Critical Care Aspects of Gallstone Disease

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ABSTRACT

Approximately twenty per cent of adults have gallstones making it one of the most prevalent gastrointestinal diseases in Western countries. About twenty per cent of gallstone patients requires medical, endoscopic, or surgical therapies such as cholecystectomy due to the onset of gallstone-related symptoms or gallstone-related complications. Thus, patients with symptomatic, uncomplicated or complicated gallstones, regardless of the type of stones, represent one of the largest patient categories admitted to European hospitals.

This review deals with the important critical care aspects associated with a gallstone-related disease.

Keywords: bile, biliary colic, biliary secretion, cholecystectomy, cholecystitis, choledocholithiasis, cholesterol crystallization, CT scan, ERCP, MRCP

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INTRODUCTION

The prevalence of gallstones in adults is about twenty per cent in developed countries [1], with a yearly increasing incidence rate of 0.60-1.39% [2]. In Europe, gallstone hospitalisation is one of the most common gastrointestinal diseases [3]. The prevalence of gallstones increases with age, and is invariably higher in women than in men [4]. Gallstones, which grow in the gallbladder and bile ducts, present as different sized solid conglomerates, consisting mainly of cholesterol monohydrate crystals, calcium bilirubinate, mucin gels, and proteins. Gallstones are classified according to their chemical composition as (1) pure cholesterol (>75%), (2) pure pigment, and (3) mixed stones. The latter contains <75% cholesterol plus varying amounts of bilirubin salts and calcium. In westernized countries, cholesterol gallstones represent about 75% of stones, whereas black pigment stones represent about 20%, and brown pigment stones only about 5% [4-7] (Figure 1).

The rising prevalence and incidence of cholesterol gallstones parallel the concomitant rise of several metabolic abnormalities, such as insulin resistance and type 2 diabetes, expansion of visceral adiposity due to overweight and obesity, and overall metabolic syndrome (MetS) [8,9].

The study of the natural history of gallstones shows that patients with gallstones remain asymptomatic in about 80% of the cases, a condition defined cholecystolithiasis [10-14]. Symptomatic gallstones or gallstone disease, by contrast, refers to gallstones causing symptoms without complications, i.e., uncomplicated biliary colic, or complicated asymptomatic gallstone disease.

The incidence of symptomatic gallstones is low, i.e., between 1-4% yearly [10,15]. Studies found that symptoms appear within five years in about 10% of patients, and within twenty years in about 20% of patients [16]. When symptoms occur, patients are liable to the risk of recurrent symptoms or complications. A previous survey by the National Cooperative Gallstone Study found that about 70% of symptomatic patients suffer from recurrent symptoms within two years of the initial episode [17]. In patients who develop an episode of biliary colic, the risk of requiring an emergency procedure increases with time, i.e., from less than 1% before week twenty to about 6% at weeks 40-52 [18].

Thus, about 20% of gallstone patients require appropriate medical or surgical procedures such as cholecys-
tectomy or endoscopic due to the onset of gallstone-related symptoms or complications [19-21].

### Symptomatic, Uncomplicated Gallstone Disease

#### Biliary colic

The diagnosis of this clinical event is based on several matters [22]. Non-specific symptoms, usually not related to the presence of gallstones include isolated heartburn, acid regurgitation, belching, nausea and vomiting, bloating, abdominal distension, chest pain, postprandial fullness and early satiety, and flatulence [23-26]. Visceral pain originates from the impact of the stone, or microlithiasis, or sludge in the cystic duct or the ampulla of Vater. This leads to the distension and contraction of the gallbladder and the biliary tract. The intermittent increase of the pressure in the gallbladder activates visceral sensory neurons [27]. The pain is relieved if the stone travels back into the gallbladder lumen, or passes through the ampulla into the duodenum, or travels back into the common bile duct [1, 27]. The pain develops as an intense and dull discomfort either continuous or intermittent with painful episodes ranging from hours to years [28]. The pain can be postprandial, usually occurring about two hours after a meal and especially after a heavy meal. However, a painful episode may be unrelated to a meal and can follow a distinctive timing and pattern for individual patients [29, 30]. The intensity of pain is variable: it can increase and plateau to a high level (9 cm on a 0-10 cm scale). Some patients may ignore symptoms if the intensity is moderate.

The pain frequently starts in the right upper quadrant of the abdomen or at the epigastrium. These sites are T8/9 representative dermatomes. Chest pain onset is rare, but when it occurs, consideration should be given to a differential diagnosis of pain arising from cardiac or esophageal problems or a peptic ulcer. The duration of the pain is usually longer than 15-30 minutes and then slowly subsides. Special attention is required if the pain lasts several hours as this is often related to complications associated with gallstones.

During painful episodes, some non-specific gastrointestinal symptoms may occur. In about 60% of cases, pain radiates to the angle of the right scapula or shoulder, and in less than 10% of cases to the retrosternal area [27, 31]. In two-thirds of patients, a colicky pain may be associated with the urgency to walk [32]. Nausea and vomiting [27, 28, 32], as well as diaphoresis may be related symptoms, while pain is usually not relieved by flatus or bowel movements [28]. Following a painful attack, physical examination may be normal or demonstrate the persistence of mild abdominal tenderness.

#### Critical care aspects

The early diagnosis of biliary pain is essential since the clinical picture represents a medical emergency and the clinician must avoid any delay in providing appropriate therapy. The definition of the characteristics of symptoms can help the diagnosis [33, 34]. In the uncomplicated form, the physical examination of a gallstone patient can be negative, except for a residual abdominal tenderness. If the gallbladder wall is not swollen, the pain may be dull, with a negative Murphy’s sign, because of the visceral origin [35]. If a biliary colic lasts longer than about three hours or is associated with...
more severe symptoms such as fever, nausea, vomiting, jaundice, and leukocytosis, the possibility of a gallstone-related complication exists.

Blood analyses can be abnormal during an attack of uncomplicated biliary colic or even between attacks. Analyses should be targeted to rule out acute cholecystitis, liver disease, significant inflammation pancreatitis and renal or ureteral involvement.

The therapy of biliary colic is based on fast-acting narcotic analgesics, with nonsteroidal anti-inflammatory drugs (NSAIDs) being the first-line therapy. There is evidence that NSAIDs are superior to antispasmodics [36, 37]. The risk of complications such as acute cholecystitis, decreases with the initiation of early therapy [36, 38-40]. Opioids such as meperidine [41], butorphanol [42], or hydromorphone are valid alternative to NSAIDs. This is the best option in patients in which NSAIDs are contraindicated or ineffective [37]. Fasting is necessary during the period of pain, in order to avoid the release of endogenous hormones such as cholecystokinin, which can further stimulate the gallbladder contraction.

SYMPTOMATIC, COMPLICATED GALLSTONE DISEASE

A subgroup of gallstone patients develop complications which include acute cholecystitis, gallstone ileus, chronic cholecystitis, choledocholithiasis, cholestatic jaundice, acute cholangitis, acute biliary pancreatitis, cholesterolosis, gallbladder polyps, gallbladder carcinoma, porcelain gallbladder, recurrent pyogenic cholangitis, and acalculous cholecystitis (Table 1).

Specific categories of patients are at increased risk of developing complications from gallstones. Patients with diabetes mellitus have an increased risk of gangrenous cholecystitis [43], and patients with chronic haemolysis, i.e., hereditary spherocytosis or sickle cell disease, may develop pigment stones due to the accumulation of bilirubin in bile, and are more at risk of becoming symptomatic [22].

Native Americans [44], as well as patients with large gallbladder adenomas [45], pancreatic ductal draining into the common bile duct, porcelain gallbladder, or choledochal cysts, Caroli’s disease, or carrying S. thyphii [46], are at increased risk of cholangiocarcinoma and gallbladder cancer. In this subgroup, a prophylactic cholecystectomy is advisable [47]. Also, obese patients undergoing gastric bypass surgery present with increased mobilisation of body cholesterol during weight loss. About one-third of patients develop cholesterol gallstones and are at risk of gallstone-related symptoms [48, 49].

Acute cholecystitis

In a patient with cholecystolithiasis, symptoms of acute calculous cholecystitis include gallbladder inflammation, pain in the right upper quadrant, fever and leukocytosis. Acute cholecystitis is the most frequent complication of gallstone disease occurring in up to 11% of gallstone patients over a median follow-up of 7-11 years [16].

Several predisposing conditions are associated with increased risk of acute cholecystitis [50-56], (Table 2) with complications including infection of the gallbladder with empyema, due to E. coli, Pseudomonas, streptococci, Klebsiella, and staphylococci, gangrene with perforation, pericholecystic abscess or peritonitis, in up to 20% of cases. These occur mainly in diabetes and older patients [43] or emphysematous cholecystitis [57] secondary to gas-producing micro-organisms such as the Clostridium welchii. Complications such as cholecystoenteric fistulas and gallstone ileus may occur following perforation of the gallbladder.

The diagnosis of acute cholecystitis is based on the history of risk factors, clinical manifestations [58, 59], imaging, and blood analyses which may include increased platelet count, bilirubin, blood urea nitrogen, creatinine, decreased prothrombin time-international normalised ratio, and abnormal arterial blood gas analysis [60, 61].

The choice of the best diagnostic imaging techniques for acute cholecystitis is given in Table 3. Abdominal

$\textbf{Table 1. Complications of gallstones}$

\begin{tabular}{|l|}
\hline
\textbf{Complications} \\
Acute cholecystitis* \\
Acute biliary pancreatitis* \\
Acute cholangitis* \\
Acute acalculous cholecystitis* \\
Biliary enteric fistula and gallstone ileus* \\
Choledocholithiasis \\
Cholestatic jaundice* \\
Cholesterolosis and gallbladder polyps \\
Chronic cholecystitis \\
Gallbladder carcinoma and porcelain gallbladder \\
Recurrent pyogenic cholangitis* \\
\hline
\end{tabular}

*Conditions characterized by critical care aspects.
ultrasonography is usually the first-choice technique. Additional imaging includes cholescintigraphy (HIDA) scan, magnetic resonance cholangiopancreatography, and computed tomography.

**Critical care aspects**

Aspects related to critical care become evident especially in the presence of complications developing as life-threatening conditions [62].

Management of acute cholecystitis is described in Figure 2 and is based on the work of Hirota et al. (2007) as expressed in the Tokyo Guidelines [58, 60, 61, 63]. Because of the potential life-threatening characteristics of acute cholecystitis, patients require careful monitoring and supportive care. Antimicrobial therapy is required, and in cases of moderate to severe intensity, the treatment plan is based on culture and sensitivity results [58, 64]. In the most severe cases, when there is the presence of signs of severe inflammation, acute renal injury, shock, liver injury, and disseminated intravascular coagulation (DIC), treatment should also include monitoring of respiratory function and hemodynamics and appropriate organ support [61, 65]. Hirota M et al. (2007) suggest that surgery should play an essential role in treating patients with acute cholecystitis. Early laparoscopic cholecystectomy is indicated in patients fulfilling the criteria for surgery during initial hospitalisation within one week. In this context, there is no increased rate of serious complications, as compared to delayed laparoscopic cholecystectomy. However, the hospital stay is shortened [66-70]. There is evidence that morbidity is higher if cholecystectomy is performed between seven and forty-five days compared with early cholecystectomy.

**Table 2. Conditions predisposing to increased risk of acute cholecystitis**

<table>
<thead>
<tr>
<th>Acute non-biliary diseases</th>
<th>Immunocompromised illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute renal failure</td>
<td>Infections (hepatitis B virus, ascariasis in developing countries)</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>Major surgery</td>
</tr>
<tr>
<td>Biliary sludge</td>
<td>Female gender</td>
</tr>
<tr>
<td>Cardiovascular disease (history of ischemic stroke, cerebral hemorrhage)</td>
<td>Multiple trauma</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Gallstones</td>
<td>Severe burns</td>
</tr>
<tr>
<td>Hormonal replacement therapy</td>
<td>Systemic vasculitis</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>Total parenteral nutrition, long term fasting</td>
</tr>
</tbody>
</table>


**Table 3. Imaging techniques for acute cholecystitis**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Major findings</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal ultrasonography</td>
<td>Enlarged gallbladder size</td>
<td>First choice</td>
</tr>
<tr>
<td></td>
<td>Gallbladder wall thickening (&gt;4mm)</td>
<td>Moderate sensitivity (88%-90%) and specificity (80%) [63, 122-124]</td>
</tr>
<tr>
<td></td>
<td>Incarcerated gallstone(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intraluminal debris echoes</td>
<td></td>
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<tr>
<td></td>
<td>Pericholecystic fluid collection or abscess</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive “sonographic” Murphy sign</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sonolucent “double wall sign”</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary scintigraphy (technetium iminodiacetic acid or hydroxyiminodiacetic acid)</td>
<td>Compound given intravenously and excreted by the liver</td>
<td>Highest sensitivity and specificity (=90-95%) [123]</td>
</tr>
<tr>
<td></td>
<td>Test is positive if the gallbladder is not visualized (i.e., cystic duct obstruction due to edema by acute cholecystitis) [63]</td>
<td>Not easily available</td>
</tr>
<tr>
<td>Computed Tomography (CT)</td>
<td>Gallbladder wall edema</td>
<td>High sensitivity 94%</td>
</tr>
<tr>
<td></td>
<td>Pericholecystic fluid</td>
<td>Low specificity 59% [123, 126]</td>
</tr>
<tr>
<td></td>
<td>Other complications [125]</td>
<td></td>
</tr>
<tr>
<td>Magnetic Resonance Cholangio-Pancreatography (MRCP)</td>
<td>Gallstones are likely passed in the common bile duct [127]</td>
<td>Moderate accuracy [123]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not easily available [123]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Under evaluation</td>
</tr>
</tbody>
</table>

Thus, when early cholecystectomy is not possible because of late diagnosis or high risk of surgery, it is advisable to delay cholecystectomy for another six weeks.

When patients with acute cholecystitis are too ill and show organ dysfunction or are considered to be non-responsive to initial medical treatment, therapy includes biliary drainage such as percutaneous transhepatic gallbladder drainage or open cholecystostomy and drainage, as well as percutaneous gallstone extraction, or delayed cholecystectomy. Endoscopic nasobiliary gallbladder drainage is an option in critically ill patients unfit for urgent or early cholecystectomy.

**Biliary-enteric fistula and gallstone ileus**

In a small subgroup of less than 0.5% of patients who undergo recurrent episodes of cholecystitis, there is the risk of developing biliary-enteric fistula following the perforation of the gallbladder into the intestinal lumen. The fistula is most often cholecystogastric, cholecystoduodenal or cholecystocolonic.

**Critical care aspects.**

Following the development of an enteric fistula, stone(s) may enter the bowel. A potential complication arises if the stone impacts the ileocecal valve, a condition causing the gallstone ileus. The clinical picture may present as mechanical bowel obstruction associated with a high rate of morbidity and mortality in elderly patients [72].

**Cholestatic jaundice**

Stones found in the common bile duct can be part of either primary or secondary choledocholithiasis, the latter being due to the migration of gallstones from the gallbladder into the common bile duct. The stone can cause bile duct obstruction, a condition leading to cholestatic jaundice which is associated with increased serum conjugated and unconjugated bilirubin [73].

**Critical care aspects**

The Mirizzi syndrome occurs when a stone is impacted in the cystic duct or the Hartmann’s pouch, leading to compression and obstruction of the common hepatic duct or common bile duct [74], with the possible development of a cholecystoenteric fistula progressing to gallstone ileus.

**Acute cholangitis**

Acute cholangitis also named ascending cholangitis, occurs because of bacterial translocation from the intestine, vascular and lymphatic system. Predisposing conditions are bile stasis and infection in the biliary tract. Biliary stones represent the most frequent cause of biliary obstructions, ranging from 30 to 70%. Other non-stone related conditions, besides bile duct stents leading to increased risk of acute cholangitis, are benign biliary strictures and tumors.
Acute cholangitis is a clinical picture ranging from mild to life-threatening. The clinical diagnosis is suspected in a patient with fever, abdominal pain, and jaundice (the Charcot’s triad). Essential laboratory tests include complete blood count, electrolytes, a metabolic panel, prothrombin time (PT), and PT-international normalised ratio. Blood cultures are required when cholangitis is suspected; the result can allow direct antibiotic therapy. Cultures can also be obtained from bile or stents removed at ERCP. The grade of disease severity depends on evidence of systemic infection and cholestasis, imaging (abdominal ultrasound, CT findings, or MRCP for finding dilatation of the common bile duct and evidence of stones), and dysfunction of different organs/systems [61, 75, 76]. In selected cases, i.e., patients cannot undergo MRCP but have evidence of biliary obstruction and increased serum conjugate bilirubinemia, ERCP or endoscopic ultrasound are required for confirmation of the diagnosis and biliary drainage. Management of acute cholangitis is based on the grade of disease severity that is usually classified as severe, moderate, and mild (Figure 3). The therapy requires some combination of medical therapies, including hydration, correction of electrolyte disorders, pain control by analgesics, follow-up for organ dysfunction and septic shock, and a series of antibiotics active against enteric streptococci, anaerobes, and coliforms. The choice of antibiotics relies on the possibility that the infection is community-acquired or healthcare-associated, individual risk factors and additional risk of antibiotic-related side effects. Initial empiric antibiotic regimens include single-agent regimens, i.e., piperacillin-tazobactam, or combination regimens, i.e., cefuroxime, ceftriaxone, ciprofloxacin, or levofloxacin plus metronidazole. The antibiotic treatment is subsequently tailored, depending on the results of culture and susceptibility, and continued for 4-5 days [77]. Additional management includes organ support and additional procedures which include endoscopic, percutaneous, and surgical drainage [60, 63, 65, 78, 79]. A particular concern is that of pregnant women with acute cholangitis. In general, these patients are managed in the same way compared to non-pregnant women, i.e., with antibiotics and biliary drainage. The choice of the antibiotic, however, is tailored to the possibility of foetal toxicity. If fluoroscopy is required, foetal shielding is used. The mortality rates have dropped from more severe acute cholangitis

**Severe acute cholangitis**

At least one of the following:

- **Cardiovascular dysfunction**
  Hypotension requiring dopamine ≥5 μg/kg/min, or any dose of norepinephrine

- **Respiratory dysfunction**
  PaO₂/FiO₂ ratio <300

- **Neurological dysfunction**
  Disturbance of consciousness

- **Hematological dysfunction**
  Platelet count <100,000/mm³

- **Renal dysfunction**
  Oliguria, serum creatinine >2.0 mg/dL

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**Moderate acute cholangitis**

At least one of the following:

- Abnormal WBC count
  >12,000/mm³, <4,000/mm³

- Fever
  39°C

- Age
  ≥75 years

- Hyperbilirubinemia
  Total bilirubin ≥5 mg/dL

- Hypoalbuminemia

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**Mild acute cholangitis**

Lacks criteria for moderate or severe cholangitis at initial diagnosis

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Fig. 3. Definition of severity of acute cholangitis.
than 50% to about 11%, due to overall improved management of disease [80]. However, a higher mortality rate (20-30%) is reported in patients with severe acute cholangitis [81].

**Acute biliary pancreatitis**

Gallstones account for 35%-40% of patients with acute pancreatitis [82, 83], and the risk increases further in patients with small gallstones [84].

Bile reflux into the pancreatic duct is a true predisposing factor for biliary pancreatitis; the three leading causes include temporary or constant obstruction due to ampullary gallstone(s), and oedema secondary to gallstone passage [85]. Clinical signs occur when a gallstone is impacted within the ampulla of Vater, leading to occluding drainage of the pancreatic duct.

**Critical care aspects**

Acute biliary pancreatitis can be a life-threatening condition and can be associated with increased morbidity, making early recognition of the condition paramount importance. Patients develop a steady pain in the mid-epigastrium or right upper quadrant. In some cases, the pain is diffuse or in the left side. It reaches maximum intensity in about twenty minutes and can last for several days, with possible band-like radiation onto the back. Bending forward can give some pain relief. Biliary colic may occur before acute pancreatitis or may proceed it. The associated symptoms are agitation, nausea and vomiting for several hours [86-90]. In addition to an increase in serum amylase and lipase levels, an elevated serum alanine aminotransferase (ALT) concentration of more than three times is highly suggestive of a biliary etiology. Patients hospitalization for gallstone pancreatitis are at low risk of stones in the common bile duct if bilirubin levels normalized after two days of admission [91]. The use of abdominal ultrasound is often the first line of the investigation, but it should be noted that it has a low sensitivity for the detection of common bile duct stones. Ultrasonography, however, reliably identifies common bile duct dilatation, a finding which is frequently associated with cholecystolithiasis. Additional imaging studies include an abdominal CT scan and MRCP, both of which can detect gallstones or dilatation of the common bile duct due to choledocholithiasis [92-96].

For the identification of bile duct stones in patients with gallstone pancreatitis without cholangitis or biliary obstruction and at risk of choledocholithiasis, endoscopic ultrasound and MRCP are the best imaging modalities. Endoscopic ultrasound is less costly compared to ERCP and carries a lower risk of complications. If cholecystectomy is planned, choledocholithiasis can be detected by intraoperative cholangiography [92, 93, 97].

ERCP with papillotomy is particularly useful for the removal of bile duct stones if undertaken within 24 hours of the patient being admitted. For patients with acute biliary pancreatitis and concomitant cholangitis, this approach has benefits regarding reducing both morbidity and mortality [97, 98].

Following the first episode of gallstone pancreatitis, the risk of cholecystitis or cholangitis increases, and may occur in up to 30% of patients. Cholecystectomy is advisable, and is usually performed in all operable patients after recovery [67, 82, 99-101], even after endoscopic sphincterotomy [102]. In patients with mild pancreatitis, cholecystectomy is indicated after symptoms have subsided and laboratory tests have normalized, usually within one week and during the same hospitalization period. If the episode of acute pancreatitis is severe and necrotizing, cholecystectomy is delayed until active inflammation subsides and fluid collections have resolved or stabilized [103].

Hirota et al. (2007) also suggest that severe pancreatitis associated with ongoing multisystem organ failure is a condition requiring the immediate clearance of any biliary obstruction. Supportive care is indicated until the patient recovers sufficiently to tolerate cholecystectomy. Sometimes patients who have had an attack of acute pancreatitis and a transient elevation of serum amylase and lipase levels show no exact cause of acute pancreatitis. The presence of biliary sludge requires timely attention and, if sludge exists, cholecystectomy is recommended [104-107].

The initial care of patients with acute pancreatitis is based on:

**Pain control with opioids.** Intravenous infusion allows fast and optimal relief. Hydromorphone in opioid naive is usually started at 0.2-1.0 mg every 2 to 3 hours and then titrated as needed. Higher initial doses can be required in patients with prior opioid. Fentanyl has better safety profile. The bolus infusion is based on 20-50 ug (with an interval of 10 min until next bolus is scheduled by the machine). The continuous infusion usually starts at a low dose. Alternatively, other modalities include the regular interval regimen or the infusion by patient control. The initial doses can be titrated until the desired effect is achieved, always checking for
opiate-related side effects (e.g., depression of respiratory drive, CNS-depressant effects, hypotension, ileus, urinary retention, nausea and vomiting). Meperidine (initial dose 25-50 mg i.v.) has shorter half-life but puts the patients at higher risk of metabolite accumulation (neuromuscular side effects if repeated doses are used.)

**Fluid resuscitation:** 5-10 mL/Kg/hr of isotonic crystalloid solution, with checks for cardiovascular and renal morbidities and adequate response.

**Nutritional support:** enteral feeding in patients who do not tolerate oral feeding.

Patients with acute pancreatitis require frequent monitoring, especially in the first 24-48 hrs. Monitoring should include testing vital signs, electrolytes, serum glucose and urine output. If an infection is suspected, therapy includes antibiotics and suture-guided medications. Prophylactic antibiotics are not recommended in patients with any type of acute pancreatitis [108].

**Recurrent pyogenic cholangitis**

Recurrent bouts of cholangitis are classified as recurrent pyogenic cholangitis.

Recurrent inflammatory episodes can ultimately result in stricture of the biliary tree and obstruction. The obstruction often causes proximal bile stasis with recurrent cholangitis and pyogenic inflammation of bile ducts. Pyogenic cholangitis is frequent in Southeast Asia or in immigrants from that region [109]. There is a similar gender prevalence. The aetiology of pyogenic cholangitis includes parasitic infection with *Clonorchis sinensis*, *Fasciola hepatica* or *Opisthorchis* species, although the actual association is still debated.

Episodes of transient portal bacteremia may transfer bacteria to the biliary ducts. This condition may start a local infection and lead to stone formation and related infection and obstruction. Detected bacteria in bile include *E. coli*, *Klebsiella*, *Proteus* species, *Pseudomonas* or anaerobes.

Bile duct stasis is another predisposing factor. Bile duct strictures might also follow repeated episodes of inflammation, and the formation of intrahepatic pigment stones can be a consequence of pyogenic cholangitis. Another cause, facilitating the inflammatory process, is a defect of hepatic phospholipid transporter [110].

The diagnosis of recurrent pyogenic cholangitis relies on imaging such as abdominal ultrasound, CT scan, ERCP, MRCP, and percutaneous transhepatic cholangiography.

**Critical care aspects**

Clinical features of pyogenic cholangitis are extra- or intrahepatic ductal dilatation, focal stenotic areas of the intrahepatic bile ducts, development of purulent bile enriched in bile pigments and debris, bacterial concentration, and intrahepatic stones in the right and left lobes, and extrahepatic ducts.

Clinically, patients with recurrent pyogenic cholangitis are exposed to sepsis, biliary inflammation, and liver cirrhosis with an increased risk of cholangiocarcinoma [111]. The management of patients is multidisciplinary. Acute complications require intravenous fluids, antibiotics, and biliary drainage (ERCP, PTC, or surgical). The prevention of long-term complications includes stone removal or if required, surgical resection of the hepatobiliary segment, which is affected by biliary-enteric anastomosis and the clearance of stones.

**Acalculous cholecystitis**

Acute cholecystitis occurring in the absence of gallstones is termed acalculous cholecystitis and occurs in approximately 10% of patients with acute cholecystitis [112]. However, the ongoing acute necro-inflammatory process of the gallbladder shows greater morbidity and mortality rates in acalculous cholecystitis than in calculous cholecystitis.

**Critical care aspects**

Acalculous cholecystitis is frequently encountered in patients with serious medical comorbidities, i.e. patients in the ICU setting [113-119]. Predisposing factors are depicted in Figure 4 and include the critically ill patient, serious illness, drugs, chronic conditions, and surgery. The potential disease mechanisms include gallbladder stasis and ischemia, local damage of concentrated bile acids [120, 121], and local inflammatory changes occurring in the gallbladder wall. Therefore, necrosis and perforation of gallbladder wall may develop. The mortality in patients with acalculous cholecystitis is related to the underlying medical and surgical conditions. The mortality rate ranges from 10% in community-acquired cases to 90% in critically ill patients [62, 112].
CONCLUSIONS AND PERSPECTIVES

Due to the rise in the prevalence of metabolic abnormalities such as insulin resistance, obesity, and diabetes, the prevalence of gallstone disease is increasing worldwide. This trend occurs in both developed and developing countries and globally represents a significant financial and social burden. Although 75 to 80% of subjects with gallstones remain asymptomatic, symptoms such as biliary pain or other complications occur in about 20% of patients. These patients require immediate attention, speedy and appropriate diagnosis, and accepted therapies including medical endoscopic, and surgical treatments. Critical care aspects, which include acute cholecystitis, gallstone ileus, cholestatic jaundice, acute cholangitis, acute biliary pancreatitis, and recurrent pyogenic cholangitis, must be adequately recognised.

Several predisposing conditions exist and put patients at risk of very severe and often life-threatening complications.

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CONFLICT OF INTERESTS

None to declare

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