

# Diagnosis and Management of Acute Cholangitis

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**Abstract** Acute cholangitis is a potentially life-threatening systemic disease resulting from a combination of infection and obstruction of the biliary tree, secondary to different underlying etiologies. Common causes of cholangitis (eg, gallstones, benign and malignant biliary strictures) are well known. However, others (eg, immunoglobulin-G subclass-4-related sclerosing cholangitis) have been described only recently, are still under evaluation, and need to gain broader attention from clinicians. The diagnosis of acute cholangitis is based on clinical presentation and laboratory data indicating systemic infection, as well as diagnostic imaging modalities revealing signs of biliary obstruction and possibly an underlying etiology. The clinical presentation varies, and initial risk stratification is important to guide further management. Early medical therapy, including fluid resuscitation and appropriate antibiotic coverage, is of major importance in all cases, followed by a biliary drainage procedure and, if possible, definitive therapy of the underlying etiology. The type and timing of biliary drainage should be based on the severity of the clinical presentation, and the availability and feasibility of drainage techniques, such as endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and open surgical drainage. ERCP plays a central role in the management of biliary obstruction in patients with acute cholangitis. Endoscopic ultrasound-guided biliary drainage recently emerged as a possible alternative to PTC for second-line therapy if ERCP fails or is not possible.

**Keywords** Cholangitis · Acute cholangitis · Biliary obstruction · Biliary stricture · Sphincterotomy · Endoscopic retrograde cholangiopancreatography · Percutaneous transhepatic cholangiography · Endoscopic ultrasound-guided biliary drainage · Magnetic resonance cholangiopancreatography · Choledocholithiasis · Biliary drainage

## Introduction

Acute cholangitis is a systemic infectious disease characterized by acute inflammation and infection in the bile ducts. Other terms (eg, suppurative cholangitis or ascending cholangitis) are also used for this condition. Acute cholangitis was first described by Charcot as “hepatic fever” in 1877 [1]. As a result, the typical signs and symptoms of acute cholangitis—intermittent fever with chills, right upper quadrant pain, and jaundice—are known as Charcot’s triad.

Acute cholangitis results from a combination of biliary obstruction and bacterial growth in bile. Its clinical presentation ranges from mild forms responding to medical treatment to severe, life-threatening forms that require intensive care and urgent biliary drainage. Advances in intensive care, antibiotic treatment regimens, and biliary drainage techniques have dramatically improved the mortality rate of more than 50% prior to the 1970s [2, 3] to less than 7% in the 1980s [4, 5]. However, the mortality rate in severe cholangitis remains significant without appropriate management. Early diagnosis based on clinical symptoms, laboratory data, and imaging findings is important for timely initiation of treatment. The type and timing of treatment should be based on the grade of severity of the disease [6•]. Universally accepted guidelines for the

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diagnosis of acute cholangitis, severity assessment, and treatment were lacking in the past. A recent attempt to establish consensus guidelines for the diagnosis and management of acute cholangitis resulted in the publication of the “Tokyo Guidelines” [6•].

## Etiology and Pathogenesis

Acute cholangitis results from a combination of biliary infection and partial or complete obstruction of the biliary system. Although biliary infection alone does not inevitably lead to clinical cholangitis, progressive biliary obstruction causes an increase of the intraductal pressure, which eventually leads to cholangiovenous and cholangiolymphatic reflux [7]. Translocation of bacteria into the bloodstream results in septicemia, an often fatal complication of acute cholangitis.

Biliary obstruction can result from etiologies such as choledocholithiasis, benign and malignant stenoses, biliary stent obstruction, strictured biliary-enteric anastomoses, and parasitic colonization of the bile duct. Table 1 summarizes

the most important causes of biliary obstruction resulting in acute cholangitis. Most are well-known. However, other conditions predisposing to acute cholangitis, such as immunoglobulin-G subclass-4 (IgG-4)-related sclerosing cholangitis have been described only recently [8•].

Under physiologic conditions, several mechanisms are involved in maintaining the sterility of bile. Bile salts have bacteriostatic properties [9, 10]. The sphincter of Oddi controls the direction of bile flow and serves as a barrier between the sterile bile duct and the nonsterile duodenum. Infection results from bacterial colonization of the biliary system. Gram-negative bacteria, such as *Escherichia coli*, *Klebsiella* spp, and gram-positive enterococci, are commonly found in biliary cultures. Other bacteria, such as *Enterobacter*, *Proteus*, *Pseudomonas*, and *Bacteroides* spp, are less frequently isolated from bile [11–15]. However, colonization of a biliary system by bacteria in the absence of obstruction (ie, infected, but not obstructed) does not usually progress to clinical cholangitis [16]. On the other hand, it is not always obvious how bacteria enter an obstructed biliary system, unless interventions such as surgery, endoscopic retrograde cholangiopancreatography

**Table 1** Etiology of biliary obstruction in acute cholangitis

Etiology	Important risk factors
Gallstones	With origin in gallbladder Primary bile duct stones
Malignant biliary strictures	Common risk factors for gallstones Biliary stasis, strictures, hemolysis, parasites
Benign biliary strictures	Older age, primary sclerosing cholangitis (for cholangiocarcinoma)
Parasitic	Pancreatic cancer Cholangiocarcinoma Gallbladder cancer Ampullary tumor Duodenal malignancy Metastasis to liver or portohepatic lymph nodes
Other	Complicated cholecystectomy, liver transplantation
	Autoimmune pancreatitis Mirizzi syndrome
	Endemic areas, immigrants, travelers
	Older age Coagulopathy, instrumentation of bile duct Obstruction by food after bilioenteric anastomosis
	Sump syndrome
	Biliary stent obstruction

(ERCP), or percutaneous transhepatic cholangiography (PTC) have been performed, resulting in loss of the physiologic barrier between the bile duct and intestine (eg, biliary sphincterotomy or stent placement, surgical sphincteroplasty, bilio-enteric anastomosis). Patients with incomplete biliary obstruction have been shown to have a higher positive bile culture rate than those with complete obstruction [17]. Thus, bile infection is unusual in jaundice due to malignant biliary obstruction (eg, pancreatic cancer, ampullary neoplasm, and cholangiocarcinoma) unless diagnostic or therapeutic interventions of the biliary system have been performed. The latter is an issue that will likely increase in importance with the spread of advanced endoscopic techniques, such as endoscopic ultrasound with fine-needle aspiration and cholangioscopy.

The long-term effects of ablating the sphincter of Oddi are still poorly understood. However, exposing the biliary tree to duodenal contents may lead to long-term complications including stone formation, cholecystitis, and sphincterotomy site stenosis (with recurring cholangitis) [18]. No data are available to quantify the potential risk for future acute cholangitis after biliary sphincterotomy.

## Diagnosis

Standard diagnostic criteria for acute cholangitis have been lacking, and various definitions for the disease have been used in the past. Although some authors have suggested basing the diagnosis mostly on clinical signs, such as Charcot's triad (fever, jaundice, abdominal pain) or the pentad of Reynolds (severe form in septic shock, adding hypotension and confusion to Charcot's triad), others have relied on diagnostic radiologic or endoscopic tests revealing pus in the biliary system and/or biliary obstruction. The "Tokyo Guidelines" recently recommended a more systematic approach, using a combination of clinical features, laboratory data, and imaging findings to diagnose acute cholangitis (Table 2) [6•].

### Clinical Presentation

Fever and abdominal pain have been reported to be the most frequent symptoms in acute cholangitis, with an incidence of 80% or more in most reports. Jaundice was less frequently seen (reported in 60%–70% of cases), and severe forms with shock and altered mental status are rare (3.5%–7.7% of reported cases) [19–22]. Thus, the typical clinical picture of Charcot's triad is not always present in patients with acute cholangitis, and further diagnostic testing may be required before the diagnosis can be established. This specifically applies to acute cholangitis in elderly patients, who often present atypically, leading to

**Table 2** Diagnostic criteria for acute cholangitis<sup>a</sup>

A. Clinical context and manifestations	1. History of biliary disease 2. Fever and/or chills 3. Jaundice 4. Abdominal pain
B. Laboratory data	5. Evidence of inflammatory response (abnormal white blood cell count, elevated C-reactive protein) 6. Abnormal liver function tests
C. Imaging findings	7. Biliary dilatation, or evidence of an etiology
Suspected diagnosis	Two or more items in A
Definite diagnosis	1) Charcot's triad (2+3+4) 2) Two or more items in A+both items in B and C

<sup>a</sup> The "Tokyo guidelines" [6•]

a delay in diagnosis and treatment [23]. The severity of acute cholangitis varies significantly, from mild, self-limiting forms to severe, life-threatening forms with septic shock. Stratification into three severity grades has been proposed, based on two different criteria: 1) "response to initial medical management," indicating mild (grade I) severity and 2) "onset of organ dysfunction," indicating severe (grade III) severity. The absence of both criteria indicates moderate (grade II) severity [6•].

### Laboratory Data

Laboratory data in acute cholangitis typically indicate inflammation (ie, leukocytosis and/or elevated C-reactive protein level) and cholestasis (ie, hyperbilirubinemia and abnormal liver function tests, with predominant elevation of aspartate alanine aminotransferase [ALT],  $\gamma$ -glutamyl transpeptidase [GGT], and alkaline phosphatase [ALP]). GGT and ALP have been shown to be elevated in more than 90% of patients with acute cholangitis [24], and total bilirubin levels are proportional to the severity of obstruction and length of illness. The highest bilirubin levels are found in complete biliary obstruction due to malignancy [25], whereas levels are typically less than 15 mg/dL in intermittent forms of obstruction, as seen in choledocholithiasis. Profound elevation of serum transaminase levels (eg, > 2000 IU/L) mimicking acute hepatitis is rare, but has been described [26].

### Diagnostic Imaging

Imaging modalities such as transabdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), endoscopic

retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiography (PTC) are frequently used when acute cholangitis is suspected. Because these tests do not directly identify bile infection (unless bile is aspirated for testing during ERCP or PTC), their main role is the detection of biliary obstruction and its etiology, such as pancreaticobiliary malignancy or cholelithiasis. The sequence in which these tests are used is not standardized, and varies widely depending on the clinical presentation, availability of procedures, expertise, and physician preference. In patients presenting with mild symptoms, less invasive tests (eg, US, CT, MRI/MRCP, and EUS) are often used to establish the diagnosis and guide further management. The recent literature has emphasized that more invasive modalities should now be reserved for patients with an indication for therapeutic intervention [26]. However, in severely ill patients with biliary sepsis, urgent intervention is indicated, either using ERCP or a second-line procedure (eg, PTC or EUS-guided drainage), if ERCP

is unavailable, has previously failed, or is likely to fail because of local anatomic issues. A combination of EUS and ERCP is now more frequently used if the indication for immediate biliary decompression or other endoscopic interventions is uncertain, or when pancreaticobiliary malignancy is suspected, and tissue diagnosis or tumor staging is desired at the same time [27]. Table 3 summarizes advantages and disadvantages of the different imaging tests. A suggested diagnostic and therapeutic approach is presented in Fig. 1.

### Therapeutic Management

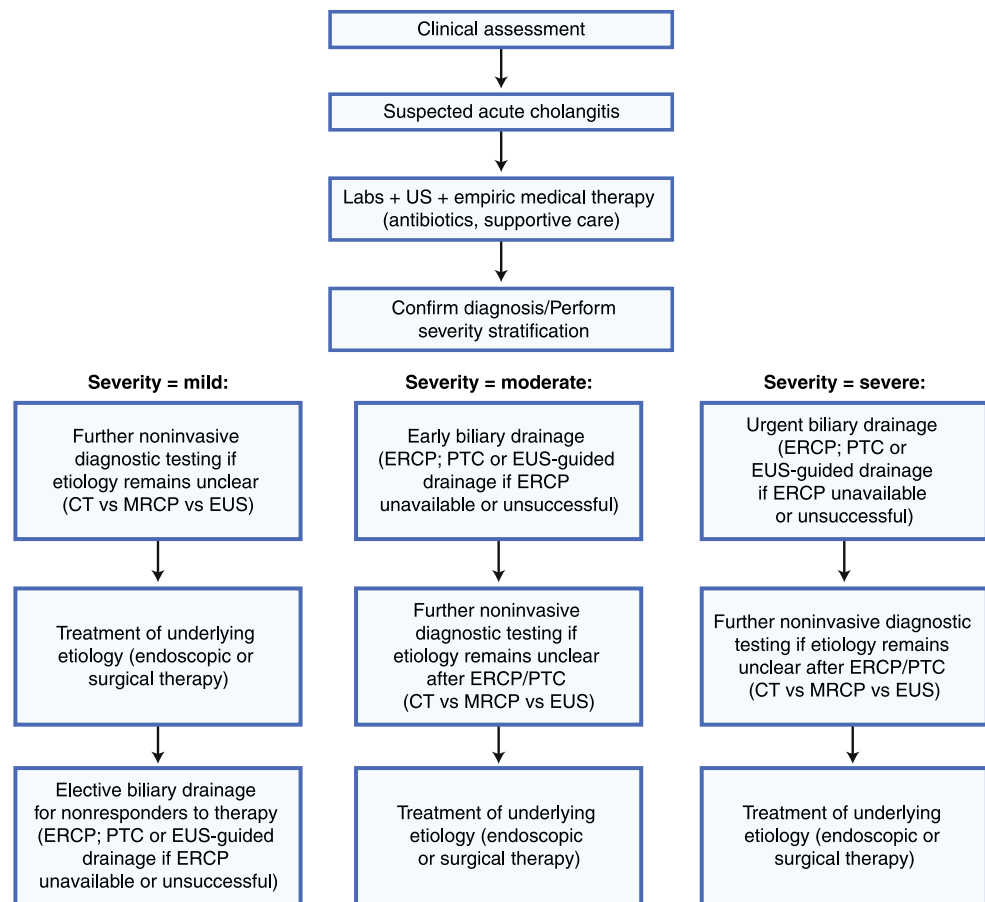
The therapy of acute cholangitis is directed toward the two main etiologic components of the disease—biliary infection and obstruction—and therefore comprises systemic antibiotic therapy and biliary drainage procedures, with appropriate supportive care.

**Table 3** Imaging modalities in suspected acute cholangitis

	Advantages	Disadvantages
Transabdominal ultrasound	Readily available, noninvasive, inexpensive	Low sensitivity for choledocholithiasis (25%–63%) and etiology of biliary obstruction
	High sensitivity for detection of gallbladder stones and biliary dilation	Operator dependent
CT	Noninvasive	No therapeutic capability or tissue acquisition in suspected malignancy
	Higher sensitivity for detecting location of obstruction and underlying etiology, including neoplasms	Radiation risk
		Contrast media may be required (nephrotoxicity, allergies)
MRCP	Noninvasive, no radiation risk, safe in pregnancy	Low sensitivity only for cholelithiasis
	High sensitivity for biliary obstruction and detection of bile duct stones >6 mm	No therapeutic capability
	Can be combined with abdominal MRI and thereby adopt advantages of CT at same time	No tissue acquisition in suspected malignancy
EUS	High sensitivity for large and small bile duct stones and pancreaticobiliary malignancy	Not possible in patients with ferromagnetic implants or severe claustrophobia
	Can establish tissue diagnosis	Limited availability
	Can be combined with ERCP	More invasive
ERCP	Provides biliary drainage	Operator dependent
	High sensitivity for location of biliary obstruction	Invasive, potential for procedure-related complications
	Tissue acquisition in suspected malignancy possible	Problematic if complete biliary drainage fails
PTC	Provides biliary drainage	Operator dependent
	High sensitivity for location of biliary obstruction	Invasive, potential for procedure-related complications
		Limited in case of coagulopathy
		Higher complication rate and more patient discomfort compared to ERCP
		Operator dependent

CT computed tomography, ERCP endoscopic retrograde cholangiopancreatography, EUS endoscopic ultrasound, MRCP magnetic resonance cholangiopancreatography, MRI magnetic resonance imaging, PTC percutaneous transhepatic cholangiography

**Fig. 1** Algorithm for management of patients with suspected acute cholangitis. *CT* computed tomography, *ERCP* endoscopic retrograde cholangiopancreatography, *EUS* endoscopic ultrasound, *MRCP* magnetic resonance cholangiopancreatography, *PTC* percutaneous transhepatic cholangiography, *US* ultrasound



## Antibiotic Therapy

Antibiotic agents should be given empirically to all patients with suspected acute cholangitis as early as possible. Blood and bile cultures should be performed at the earliest opportunity. The selection of the agent should be based on potentially infecting bacteria, the severity of the disease, and presence or absence of comorbidities such as hepatic or renal failure, patient allergies, local susceptibility patterns, and past history of antibiotic use by the patient [6•]. Biliary penetration of antibiotic agents should be considered as well, but is less important than efficacy against suspected bacteria. The clinical context also must be appreciated, because it has been shown that anaerobic bacteria are found more frequently in severe cholangitis than in mild cases [28–30]. Similarly, hospital-acquired cholangitis is often caused by multiple and/or resistant organisms, such as *Pseudomonas* spp, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococci, whereas the infection in community-acquired cases is mostly caused by a single species of intestinal microorganism, such as *E. coli*, *Klebsiella*, and *Enterococcus* spp. The type and duration of antibiotic therapy should be based on the severity of the

disease. For mild cases, a 2- to 3-day course of monotherapy with a penicillin/ $\beta$ -lactamase inhibitor combination (ie, piperacillin/tazobactam or ampicillin/sulbactam) is usually sufficient. Moderate and severe disease should be treated for a minimum of 5 to 7 days with broad-spectrum agents, such as third- and fourth-generation cephalosporins or penicillin/ $\beta$ -lactamase inhibitors. If the drug of first choice is ineffective, fluoroquinolones and carbapenems are alternatives [6•]. The duration of treatment in all cases ultimately depends on the response to treatment. If results of biliary or blood cultures become available, empirically initiated broader antibiotic regimens should be changed to narrower-spectrum agents.

## Biliary Drainage

The presence of biliary obstruction acts as a persistent source of infection in acute cholangitis. In addition, obstruction may impair the biliary penetration of antibiotics [31, 32] and cause other symptoms (eg, painful jaundice). The mortality of acute cholangitis used to be very high (up to 100%) with conservative therapy before biliary drainage procedures were readily available [33, 34], which empha-

sizes the utmost importance of biliary drainage in the treatment of acute cholangitis.

Biliary drainage can be achieved by ERCP, PTC, EUS-guided drainage, or open surgical drainage. Open drainage is more invasive and has obvious disadvantages compared to endoscopic and percutaneous drains [6•]. Therefore, ERCP and PTC have become the most commonly performed methods for biliary drainage. Randomized studies comparing ERCP and PTC are lacking. However, given the potential for serious complications of PTC (eg, intraperitoneal hemorrhage, biliary peritonitis) [35, 36], the longer hospitalization after PTC [37], and the obvious discomfort for the patient associated with a percutaneous catheter, endoscopic drainage is the procedure of choice whenever available. Different options for endoscopic drainage during ERCP include biliary stent placement and nasobiliary drain placement, with or without biliary sphincterotomy. No significant difference in efficacy has been shown between stents and nasobiliary drains. However, patient discomfort appears to be higher with nasobiliary drains [38, 39]. Biliary drainage can be successfully achieved by stent placement alone without sphincterotomy [40]; biliary sphincterotomy is associated with increased risk of complications, including bleeding, pancreatitis, and perforation. Therefore, the decision to perform biliary sphincterotomy should be individualized according to the patient's condition and the etiology of biliary obstruction. In emergency ERCP procedures on critically ill patients, time-consuming therapeutic interventions (eg, attempts at lithotripsy of large stones) should be postponed until a second session (typically a few days later), when the patient is more stable.

If ERCP fails or is not available, PTC most frequently serves as the second-line alternative for biliary drainage. EUS-guided biliary drainage recently was proved a feasible alternative to percutaneous transhepatic biliary drainage or surgery in centers with specific expertise when ERCP fails [41•]. However, the widespread adoption of EUS-guided biliary decompression has been delayed by the lack of appropriate tools (accessories) to do the job, and the need for well-done studies comparing this approach with existing options. Open surgical drainage should be reserved for patients in whom ERCP, PTC, or EUS-guided drainage are unsuccessful or contraindicated.

There are no evidence-based recommendations regarding the timing of biliary drainage. However, the “Tokyo guidelines” suggest, based on expert opinion, that drainage should be performed as soon as possible in patients with moderate and severe cases [6•]. For mild cases in patients with a favorable response to medical therapy, it is recommended that biliary drainage be performed within 24 to 48 h [26].

## Conclusions

Acute cholangitis is a potentially life-threatening systemic disease resulting from a combination of infection and obstruction of the biliary tree secondary to different underlying etiologies. The diagnosis is based on the patient's clinical presentation and laboratory data indicating systemic infection, as well as diagnostic imaging modalities revealing signs of biliary obstruction and often an underlying etiology. The clinical presentation varies, and initial risk stratification is important to guide further management. Early medical therapy, including appropriate antibiotic coverage, is of major importance in all cases, followed by a biliary drainage procedure and, if possible, definitive therapy of the underlying pathology. The type and timing of biliary drainage should be based on the severity of the clinical presentation and the availability and feasibility of drainage techniques. ERCP plays a central role in the management of biliary obstruction in patients with acute cholangitis. EUS-guided biliary drainage recently emerged as a possible alternative to PTC for second-line therapy if ERCP fails or is technically impractical or impossible.

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