mass as the cause of initial obstruction, but this would be performed after recovery from infection.

Computerized tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) have the ability to diagnose a dilated biliary tract. CT can identify the site of obstruction but not necessarily the cause. It provides a global evaluation of abdominal anatomy and pathology. It has a poor sensitivity for intraductal stones. MRCP has greater sensitivity for choledocholithiasis, and it is the ideal test to characterize biliary strictures. However, both of these are unnecessary tests in the initial workup of acute cholangitis because transabdominal ultrasound and clinical presentation are sufficient for diagnosis before intervention. MRCP can be a valuable modality to confirm a stone has passed when the clinical picture is not clear.

After appropriate noninvasive imaging with transabdominal ultrasound, further indicated imaging consists of modalities that are also therapeutic, including ERCP or percutaneous transhepatic cholangiography (PTC) with percutaneous biliary drain (PBD). Both modalities allow for identification of obstruction location, drainage, culture, and biopsy or brushings.

PRINCIPLES OF MANAGEMENT

Patients with cholangitis require treatment on an inpatient basis. Therapy consists of three main components, including resuscitation, antibiotics, and biliary drainage outlined in the management algorithm (Figure 1). Treatment for severe cases should be implemented in the intensive care unit (ICU). Resuscitation begins with fluid, correction of electrolyte abnormalities and coagulopathies, and externalization of pre-existing biliary drains. Antibiotics should be given immediately. Ideally, cultures are drawn before antibiotics are started, but cultures should not cause a significant delay in treatment.

Antibiotic coverage should start broad covering gram-negative and gram-positive bacteria as well as anaerobes. Antibiotics can be tapered on the basis of final culture results. The length of treatment is based on clinical response and typically concludes after 7 to 14 days.

Several appropriate antibiotic choices exist for empiric therapy. Options include fluoroquinolones (ciprofloxacin, levofloxacin) alone or with metronidazole, carbapenems (imipenem or meropenem), extended-spectrum penicillins (piperacillin), penicillin/beta-lactamase inhibitor combinations (piperacillin and tazobactam, ampicillin and sulbactam, ticarcillin and clavulanate), and ampicillin with gentamicin. Gentamicin-based regimens are avoided because of the substantial risk of aminoglycoside-induced nephrotoxicity. Second-generation and third-generation cephalosporins have excellent activity against gram-negative bacteria, although poor coverage against *Enterococcus* species, and are not recommended. Zosyn is a great choice given its broad gram-negative, gram-positive, and anaerobic coverage; penetration into bile; and ease of administration.

All patients with signs or symptoms consistent with cholangitis, no matter the severity, should be started on broad-spectrum antibiotics and undergo transabdominal ultrasound. Once the patient is stabilized, biliary drainage should be considered based on severity. Remember some patients will not stabilize until the duct is cleared of obstruction. The severity assessment described in the Tokyo

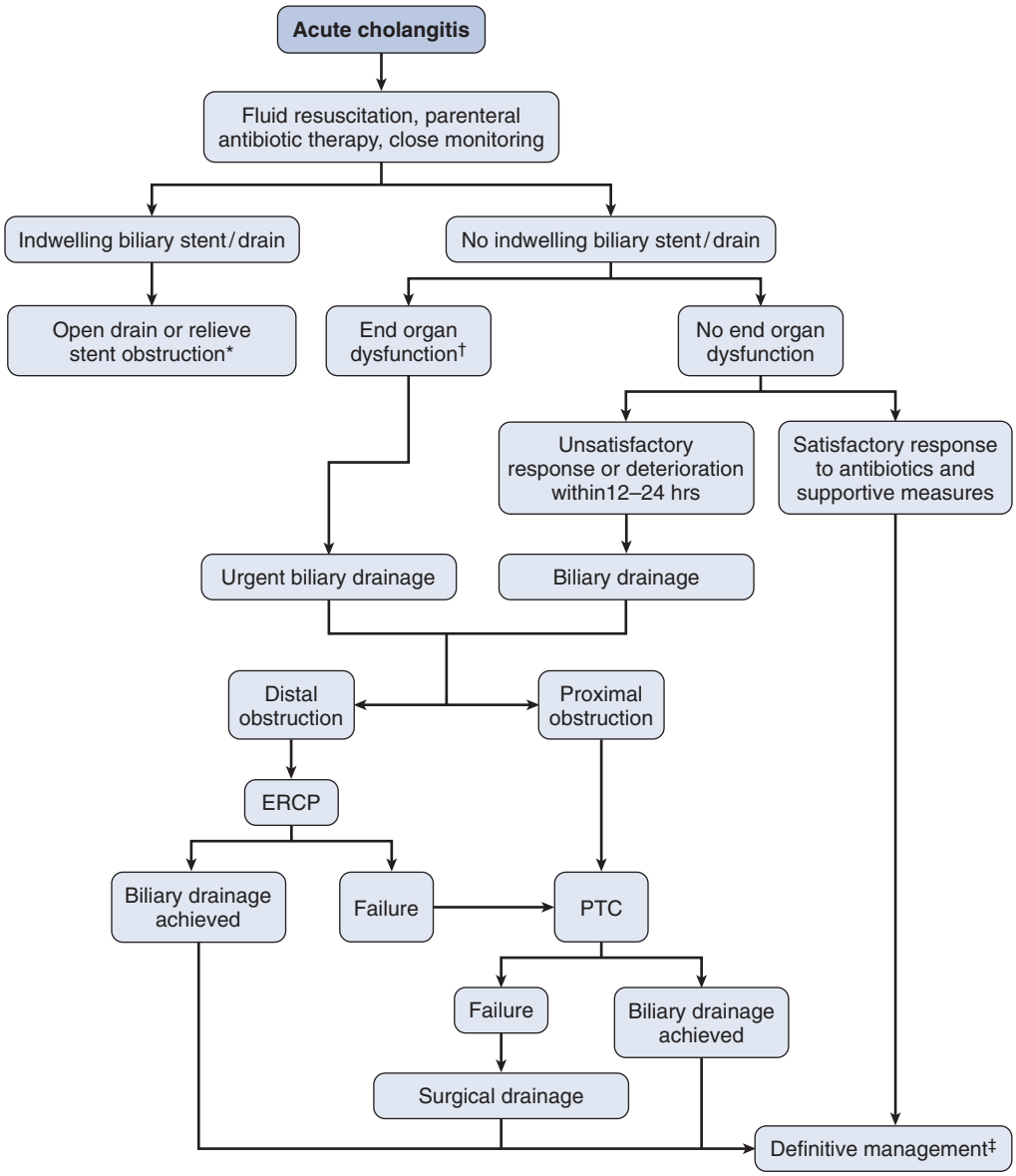

FIGURE 1 Clinical algorithm for management of acute cholangitis. *ERCP,* Endoscopic retrograde cholangiopancreatography; *PTC,* percutaneous transhepatic cholangiography.

*For changing internal stents, urgency is determined by presence or absence of end-organ dysfunction.

†For example, altered mental status or hemodynamic lability.

‡Timing of definitive management is determined by the severity of the episode of cholangitis and the comorbidities of the patient.

guidelines is shown in Box 3. Mild cases do not require drainage unless the patient has ongoing evidence of obstruction or relapse of infectious symptoms after medical therapy. Moderate and severe disease both are treated with biliary drainage but in different time frames. A moderate severity case requires early biliary drainage within 24 hours. Severe disease consistent with Reynolds' pentad or any end organ dysfunction should be drained emergently within hours.

Patients with pre-existing external biliary drains should be placed to gravity drainage as soon as the diagnosis of acute cholangitis is considered**.** Biliary drainage is not required if there is clear evidence the stone has passed. This includes obvious improvement in liver function. Typically, alkaline phosphatase and total bilirubin counts will lag behind improvement in transaminitis. If the patient is improving clinically, but lab results do not suggest the duct has cleared, an MRCP is the best study to determine duct patency and need for biliary drainage.

The optimal drainage technique depends on the site of obstruction, previous drainage attempts, available equipment, and physician expertise. The gold standard is ERCP, which is 90% to 98% effective in draining the biliary tract given the majority of obstructions are in the distal CBD. ERCP is a therapeutic and diagnostic intervention. It allows for clearing the CBD of obstruction, sphincterotomy, replacement of biliary stents, and/or dilation and stenting of strictures. Diagnostic options include biopsy and brushings. PSC is the only diagnosis in which instrumentation should be avoided if possible. Again, if the patient fails to improve, biliary drainage ultimately is indicated.

Overall, ERCP has a complication rate of 7% to 15%. Theoretically after gaining access to the biliary tree, bile should be aspirated before injecting contrast to prevent increasing already elevated biliary pressures. However even with aspiration, ERCP alone will still increase biliary pressures leading to transient bacteremia. Other complications include postprocedural pancreatitis and duodenal injury.

BOX 3: Severity Assessment Criteria for Acute Cholangitis: Tokyo Guidelines

Mild (grade I) acute cholangitis, defined as acute cholangitis that responds to initial medical treatment*

Moderate (grade II) acute cholangitis, defined as acute cholangitis that does not respond to the initial medical treatment* and is not associated with organ dysfunction

Severe (grade III) acute cholangitis, defined as acute cholangitis associated with the onset of dysfunction in at least one of the following organs/systems:

1. Cardiovascular system: Hypotension requiring dopamine >5 μg/kg per min or any dose of dobutamine
2. Nervous system: Disturbance of consciousness
3. Respiratory system: PaO_2/FiO_2 ratio <300
4. Kidney: Serum creatinine >2.0 mg/dL
5. Liver: Prothrombin International Normalized Ratio >1.5
6. Hematologic system: Platelet count <100,000/μL

From Tokyo Guidelines for the management of acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Surg.* 2007;14:1-126, 2007.

NOTE: Compromised patients (e.g., patients >75 years and patients with medical comorbidities) should be closely monitored.

*General supportive care and antibiotics.

FiO_2, Fractional concentration of inspired oxygen; *PaO_2,* partial pressure of arterial oxygen.

In some instances, it is unsafe to perform a sphincterotomy, including when the patient has an uncorrected coagulopathy. Temporizing biliary drainage can be achieved with a nasobiliary drain or internal biliary stent without a sphincterotomy.

PTC with PBD placement is a secondary drainage option after ERCP. It is successful about 90% of the time. PTC should be attempted only before ERCP if the biliary tree is inaccessible via endoscopic access. This could be due to a complete obstruction, inadvertent division of the bile duct as complication from laparoscopic cholecystectomy, Roux-en-Y reconstruction, or a periampullary duodenal diverticulum. Percutaneous access is difficult if the intrahepatic ducts are not dilated. It is again important to aspirate and obtain a culture before injecting contrast into the biliary tree. Complications of PTC include intraperitoneal hemorrhage, hemobilia, and bile peritonitis.

PTC should be considered for intrahepatic biliary dilatation without extrahepatic dilatation suggestive of proximal or hilar pathology. It allows for precise drainage of sectoral ducts if necessary. Keep in mind that cholangitis rarely develops behind tumors or strictures without previous instrumentation. Therefore only areas of the liver that were instrumented previously should be drained as treatment for cholangitis.

A percutaneous cholecystostomy tube can be unpredictable and not provide adequate drainage of the entire biliary system in the setting of acute cholangitis. However, a definitive diagnosis of cholangitis is not always obtained before intervention. Cholecystostomy tube placement is appropriate if there is concern for cholecystitis as the cause of symptoms. This requires a patent, nontortuous cystic duct to drain the CBD. The location of obstruction has to be distal to the junction of the cystic duct and common hepatic duct if any drainage is to be achieved. If a cholecystostomy tube is placed and clinical improvement does not occur, ERCP or PTC still is indicated for proper drainage of the biliary tree as treatment for cholangitis.

It is common for a patient to have a transient bacteremia after percutaneous intervention. Instrumentation of the infected biliary tract causes postprocedure SIRS that requires ICU support. Although this can produce hemodynamic instability, supportive care in the ICU is typically sufficient without further intervention unless the biliary tract is not drained adequately.

Surgery is a very rare last option associated with high morbidity and perioperative mortality up to 40%. Surgical options should be considered only after all nonoperative techniques have been exhausted. One scenario includes a patient with previous Roux-en-Y gastric bypass with inadequate drainage via PTC. Surgical treatment should be attempted only at an academic medical center with experience in complicated hepatobiliary operations.

On the rare occasion surgery is required for cholangitis, the indicated procedure is choledochotomy with limited CBD exploration and T-tube placement. This can be performed either laparoscopically or open. A laparoscopic approach requires advanced laparoscopic skills beyond those required for cholecystectomy. First, the anterior surface of the CBD is exposed. Although not necessary for treatment, a cholecystectomy is technically important for exposure to the CBD. Next, place fine (4-0) sutures laterally and medially on the CBD at 2 and 10 o'clock positions, which avoids the blood supply laterally to prevent subsequent ischemic stricture. This provides traction and exposure for a 15- to 20-mm opening to be made longitudinally on the anterior aspect of the distal CBD. Then place an endoscope directly or use a 4F biliary Fogarty catheter to try to remove one or more stones. After successful clearance of the duct, close the choledochotomy over a T-tube with interrupted 3-0 or 4-0 absorbable sutures. The tube exits the CBD at the inferior end of the choledochotomy, opening away from the liver and caudal to the sutures. Remove the back portion of the T-shaped end or cut a notch to facilitate extraction. T-tubes are customized from a 16F tube or smaller tube. The T-tube is brought out linearly through the abdominal wall to facilitate subsequent access for imaging or manipulation if needed.

The postoperative management of T-tubes depends on the clinical scenario and whether there is any suspicion of persistent stones in the duct. Clinical practice regarding removal of the T-tube varies widely, from 10 days to 6 weeks after placement. T-tubes should be imaged with T-tube cholangiography to ensure patency without obstruction before removal.

All of the following procedures should be avoided in patients with acute cholangitis: formal CBD exploration, transduodenal sphincteroplasty, and biliary enteric bypass. Interval definitive surgical treatment should be delayed until the initial episode of infection has resolved completely. Definitive treatment has no role in the acute setting of cholangitis. Cholecystectomy can be performed during the same admission if there is no end-organ dysfunction and the patient responds to treatment. Cholecystectomy is indicated during choledochotomy or if the cause of cholangitis was secondary choledocholithiasis or Mirizzi's syndrome.

More complex definitive surgery should be performed at a later date after infection has resolved. Further imaging, including CT, MRI, and EUS, can be beneficial in characterizing causative pathology other than secondary choledocholithiasis. This includes cases requiring biliary reconstruction because of benign biliary strictures or periampullary tumors.

PROGNOSIS

Most cases, up to 85%, are mild and respond to conservative management without biliary drainage. Overall mortality is 2.7% to 10%, with the poorest prognosis associated with end organ damage. Mortality rates of acute cholangitis have improved from greater than 50% in 1980 likely because of better drainage techniques.

SUGGESTED READINGS

Hirota M, Tadahiro T, Kawarada Y, et al. Tokyo guidelines for the management of acute cholangitis and cholecystitis. *J Hepatobiliary Pancreat Surg.* 2007;14:1-126.

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