Chapter

Infections of Biliary Tract

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Abstract

Biliary tract infections include cholangitis and cholecystitis. They are associated with high morbidity and mortality in elderly patients with comorbid disease. The most common infecting organisms are Enterobacteriaceae ascending from the gastrointestinal tract, Gram-positive pathogens like Enterococci spp.; the infections are rarely caused by fungi, viruses, and parasites. The prime reason for biliary tract infections is the ascending infection due to the reflux of duodenal contents and also the blood-borne infection or infection spreading through the portal-venous channels. The other predisposing conditions causing biliary tract infections include critical illnesses such as trauma, burns, sepsis, HIV infection, immunosuppression, diabetes, non-biliary surgery, and childbirth. The infection is reduced by β-lactam antibiotics or their derivatives, cephalosporins, carbapenems, fluoroquinolones, etc. Empiric treatment with piperacillin/tazobactam or a cephalosporin with or without metronidazole is recommended for moderate and severe acute cholecystitis irrespective of whether there is growth by culture. Patients with severe cholecystitis are unfortunately difficult to identify properly, both clinically and radiologically, because clinical symptoms are unexpected, and imaging investigations are frequently ambiguous. However, there are significant differences in morbidity and death rates between individuals with mild cholecystitis and those with severe cholecystitis. Preventing related consequences requires early identification and effective therapy of individuals at risk of severe cholecystitis.

Keywords: acute cholecystitis, bacteria, chronic cholecystitis, antibiotics, cholangitis

1. Introduction

Biliary tract infections, such as biliary colic, cholangitis, cholecystitis, and cholelithiasis, are the most commonly encountered health disorders globally as a result of bile duct obstruction. Gallstones are relatively prevalent in the United States and many other industrialized countries, and they are usually asymptomatic. Gallstones are projected to affect 25 million adults in the United States (Everhart et al.) [1]. Bacterial infection of the bile can result in severe morbidity and mortality [Sifri and Madoff] [2]. Bile stasis, inflammation, and the loss of mechanical barriers can all lead to bacterial infection of the bile, which can end in severe morbidity and death. Obstruction is hypothesized to cause increased intraluminal pressure, impaired blood supply and lymphatic drainage, and acute inflammation in the presence of supersaturated bile (Indar and Beckingham) [3]. The pathogenesis of biliary tract infections, the microbial pathogens involved, and antibiotic treatment options are discussed in this article.

2. Current scenario

Gallstone disease is a substantial health problem in developed countries, according to existing literature. Gallstones are believed to affect 10–15% of the general population, with considerable variations across nations. Gallstone-related problems affect between 20 and 40% of individuals with gallstones, with an annual incidence of 1–3%; acute calculus cholecystitis (ACC) is the first clinical manifestation in 10–15% of cases [4].

3. Anatomy of biliary tract

The gallbladder is a part of the digestive system. The gallbladder is a thin-walled sac with three anatomic parts: the fundus, corpus, and infundibulum [1]. It is normally located between both hepatic lobes. **Figure 1** depicts the gall bladder location in the human body, and **Figure 2** represents the gall bladder anatomy. The gallbladder empties into the cystic duct, a passive conduit with a mucosa comprising spiral valves and with a diameter of about 7 mm in humans (Valves of Heister). This duct has no sphincteric structure and empties into the common bile duct. As it enters the duodenal wall and forms the ampulla of Vater, the common bile duct passes through the head of the pancreas, finishing in the sphincter of Oddi [6].

Approximately, 10% of individuals are estimated to have one or more biliary duct abnormalities; however, not all of them are difficult to identify during surgery. The so-called triple confluence, which is an abnormality defined by simultaneous emptying of the right posterior duct, right anterior duct, and left hepatic duct into the common hepatic duct [Mortele and Ros] [7], is a frequent variation of the major hepatic biliary branching. The right hepatic duct is almost non-existent in individuals with this variation. The right posterior duct and its union with the right anterior or left hepatic duct are two more common anatomic variations of the biliary tree branching.

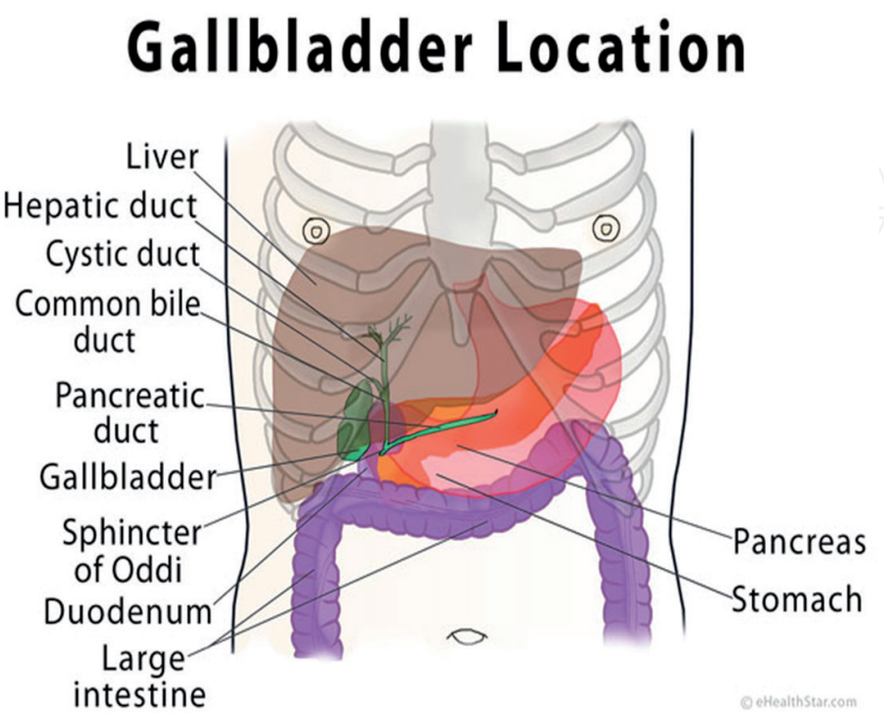

Figure 1.
Gallbladder lies beneath the lower liver edge at the bottom of the rib cage. (Jan Modric, 2017) [5].

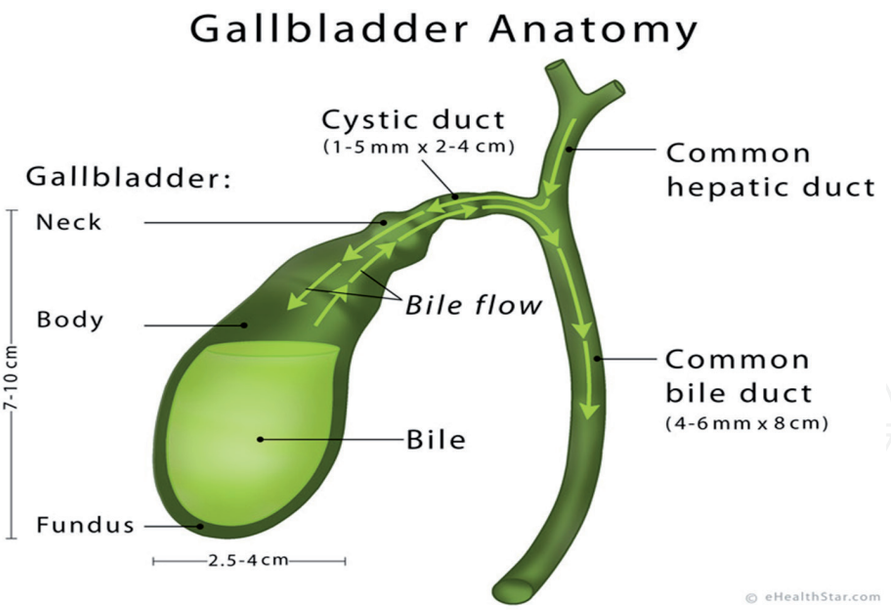

Figure 2.
Gallbladder parts and bile ducts (Jan Modric, 2017) [5].

As previously stated, the right posterior duct connects to the right anterior duct and unites it from the left to produce the right hepatic duct, which then connects to the left hepatic duct to form the common hepatic duct. The most prevalent anatomic variant of the biliary system is drainage of the right posterior duct into the left hepatic duct before its confluence with the right anterior duct.

Furthermore, various less common and usually more difficult anatomic variants of the bile ducts, which include both aberrant and auxiliary bile ducts, have been described. In a clinical setting, knowing the difference between an aberrant bile duct and an accessory bile duct is vital since an aberrant bile duct is the only bile duct draining a specific hepatic segment, whereas an accessory bile duct drains the same portion of the liver. Failure to recognize certain of these bile duct irregularities can lead to bile leakage and peritoneal membrane irritation (bile peritonitis). Endoscopic retrograde cholangiopancreatography is used to treat these leaks by inserting stents (ERCP). They can stop these leaks that arise from the common bile or cystic ducts [8–10].

4. The sphincter of Oddi: (anatomy and physiology)

The human sphincter of Oddi is approximately 10 mm in length and has a well-defined and strong musculature. The Oddi sphincter is physically and functionally distinct from the duodenum. Its myoelectrical and contractile patterns are distinct from those of the duodenum in terms of character and timing. The contractions of the human sphincter of Oddi occur at the same time; however, there may be minor variations in configuration that look peristaltic at times. Its principal function of serving as a bile flow resistor is compatible with the occurrence of synchronous contractions. Because of the sphincter of Oddi resistance, the constant hepatic production of bile is largely directed into the cystic duct and gallbladder during the fasting state, where it is stored and concentrated. During the diastolic phase, sphincter of Oddi phasic contractions and, during phase II, migrating motor complex occur when there is modest gallbladder contraction; hence, a tiny amount of bile escapes into the duodenum. The gallbladder contracts during digestion, emptying the majority of its contents, and bile is delivered to the duodenum *via* the cystic and common bile ducts, which pass *via* a relaxed sphincter of Oddi and

duodenum. Bile salts help in fat digestion and absorption in the duodenum and jejunum (triglycerides, cholesterol and phospholipids, and liposoluble vitamins). Therefore, transportation of bile salts to the terminal ileum takes place; there, most of them were recycled as part of the enterohepatic circulation through an active transport mechanism found in the terminal ileum's epithelial cells [6].

5. Sphincter of Oddi dyskinesia

Patients with sphincter of Oddi (SO) dyskinesia have biliary-like symptoms, which are frequently noticed after a cholecystectomy. The symptoms and signs of bile duct sphincter dysfunction are similar to those of temporary bile duct blockage, whereas pancreatic sphincter of Oddi dysfunction is linked to elevated pancreatic enzymes and even full-blown pancreatitis. Patients with sphincter of Oddi dysfunction are assessed with quantitative choledochoscintigraphy and/or sphincter of Oddi manometry tests to confirm the diagnosis, even if the preliminary investigation is defined by this functional entity by sphincter of Oddi manometry.

6. Chronic and acute cholecystitis

6.1 Pathogenesis

The most commonly stated hypothesis in the etiology of chronic and acute cholecystitis is that it is caused by gallstones migrating from the gallbladder obstructing the cystic duct or, in the event of big gallstones, that they intermittently obstruct the gallbladder's neck (Jose Behar) [6]. The inability to see the gallbladder in patients with acute cholecystitis has been attributed to a cystic duct occlusion. This observation has been validated clinically and pathologically in up to 97% of individuals with acute cholecystitis [Pare and Shaffer et al.] [11].

However, other explanations for this failure are more likely that.

A cystic duct obstruction would be caused by the gallbladder's acute inflammation and edema spreading to the cystic duct, or.

Because it is clogged with inflammatory fluids, an atonic gallbladder obstructs the entry of the bulk of the isotope-labeled agent. Furthermore, the severely inflamed gallbladder may be unable to distend passively due to edema or actively due to a faulty relaxation found in gallbladders with lithogenic bile containing high cholesterol contents [Xiao and Chen et al.] [12].

The appearance of cholecystitis associated only with lithogenic bile (acalculous gallbladder) or a single huge stone several times larger than the normal width of the cystic duct lumen further challenges the idea of cystic duct obstruction. Furthermore, the presence of acute inflammation on top of a chronically inflamed or atrophic fibrotic gallbladder has proven difficult to explain because it would imply recurring cystic duct obstruction events. It is more likely that the development of acute inflammation as a result of a chronic process had been in the works for a long time. Mucosal thickening, hypertrophic muscle layers, and macrophage infiltration of the lamina propria are common in gallbladders. In the absence of gallstones, chronic cholecystitis is commonly found histopathologically. They arise in people who are morbidly obese and have lithogenic bile but no gallstones. When compared with the normal mucosa in nonobese people, these gallbladders exhibit mucosal abnormalities consistent with chronic cholecystitis [Csendes et al.] [13]. The pathogenesis of chronic cholecystitis is shown in **Figure 3**. The gallbladder

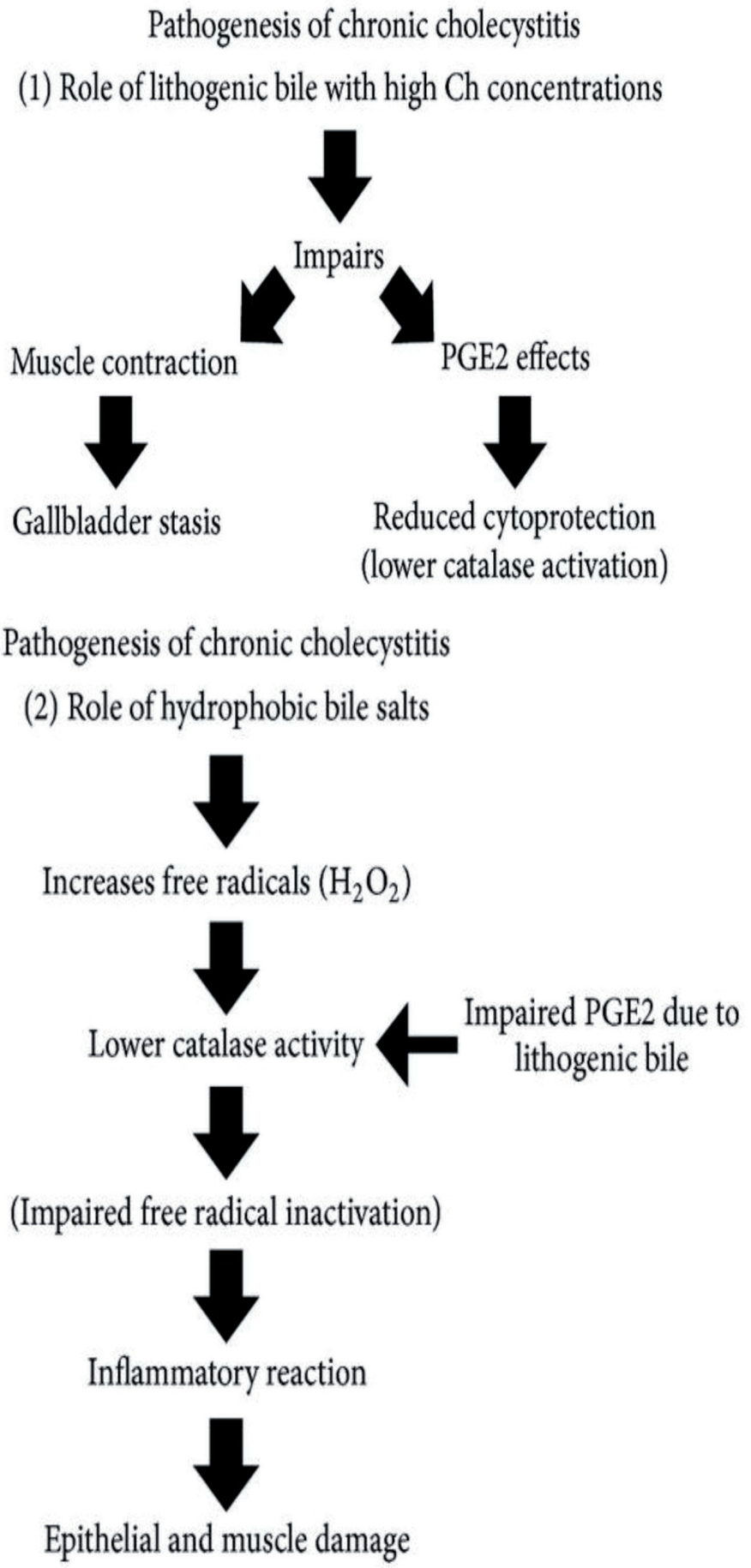

Figure 3.
Pathogenesis of chronic cholecystitis.

motility and cytoprotective functions are impaired by lithogenic hepatic bile with excess cholesterol, allowing the hydrophobic bile salts to induce chronic cholecystitis.

Finally, the results of the aforementioned human and animal studies strongly suggest that cholecystitis develops in the presence of lithogenic bile with high cholesterol concentrations, which creates a permissive environment for hydrophobic bile salts to increase oxidative stress levels and initiate the inflammatory process. Continuous entrance of hydrophobic bile salts into the diseased gallbladder is required for this inflammatory process [14].

7. Chronic cholecystitis clinical symptoms

Chronic cholecystitis patients may be asymptomatic or experience recurring episodes of epigastric and right upper quadrant (RUQ) discomfort that radiates often around the waist and toward the scapula. The pain is moderate to severe, and it is not postprandial but rather nocturnal in nature. It does not happen every day; instead, it happens every two to 3 weeks. Ultrasonography is usually used to make the diagnosis. Gallstones and gallbladder wall thickening can be detected using this test. Laboratory tests are normal. Gallstones are often asymptomatic, but because they are easily discovered in gallbladders by imaging investigations, they are blamed for a range of upper gastrointestinal problems. Gallstones are frequently blamed for nonspecific gastrointestinal symptoms such as persistent dyspepsia, gastroparesis, and irritable bowel syndrome. Patients with these functional disorders typically experience everyday upper gastrointestinal symptoms, which are often postprandial and triggered by fatty foods or large meals. Epigastric pain, nausea, and bloating are common complaints among these patients. Even while pathological investigations may indicate gallstones and histological evidence of persistent cholecystitis, cholecystectomy does not relieve these symptoms. Gallstones can go unnoticed for lengthy periods of time, according to several investigations, including autopsy studies. Most patients with asymptomatic gallstones remained symptom free for the whole 8-year follow-up period in a prospective Italian research [15–19].

8. Acute cholecystitis

In acute cholecystitis, chronic cholecystitis is the most prevalent risk factor. These patients often have abrupt onset of severe pain, which is commonly accompanied by nausea in 90% of instances and vomiting in 50% of cases.

Physical examination indicates epigastric, right upper quadrant, and positive Murphy sign pain, with rebound soreness in severe instances. However, doctors must rule out other acute abdominal diseases such as acute appendicitis, particularly with a retrocecal appendix, acute pancreatitis, localized perforated peptic ulcer, intestinal perforation, or ischemia before considering this diagnosis. These clinical entities exhibit comparable characteristics in terms of demographics and risk factors. Physical examination indicates abdominal pain that can be localized or widespread, as well as a significant decrease in bowel sounds, in these individuals who complain of severe stomach pain, nausea, and vomiting.

Acute cholecystitis is defined as an acute inflammation of the gall bladder. Chronic cholecystitis, acute pancreatitis, diverticulitis, colitis, appendicitis, Fitz-Hugh-Curtis syndrome, ureteral stone, and omental infarction are all illnesses that can cause acute right upper quadrant (RUQ) discomfort [20, 21]. It can occur abruptly in conjunction with gallstones (acute calculous cholecystitis) or less

frequently without gallstones (acute calculous cholecystitis) (acalculous cholecystitis). Gallstones affect more than 80% of persons who are asymptomatic. Acute cholecystitis is a complication of gallstone disease that usually arises in people who have had symptomatic gallstones in the past. Delayed management can lead to increased morbidity, due to progression to severe cholecystitis, such as gangrenous change, abscess formation, and gallbladder perforation [4].

9. Microorganisms in biliary tract infections

The majority of cases of acute cholecystitis are caused by an impacted gallstone blocking the gallbladder outlet, resulting in an increase in intraluminal pressure, gallbladder distension, and wall edema, and eventually gallbladder necrosis. During the early stages of acute cholecystitis, bile is normally sterile, and infection occurs as a side effect.

Biliary tract infection is a prevalent cause of bacteremia and is linked to a high rate of morbidity and mortality, especially in elderly individuals with comorbid conditions or when diagnosis and treatment are delayed. Enterobacteriaceae, which climb from the gastrointestinal system, are the most prevalent infectious organisms. Complications such as acute renal failure and septic shock are more likely in patients with bacteremia.

9.1 Bacterial causes of biliary tract infections

The most frequently identified pathogens are Gram-negative microorganisms, primarily *Escherichia coli*, *Salmonella enteritidis*, *Acinetobacter baumannii*, *Citrobacter freundii*, *Enterobacter cloacae*, and *Klebsiella* species. Within Gram-positive microorganisms, *Clostridium perfringens* is most commonly observed. Previous research has linked biliary infection with gallstone development and indicated that bacteria may act as the nucleating factor initiating the formation of both pigment and cholesterol gallstones. Many studies [22, 23] had established the coexistence of biofilm-forming bacteria in bile and gallbladder/gallstones (*Pseudomonas aeruginosa, E. coli, Klebsiella pneumoniae, Enterococcus* spp. and *Acinetobacter* spp.) in different combinations, and the presence of *Capnocytophaga* spp., *Lactococcus* spp., *Bacillus* spp., *Staphylococcus haemolyticus*, *Enterobacter* or *Citrobacter* spp., *Morganella* spp., *Salmonella* spp., and *Helicobacter pylori*.

All of the microbiological studies that led to the selection of these antibiotic regimens were carried out using standard culture methods. Recent studies of microbial detection by culture- vs. culture-free identification of microbial DNA by next-generation sequencing (NGS) for various purulent diseases have shown that traditional culture only identifies a portion of the bacteria present. Additionally, in some Asian countries, the presence of *H. pylori* has been detected infrequently in the gallbladder by PCR. Other molecular tools like RAPD fingerprinting, *cagA* gene detection, which represent a good marker for genome-sequencing projects, are available nowadays to detect the microbial strains causing infections in AC patients [24].

9.2 ESKAPE pathogens and role of bile in development of drug resistance

Bile has bactericidal activity. However, many pathogens are known to resist the bactericidal activity of bile and utilize this host component as a localization signal to regulate virulence gene expression and enhance infection. Furthermore, strategies employed by pathogens to resist bile align with antibiotic resistance

mechanisms. The efflux pump genes, *acrAB* in *E. coli*, *Salmonella*, *Shigella*, *Klebsiella*, and other pathogens, resist both bile salts and antibiotics, thereby making it essential for survival under extreme environmental conditions [25–28].

The ESKAPE group of pathogens (*Enterococcus, Staphylococcus, Klebsiella, Acinetobacter, Pseudomonas, and* Enterobacter) represents a significant public health threat as antibiotic resistance rates rise from the acquisition of multiple resistance mechanisms involving the gene expression of BSH, Gls24, GlsB, EmrB/QacA, PrkC, LiaFSR, BsrXRS, MnhF, WTA, OxyR, CpxAR, KpnO, KpnEF, CadC, TdcA, Gal ET, *pgaABCD*, *pqsABCDE*, ExoU, T6SS genes or through biofilm production, etc. Many ESKAPE pathogens are not known to cause infection in the gastrointestinal system; nevertheless, isolation from bile, the gallbladder, pancreatic or biliary stent biofilms, and bile duct infections have been described, and antibiotic resistance is frequently identified. Given a previous research that found positive bile cultures in 22.2% of the cases following elective gallbladder removal surgery, the findings are not restricted to hospital-based infections. Enterococcus spp. was the most frequent bacterial isolate found in the bile samples, followed by *E. coli*, *Klebsiella* spp., *Enterobacter* spp., and *Pseudomonas* spp.; 22.7% of these isolates were antibiotic-resistant. Furthermore, bile exposure in the lungs of CF patients has been shown to affect *Staphylococcus aureus, A. baumannii,* and especially *P. aeruginosa* infection. Growth was either consistent or increased in the presence of human bile, respectively, for *E. coli* or *Enterococcus faecalis*. Furthermore, bile reduced the antimicrobial activity of ciprofloxacin, meropenem, and tigecycline for *E. coli*, while linezolid and tigecycline had reduced activity against *E. faecalis* [29].

9.3 Rare cases of acute cholecystitis caused by microorganisms

Berinson et al. [30] reported one rare case of AC caused by *Kosakonia cowanii*, formerly known as *Enterobacter cowanii*, which is a Gram-negative bacillus belonging to the order *Enterobacterales*. The species is usually recognized as a plant pathogen and has only anecdotally been encountered as a human pathogen. A cholecystectomy confirmed the diagnosis of acute cholecystitis with partial gall bladder necrosis. By MALDI-TOF, 16S-rRNA analysis, and whole-genome sequencing, a surgical material produced pure cultures of Gram-negative rods that were clearly identified as K. cowanii.

Deering et al. [31] reported a rare case of acute cholecystitis caused by *Streptococcus bovis* biotypes (I & II), a Gram-positive, catalase-negative, anaerobic coccus found as a commensal inhabitant of the digestive system in 16% of healthy people. The patient was treated with tazobactam/piperacillin and later on subjected to laparoscopic cholecystectomy.

Vogt et al. [32] reported isolated Serogroup O1 *Vibrio cholerae* in an 83-year-old man suffering from AC. The Gram stain of the body fluid specimen demonstrated rare Gram-negative rods and many polymorphonuclear lymphocytes. The organism was positive for oxidase, and the results obtained using a Neg Breakpoint Combo Panel Type 41 (NBC41) and a MicroScan WalkAway Plus system (Siemens Healthcare Diagnostics, Deerfield, IL) identified the organism as *V. cholerae*, with 97.76% probability. The isolate was also tested using a manual API 20E Gram-negative identification panel (bioMerieux, Inc.,), which yielded a code of 5,347,124, giving a presumptive identification of *V. cholerae* at 99.9%.

9.4 Viral causes of biliary tract infections

In comparison with bacterial infections, viral infections of the biliary tract are less common and less discussed. Viral infections frequently occur as a result of a

liver infection or as part of a systemic viral illness. Viruses seldom cause primary liver infection. Cholangitis, or inflammation of the bile duct, is a very frequent symptom. Despite the fact that hepatotropic viruses (A, B, C, and E) are commonly thought of as hepatocellular pathogens, cholangitic symptoms are now widely documented in conjunction with these disorders [10, 14, 23, 33]. Cholangitis is also due to systemic viral infections in different proportions to hepatitis. The human immunodeficiency virus (HIV) is linked to a variety of liver problems, including cholangitis. Other systemic viruses, most notably members of the herpes virus family, can induce hepatic illness in both immunocompromised and immunocompetent individuals, including cholangitis and potentially ductopenia [34].

9.5 Parasitic causes of biliary tract infections

Cholangitis can be caused due to a variety of reasons, including biliary calculi, strictures, parasites, post-endoscopic retrograde cholangiopancreatography (ERCP), postoperative, and so on. Biliary parasitoses, in contrast to other causes, are more prevalent in many nations. Ascaris lumbricoides, liver flukes, and Echinococcus are common parasites that affect the biliary system. The trematodes (flukes) that commonly infect the human biliary tract include *Clonorchis sinensis, Opisthorchis viverrini, Opisthorchis felineus, and Fasciola hepatica.* The majority of patients are asymptomatic. While entering through the bile duct, they cause biliary colic and obstructive jaundice. The parasites reside in the intrahepatic bile ducts and, occasionally, in the extrahepatic bile ducts, gallbladder, and pancreatic duct. The result is mechanical obstruction, inflammatory reaction, adenomatous hyperplasia, and periductal fibrosis. The parasite can be examined through radiological findings of CT and MRI [35].

9.6 Diagnosis

The diagnostic criteria include examining for signs of local inflammation, such as Murphy's sign, the presence of a mass, pain, or tenderness located in the upper right quadrant of the abdomen. The local inflammation is often accompanied by systemic inflammation, indicated by signs of fever, increased white blood cell (WBC) counts, and elevated levels of C-reactive protein. The severity of acute cholecystitis can range from mild and self-limiting to severe and potentially life threatening [36, 37]. Several imaging techniques such as ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT) are necessary to accurately diagnose both the typical and atypical cases of acute cholecystitis. Recently, Amini et al. had used high mobility group box protein 1 (HMGB1) biomarker for acute cholecystitis diagnosis [38].

9.6.1 Diagnosis of cholecystitis

For the consensus in diagnosis of cholecystitis in 2007, the Tokyo guidelines for the management of acute cholangitis and cholecystitis (TG07) were formed and widely adopted. In 2013, the updated Tokyo guidelines (TG13) for acute cholangitis and acute cholecystitis were released for severity grading of acute cholecystitis [37] (**Table 1**).

9.6.2 TG07 severity assessment criteria

The severity assessment criteria were first presented throughout the world in TG07 by Hirota and Takada, [37] where the severity grading of acute cholecystitis

Local signs of inflammation, etc.
Murphy's sign
RUQ Mass/pain/tenderness
Systemic signs of inflammation, etc.
Fever
Elevated CRP
Elevated WBC count
Imaging findings
Imaging findings characteristic of acute cholecystitis
Suspected diagnosis: One item in A + one item in B
Definitive diagnosis: One item in A + one item in B + C
Acute hepatitis, other acute abdominal diseases, and chronic cholecystitis should be excluded. RUQ-right upper abdominal quadrant, CRP-C-reactive protein, WBC-white blood cell.

Table 1.
TG13 diagnostic criteria for acute cholecystitis.

was classified into the following three categories: "mild (Grade I)," "moderate (Grade II)," and "severe (Grade III)."

Mild (Grade I) acute cholecystitis occurred in a patient with no signs of organ failure and mild gallbladder illness, allowing cholecystectomy to be performed safely and with minimal risk. The severity score for these individuals in TG07 does not fulfill the criteria for "moderate (Grade II)" and "severe (Grade III)" acute cholecystitis.

Acute cholecystitis, in which the degree of acute inflammation is expected to be linked with greater operating difficulties in completing cholecystectomy, was classified as moderate (Grade II) acute cholecystitis [8, 9, 16].

Severe (Grade III) acute cholecystitis was defined as acute cholecystitis associated with organ dysfunction (**Table 2**).

Reference: Masamichi et al. [19].

9.7 Treatment

Acute cholecystitis is often treated promptly by cholecystectomy or percutaneous cholecystostomy and antibiotic therapy in high-risk patients. Antimicrobial treatment has a different role depending on the severity of the illness and its etiology. Because it is unclear if bacteria have a role in grade I acute cholecystitis, antimicrobial treatment is used to prevent infection before cholecystectomy. Antimicrobial treatment is therapeutic and necessary for grade II acute cholecystitis until the gallbladder is removed. Most patients with bacteremia might have clinical deterioration and can be classified as grade III acute cholecystitis and are therefore not suitable for surgery. A recent meta-analysis reported that cholecystography has the highest diagnostic accuracy for detection of acute cholecystitis [39].

Previous studies have found bile to be infected in 9–42% of patients who underwent elective laparoscopic cholecystectomy, but the incidence of culture-positive bile increased to 35–65% of patients with acute cholecystitis [40]. Antimicrobial treatment is critical for reducing both the systemic septic response and local inflammation following cholecystectomy in individuals with moderate-to-severe acute cholecystitis [41]. Those with septic shock should get appropriate antibiotic treatment within 1 hour of diagnosis, and patients who are less severely sick should receive it within 6 hours. Bile culture results, however, cannot be acquired promptly after admission, and bile culture necessitates percutaneous gallbladder puncture. As a result, the most successful empiric antibiotics described in the literature are used as the basis for first antimicrobial treatment [42].

Associated with dysfunction of any one of the following organ/systems	
Cardiovascular dysfunction	**Hypotension requiring treatment with dopamine >5 ub/kg per min, or any dose of norepinephrine**
Neurologic dysfunction	Decreased level of consciousness
Respiratory dysfunction	Pa2O/FiO2 ratio < 300
Renal dysfunction	Oluguria, creatinine >2.0 mg/dl
Hepatic dysfunction	PT – INR > 1.5
Hematological dysfunction	Platelet count <100,000/mm^3
Grade II (moderate) acute cholecystitis	
Associated with any one of the following conditions: 1. Elevated white blood cell count ([18,000/mm^3) 2. Palpable tender mass in the right upper abdominal quadrant 3. Duration of complaints (72 h) 4. Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, and emphysematous cholecystitis)	
Grade I (mild) acute cholecystitis	
Does not meet the criteria of "Grade III" or "Grade II" acute cholecystitis. Grade I can also be defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.	

Table 2.
TG 13 severity grading for acute cholecystitis.

Because most infections in acute cholecystitis are limited to the gallbladder, sampling should be done directly from the infection site in order to identify the true causative pathogen. Bile specimens collected from the biliary tract using percutaneous transhepatic biliary drainage (PTBD) or endoscopic nasobiliary drainage (ENBD) are potentially associated with microbial contamination [43].

Bacterial infection is commonly reported in 50 to 90% of the cases. Most of the studies reported the involvement of polymicrobial infections in AC, which were often treated with antibiotic regimens with two or more antibiotics, but only one study had reported that monomicrobial growth was involved in AC. The most common presumptive antibiotics used in AC are ceftriaxone (2gm, IV, OD) or piperacillin/tazobactam (4.5 gm, IV, 8 hourly) or cefoperazone/sulbactam (3gm, IV, 12 hourly) for 7 to 10 days. The second-line or alternative antibiotics is imipenem (500 mg, IV, 6 hourly) or meropenem (1gm, IV, 8hourly) for 7 to 10 days. The most commonly isolated microorganisms among pathogens in positive bile cultures are Enterococci species, non-*faecium* enterococci (*Enterococcus faecalis*, *Enterococcus gallinarum*, *Enterococcus casseliflavus*, *Enterococcus avium*), *Escherichia Coli*, and *Klebsiella* species [44]. Gram-positive microbes, such as Enterococci, have become less common over time, whereas Gram-negative germs, particularly Enterobacteriales, have become more common and are most typically isolated among patients with acute cholecystitis. The results of local antimicrobial susceptibility tests, as well as information of the likely infecting microorganisms, pharmacokinetics/pharmacodynamics, and adverse reactions/effects of available medicines, must all be considered when making antimicrobial therapy decisions (local antibiogram). The severity of the illness and previous antimicrobial exposure are also important considerations in deciding the best course of treatment. β-lactam antibiotics or their derivatives, cephalosporins, carbapenems, fluoroquinolones,

and other antibiotics diminish infection. For moderate and severe acute cholecystitis, empiric treatment with piperacillin/tazobactam or a cephalosporin with or without metronidazole is advised, regardless of whether or not there is growth on culture [45].

Broad-spectrum β-lactam and β-lactamase inhibitors, such as ampicillin-sulbactam, have been recommended as the first-line drugs to treat Enterococci and non-*faecium* enterococci infections. However, these microorganisms are reported to be resistant to most of the classes of antibiotics represented earlier. VREFM (vancomycin-resistant *Enterococcus faecium*) was reported for the first time in 2021 by Suk-Won et al. [46]. The authors found that the majority of the patients were suffering from Grade II acute cholecystitis (94.7%). Hence, they recommended other antibiotics, such as linezolid and tigecycline, which provide good coverage against VREFM, should be considered for patients with such advanced infections. Tigecycline can be used in several other cases because of its broad spectrum of effectiveness against Gram-negative microorganisms, including ESBL-producing bacteria. Tasina et al. [47] reported poor effectiveness of tigecycline toward a severely ill patient with AC.

Piperacillin-tazobactam and third- or fourth-generation cephalosporins are indicated as first-line antibiotics for Gram-negative bacteria, with fluoroquinolones and carbapenems as second-line antibiotics, depending on the severity of the infection and antimicrobial susceptibility patterns. According to Gomi et al. [48], most identified strains were resistant to ciprofloxacin due to widespread use of the antibiotic by the community, whereas 20% of pathogenic bacteria were resistant to ceftriaxone. As a result, in such circumstances, piperacillin-tazobactam or cefepime, which have larger spectra and lower resistance rates, are indicated. Carbapenem and tigecycline are advised for patients who are taking antibiotics on a regular basis. However, because of widespread medication resistance and associated high morbidity and mortality rates, carbapenem-resistant strains (CRE) species have emerged as major healthcare-related diseases [49].

9.7.1 Empiric antibiotic treatment of community-acquired biliary tract infections (CA-BTI)

The most important approach in controlling the CA-BTI is the primary source controls such as biliary drainage, removal of biliary tract stones, and cholecystectomy. The primary source control can help the antibiotics to penetrate the biliary tract, resulting in a better bactericidal effect when biliary obstruction is present. While it comes to medical therapy, there are two crucial variables to consider when choosing empiric antibiotics. Administration of antibiotics is essential for the treatment of BTI, in addition to primary source control. As the BTI is caused by endogenous etiological agents, that is, gastrointestinal tract flora, such as Escherichia coli, Klebsiella spp., Enterococci spp., Bacteroides spp., antibiotics that are effective against these organisms are usually used empirically to treat BTI rather than definite therapy. However, the usage of inappropriate empiric antibiotics may also incur fatal outcomes. To elicit positive treatment responses, >80% of the presumed causative microorganisms should be sensitive to antibiotics, and for patients with septic shock, the susceptibility rates should even exceed 100% [50]. Next, the antibiotics must be present in adequate concentrations at the infection sites to have the desired antimicrobial action [51, 52]. **Table 3** shows the antibiotics usually used to treat biliary tract infections based on their biliary penetration ability (indicated by the ratio of bile-to-serum concentrations [53–55].

Augmentin = amoxicillin + clavulanate; Bile/serum = bile concentration/serum concentration; Tazocin: Piperacillin + tazobactum; Unasyn = ampicillin + sulbactum.

Good penetration efficiency (>1)		**Low-penetration efficiency (<1)**	
Antibiotics	**Bile/serum**	**Antibiotics**	**Bile/serum**
Tazocin	60	Cefotaxime	0.75
Tigecycline	38	Meropenem	0.75
Augmentin	30	Ceftazidime	0.5
Ciprofloxacin	30	Vancomycin	0.5
Unasyn	9	Amikacin	0.3
Ceftriaxone	5	Gentamycin	0.3
Levofloxacin	5	Cefipime	0.1
Penicillin G	5	Imepenem	0.01
Cefazolin	3		
Clindamycin	3		
Doripenem	1.17		
Cefuroxime	1		
Metronidazole	1		

Table 3.
Antibiotics frequently used to treat biliary tract infections and their biliary penetration ability (indicated as the ration of bile to serum concentrations).

As a result, when choosing empiric antibiotics for the treatment of BTI, both susceptibility rates and the potential of biliary penetration should be taken into account. **Table 3** lists the antibiotics often used to treat BTI, as well as their biliary penetration ability (measured as the ratio of bile-to-serum concentrations). Only individuals with a reasonable ratio (>1) of bile-to-serum concentrations (**Table 3**) could be candidates for empiric antibiotics for BTI, according to the criteria outlined earlier. The local antimicrobial susceptibility patterns of the usual causative agents for BTI should also be considered when prescribing appropriate empiric antibiotics. To ensure a positive outcome, only those with a 20% resistance rate should be used as empirical antibiotics.

Patients with severe cholecystitis are unfortunately difficult to identify effectively, both clinically and radiologically, because clinical presentations are unpredictable, and imaging findings are frequently ambiguous. However, there are significant differences in morbidity and fatality rates between patients with uncomplicated cholecystitis and those with severe cholecystitis. Preventing related consequences requires early detection and careful management of patients at risk of severe cholecystitis.

10. Conclusions

When acute cholecystitis is suspected, bile samples are taken for microbiology culture and sensitivity testing, and antibiotics are prescribed once the diagnosis has been established. The antibiotics of choice are parenteral cephalosporin or ampicillin, as well as aminoglycosides. The antibiotic regimen chosen is based on the severity of the clinical presentation. Because acute suppurative cholangitis with biliary blockage has a high pre- and postoperative mortality rate, comprehensive antimicrobial therapy is required following biliary decompression. Bile microbiological analysis is an expedient diagnostic tool for determining more suitable medication and generating local antibiotic guidelines for the treatment of biliary tract infections.

Conflict of interest

No potential conflict of interest was reported by the authors.

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References

[1] Everhart JE, Khare M, Hill M, et al. Prevalence and ethnic differences in gallstone disease in the United States. Gastroenteriology. 1999;**117**:632-639

[2] Sifri CD, Madoff LC. Infections of the liver and biliary system. In: Mandell GI, Je B, Dolin R, editors. Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases. 7th ed. Churchill Livingstone Elsevier; 2010

[3] Indar AA, Beckingham JJ. Acute cholecystitis. BMJ. 2002;**325**:639-643

[4] Wadhwa V, Jobanputra Y, Garg SK, Patwardhan S, Mehta D, Sanaka MR. Nationwide trends of hospital admissions for acute cholecystitis in the United States. Gastroenterology Report (Oxf). 2017;**5**(1):36-42. DOI: 10.1093/gastro/gow015

[5] Jan Modric. Gallbladder Anatomy and Function. 2017. Available from: https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.ehealthstar.com%2Fanatomy%2Fgallbladder&psig=AOvVaw0Bbqz_bOLIoCUjv1R7KeBM&ust=1625739131352000&source=images&cd=vfe&ved=2ahUKEwi4rNKs3NDxAhUHGCsKHfKRCRkQr4kDegQIARBc

[6] Behar J. Physiology and pathophysiology of the biliary tract: The gallbladder and sphincter of Oddi-a review. ISRN Physiology. 2013;**2013**:1-15. DOI: 10.1155/2013/837630

[7] Mortele KJ, Ros PR. Anatomic variants of the biliary tree: MR cholangiographic findings and clinical applications. American Journal of Roentgenology. 2001;**177**(2):389-394

[8] Brodsky A, Matter I, Sabo E, Cohen A, Abrahamson J, Eldar S. Laparoscopic cholecystectomy for acute cholecystitis: Can the need for conversion and the probability of complications be predicted? A prospective study. Surgical Endoscopy. 2000;**14**:755-60. 45

[9] Teixeira JP, Sraiva AC, Cabral AC, Barros H, Reis JR, Teixeira A. Conversion factors in laparoscopic cholecystectomy for acute cholecystitis. Hepato-Gastroenterology. 2000;**47**:626-30. 46

[10] Rosh A, Manko J. Cholangitis. Available from: eMedicine.com. 2006

[11] Pare P, Shaffer EA, Rosenthall L. Nonvisualization of the gallbladder by 99m Tc-HIDA cholescintigraphy as evidence of cholecystitis. Canadian Medical Association Journal. 1978;**118**(4):384-386

[12] Xiao ZL, Chen Q, Amaral J, Biancani P, Behar J. Defect of receptor-G protein coupling in human gallbladder with cholesterol stones. American Journal of Physiology. 2000;**278**(2):G251-G258

[13] Csendes A, Burdiles P, Smok G, Csendes P, Burgos A, Recio M. Histologic findings of gallbladder mucosa in 87 patients with morbid obesity without gallstones compared to 87 control subjects. Journal of Gastrointestinal Surgery. 2003;**4**(7):547-551

[14] Kinney TP. Management of ascending cholangitis. Gastrointestinal Endoscopy Clinics of North America. 2007;**17**:289-306

[15] Jones MW, Gnanapandithan K, Panneerselvam D, et al. Chronic Cholecystitis. Treasure Island (FL): StatPearls Publishing; 2021

[16] Rattner DW, Ferguson C, Warshaw AL. Factors associated with successful laparoscopic cholecystectomy for acute cholecystitis. Annals of Surgery. 1993;**217**:233-6. 48

[17] Araujo-Teixeria JP, Rocha-Reis J, Costa-Cabral A, Barros H, Saraiva AC, Araujo-Teixeira AM. Laparoscopic versus open cholecystectomy for cholecystitis (200 cases). Comparison of results and predictive factors for conversion. Chirurgie. 1999;**124**:529-535 (in French with English abstract). 49.

[18] Merriam LT, Kanaan SA, Dawes JG, Angelos P, Prystowsky JB, Rege RV, et al. Gangrenous cholecystitis: Analysis of risk factors and experience with laparoscopic cholecystectomy. Surgery. 1999;**126**:680-685

[19] Masamichi Y, Tadahiro T, Steven MS, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). Journal of Hepato-Biliary-Pancreatic Sciences. 2013;**20**:35-46

[20] Hanbidge AE, Buckler PM, O'Malley ME, et al. From the RSNA refresher courses: Imaging evaluation for acute pain in the right upper quadrant. Radiographics. 2004;**24**: 1117-1135

[21] Kim SW, Kim HC, Yang DM, et al. Cystic duct enhancement: a useful CT finding in the diagnosis of acute cholecystitis without visible impacted gallstones. AJR. American Journal of Roentgenology. 2015;**205**:991-998

[22] Lee CC, Chang IJ, Lai YC, et al. Epidemiology and prognostic determinants of patients with bacteraemic cholecystitis or cholangitis. The American Journal of Gastroenterology. 2007;**102**:563-569

[23] Flores C, Maguilnik I, Hadlich E, Goldani LZ. Microbiology of choledochal bile in patients with choledocholithiasis admitted to a tertiary hospital. Journal of Gastroenterology and Hepatology. 2003;**18**:333-336

[24] Backert S, Tegtmeyer N, Oyarzabal OA, et al. Unusual Manifestation of Live *Staphylococcus saprophyticus, Corynebacterium urinapleomorphum*, and *Helicobacter pylori* in the Gallbladder with Cholecystitis. International Journal of Molecular Sciences. 2018;**19**(7):1826. DOI: 10.3390/ijms19071826

[25] Pos KM. Drug transport mechanism of the AcrB efflux pump. Biochimica et Biophysica Acta. 2009;**1794**:782-793. DOI: 10.1016/j.bbapap.2008.12.015

[26] Seeger MA, Diederichs K, Eicher T, Brandstatter L, Schiefner A, Verrey F, et al. The AcrB efflux pump: conformational cycling and peristalsis lead to multidrug resistance. Current Drug Targets. 2008;**9**:729-749. DOI: 10.2174/138945008785747789

[27] Sistrunk JR, Nickerson KP, Chanin RB, Rasko DA, Faherty CS. Survival of the fittest: How bacterial pathogens utilize bile to enhance infection. Clinical Microbiology Reviews. 2016;**29**:819-836. DOI: 10.1128/CMR.00031-16

[28] Begley M, Gahan CG, Hill C. The interaction between bacteria and bile. FEMS Microbiology Reviews. 2005;**29**:625-651. DOI: 10.1016/j.femsre.2004.09.003

[29] Kevin Gipson S et al. The Great ESKAPE: Exploring the crossroads of bile and antibiotic resistance in bacterial pathogens. Infection and Immunity. 2020;**88**(10):5-19

[30] Berinson B, Bellon E, Christner M, Both A, Aepfelbacher M, Rohde H. Identification of Kosakonia cowanii as a rare cause of acute cholecystitis: Case report and review of the literature. BMC Infectious Diseases. 2020;**20**(1):366. DOI: 10.1186/s12879-020-05084-6

[31] Deering EM, Muravec Z, Castineira CF, O'Donoghue G. Streptococcus bovis-related cholecystitis. BML Case Reports.

2013;**2013**:bcr2013008581. DOI: 10.1136/bcr-2013-008581

[32] Vogt AP, Doshi RK, Higgins JE, Burd EM, Ribner BS, Kraft CS. Acute cholecystitis caused by nontoxigenic Vibrio cholerae O1 Inaba. Journal of Clinical Microbiology. 2010;**48**(3):1002-1004. DOI: 10.1128/JCM.02198-09

[33] Shivaprakasha S, Harish R, Dinesh KR, Karim PM. Aerobic bacterial isolates from choledochal bile at a tertiary hospital. Indian Journal of Pathology & Microbiology. 2006;**49**:464-467

[34] Gupta E, Anita C. Viral infections of the biliary tract. Saudi Journal of Gastroenterology. 2008;**14**(3):158-160

[35] Lim JH, Kim SY, Park CM. Parasitic diseases of the biliary tract. AJR. 2007;**188**:1596-1603

[36] Porter NL. Diseases of the gallbladder and bile ducts. Essentials. 2009;**64**

[37] Hirota M, Takada T, Kawarada Y, Nimura Y, Miura F, Hirata K, et al. Diagnostic criteria and severity assessment of acute cholecystitis: Tokyo guidelines. Journal of Hepato-Biliary-Pancreatic Surgery. 2007;**14**(1):78-82

[38] Amini M, Pakdaman A, Shapoori S, Mosayebi G. High mobility group box-1 (HMGB1) protein as a biomarker for acute cholecystitis. Reports of Biochemistry and Molecular Biology. 2019;**7**(2):204-209

[39] Pisano M et al. 2020 World Society of Emergency Surgery updated guidelines for the diagnosis and treatment of acute calculus cholecystitis. World Journal of Emergency Surgery. 2020;**15**:161. DOI: 10.1186/s13017-020-00336-x

[40] Ruan H-Q, Liao G-L, Peng P, Liu S-Q, et al. Microbial profiles and risk factors of preexisting biliary infection in patients with therapeutic endoscopy. Gastroenterology Research and Practice. 2019;**2019**:1527328, 8 pages. DOI: 10.1155/2019/1527328

[41] Rello J et al. Critical Care Infectious Diseases Textbook. Kluwer Academic Publishers; 2001

[42] Galili O et al. The effect of bactibilia on the course and outcome of laparoscopic cholecystectomy. European Journal of Clinical Microbiology & Infectious Diseases. 2008;**27**:797-803. DOI: 10.1007/s10096-008-0504-8

[43] Van den Hazel SJ, Speelman P, Tytgat GN, Dankert J, van Leeuwen DJ. Role of antibiotics in the treatment and prevention of acute and recurrent cholangitis. Clinical Infectious Diseases. 1994;**19**:279-286. DOI: 10.1093/clinids/19.2.279

[44] Rhodes A et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Medicine. 2017;**43**: 304-377. DOI: 10.1007/s00134-017-4683-6

[45] Yun SP, Seo HI. Clinical aspects of bile culture in patients undergoing laparoscopic cholecystectomy. Medicine. 2018;**97**:e11234. DOI: 10.1097/MD.0000000000011234

[46] Suh SW, Choi YS, Choi SH, et al. Antibiotic selection based on microbiology and resistance profiles of bile from gallbladder of patients with acute cholecystitis. Scientific Reports. 2021;**11**(1):2969. DOI: 10.1038/s41598-021-82603-8

[47] Tasina E, Haidich AB, Kokkali S, Arvanitidou M. Efficacy and safety of tigecycline for the treatment of infectious diseases: A meta-analysis. The Lancet Infectious Diseases. 2011;**11**:834-844. DOI: 10.1016/S1473-3099(11)70177-3

[48] Gomi H et al. Tokyo Guidelines 2018: Antimicrobial therapy for acute

cholangitis and cholecystitis. Journal of Hepato-Biliary-Pancreatic Sciences. 2018;**25**:3-16. DOI: 10.1002/jhbp.518

[49] Tischendorf J, de Avila RA, Safdar N. Risk of infection following colonization with carbapenem-resistant Enterobactericeae: A systematic review. American Journal of Infection Control. 2016;**44**:539-543. DOI: 10.1016/j.ajic.2015.12.005

[50] Bradley JS, Dudley MN, Drusano GL. Predicting efficacy of antiinfectives with pharmacodynamics and Monte Carlo simulation. The Pediatric Infectious Disease Journal. 2003;**22**:982e92

[51] Varghese JM, Roberts JA, Lipman J. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. Critical Care Clinics. 2011;**27**:19e34

[52] Sharma S, Kumar A. Antimicrobial management of sepsis and septic shock. Clinics in Chest Medicine. 2008;**29**:677e87

[53] Cunha BA. Antibiotics essentials. In: Brogard JM, Pinget M, Arnaud JP, Dorner M, Lavillaureix J, editors. Biliary excretion of cefuroxime. Experimental and human study. Chemotherapy. 11th ed. Vol. 27. Burlington: Jones & Bartlett Learning; 2012, 1981. p. 526e718, 18e28

[54] Hukagawa H, Noga K. A study on the concentrations of levofloxacin in the gallbladder tissue and bile of patients. The Japanese Journal of Antibiotics. 1992;**45**:253e7

[55] Nielsen ML, Justesen T. Excretion of metroindazole in human bile. Investigations of hepatic bile, common duct bile, and gallbladder bile. Scandinavian Journal of Gastroenterology. 1977;**12**:1003-1008