

Gallstone Pancreatitis: A Review

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KEYWORDS

- Gallstone pancreatitis • Biliary acute pancreatitis • Diagnosis • Management
- Early cholecystectomy

KEY POINTS

- Gallstone disease is the most common cause of acute pancreatitis in the Western world.
- The diagnosis of gallstone pancreatitis (GSP) is based on physical examination, with elevated serum pancreatic enzymes and imaging of biliary tract stones, in the absence of any other compelling etiology.
- The purpose of imaging in GSP is to detect the cause of the disease, identify complications, and gauge severity.
- Severity stratification is essential to ensure that appropriate supportive care and interventions are provided in moderate to severe cases while also not delaying care for patients with mild disease.
- The goal of cholecystectomy is to prevent recurrent GSP.
- Cholecystectomy within 48 hours of admission for mild GSP is safe and feasible.
- Patients with moderate to severe GSP and peripancreatic fluid collections should undergo delayed cholecystectomy to prevent serious infectious complications.
- Endoscopic retrograde cholangiopancreatography and laparoscopic explorations of the common bile duct are effective means of managing concomitant choledocholithiasis.

INTRODUCTION

Gallstone disease is the most common cause of acute pancreatitis in the Western world.¹⁻⁴ In most cases, gallstone pancreatitis (GSP) is a mild and self-limiting disease, and patients may proceed without complications to cholecystectomy to prevent future recurrence. Severe disease occurs in about 20% of cases and is associated

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with significant mortality, and meticulous management is critical. A thorough understanding of the disease process, diagnosis, severity stratification, and principles of management is essential to the appropriate care of patients presenting with this common disease. This article reviews these topics with a focus on surgical management, including the appropriate timing and choice of interventions.

EPIDEMIOLOGY

GSP is most common among women older than 60 years, and the number of cases reported annually is increasing worldwide, possibly as a result of the worsening obesity epidemic.^{1,5} The incidence of acute pancreatitis is estimated at 40 per 100,000 people, and 40% to 50% of cases are biliary in etiology. The burden of acute pancreatitis from all causes in the United States exceeds \$2.2 billion per year, with more than 300,000 inpatient admissions and 20,000 deaths annually.⁶⁻⁸

The prevalence of gallstone disease in the United States and Europe is 10% to 15%, and risk factors for GSP are similar to those for gallstone formation: age, gender, obesity, pregnancy, genetics and family history, fasting and rapid weight loss, and gallbladder stasis, among others.^{9,10} Although symptomatic gallstones most commonly present as biliary colic and acute cholecystitis, the incidence of developing GSP is 3% to 8%, and symptomatic gallstones carry an annual risk for developing GSP of 0.04% to 1.5%.¹¹⁻¹⁴ Once gallstones are implicated in acute pancreatitis, the disease follows a mild course in 80% of patients, and mortality is 1% to 3%. However, in 20% of patients the acute pancreatitis is severe, and mortality approaches 30%.¹⁵

PATHOPHYSIOLOGY

Gallstones have been detected in the feces of up to 90% of patients with GSP, suggesting that the causative stones usually pass into the duodenum spontaneously. The composition of these stones is primarily cholesterol, bile salts, and phospholipids.^{16,17} When bile becomes supersaturated, overabundant cholesterol precipitates as crystals, which mix with bilirubin and solidify to form biliary sludge, which may then aggregate to form gallstones.¹⁸ Although gallstone migration into the common bile duct (CBD) may be a relatively common event, the stones cause GSP with far less regularity.¹⁹

Bernard and Prince first described the relationship of gallstones and acute pancreatitis in 1852 and 1882, followed by Opie in 1901.^{4,20-22} There is an impressive body of basic science research focused on the intricacies of this relationship and the exact mechanism by which gallstones cause acute pancreatitis. Risk factors include multiple small stones less than 0.5 mm in size, and a large cystic duct.²³⁻²⁵ Multiple theories have been proposed to describe how gallstones set off the inflammatory response in acute pancreatitis, and a commonly accepted mechanism involves a transient obstruction of the bile or pancreatic duct by an impacted or passing stone. Alternatively, biliary sludge may cause cholestasis or irritate the sphincter of Oddi, causing edema and biliopancreatic outflow obstruction. This process initiates an intracellular activation of digestive enzymes within the pancreas, but the mechanism is not well understood. Biliopancreatic reflux resulting from increased ductal pressure may contribute, but this theory has been challenged based on physiologic studies demonstrating a higher secretory pressure in the pancreatic duct than in the bile duct. In addition, some researchers have observed that sterile bile under physiologic pressures is not harmful to the pancreas, although this has also been challenged.^{26,27} Nevertheless, increased intraductal pressure likely plays a role, because the extent of

pancreatic injury is related to the duration of ampullary obstruction.^{28,29} The pancreatic sphincter, exocrine secretions, mucosal barrier, and the delayed activation of trypsinogen in the duodenum are all protective elements of normal biliopancreatic physiology. In GSP, this homeostasis is altered and pancreatic injury is compounded by inflammatory cytokines, which may worsen pancreatic parenchymal damage and potentially incite the systemic inflammatory response syndrome (SIRS).

DIAGNOSIS

History and Physical Examination

Most patients presenting with GSP complain of typical symptoms of pancreatitis, and fewer may also provide a history of biliary colic. The most common complaint is sudden-onset epigastric or right upper quadrant abdominal pain that is unrelenting, and in 50% of cases radiates to the back.¹⁰ Associated symptoms are nausea and vomiting. A strong history of alcohol abuse should raise a suspicion of alcoholic pancreatitis.³⁰ Physical examination usually demonstrates impressive abdominal tenderness, and patients with severe pancreatitis may also exhibit signs suggestive of an acute surgical abdomen. Immediate evaluation is necessary in patients with peritoneal findings, because the presentation of severe acute pancreatitis may mimic intestinal perforation. As with acute cholecystitis, the pain is exacerbated by eating or drinking. Peripancreatic inflammation may result in a generalized ileus, which causes hypoactive bowel sounds and anorexia. Patients with moderate to severe disease may also present with symptoms of SIRS, including pyrexia, tachycardia, and tachypnea.

Laboratory Evaluation

Laboratory analysis is indispensable in the initial diagnosis of acute pancreatitis. Upper abdominal pain with amylase or lipase 3-times the upper normal limit is diagnostic of acute pancreatitis in many cases, and the addition of cholelithiasis on imaging may sufficiently identify the cause as biliary. Lipase is highly sensitive (>90%) in acute pancreatitis and also has an advantage over amylase in specificity, because lipase is produced primarily by pancreatic acinar cells, whereas amylase is also found in saliva. The level of amylase typically increases within 2 to 12 hours after onset and normalizes within 3 to 5 days, whereas lipase peaks at 24 hours and may stay elevated for several days.³¹ Of importance, the degree of elevation of amylase and lipase do not correlate with disease severity.³² Despite this limitation, higher levels of amylase have been observed in gallstone pancreatitis in comparison with alcoholic pancreatitis.³³

A complete blood count is likely to show leukocytosis. It has also been observed that hematocrit correlates modestly with disease severity.¹⁵ A basic metabolic panel is useful in detecting metabolic derangements, and may also demonstrate mild hyperglycemia from decreased insulin secretion and increased glucagon.⁷ Renal function is also important to consider in severe disease where organ failure is a potential sequela. In addition, patients with acute pancreatitis of any origin may present as hypovolemic, with acute kidney injury correctable by adequate volume resuscitation. Bicarbonate levels are also a marker of resuscitation and can correlate with disease severity (see [Indices of Severity](#) in the section Management).

Liver function tests are also essential in the initial evaluation. Because the underlying pathology in GSP may involve a biliary obstruction, albeit transitory in most cases, patients may present with elevated bilirubin and transaminases. Transaminases are usually only modestly elevated, unlike the high levels seen in viral hepatitis. However, in cases where a stone is impacted they may increase markedly, but normalize after

resolution within days as opposed to weeks. Except in sustained choledocholithiasis, the bilirubin level is usually less than 15 mg/dL, because the obstruction is generally incomplete or intermittent.³⁴ In 10% of cases of GSP, liver function tests (LFTs) are normal.³⁵ Although poorly sensitive (48%), an alanine aminotransferase level more than 3 times the upper limit within 24 to 48 hours of onset is the best predictor of GSP, with a positive predictive value of 95%.³⁶ In addition, alkaline phosphatase and γ -glutamyl transpeptidase may be elevated, particularly if cholestasis persists.

Initial laboratory workup for acute pancreatitis should also include triglyceride and calcium levels for the consideration of hypertriglyceridemia and hypercalcemia as possible etiologic factors. In idiopathic pancreatitis, immunoglobulin G4 may help to identify autoimmune pancreatitis.

Imaging

The purpose of imaging in acute pancreatitis is 3-fold: to detect the cause of the disease (biliary stones, neoplasms, anatomic variances), to identify complications (fluid collections, pseudocysts, hemorrhage), and to gauge the severity of the disease (peripancreatic inflammation, pancreatic necrosis).

Ultrasonography

Every patient presenting with acute pancreatitis and no obvious alternative cause should undergo transabdominal ultrasonography to isolate gallstones as the possible cause. Ultrasonography is inexpensive, sensitive, and widely available. In the past decade the technology has evolved, allowing for portable ultrasound devices with vastly improved resolution. Ultrasonography spares patients the pain of an invasive test and the ionizing radiation of computed tomography (CT). Of note, ultrasonography studies are obtained by trained technicians and are operator dependent.

In general, the presence of cholelithiasis or sludge on ultrasonography (Fig. 1), in the absence of other likely causes, is sufficient evidence to diagnose GSP when combined with a typical presentation and elevated pancreatic enzymes. Ultrasonography is 95% sensitive for cholelithiasis, but in GSP, overlying bowel gas attributable to ileus may decrease sensitivity to 60% to 80%.^{32,37} In the detection of choledocholithiasis, ultrasonography is reported to be 25% to 60% sensitive.^{38–40} Ultrasonography is useful in detecting dilated intrahepatic and extrahepatic bile ducts, which may indicate obstruction, but is less sensitive in the context of GSP because the obstruction is

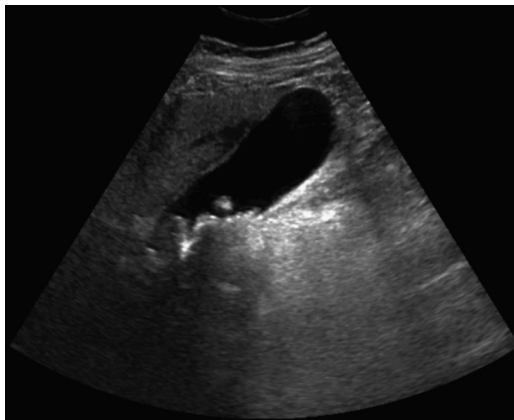


Fig. 1. Typical ultrasonogram illustrating cholelithiasis and gallbladder sludge.

acute. Ultrasonography may also fail to detect stones smaller than 4 mm, and small stones are a known risk factor for GSP.⁴¹ Despite its limitations, ultrasonography remains the standard imaging study in the diagnosis of GSP, and in imaging terms is sufficient for most patients with mild disease.

Computed tomography

The utility of CT in GSP is to detect the anatomic changes that correlate with complications and mortality.⁴² CT is often not an essential study in mild GSP, but provides more useful information in moderate to severe cases. CT is 85% to 97% sensitive and 88% to 96% specific for common duct stones when contrast is used (Fig. 2).^{43–45} The use of CT for stratification of severity and to direct management requires appropriate timing and technique. Pancreatic necrosis is best visualized on CT at 2 to 3 days after the onset of symptoms.⁴⁶ If an initial CT was obtained during diagnosis, it may need to be repeated at 3 days if the patient's pain is severe and persistent, and laboratory values fail to trend toward normal. To optimize radiographic evaluation of the pancreas, a pancreatic protocol should be specified, comprising 2- to 3-mm cuts through the pancreas, intravenous contrast, and both pancreatic and venous phases of imaging. Oral contrast should be avoided, as it causes artifact in the duodenum that limits the study. The Balthazar CT severity index was developed to help stratify patients with acute pancreatitis (see [Indices of Severity](#) in the section Management).

Magnetic resonance imaging

To understand the role of magnetic resonance imaging (MRI), it is important to differentiate between abdominal MRI and magnetic resonance cholangiopancreatography (MRCP). Whereas abdominal MRI refers to series of images of the abdomen, MRCP describes a specific protocol designed to enhance fluid within the biliary system. It is a noninvasive imaging technique that serves diagnostic aims similar to those of endoscopic retrograde cholangiopancreatography (ERCP) with comparable accuracy. MRCP produces images that clearly define the biliary and pancreatic duct anatomy to delineate anatomic abnormalities, such as pancreas divisum, a disruption of the pancreatic duct, or filling defects that may represent tumors or gallstones. MRCP is reported to be 85% to 90% sensitive in detecting CBD stones, with 93%



Fig. 2. Computed tomography scan demonstrating peripancreatic inflammatory changes and an obstructing stone (*arrow*) in a dilated distal common bile duct (CBD).

to 95% specificity.^{47,48} An advantage of MRCP is the ability to detect stones as small as 2 mm, although this modality still has limited sensitivity for most stones smaller than 5 mm. MRCP is likely to confirm choledocholithiasis, and is commonly used by clinicians to help select patients for ERCP.

Although more expensive and less available than CT, MRI is excellent at visualizing choledocholithiasis, and is particularly useful in evaluating the complications of GSP. MRI is capable of distinguishing pancreatic fluid collections from liquefied necrosis, and is also helpful in diagnosing pancreatic hemorrhage (Fig. 3).^{10,49} The effective use of MRI relies heavily on updated technology and experts in radiology who are facile at interpreting the data.

Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) is a diagnostic modality with substantial utility in diagnosing hepatobiliary abnormalities. It is performed by advancing a specialized endoscopic ultrasound probe into the upper gastrointestinal tract. The close proximity to biliopancreatic structures allows for visualization superior to that of transabdominal ultrasonography. Diagnostically, EUS is 93% to 98% sensitive and 97% to 100% specific for choledocholithiasis.^{47,50} It has a negative predictive value of 93% to 100%, and may spare patients without common duct stones unnecessary ERCP.^{51–53} EUS has also been used to exclude choledocholithiasis in pregnant patients with GSP, and in patients who have contraindications to MRCP such as implanted metallic devices. The safety profile of EUS is superior to diagnostic ERCP, and its use in the pretherapeutic ERCP setting has been strongly advocated.⁵¹

MANAGEMENT

A central principle in determining the best course of management is predicting the severity of the disease. GSP is a disease with a broad spectrum of severity, ranging from mild pancreatic inflammation that resolves within 24 hours to fulminant infected pancreatic necrosis. Self-limited pancreatitis has a mortality of 1% to 3%, and describes 80% of cases. In 15% to 25% of patients with all forms of acute pancreatitis the disease may progress to pancreatic necrosis, and some of these patients will progress further to infected pancreatic necrosis with a mortality of 30%.¹⁵ It is therefore essential to determine the severity of the disease early in the hospital course to ensure that appropriate supportive care and interventions are provided while also

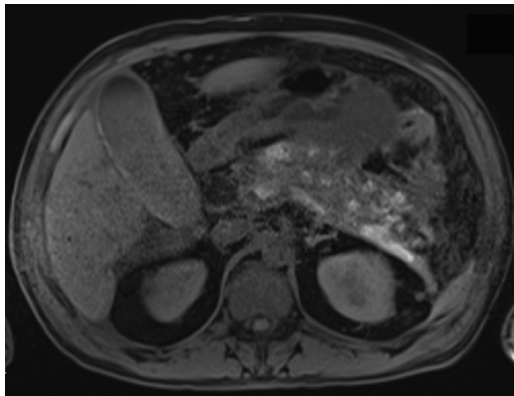


Fig. 3. Precontrast T1-weighted magnetic resonance image demonstrating severe hemorrhagic pancreatitis as extensive pancreatic enhancement.

not delaying care for patients with mild disease. Several models have been developed to assist in risk stratification and predict mortality in patients presenting with acute pancreatitis.

Indices of Severity

The Ranson score is still among the most widely used severity indices in the United States, and is calculated based on 11 parameters at the time of admission and at 48 hours. A modification of this index specifically for biliary pancreatitis uses 10 parameters, and reflects a different threshold (Table 1). A Ranson score of 3 or greater classifies a patient with severe disease. The positive predictive value has been reported to range from 37% to 70%, and one study demonstrated that the predictive power of the Ranson criteria is similar to good clinical judgment.^{56–59}

The APACHE-II score was developed to predict mortality in patients in the intensive care unit (ICU), and has been widely applied to patients with acute pancreatitis (Box 1). APACHE-II at 48 hours is reported to have a higher positive predictive value than the Ranson score.⁵⁶ In addition, the APACHE-II score may be calculated at any time during admission, and an increase or decrease in this score has been found to correlate with clinical improvement or deterioration.^{60,61} An APACHE-II score of 8 or greater indicates severe disease.

The bedside index for severity in acute pancreatitis (BISAP) is based on 5 parameters, 1 of which is the presence of SIRS. A score of 3 or greater is associated with higher mortality, and is reported to have accuracy similar to that of the Ranson and APACHE-II scores.⁵⁷

The revised Atlanta Classification of acute pancreatitis (2012) is a means of categorizing the severity of acute pancreatitis based on clinical and radiographic data. It describes an early phase, which defines the early local and systemic responses to pancreatic injury, and a late phase of acute pancreatitis, which is limited to moderate and severe pancreatitis. The classification is divided into mild, moderate, and severe pancreatitis based on the presence of local and systemic complications, and the

Parameter	All Causes of Pancreatitis	Gallstone Pancreatitis
On Admission		
Age	>55	>70
White blood cell count	>16,000	>18,000
Serum glucose (mg/dL)	>200	>220
Serum AST (IU/L)	>250	>250
Serum LDH (IU/L)	>350	>400
Within 48 h		
Base deficit (mmol/L)	>4	>5
Hematocrit decrease	>10%	>10%
BUN increase (mmol/L)	>5	>2
Pao ₂ (mm Hg)	<60	—
Sequestration of fluids (L)	>6	>4
Serum calcium (mg/dL)	<8	<8

Abbreviations: AST, aspartate aminotransferase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; Pao₂, partial pressure of arterial oxygen.

Data from Refs. ^{14,54,55}

Box 1
APACHE-II parameters

Age
 History of organ insufficiency
 History of immunocompromise
 Rectal temperature
 Mean arterial temperature
 Heart rate
 Respiratory rate
 Oxygenation
 Serum sodium
 Serum potassium
 Serum creatinine
 Hematocrit
 Arterial pH
 White blood count

presence and persistence of organ failure. The revised Atlanta Classification was proposed to facilitate communication between clinicians and to serve as an index of severity based on an understanding of the disease process.⁶² This classification takes into account the difference in mortality between transient and persistent organ failure, which is an important distinction because organ failure of less than 48 hours is associated with low mortality, whereas organ failure of more than 48 hours has a predicted mortality of 36%.⁶³

Balthazar and colleagues⁶⁴ introduced the CT severity index (CTSI) that grades severity of acute pancreatitis based on morphologic features including gland enlargement, peripancreatic inflammation, fluid collections, retroperitoneal gas, and degree of pancreatic necrosis, with prognostic implications (Table 2). Whereas clinical scores, such as Ranson, APACHE-II, and Glasgow, may have more utility in predicting

Table 2
Balthazar CT severity index and prognosis

Grade and CT Findings	Score	Mortality (%)	Degree of Necrosis (%)
A: Normal pancreas	0	3	None
B: Focal or diffuse pancreatic enlargement	1		None
C: Pancreatic/peripancreatic inflammation	2	6	<33
D: Single pancreatic/peripancreatic fluid collection	3		33–50
E: Multiple fluid collections/ retroperitoneal gas	4	17	>50

Data from Balthazar EJ, Ranson JH, Naidich DP, et al. Acute pancreatitis: prognostic value of CT. *Radiology* 1985;156:767–72; and Balthazar EJ, Robinson DL, Megibow AJ, et al. Acute pancreatitis: value of CT in establishing prognosis. *Radiology* 1990;174(2):331–6.

the course of disease early, the CTSI may be more helpful in managing patients with established disease and determining the appropriate future, as opposed to immediate, care.⁶⁵

Other predictors of severity of interest include biochemical markers. C-reactive protein has been shown to correlate with severe disease, and has been advocated as a useful single biochemical marker.⁶⁶ Other potential serum levels such as those of interleukin-6 and macrophage migration inhibitory factor have been evaluated, and further investigation may help incorporate these parameters into novel indices to predict clinical severity.

There are no perfect or universally accepted scoring methods to predict the severity of GSP, particularly early in the disease when the clinician must decide between ICU monitoring or whether to proceed with cholecystectomy. Among all patients with predicted mild pancreatitis, as many as 15% progress to severe disease.^{57,66} It is therefore incumbent on clinicians who choose to use these indices to do so selectively in combination with clinical acumen to determine the best course of management. Regardless of the method, it serves the clinician and patient well to stratify GSP as mild, moderate, or severe.

Initial Management

The general guidelines in managing acute pancreatitis apply equally to GSP. The basis of supportive care is to provide pain control, correct metabolic derangements, aggressively resuscitate with intravenous fluids, and prevent hypoxemia. Patients with an ileus may require a nasogastric tube for decompression. Those with severe disease are best served by a multidisciplinary team approach in the ICU, including gastroenterologists with ERCP capabilities, surgeons comfortable with hepatobiliary surgery, physicians with experience in critical care, and interventional radiologists. Patients with mild disease may require only adequate hydration and pain control before early cholecystectomy.

Nutrition

Patients admitted with acute pancreatitis are typically kept nil by mouth initially. However, those with mild disease benefit from a shorter length of stay in hospital with immediate oral feeding.⁶⁷ GSP patients are no exception, unless early feeding interferes with early cholecystectomy. Patients with severe disease have been shown to benefit from enteral feeding within 48 hours, without exacerbation of illness. Total parenteral nutrition is less safe, less effective, and more expensive, and should be reserved for patients who cannot tolerate enteral feeding. Jejunal feeding is preferred, but gastric feeding has also been shown to be safe.⁶⁸

Antibiotics

Appropriate broad-spectrum antibiotics are indicated pending a workup for sepsis and in infected pancreatic necrosis. In sterile pancreatic necrosis, the use of prophylactic antibiotics is controversial. There are several large studies that disagree as to whether prophylactic antibiotics impart a benefit in pancreatic sepsis and mortality, and recent literature does not recommend antibiotic use in sterile necrosis.⁶⁹⁻⁷¹ It has been shown that prolonged use of broad-spectrum antibiotics increases the risk of developing a fungal infection, so judicious use is imperative.¹⁵

Interventions

Unlike alcoholic acute pancreatitis, whereby the management is primarily to provide supportive care, the management of GSP includes several modalities that are specific

to the disease's underlying cause. These measures include cholecystectomy, exploration of the CBD, ERCP with sphincterotomy, and specific interventional radiology procedures. The goals of these procedures range from mitigating disease severity to preventing the recurrence of GSP.

Cholecystectomy

The goal of cholecystectomy is to prevent recurrence of GSP by removing the source of secondary gallstones. Although 1% to 2% of patients may recur even after cholecystectomy, the rate of recurrence in untreated patients with GSP is up to two-thirds of patients within 3 months of index presentation.^{72–75} Recurrent GSP may be graver than the initial presentation, as between 4% and 50% of cases are reported as severe, and mortality and morbidity is reported in up to 10% and 40%, respectively.^{13,76,77}

Stratifying patients as mild, moderate, or severe has a profound impact on surgical management. Historically, the recommendation was to delay cholecystectomy for 6 to 8 weeks after an attack of acute pancreatitis to allow the inflammation to subside.⁷⁸ High readmission rates for patients waiting for cholecystectomy lead to new guidelines. Although several early studies showed lower morbidity and mortality in delayed operations, the data from some of these studies is interpreted irrespective of patient stratification.^{11,78} Early cholecystectomy in GSP has now been advocated in mild disease for several decades, but what defines early timing, and the challenge of stratifying patients, have led to a great deal of discussion.

Published recommendations and references to early cholecystectomy in mild pancreatitis range from within 48 hours to within 2 to 4 weeks of presentation.^{11,58,72,79,80} Most surgical literature, however, advocates cholecystectomy during the same hospital admission. Whereas many surgeons wait for resolution of abdominal pain and normalization of pancreatic enzymes, Aboulian and colleagues⁸¹ found that laparoscopic cholecystectomy performed within 48 hours of admission for mild pancreatitis, regardless of pain or laboratory values, results in a shorter length of stay in hospital without compromising patient safety or unjustifiably challenging the surgeon's technical ability.⁸² Several other studies support performing laparoscopic cholecystectomy within 48 hours of admission in mild cases, and many others advocate early cholecystectomy within the same hospital admission.^{83,84} It is common practice for surgeons to wait for laboratory values to normalize. However, there are data demonstrating a shorter length of stay in hospital without increased morbidity when surgery is undertaken as laboratory values begin to trend toward normal.⁸⁵ Waiting for complete normalization of pancreatic enzymes may cause a delay in care and an increased length of stay.

There are compelling reasons to recommend cholecystectomy following idiopathic acute pancreatitis, as many patients may have undocumented biliary sludge or microlithiasis. This view is supported by evidence that biliary sludge and microlithiasis are also responsible for the pathologic process cited in GSP.^{86,87} Thus, for the purposes of this review, all acute pancreatitis caused by gallstones, microlithiasis, and biliary sludge is termed GSP.

Despite the compelling data to support early cholecystectomy, compliance is poor and many patients are discharged for interval cholecystectomy. In the Western world, the rate of index cholecystectomy for appropriate surgical candidates is between 10% and 60%.^{88–94} Factors associated with patients who do not undergo early cholecystectomy in the United States include old age, black race, admission to a nonsurgical service, comorbid conditions, and lack of a surgical consultation.⁹⁴ Access to appropriate medical care in certain populations may play a role.⁹⁵ Surveys of surgeons who do not perform early cholecystectomy cite reasons such as busy operating rooms,

budgetary concerns, lack of resources, and concern for a more difficult dissection.^{90,96} Contrary to these concerns, the feasibility of cholecystectomy during index admission, and at most within 2 weeks, has been studied and found to be cost neutral and practical.⁹⁷ In addition, the surgeons involved in one cohort study reported the dissection more difficult during delayed, as opposed to early, laparoscopic cholecystectomy.⁹⁸ Of note is a study with atypical findings from a busy public hospital. Clarke and colleagues⁹⁹ reported that performing index cholecystectomies put an undue strain on hospital resources, and the length of stay was in fact higher in inpatients waiting for index cholecystectomy than in patients directed toward discharge and elective surgical admission. The morbidity was the same in both groups, but 6.5% of patients in the interval laparoscopic cholecystectomy group had unplanned readmissions for mild recurrent pancreatitis.

Severe GSP is associated with significantly higher morbidity and mortality, and the disease process is such that the surgical management follows a more conservative course. Much of the morbidity and mortality reported in early studies that cautioned against early cholecystectomy is attributable to patients with severe forms of GSP. In one such study, Ranson¹⁴ excluded patients with mild pancreatic edema and only considered patients who underwent surgery with pancreatic inflammation in addition to fat necrosis or pancreatic hemorrhage, and reported high mortality. Other studies have reported similar findings whereby high rates of morbidity and mortality in patients undergoing early cholecystectomy were attributable to those patients with moderate and severe disease.¹⁰⁰

Once a patient is stratified as having moderate or severe GSP, the initial management is supportive care and management of complications. Follow-up care includes interval cholecystectomy, delayed at least 3 weeks after resolution, if clinical circumstances permit. Early cholecystectomy is contraindicated in moderate and severe GSP, and is associated with increased infectious complications and sepsis.¹⁰¹

Peripancreatic fluid collections are well recognized on CT and, when correlated to GSP severity, should dramatically influence management.^{64,102} Nealon and colleagues¹⁰³ reported that among patients with moderate to severe GSP who underwent early cholecystectomy, regardless of CT-proven peripancreatic fluid collections, 63% required reoperation and 44% had postoperative complications. Most of the reoperations were for definitive management of pseudocysts, and the infectious complications were presumably a result of pseudocysts that were sterile but became infected at the time of early cholecystectomy. These investigators thus advocate delaying cholecystectomy until it is possible to operatively manage the gallbladder and pseudocysts simultaneously. By virtue of exclusion, almost all investigators advocating early cholecystectomy specify patients with mild disease, and caution against operating too early on those with moderate or severe GSP.

Pseudocysts occur in acute pancreatitis as a result of disruption of the pancreatic duct and extravasated pancreatic excretory fluid. A fluid collection may or may not communicate with the pancreatic duct, and a fibrous wall ultimately forms around the collection (Fig. 4). Pseudocysts may be adequately diagnosed with contrast CT or MRI. A general rule is to wait 6 weeks before intervening to allow the pseudocyst wall to mature.^{103,104} Exceptions to this are cases of infected or symptomatic pseudocysts, when earlier intervention may be indicated. However, there are no universally accepted guidelines for post-GSP pseudocyst management, and a complete discussion of pseudocyst management is beyond the scope of this article. In general, the management is conservative because many of these pseudocysts will resolve spontaneously, especially if there is no patency between the pseudocyst and the pancreatic duct. Because GSP patients with peripancreatic fluid collections or

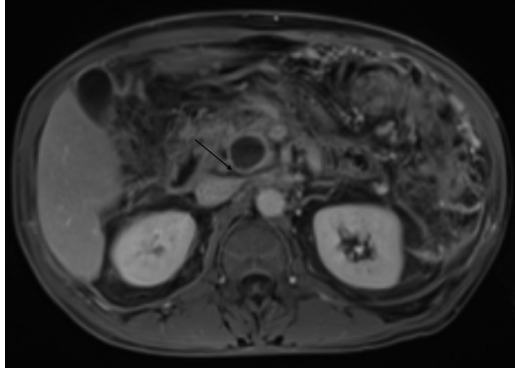


Fig. 4. Well-circumscribed pseudocyst in the pancreatic head (*arrow*) causing mechanical obstruction of the CBD.

pseudocysts are often discharged for interval cholecystectomy, appropriate follow-up is critical.

Interventional management of pseudocysts with mature walls most commonly includes gastric or proximal enteric drainage by open or endoscopic techniques. Several studies have demonstrated comparable pseudocyst resolution rates in both techniques, and the endoscopic method is favored in simple pseudocysts accessible from the gastric or duodenal lumens.^{105–110} Surgical internal drainage may be indicated in complex pseudocysts and in those not readily accessible endoscopically. The use of EUS may enhance visualization and make otherwise inaccessible pseudocysts manageable with endoscopic drainage.^{105,111} Percutaneous drainage has a role in infected pseudocysts and in symptomatic cases where endoscopic and surgical options are limited. However, this technique risks creating a controlled pancreaticocutaneous fistula, which may persist for an extended period.^{108,112}

Cholecystostomy

In high-risk patients it may be necessary to resort to other means of decompressing the biliary system. Elderly, comorbid, and/or severely ill patients may be deemed unsuitable candidates for either surgery or ERCP, yet still require emergent management of obstructing common duct stones causing biliary sepsis or aggravating acute pancreatitis. In these patients, interventional radiologists may perform percutaneous cholecystostomy, often through the use of ultrasonography and fluoroscopy. This procedure uses the Seldinger technique, and is a minimally invasive method of decompressing the biliary system. However, patients who require this degree of interventional minimalism tend to have a poor prognosis, and 30-day mortality has been reported to be as high as 15.4% in patients undergoing percutaneous cholecystostomy for acute cholecystitis.¹¹³

Intraoperative cholangiography

The role of intraoperative cholangiography (IOC) in GSP is controversial, and its use varies widely among surgeons.¹¹⁴ Some surgeons perform IOC routinely, whereas others do so only when there is a high suspicion for a common duct stone (**Fig. 5**). Although IOC is reported to be 94% specific and 98% sensitive for biliary stones, one study has demonstrated that air bubbles in the ducts can mimic stones in appearance, and routine use may be associated with a substantial false-positive rate.¹¹⁵ Many surgeons will perform an IOC if there is indirect evidence of choledocholithiasis, such as an obstructive pattern on LFTs or a relatively large common duct on

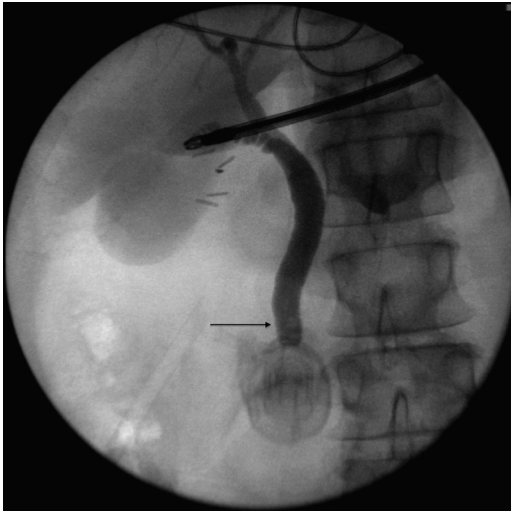


Fig. 5. Intraoperative cholangiogram demonstrating an irregular lucency in the CBD (arrow), representing a stone.

ultrasonography. The diagnosis of GSP should be considered poor indirect evidence of a duct stone, as most stones causing acute pancreatitis pass into the duodenum spontaneously. Nevertheless, the diagnosis of GSP is associated with an increased use of IOC.¹¹⁴ Johnson and Walsh¹¹⁶ found that patients with GSP who undergo IOC during cholecystectomy were more likely to have postoperative ERCP or CBD exploration during surgery, but without influencing the outcome of the pancreatitis. These findings are supported in the literature, as a recent systematic review of IOC use did not identify sufficient evidence to demonstrate a benefit.¹¹⁷ This issue is controversial and requires further investigation.

Laparoscopic exploration of common bile duct

Gallstones passing into the common duct are the offending agents in GSP, and although most pass spontaneously into the duodenum without incident, 7% to 28% of the time stones may remain in the common duct.^{21,118–121} Given sufficient evidence for choledocholithiasis coexistent with mild pancreatitis, it is safe and effective to remove the stone at the time of cholecystectomy by laparoscopic CBD exploration (LCBDE).¹²² Impacted stones causing cholangitis or aggravating severe GSP are generally removed emergently by ERCP, discussed in the next section.

LCBDE has been used for more than 2 decades, and the technology available to safely and effectively perform the procedure has evolved substantially, helping to make it as effective as ERCP in some hands.^{123–125} However, owing to the risks involved in manipulating the CBD and the exceptional level of skill required, most surgeons do not perform this procedure. LCBDE is most commonly performed by surgeons with additional hepatobiliary or laparoscopic training.

Transcystic and transcholedochal approaches are possible laparoscopically. The transcystic method is the favored approach among most surgeons performing LCBDE, and is most suitable for small stones in a small common duct. Choledochotomy is reported to be better for larger, multiple stones in a dilated common duct. Although technically more challenging, LCBDE by choledochotomy may be a more definitive approach.^{116,123,126} Refer to the article by Hardacre and colleagues, elsewhere in this issue for a detailed description of bile duct exploration.

The success of stone clearance by LCBDE has been reported in several studies to be equivalent to ERCP, with decreased morbidity, lower cost, and shorter length of stay.^{127–131} When LCBDE is not an option and patients are either diagnosed with or suspected of having common duct stones, ERCP is favored, in most cases, over open CBD exploration.

Endoscopic retrograde cholangiopancreatography

ERCP refers to the contrast imaging of the biliary and pancreatic ducts (cholangiopancreatography) using a side-viewing endoscope and fluoroscopy. When the ampulla of Vater is accessed in this manner and the CBD cannulated with a guide wire, an endoscopist may then perform endoscopic sphincterotomy or balloon dilatation of the biliary sphincter followed by extraction of stones using a balloon or basket for stones that do not pass spontaneously (**Fig. 6**). For particularly large stones, there are devices available to perform intraluminal lithotripsy to assist in extraction. For diagnostic purposes, the sensitivity of ERCP for choledocholithiasis is 90% to 97%, with 95% to 100% specificity.¹³² This diagnostic performance is similar to that of MRCP, which is noninvasive. The success rate of ERCP in extracting stones is around 95%.

ERCP has been available for more than 30 years, and has largely replaced surgical CBD exploration in cases of isolated choledocholithiasis. The role of ERCP in GSP has been discussed extensively, and it is widely accepted that in mild cases of GSP without evidence of biliary obstruction or cholestasis there is no utility for ERCP for diagnostic or therapeutic purposes.^{133–135} Most patients presenting with transiently elevated pancreatic enzymes without a sustained elevation of bilirubin may proceed to early cholecystectomy without either preoperative or postoperative ERCP. Although earlier reports advocated ERCP within 24 hours for all-comers with GSP, this strategy has been formidably challenged.¹³⁶ There is now widely accepted evidence that ERCP in patients with GSP, but without cholestasis or cholangitis, confers no benefit in terms of complications or mortality.^{137,138}

In patients with severe GSP and evidence of choledocholithiasis, including increasing LFTs, persistently elevated bilirubin, persistent pain, or visualization on

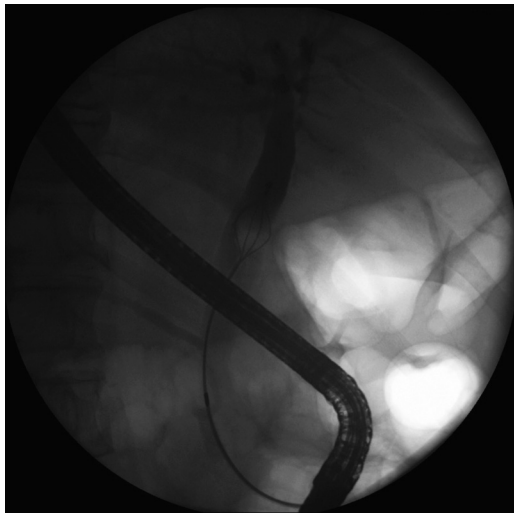


Fig. 6. Fluoroscopic image of endoscopic retrograde cholangiopancreatography during balloon extraction of a large stone.

MRCP, performing ERCP within 72 hours decreases the rate of sepsis, mortality, and complications, including pancreatic necrosis.^{134,139–142} In all patients with GSP, additional evidence of common duct stones warranting intervention includes bile-free gastric aspirate and an increasing level of serial bilirubin. Performing ERCP within 48 hours in these patients may decrease morbidity.¹⁴³ Acute cholangitis may complicate GSP in up to 10% of cases, and early ERCP is indicated to decompress the biliary system in these patients.⁵⁸

ERCP serves a role in mild GSP in patients who are unfit or unwilling to undergo surgery. Although it is well established that patients with GSP have a high rate of recurrence without cholecystectomy, ERCP with sphincterotomy is protective against recurrence of acute pancreatitis. However, because the gallbladder is left in situ, the rates of acute cholecystitis and biliary colic remain elevated.^{2,72,144,145} ERCP is thus indicated in patients with GSP who cannot undergo cholecystectomy, or will experience a prolonged delay before cholecystectomy.

Complications of ERCP include pancreatitis, hemorrhage, perforation, cholangitis, and stenosis of the sphincter of Oddi.^{127,146} Although an increased risk of cholangiocarcinoma after ERCP has been discussed in the literature, there is currently insufficient evidence to confirm this concern.

Special patient populations

As the incidence of GSP increases in the adult population, a similar increase in gallstone disease is being observed in the pediatric population. The recommendation for index-admission cholecystectomy prevails in children with mild GSP, as in adults.^{147,148}

Pregnancy is a risk factor for gallstone formation, and as many as one-third of pregnant patients presenting with biliary complaints require surgical intervention.^{149–151} Gallstone disease underlies 65% to 70% of cases of acute pancreatitis occurring during pregnancy.¹⁵² Previous recommendations warned against performing laparoscopy on pregnant patients during the first trimester, and cited limitations of intra-abdominal visualization caused by the third-trimester uterus. Thus pregnant patients presenting during the first and third trimester underwent delayed cholecystectomy. However, guidelines within the last decade endorsed by the Society of American Gastrointestinal and Endoscopic Surgeons cite substantial evidence in support of safely performing laparoscopic procedures during any trimester of pregnancy. The recommendations additionally state that the indications for laparoscopic cholecystectomy for biliary disease should also be honored in pregnancy.¹⁵³ Delaying cholecystectomy in pregnant patients carries a formidable risk of recurrent GSP, for both the patient and the fetus, which likely outweighs the poorly quantified risk of spontaneous abortion. EUS or MRCP without gadolinium contrast may be safely used in pregnancy to select pregnant patients for further intervention, including ERCP or LCBDE, if choledocholithiasis is suspected or confirmed.

It is estimated that 30% of patients older than 70 years have gallstones, and the incidence of choledocholithiasis in the elderly population is up to 20%.^{154,155} Because older patients are more likely to have gallstones and bile ducts of increased diameter, this population also has a higher incidence of GSP.¹⁵⁶ Several studies demonstrate the safety of performing laparoscopic cholecystectomy in elderly patients, yet less than 57% of older patients undergo index cholecystectomy, and it is estimated that compliance can be improved to greater than 70% while still maintaining appropriate patient selection.^{94,157,158} Recurrent GSP should be prevented in the young and elderly populations with index cholecystectomy in mild GSP, when clinically feasible.

SUMMARY

GSP is a disease with a wide spectrum of severity. Diagnosis and management have evolved over the past several decades with the advent of new and improved technology. Advancements in imaging techniques have limited the need for invasive diagnostic procedures in many cases, and diverse therapeutic options are becoming more widely available. The paradigm continues to shift toward earlier operation in mild cases, with more judicious interventions in severe disease. Risk stratification is essential to provide the best possible care for all patients, and good clinical judgment is paramount in selecting the most pertinent invasive and diagnostic procedures at the most appropriate time.

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