Choledocholithiasis, Ascending Cholangitis, and Gallstone Pancreatitis

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Gallstone disease is one of the most common and most costly digestive diseases that require hospitalization in the United States with an estimated annual direct cost of $5.8 billion [1]. Gallstone disease is newly diagnosed in more than 1 million people annually in the United States, and cholecystectomy is performed in 700,000 cases [2]. The prevalence of gallstones has ethnic variability, with prevalence rates of approximately 10% to 15% in the United States and Europe [3].

The clinical spectrum of cholelithiasis ranges from an asymptomatic state to fatal complications. Patients who have asymptomatic gallstones carry an annual risk of approximately 1% for biliary colic [4,5], of 0.3% for acute cholecystitis [4–6], of 0.2% for symptomatic choledocholithiasis [5,6], and of 0.04% to 1.5% for gallstone pancreatitis (GSP) [7,8]. These small percentages, however, represent a large number of patients, given the overall prevalence of gallstones.

Gallstone pathophysiology

Gallstones are classified into cholesterol stones and pigment stones. Stones composed mostly of cholesterol account for 80% to 90% of patients undergoing cholecystectomy in Western countries [9]. In normal bile, cholesterol is soluble in the form of mixed micelles with an optimal concentration of bile salts and phospholipids. With disproportionate concentrations, bile becomes supersaturated, and the excess cholesterol precipitates as monohydrate crystals. These crystals embed in the gallbladder mucin gel with
bilirubinate to form biliary sludge, which can aggregate eventually into a gallbladder stone [10].

Black pigment stones make up a small proportion of gallstones. These stones consist of polymerized calcium bilirubinate, precipitated as a result of exceeding the solubility of calcium and unconjugated bilirubin. Conditions that create excessive unconjugated bilirubin, such as chronic hemolysis in hemoglobinopathies, cirrhosis [11], ineffective erythropoiesis, and ileal diseases [12], predispose a patient to the formation of black pigment stones. Brown pigment stones are formed primarily in the bile duct. They result from bacterial infection that releases $\beta$-glucuronidase to hydrolyze glucuronic acid from bilirubin. This process leads to decreased solubility of deconjugated bilirubin and formation of brown pigment stones.

Risk factors for gallstones

Risk factors for gallstone formation may be modifiable or nonmodifiable (Box 1). Environmental factors and genetic predisposition probably play interactive roles in gallstone formation. An inflammatory immune response may contribute to a patient’s susceptibility to cholesterol stone formation [13].

<table>
<thead>
<tr>
<th>Box 1. Risk factors of gallstones</th>
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<tbody>
<tr>
<td><strong>Nonmodifiable factors</strong></td>
</tr>
<tr>
<td>Increasing age</td>
</tr>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>Ethnicity</td>
</tr>
<tr>
<td>Genetics, family history</td>
</tr>
<tr>
<td><strong>Modifiable factors</strong></td>
</tr>
<tr>
<td>Pregnancy and parity</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Low-fiber, high-calorie diet</td>
</tr>
<tr>
<td>Prolonged fasting</td>
</tr>
<tr>
<td>Drugs: clofibrate, ceftriaxone</td>
</tr>
<tr>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Low-level physical activities</td>
</tr>
<tr>
<td>Rapid weight loss (&gt; 1.5 kg/wk)</td>
</tr>
<tr>
<td>Hypertriglyceridemia/low high-density lipoprotein</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Gallbladder stasis</td>
</tr>
<tr>
<td>Specific diseases (ie, cirrhosis, Crohn’s disease with severe ileal involvement/resection)</td>
</tr>
</tbody>
</table>
Role of genetics

Geographic variations and ethnic differences in prevalence suggest a genetic role in the formation of gallstones. The prevalence of gallstones is increased in families and in identical twins of patients who have gallstones [3]. The genes responsible for biliary lipid transport across the hepatic canaliculi [10,14] and for lipid metabolism [3] have been identified.

Role of gallbladder stasis

Impaired gallbladder contractility has been noted in some patients who have gallbladder stones. Although gallbladder dysfunction can result from gallstone disease or from excessive cholesterol infiltration into gallbladder smooth muscle [10], gallbladder stasis, by itself, can contribute to gallbladder stone formation. Gallbladder stasis frequently is evident in patients who have risk factors for cholelithiasis, including obesity, pregnancy, rapid weight loss, and prolonged fasting [15]. Furthermore, gallbladder dysmotility seems to be an independent risk factor for recurrent gallstones in patients treated with extracorporeal shockwave lithotripsy (ESWL) [16].

Prevention of gallstones

Moderate physical activity and dietary management (high fiber intake and avoidance of saturated fatty acids) can lower the risk of cholelithiasis [17]. Daily administration of cholecystokinin in patients receiving prolonged total parenteral nutrition was shown to prevent the formation of gallbladder sludge in one small series [18]. Oral ursodeoxycholic acid (UDCA) has been demonstrated to help prevent cholelithiasis during rapid weight loss and in patients requiring long-term somatostatin therapy [17]. For secondary prevention, there currently are insufficient data to support the use of medical therapy, such as UDCA, for prevention of biliary colic or for prevention of complications in patients who have gallstones who are awaiting cholecystectomy or who are unfit for surgery [17,19].

Choledocholithiasis: special consideration

Primary versus secondary bile duct stones

In the Western world, most stones in the common bile duct arise from the passing of gallbladder stones into the common bile duct. Stones in the common duct occur in 10% to 15% of people who have gallbladder stones. Concomitant gallbladder stones and bile duct stones occur more frequently in elderly, Asian patients and in patients who have chronic bile duct
inflammation (such as sclerosing cholangitis, parasitic infestation) and, probably, hypothyroidism [20].

Primary bile duct stones are formed in the intrahepatic or extrahepatic bile ducts. They are more prevalent in Asian populations. These stones usually are brown pigment stones. Bacterial colonization of bile and bile stasis play important roles in the pathogenesis of these stones [21,22].

Clinical spectrum

Coexisting bile duct stones and gallbladder stones

Bile duct stones can be discovered incidentally during the evaluation of gallbladder stones, with an estimated prevalence of 5% to 12% [23,24]. It is difficult to determine whether the existing bile duct stones are asymptomatic in patients who present with biliary pain alone, because the pain can originate from either the gallbladder stones or bile duct stones. Approximately one third of patients have spontaneous bile duct stone passage based on stone disappearance 6 weeks after diagnosis, as determined in one study by cholangiograms using an in situ cholangiogram catheter [25]. Given the potential serious complications of bile duct stones, specific therapy generally is indicated regardless of symptoms.

Symptomatic bile duct stones

Patients who have symptomatic bile duct stones are at high risk of experiencing further symptoms or complications if left untreated. More than one half of patients who had retained bile duct stones experienced recurrent symptoms during a follow-up period of 6 months to 13 years [26], and 25% of patients developed serious complications [27].

Common clinical symptoms and signs include pain, fever, and jaundice. Biliary pain confined to the epigastrium or right upper quadrant of the abdomen is the most common presentation. Pain is variably mild to severe at onset. Severe episodes commonly require emergency medical visits and must be differentiated from cardiac or other potentially life-threatening events. Infrequently, patients present with painless jaundice and weight loss that mimics pancreatobiliary malignancy. Acute ascending cholangitis and acute pancreatitis are two serious, life-threatening complications.

Diagnosis of bile duct stones

Although advanced technologies have become more widely available, a clinically oriented approach remains paramount. Atypical as well as typical clinical symptoms should be recognized. Newer techniques of biliary imaging have simplified the diagnosis of bile duct stones. Noninvasive
methods have the lowest risk, whereas invasive techniques have the greatest accuracy.

**Blood tests**

Patients who have cholangitis or pancreatitis associated with abnormal serum liver function tests are at increased risk of having bile duct stones. Elevations of serum alkaline phosphatase and gamma-glutamyl transpeptidase levels were detected in more than 90% of symptomatic patients [28]. The intensity of pain, degree of jaundice, and serum levels of these tests can fluctuate over time. The serum bilirubin level typically is less than 15 mg/dL, because most bile duct stones cause intermittent and incomplete biliary obstruction. Rarely, the serum transaminase levels can be elevated profoundly (up to 2000 IU/L), mimicking acute viral hepatitis. With biliary stones, however, these levels tend to decline rapidly over several days [29] rather than slowly over several weeks, as occurs with viral syndromes. In this clinical setting sequential follow-up of the pattern of liver function tests may be helpful diagnostically.

**Imaging studies for diagnosis of bile duct stones**

Transabdominal ultrasound (TUS) is the most commonly used initial diagnostic tool for suspected biliary stones. Gallbladder stones, if present, generally are well visualized if the gallbladder is adequately distended and not obscured by luminal gas or obesity. TUS has low sensitivity (25%–60%) for the detection of bile duct stones, but it has a very high specificity [30,31]. Indirect evidence, such as the presence of gallstones or biliary ductal dilation, in the appropriate clinical setting is predictive of bile duct stones, but the obstructed bile duct may not be dilated with acute obstruction. CT scanning has a similarly low sensitivity in the detection of bile duct stones and is used primarily to document biliary dilation, to exclude other causes of biliary obstruction (eg, a mass lesion), and to detect local complications such as liver abscess. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) are less invasive than endoscopic retrograde cholangiography (ERC) but can detect bile duct stones with comparable accuracy. Recently, use of multidetector CT, in conjunction with oral or intravenous contrast and with reconstruction of axial and three-dimensional images, has been reported to have a sensitivity of 85% to 97% and specificity of 88% to 96% in the diagnosis of bile duct stones [43–46]. Although this accuracy is comparable to that of MRCP, this method is limited by (1) relatively frequent allergic reactions to the contrast agents, as high as 15% in one series using intravenous iotroxate [45]; (2) suboptimal ductal contrast opacification in the presence of significant jaundice (bilirubin more than two or three times the upper limits of normal) or in a patient who has undergone cholecystectomy [43,47]; and (3) limited visualization of intrahepatic duct branches, particularly when using oral contrast agents [45,48]. Table 1 summarizes the clinical
### Table 1

**Imaging studies for diagnosis of common bile duct stones**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TUS</th>
<th>CT</th>
<th>MRC</th>
<th>EUS</th>
<th>ERC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Inexpensive</td>
<td>Safe</td>
<td>Detection of concomitant intrahepatic duct stones, liver parenchymal lesions, and pancreatic lesions</td>
<td>High accuracy for duct stone detection</td>
<td>Noninvasive intrahepatic and extrahepatic duct evaluation</td>
</tr>
<tr>
<td></td>
<td>Widely available</td>
<td>Portable</td>
<td>High accuracy for duct stone detection</td>
<td>High accuracy for duct stone evaluation</td>
<td>High accuracy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Noninvasive intrahepatic and extrahepatic duct evaluation</td>
<td>Less invasive than ERC</td>
<td>Detects small stones in a nondilated duct [30]</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Low sensitivity</td>
<td>Radiation exposure</td>
<td>Expensive</td>
<td>Operator dependent</td>
<td>Higher risk than EUS</td>
</tr>
<tr>
<td></td>
<td>Operator dependent</td>
<td>Contrast allergy</td>
<td>Time consuming</td>
<td>High cost of equipment</td>
<td>False positives (air bubbles)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal impairment</td>
<td>Limited value in stones &lt; 6 mm [37]</td>
<td>Insensitive for proximal common hepatic duct / intrahepatic duct stones</td>
<td>False negatives with small stones in dilated duct</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impacted stone at the ampulla [38], dilated bile duct &gt; 10 mm [39]</td>
<td>Claustrophobia</td>
<td>Unsuccessful cannulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ferromagnetic implant</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Artifact interference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[40–42]</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ERC, endoscopic retrograde cholangiography; EUS, endoscopic ultrasound; MRC, magnetic resonance cholangiography; TUS, transabdominal ultrasound.

* Including pneumobilia, flow artifact, duodenal diverticula.
applications and limitations of imaging studies in the diagnosis of bile duct stones.

ERC is considered the reference standard for the diagnosis of bile duct stones and provides an opportunity for therapy. Because of potential significant procedure-related risks and the availability of the other, less invasive, accurate imaging modalities, ERC now is reserved for patients who have confirmed bile duct stones or who are at high risk for bile duct stones (Table 2) who probably will require therapeutic intervention [49].

**Recurrent bile duct stones**

Bile duct stones recur in about 4% to 24% of patients during a follow-up period of 15 years [42]. Stones even can recur in patients after gallbladder removal. It remains uncertain, however, what proportion of these recurrent stones are, in fact, overlooked retained/residual stones from the prior therapy. Recurrence is thought to be caused mainly by bile stasis and bacterobilia. Main duct dilation (≥ 13 mm) and the presence of a periampullary diverticulum are common risk factors for recurrent stones [42,50], perhaps resulting from increased biliary stasis. Identification and treatment of correctable risk factors, such as biliary strictures, papillary stenosis, and gallstones in patients who have gallbladder in situ, is essential to prevent recurrence.

**Detection of bile duct stones after endoscopic therapy**

After biliary endoscopic sphincterotomy (BES), the biliary system frequently is filled with air. The bile duct may be dilated persistently despite removal of all bile duct stones. These two factors may decrease the accuracy of imaging tests in detecting residual/recurrent stones after endoscopic therapy. MRCP seems to have limited value in detecting stones in an air-filled duct [51]. In this setting, intraductal EUS, in conjunction with ERC, has been reported to detect stones in the dilated duct with a greater accuracy than achieved with ERC alone [52].

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**Table 2**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>High Risk (&gt; 50%)</th>
<th>Moderate Risk (10%–50%)</th>
<th>Low Risk (&lt; 5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>Current</td>
<td>History of jaundice</td>
<td>No history of jaundice</td>
</tr>
<tr>
<td>Liver function tests</td>
<td>Persistently elevated</td>
<td>Declining</td>
<td>Normal</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>Current</td>
<td>History of fever</td>
<td>No history of fever</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Current</td>
<td>History of pancreatitis</td>
<td>No history of pancreatitis</td>
</tr>
<tr>
<td>Common bile duct diameter</td>
<td>Dilated bile duct (≥ 10 mm)</td>
<td>Borderline dilated</td>
<td>Normal</td>
</tr>
<tr>
<td>Ductal stones seen</td>
<td>Yes</td>
<td>Questionable (with small gallbladder stones)</td>
<td>None (with large gallbladder stones)</td>
</tr>
</tbody>
</table>
Therapy of bile duct stones

Biliary endoscopic sphincterotomy

Since its introduction in 1974, BES has supplanted surgery as the standard therapy for bile duct stones. About 85% to 90% of bile duct stones can be removed by balloon/basket extraction following BES. In a large, multicenter trial, the overall complication rate of BES was 9.8% in 2347 patients, including pancreatitis in 5.4%, bleeding in 2%, procedure-related cholangitis in 1%, cholecystitis in 0.5%, and perforation in 0.3% [53]. In the subgroup of 1600 patients who had common duct stones, the overall complication rate was 8%.

Treatment of difficult bile duct stones

Approximately 10% to 15% of patients have bile duct stones that cannot be removed using standard BES and balloon/basket extraction techniques. These stones generally are larger than 1.5 cm, are impacted, or are located proximal to strictures [54]. Alternative therapies have been used to manage these difficult bile stones.

Fragmentation of stones

Mechanical lithotripsy. Mechanical lithotripsy is the simplest and most widely used technique for fragmenting stones. The lithotripter unit is designed as either an integrated device or a salvage device that consists of a metal sheath with a handle applicable to lithotripsy-compatible wire baskets. In two studies, mechanical lithotripsy successfully removed 85% to 90% of “difficult” bile duct stones [55,56]. Mechanical lithotripsy usually is successful only in stones smaller than 3 cm [55]. The most common reason for unsuccessful mechanical lithotripsy is inability to capture the stones (eg, inadequate space to open the basket).

Electrohydraulic lithotripsy. An electrohydraulic lithotripsy system consists of a bipolar probe and a charge generator. Initiation of a spark causes expansion of the surrounding fluid that generates shock waves to fragment stones. Electrohydraulic lithotripsy can be operated under either fluoroscopic or direct cholangioscopic guidance. Direct visualization is preferred to permit deployment of the probe at the surface of the stone to ensure the highest efficacy and to avoid ductal injury. This technique seems to be helpful in patients who have concomitant intrahepatic duct stones or biliary strictures [57]. A disadvantage of using cholangioscopy for electrohydraulic lithotripsy is the need for two operators and the use of a fragile intraductal miniscope. Recently, single-operator cholangioscopy has been used to direct electrohydraulic lithotripsy therapy for bile duct stones; preliminary results have been encouraging [58].
Extracorporeal shockwave lithotripsy. ESWL generates a shockwave originating outside the body using piezoelectric, electrohydraulic, or electromagnetic systems. A liquid or tissue medium is required to prevent energy attenuation. Because ESWL is painful, general anesthesia or, less frequently, conscious sedation is required. Because most bile duct stones are not radiopaque and are not visualized by fluoroscopy before contrast injection at endoscopic retrograde cholangiopancreatography (ERCP), a nasobiliary tube may be required before ESWL. Complete stone clearance rates of 83% to 90% have been reported [59,60]. Most cases require several endoscopic procedures to remove the fragmented stones.

Laser lithotripsy. In laser lithotripsy, laser light at a particular wavelength is focused on the surface of a stone to achieve stone fragmentation. An oscillating plasma, consisting of a gaseous collection of ions and free electrons, is created to induce wave-mediated fragmentation of stones. Laser lithotripsy is performed under direct visualization using the cholangioscope or under fluoroscopic guidance. A recent-generation device can differentiate between the light reflection patterns of the bile duct wall and those of stones. The laser beam is stopped immediately when bile ductal tissue is contacted to prevent bile duct injury. Experience with this modality is limited, however. The success rates of bile duct stone clearance with laser lithotripsy have been reported at 64% to 97% [27].

Supplemental large-diameter biliary orifice balloon dilation

Endoscopic biliary orifice dilation (EBD) using a 6- to 8-mm diameter balloon to remove bile duct stones has a reported success rate comparable to that of BES. This success rate, however, seems to require more ERCP sessions, more frequent use of mechanical lithotripsy, and, occasionally, rescue BES. Most importantly, two meta-analyses have shown that the rate of pancreatitis is significantly higher with EBD than with BES [61,62].

Use of a large-diameter (12–20 mm) dilation balloon as an adjunctive tool to enlarge an inadequate BES orifice can aid in the removal of large or difficult bile duct stones. In a recent multicenter study of 103 patients, this technique had a success rate of 92% and a complication rate of 7.6%, with a remarkably low rate of pancreatitis of 2.2% [63]. This low rate of pancreatitis is attributed to the separate pancreatic and biliary orifices following BES, so that the pancreatic orifice is avoided during biliary balloon dilation. Although this combined technique seems to be attractive, additional clinical experience is necessary.

Surgery

Laparoscopic bile duct exploration. Patients who have concomitant gallbladder and bile duct stones are treated ideally with a single procedure: laparoscopic cholecystectomy and laparoscopic bile duct exploration. In expert hands, a single-stage laparoscopic procedure can achieve a stone clearance
rate comparable to that of ERCP. Either a transcystic approach (for stones < 8–10 mm) or direct choledochostomy with choledoschoscopy (for larger or multiple stones) can be performed. This procedure is technically demanding, however, and only a minority of surgeons perform laparoscopic bile duct exploration. The reported success rates range from 80% to 98%, with complication rates of 4% to 16%, including bile duct injury, infection, pancreatitis, and stricture [64].

Open common bile duct exploration. Open common bile duct exploration generally is performed only if endoscopic and laparoscopic approaches are unsuccessful. Additionally, choledochoenterostomy or sphincteroplasty can be performed. The former procedure is preferable for stones larger than 2 cm. Sump syndrome, which occurs when debris or food particles enter a side-to-side choledochoduodenostomy and block the distal bile duct, occurs in 1% of such cases and is managed by endoscopic therapy.

Long-term biliary stenting
Whenever stones cannot be removed completely endoscopically, biliary stents should be placed to ensure adequate biliary drainage and to prevent recurrent symptoms as well as biliary sepsis while awaiting further therapy. Alternatively, long-term biliary stenting is used in patients who have severe comorbid medical conditions that preclude surgery or who have had repeated endoscopic interventions for definitive therapy of bile duct stones [65–68]. The main goal is to prevent the impaction of stones. Additionally, long-term stenting can promote stone fragmentation, leading to decreased stone size, and, occasionally, spontaneous passage of stones [65,69]. Internal and external pigtail stents are preferred to straight stents because they migrate less frequently and maintain the patency of the biliary orifice better. Straight stents may be used selectively for stones associated with a biliary stricture. Long-term biliary stenting, however, is associated with significant mortality, ranging from 6% to 16%, mainly from cholangitis, and with morbidity of up to 40% during 3 years of follow-up [70,71]. Moreover, new bile duct stones can occur in patients who had inadvertent long-term stent placement following therapy for bile duct stones [72]. In summary, long-term stenting should be reserved as a definitive therapy for patients who are at extremely high risk for endoscopic or surgical procedures or who have a short life expectancy.

Acute ascending cholangitis
Acute cholangitis, or infection of the biliary tree, occurs as a consequence of biliary tract obstruction. The clinical presentation ranges from a mild, self-limited process to a serious, life-threatening condition requiring emergent intervention. Bile duct stones are the most common cause of acute
cholangitis in Western countries [73]. Malignant obstruction rarely presents with cholangitis do novo but can cause cholangitis after manipulation of stent occlusion from the biliary tree. Indeed, previous therapy probably is the second most common cause of acute cholangitis. Acute cholangitis is occurring increasingly, secondary to biliary stricture from biliary surgery, orthotopic liver transplantation, primary sclerosing cholangitis, or AIDS-related cholangiopathy. These conditions are beyond the scope of this discussion.

Pathophysiology

Bacterobilia occurs commonly in patients who have bile duct stones, often in the absence of clinical cholangitis. Typically, the main entry route of bacteria is ascending from the duodenum [73]; the portal venous and periportal lymphatic systems serve as the portal of entry in a minority of cases [74]. In the presence of bacterobilia, biliary obstruction plays a critical role in the pathogenesis of cholangitis. Increasing intraductal pressure leads to disruption of hepatocellular tight junctions, with subsequent translocation (reflux) of bacteria and biliary toxins into the bloodstream. The occurrence of bacteremia or endotoxemia is correlated directly with the intrabiliary pressure [75,76]. Biliary obstruction promotes bile stasis and bacterial growth and also may compromise host immune defense mechanisms [77].

Diagnosis and clinical manifestations

Charcot, in 1877, described a triad of fever, right upper abdominal pain, and jaundice; this triad occurs in 56% to 70% of patients who have cholangitis [78]. The more severe form, characterized by the additional clinical features of hypotension and alteration of consciousness (Reynold’s pentad), is uncommon and occurs in only 5% to 7% of cases [79,80]. Fever is the most common presenting symptom, found in 90% of patients. The pain in patients who have cholangitis, unlike the pain secondary to bile duct stones in the absence of infection, is relatively mild and intermittent. Elderly and immunocompromised patients can present with atypical symptoms and signs. The presence of fever, leukocytosis, and abnormal liver function tests is highly suggestive.

Laboratory tests

Leukocytosis and an elevated C-reactive protein level and erythrocyte sedimentation rate are found commonly but are nonspecific. Liver function tests invariably are elevated, with a widely variable range. Pancreatic enzyme elevations suggest that bile duct stones caused the cholangitis, with or without GSP [81].

Bile cultures are positive in 80% to 100% of patients who have cholangitis, and blood cultures are positive in 21% to 71% [82,83]. Enteric
gram-negative organisms including *Escherichia coli*, *Klebsiella*, and *Enterococcus* are isolated from bile commonly; *Staphylococcus* and *Streptococcus* are isolated infrequently. Anaerobic bacteria, such as *Clostridium* and *Bacteroides*, are isolated more commonly in polymicrobial infections in patients who have had prior biliary-enteric surgery, are elderly [73], or have severe disease [84,85]. Patients who have had recent biliary surgery or who have indwelling stents are more likely to harbor *Enterococcus* or hospital-acquired organisms such as *Pseudomonas* species, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, or fungi [86].

**Imaging tests**

The choices in imaging are the same as for the diagnosis of bile duct stones but must be done more urgently in patients who have acute cholangitis. An early CT scan is recommended to evaluate for biliary dilation and simultaneous liver abscesses.

**Management of cholangitis**

Early diagnosis and prompt appropriate therapy are essential. Close monitoring and reassessment of the treatment response are important to guide the therapy. Patients who have mild disease are managed initially with medical therapy, including antibiotics and supportive medical care. Patients who respond promptly to medical therapy should undergo biliary decompression and/or definitive therapy for bile duct stones as early as practical, preferably within 24 to 48 hours. Patients who have severe or progressive disease require urgent biliary drainage in addition to medical therapy [87]. Delay in securing biliary drainage in this subgroup may produce a fatal outcome. A treatment algorithm is suggested in Fig. 1.

**Medical therapy**

Initially, antibiotics as well as supportive therapy, including adequate hydration and correction of coagulopathy and metabolic derangements, must be provided. Medical therapy alone is effective in approximately 80% of patients; prompt additional biliary drainage is required in the others to control the clinical symptoms.

**Antibiotic therapy**

Antibiotics should be given early when acute cholangitis is suspected, even before it is definitively established, to control bacteremia and sepsis. The choice of empiric antibiotics is based on several considerations, including host factors (renal function, allergic reactions), severity of disease, local susceptibility pattern, community versus hospital-acquired infection, and the presence of prior biliary intervention or surgery. Broad-spectrum antibiotics with adequate biliary excretion such as ampicillin/sulbactam,
Acute cholangitis

Assess clinical status, prompt antibiotics, hydration, correct metabolic derangement

Mild

Close monitoring/reassessment in 6-12 hours

Favorable response

Elective ERCP with definitive therapy of bile duct stones (within 24-48 hours)

Severe/unstable

Intensive care

Urgent ERCP with biliary decompression

Altered anatomy (e.g. gastric bypass surgery)

Elective ERCP with definitive therapy (if not previously done)

Urgent ERCP with biliary decompression

Technical failure

Favorable response

Urgent ERCP with definitive therapy

Unfavorable response/

Elective ERCP

Percutaneous drainage

Fig. 1. Algorithm for management of patients who have acute cholangitis.

piperacillin/tazobactam, third- or fourth-generation cephalosporins, quinolones, and carbapenems are preferred. Antibiotics with enterococcal and anaerobic coverage may be added in patients who have advanced age, severe disease, a biliary stent in situ, or prior enterobiliary surgery. Biliary excretion of most antibiotics is compromised in the presence of biliary obstruction, however [83]. Early biliary decompression is essential to restore good biliary penetration of the antibiotics and to drain purulent bile, particularly in patients who have severe disease. Once the micro-organisms have been identified and their susceptibility has been determined, the antibiotics should be adjusted to cover the identified micro-organism and to avoid the emergence of antibiotic-resistant micro-organisms.

The duration of antibiotic therapy is based on the clinical response and the presence of bacteremia. For mild disease, antibiotics generally are continued for 5 to 7 days. For patients who have a positive blood culture, a 10- to 14-day course of antibiotics is recommended. After a clinical response, switching from intravenous to oral administration usually is appropriate. The optimal duration of antibiotic therapy following biliary drainage has not been well defined in prospective, randomized trials. One small retrospective study reported that a 3-day duration of antibiotic therapy following biliary drainage seemed to be effective in selected patients who respond promptly (with resolution of fever) to drainage procedures [88].

Biliary drainage

Biliary decompression is essential in patients who have cholangitis. Decompression can be performed by endoscopic, percutaneous, or surgical approaches or by multimodal therapy.
Endoscopic biliary decompression

An endoscopic approach offers several benefits, including defining ductal anatomy, identifying simultaneous pathology (such as biliary strictures or choledochal cysts), collecting bile for microbiologic study, providing tissue sampling, and allowing definitive therapy in most cases. In severe cholangitis biliary decompression and bile duct clearance by ERCP has lower morbidity and mortality rates than open surgery with bile duct exploration [89,90]; in one prospective, randomized trial, the morbidity of the endoscopic procedure was one half that of open surgery (34% versus 66%), and the mortality with the endoscopic procedure was one third that of the open approach (10% versus 32%) [90]. Similarly, morbidity and mortality in elderly patients are lower with EBD than with percutaneous drainage [91]. Endoscopic biliary decompression therefore is the procedure of choice, and percutaneous or surgical drainage is reserved as an alternative when endoscopic therapy is technically impossible or is unsuccessful.

Evaluation before endoscopic retrograde cholangiopancreatography. The patient’s condition is stabilized as much as possible before the procedure. Adequate hydration and prompt administration of systemic antibiotics are essential. Details of prior surgeries that alter ERCP access should be identified. Appropriate periprocedural and intraprocedural monitoring is needed. Critically ill patients may require emergency ERCP using a mobile fluoroscopic unit at the bedside in the ICU. EBD without fluoroscopy has been performed successfully in the ICU [92].

Endoscopic techniques of biliary drainage in acute cholangitis. When ERCP is performed in the presence of active cholangitis and purulent bile, care must be taken to avoid aggravating the existing high intraductal pressure. Contrast injection during biliary cannulation should be minimized. Once deep cannulation is successful, 20 to 40 mL of bile should be aspirated to decompress the bile duct and to provide a sample of bile for microbiologic analysis. Then limited contrast can be injected to fill only the extrahepatic ductal system to define the cause and location of obstruction, unless intrahepatic bile duct pathology is suspected. Definitive therapy (BES with removal of stones) is pursued in a stable patient who has confirmed bile duct stones. In an unstable patient, every effort should be made to shorten the procedure time while providing adequate biliary drainage; definitive therapy can be performed subsequently once the patient is stable. Prolonging the procedure to attempt definitive therapy in an unstable patient may increase the morbidity and mortality.

In patients who have severe cholangitis, EBD can be achieved with plastic biliary stents or with nasobiliary catheter drainage (NBD) with or without BES. Concomitant BES facilitates the placement of a larger stent (10–11.5 F) or multiple stents for more effective drainage and with a minimal risk of stent migration. A large multicenter trial, however, noted that the risk
of postsphincterotomy bleeding is correlated significantly with the presence of acute ascending cholangitis, even in the absence of coagulopathy [53]. Furthermore, one study comparing decompression by NBD alone (n = 73) versus NBD with BES (n = 93) showed comparable success rates but significantly more complications in the BES group (12% versus 2%), mainly from bleeding or cholecystitis [93]. Overall, the decision whether BES should be performed is tailored to the individual patient. If coagulopathy is present, or if the patient is unstable, placement of a biliary drainage tube alone (preferably a 7-F biliary stent or NBD), without BES, generally is recommended for short-term drainage and produces satisfactory results [93,94]. BES may be performed when placement of a large (≥ 10 F) or multiple stents is required. By separating the biliary and pancreatic orifices, BES can avoid compression of the pancreatic orifice by the stents, which otherwise could result in post-ERCP pancreatitis. In patients who have a concomitant biliary stricture that requires dilation, BES also may facilitate stent placement through the tight stricture. In patients who have cholangitis in whom ERCP is performed but no bile duct stones are identified, BES has been shown to improve outcomes compared with no therapeutic intervention, with a faster recovery and shorter hospitalization [95].

Two prospective studies demonstrated no difference in treatment outcomes between biliary stenting and NBD in patients who had acute cholangitis [96,97]. NBD provides the advantage of active decompression by intermittent or continuous negative pressure suction and the opportunity for sequential bacteriologic bile cultures. It is, however, less used frequently because of patient discomfort, the possibility of inadvertent dislodgment of the nasobiliary catheter, the risk of kinking with inadequate drainage, and the potential for electrolyte disturbances secondary to the external diversion of bile. No randomized, controlled trials have compared outcomes between straight or pigtail biliary stents or among different stent sizes (7 F versus larger size) in patients who have acute cholangitis. Theoretically, larger stents should provide better drainage, particularly if thick, purulent bile and stone debris are present. Because BES is needed for placement of larger stents, the risk of BES-related bleeding needs to be weighed against the potential benefit. Because most patients who have acute cholangitis undergo definitive therapy for bile duct stones several days or weeks following successful biliary decompression, the type or size of stent is likely to have no effect on treatment outcomes. In patients who have debilitating comorbid conditions, in whom the definitive therapy for bile duct stones is anticipated to be delayed (ie, for months) or may be unsuccessful, BES with long-term placement of multiple stents may be a reasonable alternative.

**Percutaneous transhepatic biliary drainage**

In percutaneous transhepatic biliary drainage a biliary drainage catheter is placed under ultrasound or fluoroscopic guidance into an intrahepatic
duct and/or common bile duct, with the tip downstream in the duodenum. In expert centers, the overall success rate of percutaneous drainage approaches 95% to 98% in patients who have biliary ductal dilation and is 70% to 80% in patients who do not have biliary dilation [98]. Potential serious complications include sepsis, intraperitoneal hemorrhage, peritonitis, and pancreatitis [98]. Percutaneous transhepatic biliary drainage generally is reserved for patients in whom endoscopic biliary drainage is unsuccessful or who have altered anatomy such as prior gastric bypass surgery.

Surgical drainage

Either open or laparoscopic common duct exploration may be performed. In severely ill patients, the simplest procedure (eg, T-tube placement) should be performed to shorten the procedure time. The option of definitive therapy can be determined later, when appropriate. Because of the operative risks, emergency surgical decompression rarely is performed; it is reserved for patients in whom both endoscopic and percutaneous approaches have been unsuccessful or who have altered anatomy that precludes such approaches.

Gallstone pancreatitis

Gallstones are the most common cause of acute pancreatitis in Western countries. The incidence of GSP is increased in women more than 60 years old [99]. The pathogenesis is believed to be related to increased pancreatic ductal pressure, possibly with biliopancreatic reflux, that occurred when the bile duct stone passed or was impacted at the ampulla. Multiple small gallstones (< 5 mm), a dilated cystic duct, and good postprandial gallbladder emptying are putative factors for GSP [100–102]. Anatomic variations such as a long common channel [103] or a nonpatent accessory duct [104] may be contributing risk factors.

Most stones pass spontaneously into the duodenum. Discovery of fecal stones has been reported in about 90% of patients suspected of having GSP, in comparison with 10% of controls [105]. The disease recurs, however, in approximately one third to two thirds of patients as early as 3 months after the initial episode if the underlying biliary stones are left untreated [106]. Although GSP usually is mild and self-limited, some patients have a severe, complicated course that entails substantial mortality. Management of patients who have severe disease is complex and has been debated for nearly a century.

Clinical presentation

Patients typically present with a sudden onset of unrelenting upper abdominal pain, which radiates into the back in about 50% of cases. Nausea and/or vomiting frequently occur. An elevated serum amylase and/or lipase
level three times the upper limit of normal or higher in the typical clinical setting is diagnostic. When patients experience sudden severe abdominal pain, other serious conditions should be considered and need to be excluded (Box 2). Notably, other potentially life-threatening conditions, such as a perforated viscus or bowel ischemia, can produce modest elevation of the serum amylase or lipase level.

**Diagnosis**

Recognition of GSP is crucial, because urgent endoscopic intervention may prevent complications and mortality in selected cases, and specific therapy of bile duct stones is essential to prevent recurrence. As noted earlier, the diagnosis of acute pancreatitis is based on the characteristic pain and elevated serum amylase or lipase levels. Suspicion of GSP is increased in patients who have acute pancreatitis associated with abnormal liver function tests, documented gallbladder stones, or biliary dilation in the absence of other causes [107,108]. A history of excessive alcohol use, known gallstone disease, previous/current medication use, abdominal trauma/surgery, previous episodes of pancreatitis, family history, and weight loss that suggests a malignant process should be obtained. Liver function tests, triglyceride levels, and the serum calcium level also should be obtained at presentation. In selected cases, additional blood tests to exclude autoimmune pancreatitis (anti-nuclear antibodies, IgG₄) or genetically related pancreatitis (cystic fibrosis, hereditary pancreatitis) should be considered.

**Liver function tests**

Elevation of alanine aminotransferase more than three times the upper limit of normal within 1 to 2 days after onset is the single best predictor of biliary pancreatitis, with a positive predictive value of 95% [109]. Any elevation of liver function tests in patients who have acute pancreatitis should

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**Box 2. Differential diagnosis of acute pancreatitis**

*Gastrointestinal diseases*
- Perforation of hollow viscus
- Mesenteric ischemia/infarction
- Intestinal obstruction
- Acute cholecystitis
- Acute cholangitis

*Non-gastrointestinal diseases*
- Acute inferior wall myocardial infarction
- Dissecting abdominal aortic aneurysm
- Ectopic pregnancy
raise the possibility of GSP. A normal alanine aminotransferase level does
not exclude GSP, however, because the sensitivity rate is only 48% [109].
Moreover, liver function tests are entirely within the normal range in 10% of cases [110].

**Serum amylase/lipase**

The serum amylase level rises within 2 to 12 hours after the onset of symptoms and normalizes within 3 to 5 days [111]. Serum lipase, derived mainly from pancreatic acinar cells, peaks at 24 hours and may remain elevated for several days [112]. The serum amylase level tends to be higher with GSP than with alcoholic pancreatitis [113]. Clinical use of the height of the serum amylase/lipase is limited, however, because of overlapping values. Furthermore, the amount of the serum amylase/lipase elevation is not correlated with disease severity, and daily monitoring of these levels is of limited value in predicting the progression or prognosis of acute pancreatitis [114].

**Imaging studies**

In patients suspected of having acute pancreatitis, initial imaging studies are useful mainly in confirming the diagnosis and in excluding other abdominal emergencies. In patients who have a firm diagnosis, imaging studies may be required to determine the potential cause (gallstones, bile duct dilation, underlying chronic pancreatitis, or neoplastic process) and to detect local complications (pancreatic necrosis, fluid collection) in patients who have severe pancreatitis.

**Abdominal plain roentgenograms**

Abdominal plain roentgenograms contribute little to the diagnosis. The “sentinel loop” of distended small bowel is rare and does not affect management. The primary value of plain roentgenograms is to exclude other abdominal emergencies such as intestinal perforation or obstruction. Pancreatic calcifications, indicating underlying chronic pancreatitis, or opaque gallbladder stones are detected rarely.

**Transabdominal ultrasound**

TUS is the first line of investigation for GSP because of its low cost, its availability, and its portability for bedside examination of the critically ill patient. The primary value of TUS for acute pancreatitis is to document the presence of gallbladder stones and/or bile duct dilation, suggesting GSP. Although TUS is highly accurate for the diagnosis of gallstones in the absence of pancreatitis, it is only 60% to 80% sensitive in detecting gallstones during an attack of acute pancreatitis, presumably because of overlying bowel gas [114,115]. In particular, small gallstones (mean size, < 4 mm) may be missed by TUS [116]. EUS or an interval TUS may help in this situation.
**CT scanning**

A dynamic contrast-enhanced CT scan is the optimal tool for detecting pancreatic parenchymal and peripancreatic inflammatory changes to confirm the diagnosis. Occasionally, certain causes of pancreatitis such as common duct stones, pancreatic calcifications indicating chronic pancreatitis, or a pancreatic neoplasm can be discovered. In patients who have an uncertain diagnosis, a CT scan is helpful to identify other abdominal emergencies such as intestinal perforation, obstruction, or mesenteric infarction.

Balthazar and colleagues [117–119] have combined the extent of pancreatic/peripancreatic inflammatory changes and degree of pancreatic necrosis into a CT severity index that can predict reliably the severity of disease and the prognosis (Table 3). When intravenous contrast is contraindicated, precluding an accurate evaluation of extent of necrosis, a noncontrast multislice CT seems to be informative; patients who have peripancreatic fluid collections (grade D or E on the CT severity index) had a mortality of 14% and morbidity of 54%, whereas patients who did not have fluid collections (grades A, B, or C) had no mortality and only 4% morbidity [119].

Peripancreatic fat necrosis can occur from extravasation of activated pancreatic enzymes without pancreatic necrosis [117]. In a retrospective, cohort study, CT grading of the extent of extrapancreatic inflammation (ascites, pleural effusion, and retroperitoneal inflammation) was noted to predict local complications and persistent organ failure accurately [120].

The optimal timing of the CT scan is important. Because pancreatic necrosis may not be appreciated by CT scan until at least 2 to 3 days after symptom onset [121], an earlier CT scan may underestimate the severity of disease. Also, a high-quality CT scan, with appropriate technique, is mandatory.

**MR imaging/magnetic resonance cholangiopancreatography**

Recent studies suggest that MR imaging and CT have comparable reliability in the evaluation of severity and local complications of acute pancreatitis [122,123]. MR imaging/MRCP may offer an advantage over

<table>
<thead>
<tr>
<th>CT Grading</th>
<th>Degree of Necrosis (%)</th>
<th>CT Severity Index (range)</th>
<th>Complications (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: normal pancreas</td>
<td>0 none</td>
<td>0–3</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>B: edematous pancreatitis</td>
<td>1 none</td>
<td>0</td>
<td>0–3</td>
<td>92</td>
</tr>
<tr>
<td>C: pancreatic/peripancreatic inflammation</td>
<td>2 &lt;30</td>
<td>2</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>D: one peripancreatic fluid collection</td>
<td>3 30–50</td>
<td>4</td>
<td>7–10</td>
<td>17</td>
</tr>
<tr>
<td>E: multiple peripancreatic fluid collections</td>
<td>4 &gt;50</td>
<td>6</td>
<td>7–10</td>
<td>17</td>
</tr>
</tbody>
</table>

*Data from Refs. [117–119].*
CT scanning, with better detection of pancreatic hemorrhage [122] and bile duct stones. Secretin-MRCP may help define pancreatic ductal anatomy, such as pancreas divisum, as well as pancreatic duct disruption undetected by CT scan [123]. Unlike CT scan, MR imaging reliably distinguishes a pancreatic fluid collection from liquefied necrosis [124]. The use of MR imaging has been limited by its lack of availability on an urgent basis, its technical infeasibility in critically ill patients, and its variable reliability between centers. Furthermore, most bile duct stones causing GSP are small (< 5 mm), and MRCP has limited accuracy in detection of these stones. One small, prospective series reported the sensitivity, specificity, and accuracy of MRCP in detection of bile duct stones in setting of GSP to be 80%, 83% and 81%, respectively [39].

**Endoscopic ultrasound**

EUS is a very accurate, less invasive means to detect biliary stones. Because of its accuracy in detecting bile duct stones, EUS may serve as a useful guide about whether to proceed with therapeutic ERCP for GSP. A normal EUS can obviate the need for ERCP because it has a high negative predictive value for the diagnosis of bile duct stones. The technical success rate of early EUS (median, < 3 days from admission) in 123 patients suspected of having GSP has been reported to be as high as 97.5% [125]. EUS followed by ERCP, if indicated, seems to be a reasonable approach, particularly in critically ill patients who have a borderline probability of bile duct stones, because ERCP is performed only if bile duct stones are confirmed by EUS.

Intraductal EUS with ERC has been shown to increase the diagnostic accuracy of bile duct stones to 95% to 97%, whereas the accuracy of ERC alone is 87% to 90% [39,52]. It does not obviate the need for ERCP, however. Although it is available at only a few centers in the United States, EUS may be useful in select patients (eg, postcholecystectomy) in whom the detection of stones at the time of ERCP guides therapy.

**Determining severity and predicting prognosis**

Once acute pancreatitis has been diagnosed, the severity of disease can be assessed to guide further management and to predict prognosis. Although most patients who have acute pancreatitis have mild, self-limited disease (acute interstitial pancreatitis), which carries a mortality rate of 1% to 3%, about 15% to 25% of patients develop pancreatic necrosis. If this necrotic tissue becomes infected, mortality approaches 30% [107].

Several clinical scoring systems have been used to predict the severity of pancreatitis, most commonly Ranson’s criteria (overall, and biliary pancreatitis) [126,127], Glasgow criteria [128], and APACHE-II [129]. Both Ranson’s and Glasgow criteria require a 48-hour duration to complete the assessment, which is relatively long because organ failure may be evident by this time. The APACHE-II score can be determined at admission and repeated at 24 or 48 hours. These scoring criteria provide moderate overall
accuracy. Because of the low prevalence of severe disease, these clinical predictors yield a low positive predictive value (43%–49%) [107]. The clinically based Atlanta classification of acute pancreatitis is widely accepted [130]. Severe pancreatitis is defined by the presence of organ failure (systolic blood pressure < 90 mm Hg, \( \text{PaO}_2 \leq 60 \text{ mm Hg} \), creatinine level > 2.0 mg/dL after rehydration, and gastrointestinal bleeding > 500 cm³/24 hours); local complications such as pancreatic necrosis, abscess or pseudocyst; or systemic complications such as laboratory evidence of disseminated intravascular coagulation or a serum calcium level of 7.5 mg/dL or higher. A Ranson’s score of 3 or higher or an APACHE II score of 8 or higher also predicts severe pancreatitis. The authors’ group does not use a formal grading system to manage these patients.

A distinction between transient organ failure (< 48 hours) and persistent organ failure (> 48 hours) is important [107] because the former can occur in patients who have interstitial pancreatitis with a low mortality, but the latter has been associated with a mortality of 36% and local complication rate of 77% [131]. Moreover, early (< 72 hours after symptom onset), progressive multiorgan organ failure is the most important predictive factor for mortality, with a reported mortality greater than 50% in one study [132].

Obesity, defined by a body mass index of 30 or higher, was associated with increased morbidity and mortality of acute pancreatitis in a recent meta-analysis of 739 patients from five studies [133]. Elevated hematocrit and C-reactive protein [107] are correlated modestly with severe disease. Several markers, such as interleukins, procalcitonin, polymorphonuclear elastase, and trypsinogen activation peptide, have been evaluated in limited studies but are not used routinely.

Treatment

General

Adequate hydration, prevention of hypoxemia, correction of metabolic derangements, and pain control are the mainstays of supportive care. Aggressive fluid resuscitation to preserve pancreatic microcirculation prevented or minimized pancreatic necrosis in an experimental model [134]. Oxygen supplementation generally is recommended because most patients require narcotic analgesia, which can compromise ventilatory function. Effective pain control is tailored to the individual patient. Nasogastric tube decompression is needed only in patients who have significant ileus or vomiting. Empiric proton-pump inhibitor therapy is reasonable to prevent stress-related mucosal injury, although firm supportive evidence is lacking.

Close monitoring is needed to detect early deterioration of correctable conditions (eg. hypoxia). In patients who have severe pancreatitis, treatment in an ICU using a multidisciplinary team approach (consisting of
gastroenterologists, endoscopists with expertise in ERCP, pancreatobiliary surgeons, interventional radiologists, and a critical care team) is needed to optimize outcome.

**Nutrition**

In patients who have mild pancreatitis, nutritional support is not necessary because rapid recovery is expected within several days. Optimal timing for initiating oral intake is determined according to clinical status: improving pain scores, return of appetite or active bowel function, and absence of significant nausea or vomiting.

In patients who have severe pancreatitis for whom prolonged pancreatic rest is expected, adequate nutritional support is needed to meet metabolic requirements. Early enteral feeding within 48 hours after admission is well tolerated, is safer (with fewer infectious complications), and is less expensive than parenteral nutrition [135]. In the absence of ileus, jejunal feeding is preferable, although tube placement occasionally can be difficult. Gastric feeding also seems to be feasible and safe [136]. Parenteral nutrition may be considered in patients who cannot tolerate enteral feeding or when jejunal tube placement is not feasible technically.

**Antibiotic prophylaxis**

Based on a recent guideline, antibiotic prophylaxis is recommended in patients who have suspected or confirmed bile duct obstruction undergoing ERCP [137]. Generally, empiric antibiotic prophylaxis is given to patients who have GSP when early ERCP is indicated because these patients are likely to have retained or impacted bile duct stones.

Patients who have pancreatic necrosis have a significant risk of infectious complications, which constitute a major cause of death after 2 weeks of disease. Antibiotic prophylaxis to prevent infected pancreatic necrosis therefore is an attractive concept. Several randomized, unblinded studies using either selective gut decontamination with oral antibiotics or systemic antibiotics with various regimens in patients who have pancreatic necrosis have shown conflicting results. One meta-analysis published in 2003 concluded that prophylactic antibiotics significantly reduced both mortality and pancreatic sepsis [138]. Because of the heterogenous studies (eg, different antibiotic regimens, selection criteria) included in this meta-analysis, its reliability has been questioned. Recently, two prospective, double-blind, placebo-controlled studies showed no beneficial effects of antibiotics (ciprofloxacin/metronidazole in one; meropenem in the other) on reduction of pancreatic infection or mortality [139,140]. Moreover, superimposed fungal infection is a risk emerging from the prolonged use of broad-spectrum antibiotics [107]. Currently, routine use of prophylactic antibiotics seems to be unjustified and is not recommended [107]. Rather, empiric antibiotics should be used only when infected necrosis is suspected and the work-up for sepsis is pending.
**Specific therapy**

Most patients who have GSP have a self-limited, uncomplicated course with mild to moderate disease, because the offending stone passes spontaneously into the duodenum in most patients. Routine ERCP therefore is not recommended because of its low yield and significant risks. ERCP is used in mild, self-limited GSP when the findings of other noninvasive tests such as MRCP, EUS, or an intraoperative cholangiogram performed during the interval cholecystectomy indicate the need for definitive therapy of bile duct stones.

**Urgent endoscopic retrograde cholangiopancreatography for acute biliary pancreatitis**

The extent of pancreatic injury is related to the duration of ampullary obstruction [141], and patients who have severe GSP are more likely to have retained/impacted stones [142]. Therefore early restoration of ampullary patency at ERCP is desirable to prevent further pancreatic injury. Clinically, persistent severe pain, progressive rise of liver function tests or of the serum lipase/amylase level during the 24 to 48 hours after admission, and an elevation of bilirubin to more than 1.35 mg/dL on day 2 of hospitalization have been used to predict retained bile duct stones in patients who have GSP. These predictors have variable accuracy [143,144]. With the increasing availability of MRCP and EUS, patients who are likely to have retained bile duct stones requiring ERCP can be selected more precisely.

**Clinical studies of the role of urgent endoscopic retrograde cholangiopancreatography in gallstone pancreatitis**

Four landmark randomized, controlled trials have compared urgent ERCP with conservative therapy [142,145–147]. Neoptolemos and colleagues [142] first reported a randomized trial comparing urgent ERCP within 72 hours of admission with conservative therapy plus selective ERCP after 5 days if indicated. Urgent ERCP was performed successfully in 88% of patients, and biliary stones were documented in 19 patients (32%) in this group. In patients who had predicted severe GSP, early ERCP led to a significant reduction in the overall complication rate and hospital stay compared with the control group (24% versus 61%, and 9.5 days versus 17 days, respectively). No significant difference in mortality was noted between the two groups. This study demonstrated that an expert could perform ERCP safely in the setting of acute pancreatitis.

Fan and colleagues [145] randomly assigned 195 patients who had pancreatitis, 127 of whom had GSP, to early ERCP within 24 hours after admission or to conservative therapy. Early ERCP was performed successfully in 90% of patients; bile duct stones were discovered in 38%. Notably, 18 of the patients (45%) who had predicted severe pancreatitis who were assigned to conservative therapy eventually had ERCP performed (for cholangitis/septic shock) at a median of less than 72 hours after admission. Subgroup
analysis of the 127 patients who had GSP demonstrated that the rate of complications was significantly lower in the group receiving early ERCP than in the control group (16% versus 33%), as was biliary sepsis (0% versus 12%). The reduction in biliary sepsis was confined to those who were predicted to have severe pancreatitis. There also was a trend toward lower mortality in the ERCP group (2% versus 8%; \( P = .09 \)). This study confirmed the benefits of early ERCP in patients predicted to have severe GSP, as reported in the earlier British study [142].

A large preliminary study from Poland [146] evaluated 280 patients suspected of having GSP. All patients underwent duodenoscopy within 24 hours of admission. Seventy-five patients were found to have impacted stones at the papilla and were treated immediately with BES. The remainder of the patients, who had a normal-appearing papilla, were assigned randomly to early ERCP (< 24 hours after admission) or conservative therapy. The patients who had early ERCP (including the 75 patients who impacted stones, who were immediately treated) had significantly lower complication rates (17% versus 36%) and mortality (0% versus 7%) than the patients treated with conservative therapy. The benefit of early ERCP was significant regardless of the severity of GSP and was most pronounced in patients who had ERCP less than 24 hours after the onset of symptoms. This study has not been fully published, however, and some relevant data (eg, criteria for severity, percentage of visualized bile duct stones) are not available. Hence, the clinical applicability of this preliminary report is limited.

The fourth study, reported by Fölsch and colleagues [147], evaluated 238 patients suspected of having GSP from 22 centers in Germany. Patients who had a bilirubin level greater than 5 mg/dL or high fever (\( > 39^\circ C \)) were excluded. Patients assigned to early intervention had ERCP performed within 72 hours of symptom onset. This study did not demonstrate a significant benefit of early ERCP in reduction of either morbidity or mortality. Instead, the study was terminated prematurely because the interim analysis demonstrated an increased mortality (7.9% versus 3.6%) and a higher rate of respiratory failure (12% versus 4.5%; \( P = .03 \)) in the early ERCP group. This study has been criticized, however, because of its higher rate of overall morbidity in comparison with the other three studies and an unclear association of early ERCP with respiratory distress. The expertise of the participating centers also was questioned, because 19 of the 22 centers contributed fewer than a mean of 2 patients per year to the trial [148].

Two subsequent meta-analyses concluded that early endoscopic therapy, particularly in patients who have severe disease, significantly reduces morbidity [149,150]. A significant reduction in mortality was evident only when the Polish study was included in one meta-analysis [149], with the number needed to treat for avoidance of complication being 7.6 and the number needed to treat for avoidance of death being 25.6. It is difficult to establish firm conclusions based on these meta-analyses because of the
lack of homogeneity (eg, in selection criteria, predictors of severity, and timing of intervention) among these randomized trials.

Two recent prospective, randomized studies addressing the use of early ERCP to restore biliary patency in patients who have GSP have included only patients who met the preset criteria for ampullary obstruction [144,151]. Acosta and colleagues [144] randomly assigned patients suspected of having ampullary obstruction (defined by persistent severe pain, bile-free gastric aspirate, and rising bilirubin level measured every 6 hours) to early ERCP (within 48 hours of admission if obstruction persisted more than 24 hours) versus conservative therapy with selective ERCP after more than 48 hours. Ten percent of patients in each group had severe pancreatitis. Ampullary obstruction was confirmed by early ERCP in 13 of 14 patients who met the criteria of persistent obstruction (11 had impacted stones at the ampulla; 2 had papillary edema). This study was aborted prematurely after recruiting 61 patients because the interim analysis demonstrated that morbidity (29% versus 7%; \( P = .04 \)) and immediate complications (26% versus 3%; \( P = .02 \)) were significantly higher in the conservative group than in the early ERCP group. There were no deaths in this study. Notably, most immediate complications in this study were classified as pancreatic phlegmons, which were not fully defined.

Subsequently, Oria and colleagues [151] recruited 103 patients suspected of having GSP who met criteria for ampullary obstruction (bilirubin level \( \geq 1.2 \) mg/dL and distal bile duct diameter measured by TUS \( \geq 8 \) mm) without cholangitis. Patients were assigned randomly to early ERCP (within 72 hours after admission) or to conservative therapy. Early ERCP was successful in 92% of patients. Bile duct stones were found in 66% of patients in the early ERCP group versus 40% in the conservative group (who underwent elective cholecystectomy with intraoperative cholangiogram). This study showed no significant benefit from early ERCP in reduction of organ failure, local complications (6% versus 6%), overall morbidity (21% versus 18%; \( P = .8 \)), and mortality (6% versus 2%; \( P = 1 \)). The timing of early ERCP (within 72 hours) was relatively delayed in this study as compared with the former study. The validity of their criteria for biliary obstruction is unknown, because the rate of documented bile duct stones seems to be similar to that of previous studies without the preset criteria of biliary obstruction [150,152]. In addition, it is unclear how many patients in this study actually had evidence of bile duct obstruction, rather than merely having bile duct stones. The accuracy of TUS in measuring the distal bile duct also has been questioned, particularly in the setting of acute pancreatitis, when overlying bowel gas commonly is present.

These six studies are summarized in Table 4. In summary, early ERCP seems to be beneficial, particularly if performed within 24 to 48 hours of admission or symptom onset in patients who have GSP and who have simultaneous acute cholangitis or persistent biliary obstruction (persistent severe pain and elevation of liver function tests). In patients who have severe,
Table 4
Prospective randomized, controlled trials: urgent endoscopic retrograde cholangiopancreatography (ERCP) in gallstone pancreatitis (GSP)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Criteria of predicted severe GSP</th>
<th>Timing of ERCP</th>
<th>Success rate of early ERCP (%)</th>
<th>Documented stones at early ERCP (%)</th>
<th>Complications (%)</th>
<th>Mortality (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoptolemos et al [142]</td>
<td>146</td>
<td>&gt; Three modified Glasgow’s criteria</td>
<td>72 hours after admission</td>
<td>88</td>
<td>32</td>
<td>12/24&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>2</td>
<td>8 Decreased morbidity in predicted severe GSP Shortened hospital stay (9.5 days for ERCP versus 17 days for controls)</td>
</tr>
<tr>
<td>Fan et al [145]</td>
<td>195/127</td>
<td>On admission: serum urea &gt; 45 mg/dL or plasma glucose &gt; 198 mg/dL &gt; Three Ranson’s criteria</td>
<td>24 hours after admission</td>
<td>90</td>
<td>38</td>
<td>16&lt;sup&gt;a&lt;/sup&gt;/0&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>5</td>
<td>9 Early ERCP significantly reduces morbidity in patients predicted to have severe GSP</td>
</tr>
<tr>
<td>Nowak et al [146]</td>
<td>280</td>
<td>Not mentioned</td>
<td>24 hours after admission</td>
<td>Not mentioned</td>
<td>42 (impacted stones)</td>
<td>17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13&lt;sup&gt;a&lt;/sup&gt; Decreased complication rate and mortality in both predicted mild and severe cases</td>
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<td>Study</td>
<td>Sample Size</td>
<td>Criteria/Definition</td>
<td>Follow-up</td>
<td>Mortality</td>
<td>Complications</td>
<td>Main Complication</td>
<td>Findings</td>
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<td>Fölsch et al [147]</td>
<td>121</td>
<td>$\geq$ Three Glasgow criteria</td>
<td>72 hours</td>
<td>96</td>
<td>46</td>
<td>46 51 7.9 3.6</td>
<td>Significantly higher rate of respiratory failure in the early ERCP group</td>
<td></td>
</tr>
<tr>
<td>Acosta et al [144]</td>
<td>61</td>
<td>Ranson’s and Acosta criteria; selected patients with suspected ampullary obstruction(^d)</td>
<td>&lt; 48 hours</td>
<td>100</td>
<td>93</td>
<td>29(^a) 7(^a) 0 0</td>
<td>Excluded cholangitis (biliary sepsis)</td>
<td>Main complication in control group was pancreatic phlegmon</td>
</tr>
<tr>
<td>Oria et al [151]</td>
<td>102</td>
<td>APACHE-II, selected patients with suspected ampullary obstruction(^e)</td>
<td>&lt; 72 hours</td>
<td>92</td>
<td>66</td>
<td>21 18 6 2</td>
<td>Excluded acute cholangitis</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Numbers are statistically significantly different.
\(^b\) All severity/ predicted severe.
\(^c\) Total complications/ biliary sepsis.
\(^d\) Defined by severe persisting pain, bile-free gastric aspirate, and elevated serum bilirubin.
\(^e\) Defined by distal bile duct measuring $\geq$ 8 mm by ultrasound with a total bilirubin $\geq$ 1.2 mg/dL on admission.
nonobstructive GSP, the benefit of urgent ERCP is controversial. Practice varies among experts and centers, and recommendations are inconsistent [49,107,113,152,153]. The authors perform urgent ERCP on selected cases in this situation when retained bile duct stones are suspected based on persistent elevation of liver function tests for more than 24 to 48 hours. Patients who have spontaneously resolving liver function tests may not require urgent ERCP.

Finally, whether BES should be performed when bile duct stones are not visualized is unclear, and each case should be judged individually. Because of possibility of overlooking tiny bile duct stones, particularly in a dilated duct, performing BES empirically in severe GSP seems reasonable. Furthermore, BES may prevent recurrent episodes of pancreatitis, particularly if cholecystectomy cannot be performed in the near future or is impossible because of the high surgical risk. Indeed, one guideline advocates BES in patients who have severe GSP, regardless of the presence or absence of bile duct stones [153].

An algorithm for endoscopic intervention in acute GSP is proposed in Fig. 2.

**Cholecystectomy for gallstone pancreatitis**

The primary objective of cholecystectomy is to prevent recurrent GSP. Early laparoscopic cholecystectomy seems to be safe and effective in preventing recurrent attacks in patients who have mild GSP [154]. Early

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**Fig. 2. Algorithm of endoscopic therapy in acute gallstone pancreatitis.**
cholecystectomy may be unsafe in patients who have severe disease, however, because overall complication rates and sepsis were significantly higher in those undergoing early surgery than in those undergoing delayed surgery (44% versus 5.5% and 47% versus 7%, respectively) [155].

Because of the high recurrence rate of GSP unless gallstones are removed, it currently is recommended that cholecystectomy should be performed in the same hospitalization, when pancreatitis subsides, or within 2 to 4 weeks after discharge [152,153]. Patients who have little evidence of retained ductal stones (resolved pain, fully normalized serum liver chemistries) may proceed directly to laparoscopic cholecystectomy and intraoperative cholangiogram. If any bile duct stones are documented, they can be managed by intraoperative or postoperative ERCP or by laparoscopic bile duct exploration, depending on the local expertise.

**Gallstone pancreatitis after cholecystectomy**

In patients who have had cholecystectomy, other causes such as sphincter of Oddi dysfunction, pancreas divisum, and pancreatic neoplasms need to be excluded. Less invasive investigations, such as MRCP or EUS, should be considered to guide further management. If these tests do not confirm the presence of common duct stones, a presumptive diagnosis of idiopathic pancreatitis should be made. Further discussion of this issue is beyond the scope of this article. Because of the frequent need for complex biliary procedures, such as biliary and pancreatic manometry, and for minor/major pancreatic sphincter therapy, and because of the high frequency of serious procedure-related complications, management of these patients should be undertaken by experienced hands.

**Summary**

Gallstone disease is encountered commonly in clinical practice. The diagnosis of biliary stones has become less problematic with current, less-invasive imaging methods. The relatively invasive endoscopic techniques should be reserved for therapy and not used for diagnosis. Acute cholangitis and GSP are two major complications that require prompt recognition and timely intervention to limit morbidity and prevent mortality or recurrence. Appropriate noninvasive diagnostic studies, adequate monitoring/supportive care, and proper patient selection for invasive therapeutic procedures are elements of good clinical practice.

**References**


Lyons MA, Wittenburg H. Susceptibility to cholesterol gallstone formation: evidence that LITH genes also encode immune-related factors. Biochim Biophys Acta 2006;1761:1133–47.


