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Review

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Acute cholangitis: a state-of-the-art review

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Abstract

Acute cholangitis is a potentially life-threatening bacterial infection of the intra and/or extrahepatic bile ducts. It remains the second and third cause of community-acquired and hospital-acquired bacteremia, respectively, and is associated with mortality rates of up to 15%, despite advances in broad-spectrum antimicrobial therapy and improved access to emergency biliary tract decompression procedures. Even though not much has changed in recent years in terms of diagnosis or treatment, new data have emerged regarding multidrug-resistant bacteria that serve as etiologic agents of cholangitis. Moreover, different approaches in antibiotic regimes depending on severity grading and bile sample cultures as well as novel minimally invasive endoscopic procedures that can help when consecrated treatments such as endoscopic retrograde cholangiopancreatography (ERCP) fail, cannot be performed, or are unavailable have been proposed. This state-of-the-art review aims to offer a complete and updated assessment of the epidemiology, novel diagnostic and therapeutic methods, complications, and prognostic variables of acute cholangitis. The authors will review the prognostic implications of unusual complications, the relevance of regular bile samples and antibiograms, and their new role in guiding antibiotic therapy and limiting antibiotic resistance to present an organized and comprehensive approach to the care of acute cholangitis.

Keywords: acute cholangitis, antibiogram, antibiotic resistance, bile sample cultures, gallstone disease

Introduction

Acute cholangitis (AC), a severe inflammatory disease of the biliary duct, is a potentially fatal medical emergency. It is caused by biliary tract blockage, usually biliary gallstones, and is associated with various pathophysiological causes[1]. The pathophysiology and treatment options of AC have received in the past years substantial attention from the medical community, requiring an up-to-date and comprehensive assessment. Two major underlying processes can explain acute cholangitis: biliary tract obstruction, which affects normal bile flow and generates increased pressure within the ducts, and bacterial growth[2].

Symptoms vary in degree and intensity. The most frequently encountered symptom is severe pain in the right upper quadrant (RUQ) of the abdomen, which may radiate to the back or to the right shoulder[3]. Patients may struggle to feel comfortable and adopt a fetal posture to relieve pain. Due to the urgent nature of AC, diagnosis and therapy require careful examination and adherence to established international recommendations, such as the Tokyo Criteria[4]. Treatment typically involves a combination of antibiotics to treat the infection and procedures to relieve biliary blockage, such as endoscopic biliary drainage.

This state-of-the-art review aimed to offer a complete and updated assessment of the etiology, pathophysiology, novel diagnosis, therapeutic methods, complications, and prognostic

HIGHLIGHTS

- Acute cholangitis remains a potentially life-threatening condition.
- Its management is frequently complicated by the emergence of antimicrobial resistance.
- Herein, we provide a state-of-the-art review of the current knowledge regarding acute cholangitis, with a particular focus on pathogen-driven antimicrobial treatment.

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variables associated with acute cholangitis. We will discuss the latest treatment options, including antibiotics and endoscopic biliary drainage. Other topics included the prognosis of complications, the relevance of regular bile samples, and their new role in better choosing guided antibiotic therapy and limiting antibiotic resistance.

Pathophysiology of gallstone disease

Risk factors

The traditional risk factors for gallstone disease are commonly known as the four "F's": being female, fertile, overweight (fat), and around the age of forty. These factors have been extensively studied for many years and are well-established. However, recent research suggests that being fair-skinned could also be added to the list (the fifth "F")[5]. Cholesterol and pigment gallstone formation are influenced by a complex combination of genetic, environmental, and metabolic factors[5,6]. In Western populations, cholesterol gallstones account for 90–95% of all gallstones. Black pigment stones are the predominant type in patients with chronic hemolytic disorders or cirrhosis, although most patients with black pigment stones do not have these conditions. Cholesterol and black pigment stones are usually formed in the gallbladder, whereas brown pigment stones primarily develop in the main bile duct[7,8].

Age, sex, and ethnicity

Gallstones are more prevalent in individuals over the age of 40, with the likelihood increasing tenfold after that age. The occurrence of cholesterol gallstones also increases steadily with age in both sexes, reaching approximately 50% among women aged more than 70 years old. Additionally, older adults are at a higher risk of complications and surgical mortality. This can be attributed to two factors: a decrease in the activity of cholesterol 7-α-hydroxylase, the enzyme responsible for bile acid synthesis, and an increase in the biliary secretion and intestinal absorption of cholesterol. Furthermore, there is a decrease in hepatic synthesis and secretion of bile salts as well as reduced gallbladder motility. Epidemiological research has consistently shown that women are twice as likely to develop cholesterol gallstones at all ages as men. This disparity begins during puberty and persists throughout the childbearing years owing to the influence of female sex hormones and differences in cholesterol metabolism by the liver in response to estrogen[5,9–12].

Diet

A "Western-style" diet, which usually consists of high intakes of refined carbohydrates, saturated fatty acids, cholesterol, meat, and salt has been identified as one of the strongest determinants for developing cholesterol gallstones, regardless the age or sex. Large prospective epidemiological studies have reported a strong positive correlation between calorie consumption or chronic hypernutrition and gallstone formation. The mechanisms involved are usually increased cholesterol synthesis and secretion and impaired intestinal and gallbladder motility. In contrast, diets rich in unsaturated fats, fish oil, fresh fruits and vegetables, and nuts (rich sources of dietary fiber) have been found to reduce the risk of cholesterol gallstones. Data on coffee and tea intake are scarce and controversial. Currently, there is no indication for ursodeoxycholic acid (UDCA) of statins in the general population for the primary prevention of gallstone disease. The same rule applies to ascorbic acid and ezetimibe, a selective cholesterol absorption inhibitor acting on the intestinal *Niemann–Pick C1-like 1 protein*, where data is still incomplete, inconsistent, and needs further research[5,9].

Lipid profile

Numerous studies have been conducted to elucidate the association between lipid levels and the occurrence of gallstones. However, the findings remain contentious, with some studies suggesting a positive link between elevated cholesterol levels and the development of cholesterol gallstones, whereas others have reported an inverse correlation. Similar contradictions exist regarding high-density lipoprotein (HDLc) cholesterol and triglyceride levels. Although some studies present conflicting data, epidemiological investigations have demonstrated that plasma HDLc levels are inversely associated with the prevalence of cholesterol gallstones. Conversely, hypertriglyceridemia was positively associated with an increased gallstone prevalence[5,13].

Obesity and rapid weight loss

Multiple prospective cohort studies have demonstrated that obesity, expressed by the BMI, is an important risk factor for gallstone formation, especially in women, where a BMI greater than or equal to 30 kg/m^2 is responsible for a two-fold increased risk and one greater than or equal to 45 kg/m^2 for a seven-fold increased risk of having symptomatic gallstones. Moreover, central adiposity, relative to upper- and lower-extremity adiposity, plays an important role. The mechanisms by which this occurs are various and not yet completely understood, including increased mucin and calcium content in the bile, altered gallbladder emptying, supersaturation of bile with cholesterol, and promotion of stone aggregation. Weight loss was linked to a reduction in gallstone incidence unless it was sudden ($>$ 1.5 kg/week) or exaggerated ($>$ 25% of body weight). As many as 50% of obese patients who undergo bariatric surgery will eventually develop gallstones after a 6-month follow-up period, and ~40% of these will experience symptoms related to gallstones in the same period. In this category of patients, UDCA at a median dose of 600 mg/day was shown to reduce the prevalence of gallstones in obese patients on a very low-calorie diet. Prophylactic cholecystectomy is not routinely recommended and is usually reserved for patients with symptoms related to gallstones or complications (e.g. chronic cholecystitis)[13,14].

Total parenteral nutrition (TPN)

Sludge or even small gallstones can appear as early as 3 weeks after TPN, leading to a prevalence of ~45% after 3–4 months of prolonged fasting. Usually, after restoration of the oral diet, both sludge and small gallstones disappear. In most cases, patients requiring TPN also have a jeopardized clinical status, which makes them unsuitable for cholecystectomy; therefore, prophylactic treatment is taken into consideration. While stimulation of gallbladder motility with cholecystokinin (CCK) octapeptide has proven to be effective, safe, and cost-effective, literature data are scarce and contradictory. Furthermore, there is no indication for prophylactic treatment with UDCA in patients with long-term TPN[14,15].

Systemic conditions

Diabetes mellitus (DM): Because DM is highly associated with hypertriglyceridemia, obesity, and other risk factors for gallstone disease, DM has long been considered an independent risk factor for developing gallstones. This statement is difficult to demonstrate, but it has been shown in multiple case-control studies that DM is more prevalent in patients with gallbladder disease. Mechanisms are not well understood but are thought to be common with other common DM complications, such as increased hepatic secretion of biliary cholesterol and impaired gallbladder motility due to autonomic neuropathy[5,14,16].

Diseases of the ileum: Most bile salt absorption takes place in the terminal ileum through a series of specific bile salt transporters, such as the ileal apical sodium-dependent bile acid transporter. Therefore, in patients with intestinal resection or damaged ileal mucosa, as in the case of patients with Crohn's disease, bile salt absorption is impaired, resulting in excessive bile salt excretion in feces, an increased concentration of bilirubin conjugates, unconjugated bilirubin, and total calcium in the gallbladder bile, and a diminished bile salt pool size. This is associated with an increased risk of pigment gallstone disease, with a prevalence of greater than 26% in patients with Crohn's disease[5,17].

Cirrhosis: In general, cirrhosis promotes the formation of pigment gallstones through impaired synthesis and transport of bile salts, postprandial gallbladder hypomotility, and high estrogen levels. This translates to a prevalence of almost 30%, which increases with the severity of cirrhosis and with the patient's BMI[14].

Spinal cord injuries: Gallbladder hypomotility and decreased intestinal peristalsis alter the hepatic-entero-hepatic circulation and normal biliary secretion, which ultimately leads to a prevalence of 30% of gallstone disease among these patients[5,14].

Celiac disease: Damage to the duodenal mucosa found in patients with celiac disease (autoimmune enteropathy caused by intolerance to dietary gluten in genetically predisposed individuals) causes impaired CCK secretion and, therefore, an inadequate emptying response of the gallbladder after a fatty meal. Thus, celiac disease is a risk factor for the development of cholesterol gallstones. The risk can be greatly reduced by early diagnosis and therapy following a strict gluten-free diet[5,9].

Pregnancy: Pregnancy is a risk factor for gallbladder disease due to increased levels of estrogen and progesterone, which in turn alters the hepatic cholesterol secretion, cholesterol bile concentration, and gallbladder motility. The risk increases with the frequency and number of pregnancies and is usually the highest in the third semester[9,14].

Genetic susceptibility

Family history is often positive in many of the patients with gallstone disease, as shown by a study that demonstrated that in the case of patients with gallstone disease, ~15% of their first-degree relatives also had cholelithiasis visualized on abdominal ultrasound (US). Therefore, it has been suggested that genetic factors play an important role in the development of gallstones. Among the gene mutations most frequently involved are *ATP binding cassette subfamily B member 4* (ABCB4/MDR3), a rare mutation also referred to as low phospholipid-associated cholelithiasis, described below), *ATP binding cassette subfamily G member 8* (ABCG8), and *UDP Glucuronosyltransferase Family 1 Member A1* (UGT1A1)[13,18,19].

Drugs

Long-term therapy with somatostatin or analogs: Approximately 25% of the patients requiring long-term use of octreotide or other various somatostatin analogs (used for acromegaly or neuroendocrine neoplasms treatment) develop asymptomatic gallstone disease or sludge during the first 18 months of therapy. Mechanisms include prolonged intestinal peristalsis, reduced cholecystokinin release, impaired gallbladder emptying, and lithogenic changes in the bile composition. Concomitant prophylactic treatment with UDCA should be considered[13,14].

Ceftriaxone: As 40% of ceftriaxone, a third-generation cephalosporin, is secreted unmetabolized in bile, it reaches up to 200 times the serum concentration. For this reason, ceftriaxone can exceed its saturation level in the bile and form insoluble ceftriaxone-calcium precipitates. This becomes problematic in patients from the intensive care unit who are also fed TPN[9,13].

Hormone replacement therapy: Estrogen-replacing therapy is broadly used in women, especially for controlling menopausal symptoms and preventing cardiovascular disease, osteoporosis, and dementia, as well as in men for the treatment of prostatic neoplasia. Chronic estrogen therapy has been associated with an increased risk of symptomatic gallstone disease, particularly in postmenopausal women. The mechanism involves stimulation of the hepatic estrogen receptor α, which induces hepatic secretion of newly synthesized cholesterol and supersaturation of bile. However, prophylactic treatment with UDCA has not yet been taken into consideration[5,14].

Lipid-lowering drugs: Fibrates inhibit *cholesterol 7-alpha-hydroxylase*, an enzyme responsible for limiting bile acid synthesis. This results in cholesterol-supersaturated bile and gallstone precipitation, making chronic treatment with clofibrate or fenofibrate an independent risk factor for gallstone disease. Cholestyramine and nicotinic acid are other lipid-lowering agents, but there are no available studies regarding their role in gallstone pathophysiology[13,14].

Protective factors

Physical activity

Physical activity appears to be a protective factor against gallstone formation, while, at the same time, lack of regular activity has the opposite effect. Various large prospective cohort studies have shown that 30 min of endurance-type exercise (e.g. running or cycling) five times per week can lower the incidence of symptomatic gallstones in men by 34% and that 2–3 h of recreational exercise per week can reduce the risk of cholecystectomy by ~20%. This may be partially due to increased bile salt excretion, enhanced gut motility, increased HDLc, and improved plasma triglyceride levels and insulin release[5,9].

Coffee

Two large observational prospective studies have shown that consuming 2–3 cups of regular coffee per day is associated with a 40% risk reduction for developing symptomatic gallstones. No benefits have been demonstrated for drinking decaffeinated coffee[9,13].

Table 1 summarizes the main risk factors and protective factors for gallstone disease.

Table 1

Main risk factors for and protective factors against gallstone disease.

Risk factors	Age, sex, and ethnicity	• Incidence of GS disease increases ten folds over the age of 40 • Women are twice as likely to develop cholesterol GS	
	Diet	• A "Western-style" diet represents one of the strongest determinants for developing Chl-GS • Strong positive correlation with caloric consumption or chronic hypernutrition • Diets rich in unsaturated fats, fish oil, fresh fruits and vegetables, and nuts reduce the risk of Chl-GS	
	Lipid profile	• Plasma HDLc levels are inversely associated with the prevalence of Chl-GS • Hypertriglyceridemia was positively associated with an increased GS prevalence	
	Obesity and rapid weight loss	• a BMI $\geq$ 30 kg/m^2 is responsible for a two-fold increased risk and one $\geq$ 45 kg/m^2 for a seven-fold increased risk of having symptomatic GS • Weight loss was linked to a reduction in GS incidence unless it was sudden ($>$ 1.5 kg/week) or exaggerated ($>$ 25%) • UDCA at a median dose of 600 mg/day was shown to reduce the prevalence of GS in obese patients on a very low-calorie diet	
	TPN	• Prevalence of ~45% after 3–4 months • There is no indication for prophylactic treatment with UDCA	
	Systemic conditions	T2DM	Increased hepatic secretion of biliary Chl, impaired GB motility due to autonomic neuropathy and association with hypertriglyceridemia and obesity
		Diseases of the ileum	Impaired BS absorption, excessive BS excretion in feces, an increased concentration of BLB conjugates, uBLB, and total Ca^+ in the GB bile, and a diminished BS pool size
		Cirrhosis	Impaired synthesis and transport of BS, postprandial GB hypomotility, and high estrogen levels
		Spinal cord injuries	GB hypomotility and decreased intestinal peristalsis
		Celiac disease	Impaired CCK secretion and, therefore, inadequate emptying response of the GB
		Pregnancy	Increased levels of estrogen and progesterone, altered the hepatic Chl secretion, Chl bile concentration, and GB motility
	Genetic susceptibility	• Seen in up to 15% of the cases. • Among the gene mutations most frequently involved are ABCB4/MDR3, ABCG8, and UGT1A1	
	Drugs	Long-term therapy with SST or analogs	• Seen in up to 25% of the patients during the first 18 months of therapy. • Mechanisms include prolonged intestinal peristalsis, reduced CCK release, impaired gallbladder emptying, and lithogenic changes in the bile composition. • Concomitant prophylactic treatment with UDCA should be considered
		Ceftriaxone	Secreted unmetabolized in bile, it forms insoluble ceftriaxone-Ca^+ precipitates.
		Hormone replacement therapy	Stimulation of the hepatic estrogen receptor α induces hepatic secretion of newly synthesized Chl. and supersaturation of bile.
		Lipid-Lowering Drugs	Fibrates inhibit *cholesterol 7-alpha-hydroxylase*, an enzyme responsible for limiting bile acid synthesis which results in Chl-supersaturated bile and GS precipitation.
Protective factors	Physical Activity	30 min of endurance-type exercise five times per week can lower the incidence of symptomatic GS in men by 34%	
	Coffee	consuming 2–3 cups of regular coffee/day is associated with a 40% risk reduction for developing symptomatic GS	

ABCB4/MDR3, ATP binding cassette subfamily B member 4; ABCG8, ATP binding cassette subfamily G member 8; BLB, bilirubin; BS, bile salts; CCK, cholecystokinin; Chl, cholesterol; HDLc, high-density lipoprotein cholesterol; GB, gallbladder; GS, gallstone; SST, somatostatin; T2DM, type-2 diabetes mellitus; TPN, total parenteral nutrition; uBLB, unconjugated BLB; UDCA, ursodeoxycholic acid; UGT1A1, UDP glucuronosyltransferase family 1 member A1.

Types of gallstones

Cholesterol gallstones

The main factors that contribute to the formation and growth of cholesterol gallstones are:

(1) Genetic factors (previously mentioned)
(2) Cholesterol supersaturation in bile
(3) Impaired gallbladder motility
(4) Cholesterol nucleation and crystallization
(5) Alteration of normal hepatic-entero-hepatic bile salts circulation[9,20]

Cholesterol supersaturation of bile (i.e. a cholesterol concentration at which bile salts and phospholipids can no longer solubilize) represents a critical event in cholesterol gallstone pathophysiology. This is a result of (1) the excess secretion of biliary cholesterol by the liver, (2) decreased concentrations of biliary bile salts or phospholipids, or (3) a combination of the first two. Gradually, as a result of an imbalance between the factors that promote and inhibit nucleation, cholesterol molecules can undergo crystallization, ultimately leading to the formation of macroscopic stones[9,20–22].

Mucin is a glycoprotein that forms a protective layer covering the gallbladder cells and acts at the same time as an important pro-nucleating agent, functioning as a matrix for the growth of gallstones. Additional pro-nucleating agents include *amphipathic anionic polypeptide fraction/calcium-binding protein*, *group II phospholipase A2*, *albumin-lipid complexes*, and *calcium*. In contrast, *UDCA* and *lectin* have been shown to protect against cholesterol crystallization. The pro- and anti-nucleating activity of these agents has been demonstrated in numerous "in vitro" studies, but theirs real "in vivo" ability of these agents to generate or protect against gallstones is still uncertain[23–26].

Gallbladder motility dysfunction is another factor that contributes to gallstone formation. In a fasting state, the gallbladder can store up to 25–30 ml of bile, and after a meal, it promptly releases its contents and subsequently refills multiple times. Cholescintigraphy and US evaluation showed that in patients with cholesterol gallstones, a large gallbladder volume during fasting, high residual gallbladder volume, and incomplete emptying are more prevalent. These changes appear both through gallbladder smooth muscle dysfunction due to increased absorption of cholesterol from the gallbladder lumen and

through abnormalities in the plasma membrane CCK-1 receptors[27–29].

Pigment gallstones

Pigment gallstones are formed by the precipitation of calcium salts. They can be classified, according to their color, into "black" or "brown," depending on the composition, polymerization, and oxidation processes involved in their formation. Although less frequent than cholesterol stones, they are an important cause of cholelithiasis and cholangitis in Western European and Eastern Asian populations. Each type of pigment gallstone has a specific composition and physical characteristics that may influence the evolution of the disease[30].

Black stones are hard, amorphous gallstones formed at the level of sterile bile owing to the precipitation of calcium salts from unconjugated bilirubin. Chronic hemolytic processes (sickle cell anemia, Gilbert's syndrome, etc.) that lead to an increase in the level of unconjugated bilirubin can favor the appearance of these types of gallstones as a result of oversaturation of bile conjugation mechanisms. Inefficient erythropoiesis or induced enterohepatic circulation of unconjugated bilirubin represents another cause of hyperbilirubinemia that can favor the precipitation of calcium salts and the formation of stones. The secondary causes of black stone formation include diabetes mellitus, truncal vagotomy, and parenteral nutrition. The presence of several such conditions in the same patient increases the risk of black stone formation.

Brown stones, as opposed to black ones, are more friable and are formed by the association of calcium salts, biliary acids, and cholesterol at the biliary tree level. Their formation is often the result of bile stasis caused by anaerobic bacterial or parasitic agents. There are numerous mechanisms through which these types of calculus are formed, including bacterial secretion of enzymes (phospholipase-A, beta-glucuronidase, or bile acid hydrolase) that increase the level of unconjugated bilirubin. AC caused by impacted brownstones is frequently followed by secondary infection and severe complications. *Caroli syndrome* and *isolated biliary cysts* are other scenarios linked to an increased risk of brownstone formation in the absence of an identifiable infection[30–32].

The mechanisms involved in the generation of gallstones is depicted in Fig. 1.

Etiology of acute cholangitis

Mechanism: Two hallmark mechanisms are necessary for AC. First, it involves obstruction of the biliary tract, which disrupts the normal flow of bile and results in increased pressure within intrahepatic and extrahepatic bile ducts. This alters the secretion of bile and its reflux into venous and lymphatic systems. These changes in the biliary circulation are responsible for the clinical and paraclinical presentation of acute cholangitis.

The second mechanism involves bacterial proliferation within the bile. Normally, the biliary system is sterile, although some colonization may occur in individuals without a biliary tract infection. Bacterial contamination can occur in two ways: ascending contamination from the normal duodenal flora or hematogenous contamination from the portal venous blood. Elevated biliary pressure promotes the translocation of bacteria from the bile system to the bloodstream. It is important to note that reflux cholangitis, which is characterized by transitory obstruction caused by the reflux of food debris, is an exception in the context of cholangitis and is more difficult to identify[13,33,34].

Causes: The primary cause of acute cholangitis secondary to biliary obstruction is choledocholithiasis, which refers to the presence of gallstones in the common bile duct. Other causes include malignant or benign strictures of the intra-or extrahepatic bile ducts, cephalopancreatic neoplasm, ampullary adenoma or adenocarcinoma, tumors, metastases of hilar lymphadenopathy, obstruction of a biliary stent (resulting from microbial biofilm deposits, reflux of duodenal contents, biliary sludge, or tumor infiltration), and amyloid deposits. Other causes include primary sclerosing cholangitis, Mirizzi syndrome (compression of the common bile duct or common hepatic duct due to a gallstone impacted in the cystic duct or neck of the gall bladder [discussed below]), Lemmel's syndrome (distal biliary obstruction caused by a peri-ampullary diverticulum), infestation of the bile duct by roundworms (*Ascaris lumbricoides*) or tapeworms (*Taenia saginata*), acquired immunodeficiency syndrome cholangiopathy, and stricture in bilioenteric anastomoses. Risk factors for acute cholangitis include choledochoceles and narrow-caliber bile ducts. Inefficient cleaning of endoscopic equipment can also play a role, as shown by *Epstein* and colleagues, who reported an outbreak of cholangitis caused by *carbapenem-resistant Enterobacteriaceae* (CRE) associated with exposure to contaminated duodenoscopes. As much as 0.5–2.4% of patients after post-endoscopic retrograde cholangiopancreatography (ERCP)[35–39].

Microorganisms causing acute cholangitis: The predominant pathogens identified in cases of acute cholangitis are Gram-negative bacteria that are members of normal intestinal commensal flora, including *Escherichia coli* (25–50%), *Klebsiella* species (15–20%), *Enterococcus* species (10–20%), and *Enterobacter* species (5–10%). In some cases, anaerobic bacteria, such as *Bacteroides fragilis* and *Clostridium perfringens* can also contribute to the development of AC, especially in patients with a history of biliary surgery, previous endoscopic procedures, or in the elderly population. Additionally, parasitic infestations of the biliary system caused by liver flukes, such as *Opisthorchis felineus*, *Opisthorchis viverrini*, *and Clonorchis sinensis,* and roundworm infestation by *Ascaris lumbricoides*, have been associated with the occurrence of cholangitis[40–43].

Figure 2 depicts the pathophysiology of acute cholangitis.

Syndromes associated with cholangitis and gallstone disease

Gallstone disease and cholangitis are complicated illnesses that can be linked to a variety of syndromes, each with its own etiology and clinical manifestations (Table 2).

Low phospholipid-associated cholestasis and cholelithiasis (LPAC) syndrome is a rare type of biliary lithiasis characterized by reduced phosphatidylcholine (PC) synthesis, resulting in the formation of cholesterol crystals and eventually gallstones in both the intrahepatic ducts and gallbladder. LPAC syndrome can be diagnosed using specific clinical criteria and is often effectively treated with UDCA.

Although uncommon, hemolytic-uremic syndrome (HUS) can be associated with gallstone disease when bacterial toxins are produced, leading to bile duct blockage. This results in severe hemolytic anemia, acute kidney injury, and thrombocytopenia.

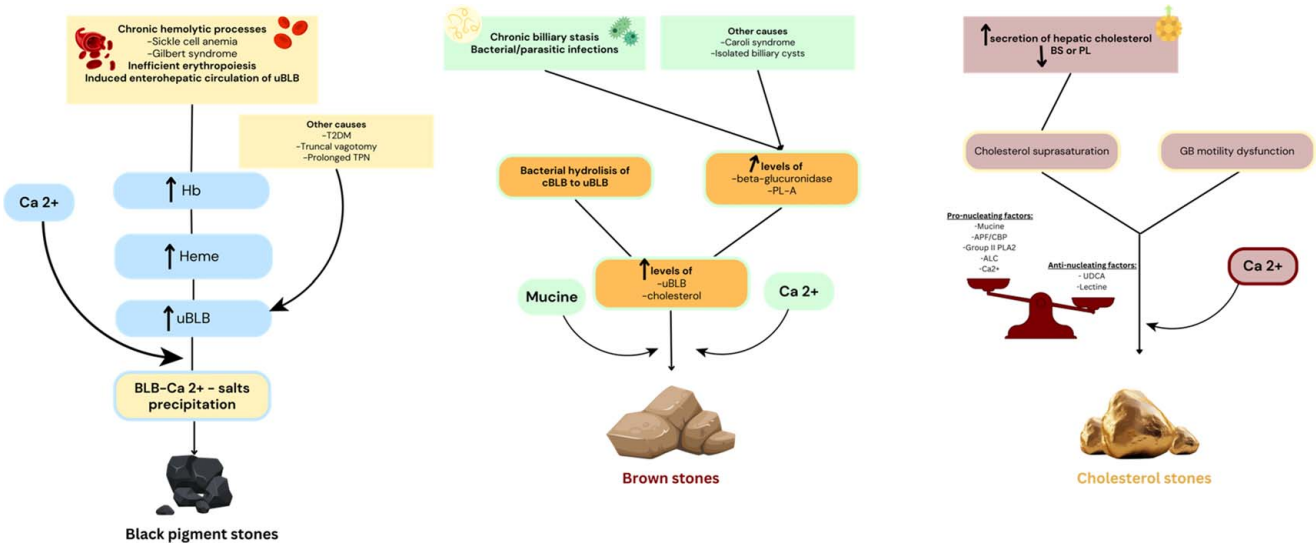

Figure 1. Mechanisms of formation of different types of gallstones. ALC, albumin-lipid complexes; APF/CBP, amphipathic anionic polypeptide fraction/calcium-binding protein; BLB, bilirubin; BS, bile salts; cBLB, conjugated bilirubin; GB, gallbladder; Hb, hemoglobin; PL-A, phospholipase-A; T2DM, type-2 diabetes mellitus; TPN, total parenteral nutrition; uBLB-unconjugated bilirubin; UDCA, ursodeoxycholic acid.

LPAC syndrome

LPAC syndrome, a distinctive variant of biliary stone disease, was first described by Rosmorduc and colleagues in 2001. It arises from a mutation in the ABCB4 gene (chromosome 7q21), resulting in a reduction in the secretion of PC into the bile, which in turn leads to the formation of stones not only in the gallbladder but also within the intrahepatic bile ducts. This uncommon condition primarily affects individuals under the age of 40 years and is characterized by recurrent episodes of biliary colic, cholecystitis, and pancreatitis, which can persist even after the removal of the gallbladder[44–46].

A diagnosis of LPAC syndrome should be suspected when a minimum of two of the following criteria are met:

(1) Symptoms appear before the age of 40.

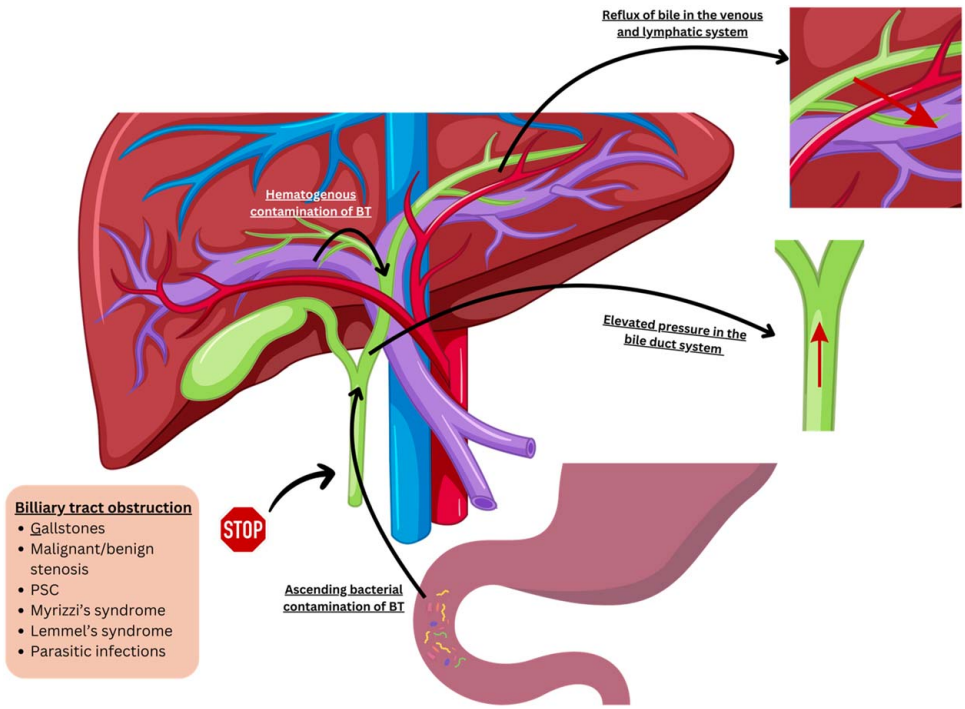

Figure 2. Pathophysiology of acute cholangitis. BT, biliary tract; PSC, primary sclerosing cholangitis.

Table 2

Syndromes associated with gallstone disease and cholangitis.

Associated syndrome	Etiology and pathophysiology	Clinical features	Diagnosis and treatment
LPAC syndrome	Mutation in ABCB4/MDR3 gene, leading to a reduction in the secretion of PC in bile	Recurrence of biliary symptoms after cholecystectomy	US is the diagnostic method of choice. Treatment includes usually UDCA
HUS	Secondary complication of gallstone disease with the release of bacterial toxins	Severe stomach pain, fever, jaundice, pallor in addition to the clinical features seen in HUS	Specific tests for bacterial toxins. Treatment includes addressing the cholangitis, removal of gallstones, and supportive care

ABCB4/MDR3, ATP binding cassette subfamily B member 4; HUS, hemolytic-uremic syndrome; LPAC, low phospholipid-associated cholestasis and cholelithiasis; PC, phosphatidylcholine; UDCA, ursodeoxycholic acid; US, ultrasound.

(2) Reappearance of symptoms following cholecystectomy.
(3) The presence of intrahepatic stones as evidenced by hyperechoic foci, comet-tail images, or the presence of biliary sludge on the liver US.

These criteria were established using a small sample size to predict MDR3/ABCB4 mutations. However, it's worth noting that a significant proportion of patients, (often more than 50%), do not have these gene mutations. As a result, these criteria may not fully represent the actual situation. Therefore, there is a need for a more comprehensive characterization of the various clinical aspects of individuals with this syndrome[47].

In all cases of LPAC syndrome, it is advisable to promptly initiate long-term curative or prophylactic therapy involving UDCA, which is intended to proactively prevent the occurrence or recurrence of the syndrome and its associated complications. In a study by Gille and colleagues, UDCA has shown 94% efficacy, with an average onset of action of 3–4 weeks. UDCA is generally well-tolerated, and adverse effects such as diarrhea and nausea are relatively infrequent. It is important to note that UDCA is a long-term therapy that should be continued, even if all symptoms have resolved. Cholecystectomy is recommended if symptomatic gallstones are present. In situations where there are symptomatic intrahepatic bile duct dilatations filled with gallstones, biliary drainage or partial hepatectomy may be considered as appropriate interventions. Patients who have reached an advanced stage of liver disease may be evaluated as potential candidates for liver transplantation[45,48–50].

The exact incidence of long-term complications such as cirrhosis or malignant transformation remains unclear. However, isolated instances of such complications have been documented in the literature. Prolonged irritation of the bile epithelium due to the prolonged presence of stones and the effects of hydrophobic bile acids can result in chronic inflammation, which is a known factor in the development of secondary biliary cirrhosis and sclerosing cholangitis. Additionally, chronic inflammation can lead to the development of dysplasia, and instances of cholangiocarcinoma have been reported in individuals with LPAC[49,51–55].

Hemolytic-uremic syndrome and its relation to gallstone disease

HUS is an uncommon but severe disorder that is associated with gallstone disease in certain circumstances. HUS is distinguished by the triad of hemolytic anemia, acute kidney injury, and thrombocytopenia. The condition may be primary (induced by an infection) or secondary (linked to other conditions or triggers)[56].

HUS can develop as a consequence of gallstones. The underlying process is believed to involve the release of bacterial toxins from the gastrointestinal system because of gallstones that block the bile ducts. Bacteria such as *Escherichia coli* and *Shigella* can produce toxins that enter circulation and cause HUS. The symptoms of HUS in the context of gallstone disease can first mirror those of cholangitis, such as severe stomach pain, fever, and jaundice. However, as the disease worsens, hemolytic anemia and thrombocytopenia become visible. Patients may experience weakness, fatigue, and pallor due to the breakdown of red blood cells. Furthermore, a low platelet count may cause bruising and bleeding. Acute kidney injury can result in reduced urine production, peripheral edema, and electrolyte imbalances[56–58].

Diagnosis and management

Diagnosis of HUS in the context of gallstone disease requires a high level of suspicion, especially when a patient shows signs and symptoms of AC but does not respond to standard therapy. Complete blood counts, peripheral blood smears, and kidney function tests are critical for diagnosis. Testing for particular bacterial toxins, such as Shiga toxin, may also help to confirm the diagnosis. HUS associated with gallstone disease is managed by addressing the underlying problems (i.e. treating cholangitis and removing gallstones to restore normal bile flow). Supportive treatment, including blood transfusions and the monitoring and management of renal function, is also required. Dialysis may be necessary in extreme situations to maintain renal function[57,58].

Epidemiology and physiopathology of acute cholangitis

In general, the incidence of AC has been observed to increase over time, which could be attributed to several factors such as improved diagnostic methods, aging populations with a higher prevalence of gallstones (the primary cause of biliary obstruction), and increased use of invasive biliary procedures. Unfortunately, accurate and up-to-date epidemiological data on AC are relatively scarce, mainly because of underdiagnosis and underreporting of the condition.

Despite limitations in the available data, the annual incidence rate of AC in the United States has been reported to range from 12 to 35 cases per 100 000 individuals, making it a relatively common cause of hospital admission. Globally, the incidence rate appears to be similar, with a study in the Netherlands reporting an annual incidence of 28 cases per 100 000 individuals.

In particular, the prevalence of AC varies among different age groups, with a higher incidence noted among older adults. This is primarily due to the increased likelihood of gallstone disease and malignancies, the two major risk factors for biliary obstruction in

this category. Furthermore, some studies have indicated a higher incidence of the disease among males, although this sex preference is not universally accepted. However, bacterial infection, the key catalyst for AC, can be promoted by several factors. Immunosuppression is a notable risk factor, as a weakened immune system can struggle to control bacterial populations within the biliary tract, resulting in overgrowth and possible infections. Invasive procedures in the biliary tract, such as ERCP or percutaneous transhepatic cholangiography (PTC), can also introduce bacteria into the biliary system or cause trauma to the ducts, increasing the risk of infection[3,59–62].

AC, a global health concern, has a significantly higher incidence in Western countries, particularly in Europe and the United States. This geographical predisposition can be attributed to a multitude of factors. A Western diet, characterized by a high intake of fats and cholesterol and a low intake of fiber, increases the risk of gallstone formation, subsequently increasing the risk of AC. Lifestyle choices prevalent in these regions, including sedentary behavior and over-consumption of hypercaloric foods, contribute to obesity rates. Obesity is associated with metabolic syndrome, an entity composed of a constellation of factors, including insulin resistance, hyperlipidemia, and hypertension, which predisposes patients to gallstone disease and subsequent cholangitis. Furthermore, hepatobiliary malignancies, another significant risk factor for acute cholangitis, are also more frequently diagnosed in these regions owing to the increased incidence of risk factors, including cirrhosis, hepatitis, and certain lifestyle behaviors such as smoking and alcohol consumption. Despite these observations, it is important to note that further research is necessary to fully understand the relationship between geography, obesity, and AC[63].

AC is a major health concern that is likely to increase in incidence due to factors such as an aging population, increasing prevalence of gallstones, and more frequent use of invasive biliary procedures. The condition is seen worldwide and affects both sexes; however, older adults are at a higher risk. Although the exact epidemiology of the disease remains to be fully elucidated owing to issues such as underdiagnosis and underreporting, it is clear that efforts to improve its early recognition and management are crucial to reducing its associated morbidity and mortality. Studies investigating the potential impact of modifiable risk factors, such as diet and lifestyle, the role of emerging diagnostic technologies in improving the recognition of the disease, and the effectiveness of various management approaches in different population subgroups can pave the way for future exploration of the topic[62,63].

Diagnosis and the role of the Tokyo guidelines

Rapid progression requires prompt diagnosis and management to prevent severe morbidity and organ dysfunction. Patients with cholangitis often have a primary complaint of fever, abdominal pain (especially in the RUQ), and jaundice, as originally described in the Charcot triad of cholangitis. The patient may also have reported a history of cholangitis or other obstruction/infections of the bile duct. In rare prolonged cases, patients may present with symptoms associated with septic shock and decreased consciousness. Although the symptoms described in Charcot's triad have been used for a long time, recent studies have reported only moderate sensitivity and lower diagnostic rates. This makes Charcot's triad unsuitable for the diagnosis of AC, as the consequences of missed diagnosis can be life-threatening.

To address this issue, a group of scientists have met several times to formulate and continuously update a worldwide standard for diagnosing and managing acute cholangitis. The Tokyo Guidelines, established in 2007 and revised in 2013 and 2018 (TG18), serve as a comprehensive classification system to assist clinicians in diagnosing and managing AC and its complications. They are dynamic and continually adapt to reflect the latest understanding and technological advances in AC diagnosis, severity classification, and management. Their focus was on four main aspects: diagnosis, severity classification, therapeutic interventions, and management algorithms[1,9,13,64–67].

The diagnosis and severity grading criteria as well as the main antibiotic recommendations are summarized in Table 2.

Therapeutic interventions

The guidelines underline the importance of early diagnosis and rapid antibiotic therapy, which is crucial in initial management. Although the guidelines indicate the most efficient empirical regime based on available international data, the choice of the antibiotic regime should always be guided by local microbiological characteristics and antibiotic resistance patterns if bile cultures and antibiograms cannot be performed. The primary etiology, usually biliary obstruction, must be addressed immediately. Biliary drainage methods vary and are influenced by the severity of the condition, local expertise, and patient-specific factors[68].

Management algorithms

The Tokyo Guidelines provide an easy-to-follow algorithm for diagnosing and managing AC (Table 3). It outlines the steps from initial diagnosis, based on clinical, laboratory, and imaging criteria, severity classification, immediate treatment (including fluid resuscitation and antibiotics), and further definitive treatment options, such as ERCP, PTC, or classic surgery[69]. Although the Tokyo Guidelines have undoubtedly facilitated better and more standardized care for patients with AC, there is some criticism. Some researchers argue that these guidelines do not sufficiently consider patient comorbidities, which are significant determinants of outcomes. There is also discussion on the optimal timing and method of biliary drainage. These are the areas of future iterations that the guidelines may focus on.

Management

AC treatment requires addressing two main factors: bacterial colonization and obstruction of the biliary tract. Prompt initiation of empiric antibiotic therapy can effectively address bacterial presence. However, de-obstruction of the main bile duct requires more expertise and must be performed in the endoscopic emergency unit. This can be achieved either through a traditional percutaneous surgical approach or endoscopically by ERCP, a common procedure performed in the majority of healthcare units. In addition to these fundamental principles, supportive management actions should be taken as soon as possible based on the severity of cholangitis. These actions include intravenous fluid repletion, correction of electrolyte imbalances, and careful monitoring of vital signs, such as blood pressure, heart rate, and

Table 3

Diagnosis and severity grading criteria, and the main antibiotic recommendations from the TG18[64–67]

	Community-acquired and healthcare-associated biliary infections			
Severity grading	Grade I (mild) acute cholangitis	Grade II (moderate) AC—associated with any two of the following conditions	Grade III (severe) AC—disfunction in any one of the following organs/systems:	
	Does not meet the criteria of "Grade III" or "Grade II" AC at initial diagnosis	1. Abnormal WBC count ($>12\,000/mm^3$, $<4000/mm^3$) 2. High fever ($\geq 39°C$) 3. Age ($\geq$ 75 years) 4. Hyperbilirubinemia (tBLB $\geq$ 5 mg/dl) 5. Hypoalbuminemia (< STD 9 0.7)	1. Cardiovascular dysfunction: hypotension requiring dopamine $\geq$ 5 mg/kg per min, or any dose of norepinephrine 2. Neurological dysfunction: disturbance of consciousness 3. Respiratory dysfunction: PaO_2/FiO_2 ratio <300 4. Renal dysfunction: oliguria, serum creatinine > 2.0 mg/dl 5. Hepatic dysfunction: PT-INR > 1.5 6. Hematological dysfunction: platelet count <100 000/mm^3	
Management	• Antibiotics are usually sufficient • Most patients do not require BD (but should be considered if a patient does not respond to initial treatment)	• Early BD is indicated, after the patient's general condition has improved	• Appropriate respiratory/circulatory management (tracheal intubation followed by artificial ventilation and the use of hypertensive agents, if needed) • BD should be performed as soon as possible after the patient's condition has been improved by initial treatment and respiratory/ circulatory management • Treatment for the underlying etiology should be provided after the patient's general status has improved	
	Community-acquired biliary infections			
Antibiotic agents	Grade I AC	Grade II AC	Grade III[a] AC	Healthcare-associated biliary infections[a]
Penicillin-based therapy	Ampicillin/sulbactam[b] is not recommended if > 20% RT	Piperacillin/tazobactam	Piperacillin/tazobactam	Piperacillin/tazobactam
Cephalosporin-based therapy	Cefazolin[c]/Cefotiam[c]/Cefuroxime[c] /Ceftriaxone/Cefotaxime ± Metronidazole[d]/Cefmetazole[c]/ Cefoxitin[c]/Flomoxef[c]/ Cefoperazone/sulbactam	Ceftriaxone/Cefotaxime/Cefepime/ Cefozopran/Ceftazidime ± Metronidazole[d]/ Cefoperazone/sulbactam	Cefepime/Ceftazidime/ Cefozopran ± Metronidazole[d]	Cefepime/Ceftazidime/Cefozopran ± Metronidazole[d]
Carbapenem-based therapy	Ertapenem	Ertapenem	Imipenem/cilastatin/ Meropenem/ Doripenem/Ertapenem	Imipenem/cilastatin/Meropenem/ Doripenem/Ertapenem
Monobactam-based therapy	—	—	Aztreonam ± Metronidazole[d]	Aztreonam ± Metronidazole[d]
Fluoroquinolone-based therapye[e]	Ciprofloxacin/Levofloxacin/ Pazufloxacin ± Metronidazole[d] Moxifloxacin	Ciprofloxacin/Levofloxacin/ Pazufloxacin ± Metronidazole[d] Moxifloxacin	—	—
Duration of antibiotic therapy	Once source of infection is controlled, duration of 4–7 days is recommended. If bacteremia with *Enterococcus spp.* or Streptococcus spp. is present, duration of minimum 2 weeks is recommended.			If bacteremia with *Enterococcus spp.* or *Streptococcus spp.* is present, a duration of a minimum 2 weeks is recommended.

AC, acute cholangitis; BD, biliary drainage; RT, resistance rate; tBLB, total bilirubin; WBC, white blood cells.

[a]Vancomycin is recommended to treat Enterococcus spp. for grade III community-acquired acute cholangitis, cholecystitis, and healthcare-associated acute biliary infections. Linezolid or daptomycin is recommended if vancomycin-resistant Enterococcus (VRE) is known to colonize the patient if previous treatment includes vancomycin and/or if the organism is common in the community.

[b]Ampicillin/sulbactam has little activity left against Escherichia coli. It is removed from the North American guidelines[43,49].

[c]Local antimicrobial susceptibility patterns (antibiogram) should be considered for use.

[d]Anti-anaerobic therapy, including the use of metronidazole, tinidazole, or clindamycin, is warranted if biliary-enteric anastomosis is present. The carbapenems, piperacillin/tazobactam, ampicillin/Sulbactam, cefmetazole, cefoxitin, flomoxef, and cefoperazone/sulbactam have sufficient anti-anaerobic activity.

[e]Fluoroquinolone use is recommended if the susceptibility of cultured isolates is known or for patients with β-lactam allergies. Many extended-spectrum b-lactamase (ESBL)-producing Gram-negative isolates are fluoroquinolone-resistant.

urine volume. Analgesics can be administered early, and fasting should only be implemented if immediate emergency drainage is scheduled. However, caution must be exercised when administering analgesics, such as morphine hydrochloride and pentazocine, as they can increase pressure in the biliary system by stimulating the sphincter of Oddi.

Initial evaluation and severity grading

The patient's medical history should include a thorough assessment of history related to the biliary system, such as previous episodes of cholangitis, history of biliary tract disorders, jaundice, or prior interventions related to the biliary tract, such as ERCP, endoscopic ultrasound (EUS), or percutaneous transhepatic biliary catheterization. It is important to note if the patient has undergone any biliary tract surgery, which can result in changes to the normal anatomy and potentially make ERCP more challenging. Billroth procedures or choledochojejunostomy, can fall into this category. Routine laboratory tests, including complete blood count, coagulation profile, electrolyte, and renal function assessments, as well as blood cultures, should be conducted. These examinations are crucial for the comprehensive evaluation and assessment of severity.[2,70–73].

Antibiotic therapy

Empiric antibiotic therapy should be promptly initiated before blood or bile cultures are obtained (discussed later). The selection of the antimicrobial agent should be based on various factors, including the severity of the disease, type of infection (community or hospital-acquired), patient's age, presence of underlying hepatobiliary disease (such as a history of biliary instrumentation or surgery), immune status, allergies, and local susceptibility patterns. Therefore, it is important to consider the clinical context. Hospital-acquired infections may involve multiple and/or highly resistant microorganisms, such as *methicillin-resistant Staphylococcus aureus* (MRSA), *Pseudomonas spp*., or *vancomycin-resistant Enterococcus* (VRE), whereas community-acquired infections are typically caused by a single species of commensal microorganisms, such as *Enterococcus spp*, *E. coli* or *Klebsiella*. Anaerobic bacteria are more commonly found in severe forms in older patients with an altered biliary anatomy. Once the results of the bile/blood cultures are available, the initial empiric antibiotic treatment should be adjusted to narrow-spectrum agents. In the past, agents with good biliary penetration, such as penicillins, were considered better and preferred alternatives to newer and more potent agents. However, recent data suggest that mechanical biliary obstruction leads to a decrease or even a halt in the secretion of these antibiotics into the bile. Hence, although biliary permeability is a relevant factor, it should not be an exclusive decisive factor. The latest recommendations for antibiotic therapy are summarized in Table 2[70–74].

Biliary drainage

Biliary obstruction is a key factor in AC; thus, biliary drainage is necessary when an obstruction is detected through imaging. The purpose of this drainage is to eliminate the infection source, enhance the excretion of antibiotics in the bile, and prevent complications, such as septic shock, hepatic abscesses, or even death. The urgency of performing endoscopic or surgical drainage depends on the severity of the disease: it can be done on an elective basis for patients with mild cholangitis, within 24–48 h of presentation for those with mild to moderate cholangitis, and urgently (in the first few hours) for individuals with severe cholangitis who do not respond to first-line antibiotics[2,70–72].

Endoscopic biliary drainage

In the past, biliary drainage was typically performed using the traditional surgical approach. However, in recent years, minimally invasive endoscopic procedures like ERCP and EUS have gained prominence due to their improved safety and effectiveness. Current practical guidelines, supported by evidence from the literature, indicate that surgery carries a significantly higher risk of complications and in-hospital mortality (up to 40%) compared to endoscopic therapy. Therefore, surgical biliary decompression is no longer considered a suitable routine treatment for AC. Therefore, endoscopic procedures are the preferred method for biliary decompression with a success rate of 98%. After successful cannulation of the common bile duct, it is important to aspirate the bile samples before injecting the contrast agent for microbiological analysis. This procedure is quick, cost-effective, does not require additional materials, and can guide empirical antibiotic therapy in cases involving multidrug-resistant bacteria, thereby promoting faster healing and preventing the development of antibiotic-resistant micro-organisms[69,75].

During ERCP, endoscopic drainage can be performed in two ways: placement of a transpapillary biliary stent, or placement of a nasobiliary drain. Both methods showed similar efficacy. A nasobiliary catheter permits active decompression via nasobiliary suction and facilitates the ongoing observation and analysis of bile drainage. Although nasobiliary catheters can be placed without sphincterotomy, which carries a risk of complications such as bleeding, pancreatitis, or perforation, and may still be an option in severe cases, their usage has significantly declined in recent years. Compared with transpapillary stents, nasobiliary catheters have several drawbacks. These include patient discomfort, high nursing care demands leading to increased medical expenses, potential electrolyte imbalances resulting from external bile diversion, and a tendency to be often displaced.

Consequently, transpapillary stents have largely replaced nasobiliary tube placement. A critical consideration during ERCP is the injection of contrast agent into the biliary tract to make it visible on radiography. Injecting contrast agents into an obstructed biliary system can raise intrabiliary pressure, leading to the reflux of infected bile into the systemic circulation or upstream in the small bile ducts, resulting in complications such as septic liver abscess or bacteremia. Therefore, contrast injection is recommended only when there is secure communication between the duodenum and biliary tract through a guide wire, which allows for stent implantation, and only after the level and nature of the obstruction have been determined by EUS or Magnetic Resonance Cholangiopancreatography (MRCP). If ERCP fails, there are two remaining options: (1) PTC, potentially followed by endoscopic stent placement using the 'rendez-vous' technique, which allows for the removal of external drainage, or (2) EUS-guided biliary drainage[68–70,72–75].

Percutaneous transhepatic cholangiography

PTC involving placement of a percutaneous biliary drain is considered the second-line approach for biliary drainage. It is frequently utilized when ERCP fails due to modified anatomy

resulting from prior surgical interventions, unavailability within a reasonable timeframe, or contraindications, such as allergic reactions to contrast agents. The success rate of PTC can be as high as 90%. Notably, no randomized studies have directly compared ERCP with PTC. However, it is important to acknowledge that PTC carries a higher risk of complications than ERCP does. Reports have indicated morbidity rates of up to 80% and mortality rates of 15% associated with PTC. Complications include hemobilia, bile peritonitis, discomfort at the drainage site, and intraperitoneal hemorrhage. Furthermore, PTC patients often experience prolonged hospital stays, and the presence of a percutaneous catheter is associated with high pain levels[70–72].

EUS-guided biliary drainage/role of EUS

The technique known as EUS-guided biliary drainage has become increasingly popular in recent years. It is used when ERCP is not feasible. There are two primary techniques for EUS-BD.

A. "Rendez-vous" technique: Under EUS guidance, a guidewire is carefully inserted into the bile duct through the wall of the stomach. The guidewire was then advanced anterograde through the papilla in the duodenum, allowing it to be grasped using a standard duodenoscope. This enables biliary access for a regular ERCP procedure and facilitates stent placement.

B. EUS-guided choledochoduodenostomy: Under EUS guidance, from the duodenal bulb, a guidewire is subsequently inserted into the common bile duct to facilitate the placement of a biliary stent.

Based on the latest research findings, the „rendez-vous" procedure has a success rate of 80% and a complication rate of 4%. Similar challenges arise with regular ERCP-guided biliary drainage, which exhibits a success rate of 94%, but carries a risk of complications of 15% (such as bile peritonitis and pneumoperitoneum). However, based on EUS guidelines, choledochoduodenostomy proves to be a safe and effective alternative, with a success rate of 94% and a lower risk of complications Additionally, there has been documented cases of EUS-guided hepaticogastrostomy. While these procedures have shown promising outcomes, their utilization should be limited to hospitals with significant experience in therapeutic EUS procedures, and only when conventional drainage methods are not feasible until conclusive data become available[3,59,70–72,76,77].

Classic surgical approach

In extreme and rare situations, choledochotomy and Kehr T-shaped tube placement can be used to decompress the biliary tree, followed by definitive secondary surgery[2,69,74].

Complications and prognosis

Biliary drainage using ERCP has reduced the overall mortality of AC from 50% of cases to less than 10% due to early available endoscopic intervention. However, emergency surgery for severe AC still has a mortality rate of 30%. The overall mean mortality at 30 days caused by AC ranges from 2.6 to 5%, indicating the possible severity of the disease despite improved treatment strategies.

Several factors reported in the literature that result in a poor prognosis in patients with AC include hypoalbuminemia, organ dysfunction, Charlson score greater than 3, neoplastic obstruction, inappropriate antibiotic therapy, intrahepatic obstruction, serum interleukin-7 level less than 6 pg/ml and serum procalcitonin greater than 0.5 ng/ml.

The most commonly reported complications of AC were acute biliary pancreatitis (7.6%), liver abscess (2.5%), and endocarditis (0.26%). Other less frequent complications include portal venous thrombosis, liver failure, acute kidney failure, and bacteremia/septicemia. A case of bacterial meningitis resulting from acute cholangitis has been reported[3,63,72,78–81].

Uncommon complications of gallstone disease and acute cholangitis

Mirrizi syndrome

Mirizzi syndrome is an uncommon disorder characterized by external compression of the common bile duct (CBD) or common hepatic duct (CHD) by one or more gallstones impacted by Hartman's pouch. Because symptoms are similar and imagistic diagnosis is difficult, it can be mistaken for other etiologies of cholangitis, such as CBD/CHD stones or stenoses.

Internal fistulas from the gallbladder to the CBD, CHD, or duodenum may form as this illness worsens. Several stages of Mirizzi syndrome have been divided into the following categories using a defined categorization system: Type I indicates no fistula, whereas subtypes IA and IB are distinguished by the presence or absence of the cystic duct. Types II through IV indicate the presence of a fistula; Type II shows a defect of less than 33% of the CHD diameter, Type III shows a defect of 33–66% of the CHD diameter, and Type IV shows a defect of more than 66% of the CHD diameter[82,83].

Clinical features

Mirizzi syndrome often manifests as acute or chronic cholecystitis, associated with jaundice and/or symptoms of cholangitis. Symptoms usually appear in the evening and typically last for weeks or months. Chronic cholecystitis is characterized by dull discomfort in the RUQ of the abdomen, which can spread back. It is commonly associated with the consumption of fatty foods. Nausea and vomiting may also occur. The traditional physical examination usually reveals a positive Murphy's sign (discomfort in the right upper abdomen with deep palpation)[84].

Diagnosis and treatment

Abdominal ultrasound is the most effective diagnostic technique to detect gallstones and ensuing acute cholecystitis. It can detect gallbladder polyps, sludge, and stones as small as 2 mm with a specificity of 90%. AC rather than cholelithiasis is suggested by US findings such as a positive sonographic Murphy sign, pericholecystic fluid, and gallbladder wall thickness greater than 3 mm. computed tomography (CT) and MRI are also commonly used to detect gallstones; however, they are less sensitive for the diagnosis of acute cholecystitis. Gallstones may also show up in as much as 10% of normal abdominal X-rays due to their high calcium concentration. MRCP should be performed if cholelithiasis is detected in the CBD. If the diagnosis is confirmed, ERCP should be performed. PTC is also considered as an alternative if ERCP is not feasible. In most cases, however, Mirizzi syndrome is misinterpreted during a preoperative examination as a straightforward CBD stone or is entirely missed.

Cholecystectomy is the treatment of choice for Mirizzi syndrome. Although laparoscopic cholecystectomy is currently an obvious option, open cholecystectomy may be necessary if the condition has progressed. In severe and prolonged cases, partial cholecystectomy should be considered. This would include removing the gallbladder body and gallstones while leaving the Hartman's pouch in place. This reduces the risk of further bile duct injury[85,86].

Cholecystoenteric fistula

Cholecystoenteric fistula (CEF) is a rare complication of cholecystitis, characterized by fistulous communication between the gallbladder and surrounding gastrointestinal tract, particularly the duodenum. It is one of the late complications of cholecystitis and occurs most commonly in elderly women; however, few cases have been documented in the younger population. The overall incidence of CEF ranges between 3% and 5% in patients with cholecystitis[87–89].

The clinical manifestations of CEF are nonspecific and variable, making the preoperative diagnosis challenging. Patients with CEF usually experience pain, nausea, and vomiting in the RUQ and symptoms that are indistinguishable from acute cholecystitis. However, CEF may also co-exist with biliary ileus, in which case the above-mentioned symptoms are associated with constipation and inability to pass intestinal gases.

Despite modern imaging equipment and techniques, preoperative diagnosis of CEF remains challenging. Huang and colleagues described the following points to facilitate the diagnosis of CEF preoperative. (1) A history of repeated episodes of cholecystitis, particularly longer than 5 years, (2) thick gallbladder wall, pneumobilia, or pneumo-gallbladder, along with atrophy of the gallbladder, are signs suggestive of CEF on US, (3) coronal reconstruction of abdominal CT effectively identifies an ill-defined border between the gallbladder and the digestive tract, (4) MRCP for CEF is important in the setting of choledocholithiasis or Mirizzi syndrome, (5) gastroscopy or duodenoscopy should be considered for direct visualization of the fistulous opening, and (6) Presence of Rigler's triad in the setting of intestinal obstruction is highly suggestive of CEF. Furthermore, the treatment of CEF varies depending on the presence or absence of biliary ileus. Traditionally, open surgical closure of the fistula is preferred in patients without intestinal obstruction; however, laparoscopic repair is not contraindicated. The treatment of CEF in the presence of bowel obstruction has been discussed in the section on biliary ileus[89].

Biliary ileus

Biliary ileus, also called gallstone ileus, is a mechanical obstruction of the intestinal tract after impaction by one large gallstone or multiple gallstones. Biliary ileus has an incidence of 0.3–0.5% in patients with cholelithiasis and is particularly common in the elderly population. It is preceded by a history of acute cholecystitis, which causes inflammatory changes in the wall of the gallbladder, adhesions, and the formation of fistulas between the gallbladder and surrounding gastrointestinal structures. Gallstones may also impact the duodenum by entering through the dilated ampulla of Vater.

Biliary ileus presents as an acute, chronic, or intermittent episode of gastrointestinal obstruction. Symptoms of biliary ileus may be nonspecific and intermittent due to the changing position of the gallstone in the gastrointestinal tract, which is termed the 'tumbling phenomenon'. Nausea, vomiting, intermittent cramps, and abdominal distention are symptoms that may suggest biliary ileus when preceded by a history of acute cholecystitis. In patients with biliary ileus, the following surgical procedures are performed: (1) enterolithotomy; (2) one-stage cholecystectomy with fistula repair; and (3) two-stage enterolithotomy, cholecystectomy, and fistula repair. The consensus suggests that enterolithotomy is the most suitable procedure for most patients; however, a one-stage procedure can be considered for those who are low-risk and have a good overall condition. In patients with persistent symptoms despite enterolithotomy, a two-stage procedure may be performed[90–94].

Future perspective on antibiotic resistance

Despite the recent improvements in the diagnosis and treatment of acute cholangitis, mortality still exceeds 15% in some categories of patients. Currently, microorganisms can be isolated relatively easily by collecting bile samples during minimally invasive endoscopic procedures. Antibiograms can be used to guide initial empirical antibiotic treatment, accelerate healing, and avoid the emergence of antibiotic resistance. The latest data from the literature show that, in recent years, there has been a spread of extended-spectrum β-lactamase-producing organisms, carbapenemase-producing bacteria, multidrug-resistant Acinetobacter, VRE, and methicillin-resistant Staphylococcus aureus, both in the community and in the nosocomial setting. Independent of other prognostic variables, such as malignant biliary obstruction and severe illness related to a poor result, a longer hospital stay, and a high death rate, an episode of infection with antibiotic-resistant bacteria was an episode. Even if international practical guidelines (such as TG18) provide a useful framework that helps many physicians choose the best empirical antibiotic therapy, without guidance from cultures and antibiograms from blood or bile aspirates, or even local susceptibility data, it is difficult to choose an appropriate antibiotic regimen. The latest data from the literature show that resistance to third-generation cephalosporins, the most used antibiotics in patients with acute cholangitis, reached up to 15%, E. coli-producing extended-spectrum beta-lactamases (ESBL) was detected in 31% of the patients, and that multiresistant Gram-negative bacteria were detected in up to 41% of the patients. Since antibiotic resistance rates vary greatly from country to country or region to region, national and local records are needed to provide guidance to physicians and limit antibiotic resistance[95,96].

Conclusion and future research directions

AC remains a serious, multifactorial, and life-threatening systemic disease that requires rapid diagnosis and an urgent and comprehensive approach. The diagnosis today is much simpler and more precise, with the help of more sensitive investigations, such as EUS or MRCP. Treatment is multidisciplinary, combining a powerful and guided antibiotic therapy with a much more modern, minimally invasive biliary de-obstruction technique that, once obtained, in most cases, ensures quick healing and thus prevents the occurrence of systemic or local complications. ERCP and EUS-guided procedures are the latest innovations that constitute the vast majority of treatment measures for these patients, leaving behind the classic surgical approach. In recent years, this

novel therapeutic procedure has led to the possibility of bile aspirates, microbiological cultures, and antibiograms, which can guide antibiotic therapy, accelerate healing, and prevent the emergence of antibiotic resistance.

There exist several gaps in literature surrounding acute cholangitis which we feel would be important to explicitly restate as potential research areas. Broadly speaking, there is a need for studies investigating the potential impact of modifiable risk factors, such as diet and lifestyle, the role of emerging diagnostic technologies in improving the recognition of the disease, and the effectiveness of various management approaches in different population subgroups. More specifically, some contradictory reports are observed and would benefit from systematic reviews and meta-analyses, speaking from the top of the hierarchy of evidence-based medicine, to provide pooled findings and clarity with consensus on such matters. These conflicting thoughts revolve around the association between lipid levels, coffee and tea intake and the occurrence of gallstones. Similarly, original studies could be based on establishing the role of cholestyramine and nicotinic acid in gallstone pathophysiology, the potential role of ursodeoxycholic acid, ascorbic acid and ezetimibe in the primary prevention of gallstone disease, an in-depth characterization of low phospholipid-associated cholestasis and cholelithiasis syndrome as part of the cholangitis associated syndromes, and the role of gall bladder stimulation with cholecystokinin octapeptide in patients under total parenteral nutrition. While these may not be exhaustive, the aforementioned form part of the key focus research areas that could be explored by future authors.

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Conceptualization and methodology: M.-A.C. and C.C.D. validation, M.-A.C., M.-A.G., and C.C.D.; formal analysis: M.-A.C., B.S.S., and A.D.; investigation: M.-A.C., M.R.M., A.N., and M. D.M.M.; resources: M.-A.C., R.C.S., and L.V.S.K.; data curation: M.-A.C., A.M.G., M.-A.G., and C.K.; writing—original draft preparation: M.-A.C., M.-A.G., and A.M.G.; writing—review and editing: M.-A.C., A.M.G., and C.C.D.; visualization: M.-A.C. and C.C.D.; supervision: M.-A.C., A.M.G. and C.C.D.; project administration: M.-A.C. and C.C.D; All authors have read and agreed to the published version of the manuscript.

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