CHAPTER 6

Gallstone pancreatitis: diagnosis and treatment

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Abbreviations

ALT	alanine transaminase
AP	acute pancreatitis
CBD	common bile duct
CCY	cholecystectomy
CT	computed tomography
ERCP	endoscopic retrograde cholangiopancreatography
ES	endoscopic sphincterotomy
EUS	endoscopic ultrasound
IOC	intraoperative cholangiogram
MRCP	magnetic resonance cholangiopancreatography
SIRS	systemic inflammatory response syndrome
TUS	transabdominal ultrasound
US	ultrasound

Summary

Acute pancreatitis (AP) is the leading gastrointestinal disorder requiring hospitalization in the United States, and gallstone disease is the most common etiologic factor worldwide [1]. Recurrence and complications of gallstone pancreatitis may be avoidable with proper diagnosis and treatment. Clinical history coupled with laboratory and imaging is accurate in diagnosing gallstone disease, particularly with the advent of magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS). While less utilized as a diagnostic test, endoscopic retrograde cholangiopancreatography (ERCP) remains the preferred approach for the treatment of choledocholithiasis and concomitant cholangitis or biliary obstruction in the setting of severe AP. When performed in a timely manner, cholecystectomy (CCY) is highly effective in preventing recurrent gallstone pancreatitis. Among poor operative candidates, ERCP with biliary sphincterotomy is a reasonable surrogate. This chapter reviews the current evidence for diagnosing and treating acute gallstone pancreatitis.

Introduction

Gallstone disease represents the single leading cause of acute pancreatitis (AP), accounting for approximately 50% of cases in the Western world [2, 3]. The majority of AP patients will experience a benign course and rapid recovery with supportive management. However, up to 20% develop severe pancreatitis with systemic (organ failure) or local complications that may result in mortality, with rates quoted as high as 15% [4]. Although there is a definite correlation between gallstones and AP, the precise pathophysiology of gallstone (a.k.a., biliary) pancreatitis remains unclear. The most important purported mechanisms include (i) transient or sustained occlusion of the pancreatic duct leading to an increase in intraductal pressure and (ii) bile reflux into the pancreatic duct [5].

When a patient presents with AP, the clinician often jumps to the conclusion that the underlying cause is alcohol or gallstones. While there are numerous alternative etiologies that will be discussed in other chapter(s), our discussion is organized by several key

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questions that should be considered by the treating physician:

1 How is gallstone pancreatitis diagnosed?
2 What tests are available to evaluate for common bile duct (CBD) stones?
3 For patients with gallstone pancreatitis, what is the role of ERCP in the acute setting?
4 What is the impact of CCY for the prevention of recurrent gallstone pancreatitis, and when should it be performed?
5 What is the benefit of ERCP for patients who are poor candidates for CCY?

In this chapter, we review the definition of gallstone pancreatitis and the methods by which gallstones may be implicated as the cause. We underscore the indications for ERCP and CCY and alternative strategies to attenuate the disease course and prevent its recurrence.

How is gallstone pancreatitis diagnosed?

Once a diagnosis of AP is established, identifying gallstones as the underlying cause is crucial since complications and recurrence may be avoidable with interventions such as CCY and ERCP (Figure 6.1) [6]. CCY is highly effective in preventing recurrent episodes of AP, but only when the etiology is gallstones [7]. Therefore, gallstone pancreatitis should be confirmed by documenting gallbladder stones on cross-sectional imaging, transient fluctuation in liver chemistries >3× upper limit of normal, or both. If neither is present, the benefit of empiric CCY is unproven [8].

Laboratories

An early clue that gallstones are the primary etiology is the relative elevation of serum amylase, which is often disproportionately higher in comparison to other etiologies [9]. However, amylase levels tend to drop rapidly and even normalize within 24 hours. In contrast, lipase remains elevated for a longer period; among patients who present several days after symptom onset, the amylase may have normalized/near-normalized while the lipase remains elevated [10]. Serum lipase is more sensitive and specific than amylase for establishing the diagnosis of AP since lipase persists longer than amylase, and there are fewer nonpancreatic etiologies for elevations in serum lipase (Table 6.1) [11].

Beyond characterizing the pattern of pancreatic chemistry elevation, marked increases (>3× upper limit of normal) in liver chemistries are useful for distinguishing gallstones from alternative etiologies. Alanine transaminase (ALT) is probably the single most reliable test, having a positive predictive value of 93% for a biliary cause when elevated threefold [12, 13]. However, up to 15% of patients with biliary pancreatitis have normal liver chemistries at presentation, and any cause for AP may induce elevation of these parameters simply by extrinsic compression of the extrahepatic biliary tree [14].

Cross-sectional imaging

Given its wide availability, lack of ionizing radiation, low cost, minimal interoperator variability, and high sensitivity/specificity (>95%) for gallbladder stones, transabdominal ultrasound (TUS) is the preferred initial imaging modality for patients with suspected gallstone pancreatitis [15]. However, in the setting of AP, the sensitivity is reduced to approximately 60% due to bowel distension and poor patient compliance with the examination: deep probing of the upper abdomen with the ultrasound (US) transducer is rarely feasible in such individuals. In addition, the sensitivity for diagnosing bile duct stones is even lower (20–50%), particularly in the setting of obesity. Moreover, the lack of biliary dilation does not rule out a biliary etiology during the first 48 hours [16].

Compared to TUS, computed tomography (CT) is marginally better for detecting CBD stones. While useful for diagnosing local complications of AP, CT during the first 48 hours of AP should be reserved for uncertain diagnoses, since iodinated contrast may precipitate renal failure or even pancreatic necrosis [17].

Although sonographic characteristics of gallstones are the same when detected by TUS or EUS, the latter has a higher sensitivity (85–100%) in diagnosing gallbladder stones (especially small stones and sludge) due to the proximity of the US transducer to the gallbladder [18]. MRCP is also more sensitive than TUS and can identify local complications of AP and pancreatic ductal anatomy at the same time [19].

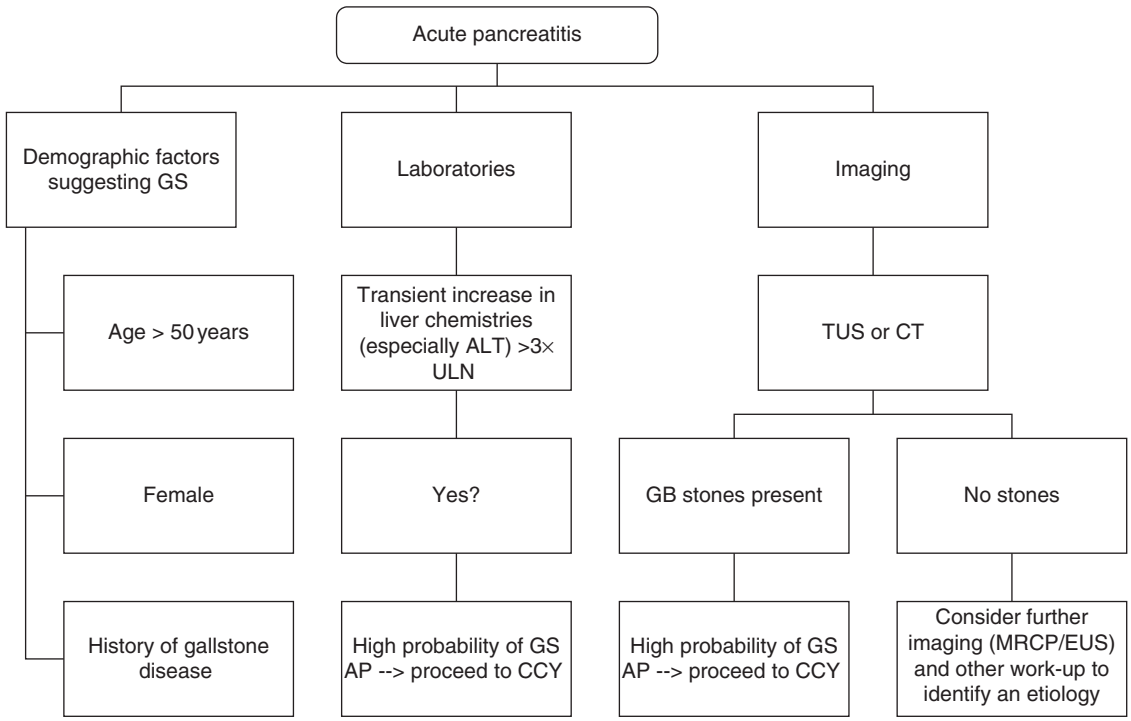

Figure 6.1 Confirming a diagnosis of gallstone pancreatitis. TUS, transabdominal ultrasound; CT, computed tomography; CCY, cholecystectomy; GS, gallstone; GB, gallbladder; MRCP, magnetic resonance cholangiopancreatography; EUS, endoscopic ultrasound; ULN, upper limit normal; AP, acute pancreatitis; ALT, alanine transaminase.

Table 6.1 Nonpancreatic etiologies for elevation in serum amylase or lipase.

Causes	Amylase	Lipase
Abdominal pathology	Peptic ulcer disease Mesenteric ischemia Acute appendicitis Cholecystitis Intestinal obstruction Gynecological disorders	Peptic ulcer disease Mesenteric ischemia Acute appendicitis
Extra-abdominal pathology	Salivary gland disease Pneumonia Head injury	Bone fractures Crush injury Fat embolism
Metabolic disorders	Renal failure Liver failure Diabetic ketoacidosis Anorexia nervosa and Bulimia	Renal failure
Others	HIV Macroamylasemia Cigarette smoking Neoplasms: lung, gastric, breast, and myeloma	

Since there are fewer causes for elevation in serum lipase (specificity), and it remains elevated longer than serum amylase (sensitivity), lipase is considered more specific and sensitive for the diagnosis of acute pancreatitis.

What tests are available to evaluate for common bile duct stones?

While CCY is highly effective in preventing recurrent bouts of gallstone pancreatitis, unrecognized CBD stones are likely to cause additional complications – including AP – even following CCY. In all cases of gallstone pancreatitis, the possibility of choledocholithiasis must be considered in any management algorithm (Figure 6.2). Usually, gallstone pancreatitis is

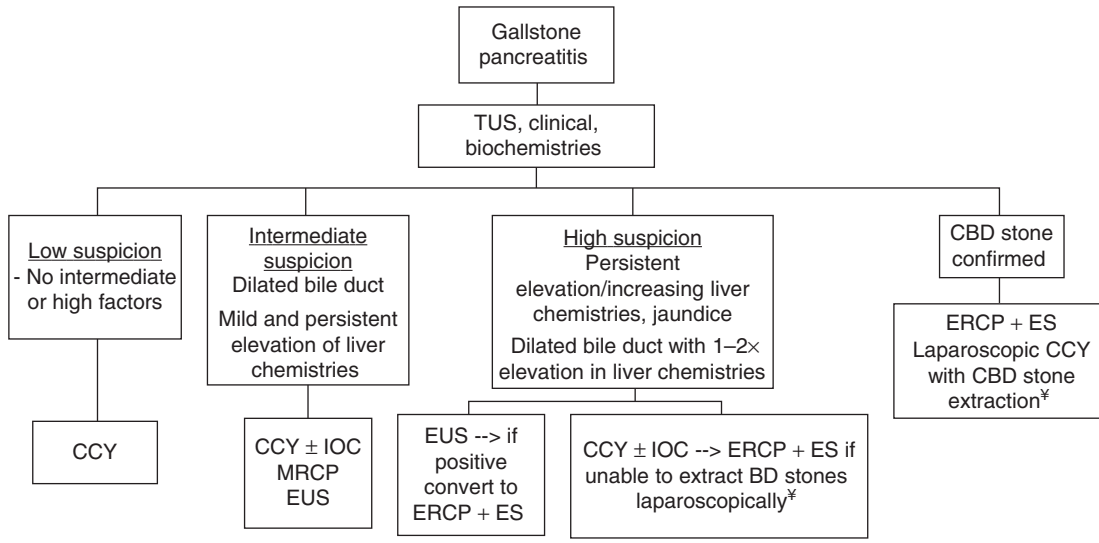

Figure 6.2 Recommended algorithm for diagnosing choledocholithiasis. TUS, transabdominal ultrasound; CCY, cholecystectomy; IOC, intraoperative cholangiogram; MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; CBD, common bile duct. IOC is an option; the CBD should be imaged by some modality, that is, MRCP, ERCP, and IOC. ¥Being highly operator dependent, the best strategy between laparoscopic and endoscopic stone extraction will be determined by the availability of local expertise and technology.

caused by the spontaneous passage of a CBD stone into the duodenum. Since the majority of patients do not have retained CBD stones, diagnostic testing should be titrated to the level of clinical suspicion (Figure 6.2).

ERCP

ERCP is the gold standard for diagnosing CBD stones, but its risk profile [20] and the advent of less invasive imaging modalities have significantly reduced its utility as a purely diagnostic test. Furthermore, cholangiography may miss small gallstones [21]; in cases where there is a very high suspicion for or prior confirmation of CBD stones, ERCP with endoscopic sphincterotomy (ES) and balloon sweep is typically performed. If available, laparoscopic surgical expertise with CBD stone extraction actually appears preferential to an ERCP-first strategy; in this scenario, the surgeon performs a CCY and attempts to clear the CBD laparoscopically, using ERCP with sphincterotomy only if unsuccessful. Even when the pretest probability of CBD stones approaches 100%, an intraoperative cholangiography (IOC)-first as opposed to ERCP-first strategy is more cost effective [22]. In our experience, most surgeons prefer to have the CBD cleared preoperatively via ERCP when this is readily available so as to minimize the morbidity of CCY.

Regardless of local expertise, ERCP should no longer be considered a diagnostic test for bile duct stones. The availability of EUS and MRCP, lower-risk and highly sensitive imaging modalities for suspected choledocholithiasis, has relegated ERCP to a therapeutic intervention when stones are present assuredly.

Intraoperative cholangiography (IOC)

In the United States, IOC is performed in approximately 30% of individuals undergoing CCY. Its sensitivity varies from 59% to 100% and specificity from 93% to 100% in detecting CBD stones and is highly operator dependent [23, 24]. In patients with mild gallstone pancreatitis but no ongoing biliary obstruction, the optimal approach to clearing the CBD is to perform CCY with IOC first using ERCP to clear stones that are retained postoperatively [25]. Since most stones have already passed into the duodenum and only a minority of patients have CBD stones at the time of CCY, ERCP is unnecessary for most patients presenting with acute gallstone pancreatitis [26, 27]. By performing IOC first, fewer patients undergo unnecessary ERCP (and other diagnostics), and the length of hospitalization can be shortened.

However, many surgeons perform IOC infrequently – and fewer are comfortable with laparoscopic removal of bile duct stones [22, 25, 28–32]. Some surgeons have proposed laparoscopic CBD exploration as an excellent single-step approach for CBD stone clearance [33, 34], but this technique is infrequently performed [35]. The single-stage laparoendoscopic treatment (a.k.a., "rendezvous technique") is an alternative to laparoscopic stone extraction. During IOC, a guidewire can be advanced under fluoroscopic guidance and in an antegrade manner across the sphincter of Oddi. A duodenoscope is advanced *per os* to the major papilla, where the wire is grasped and the bile duct accessed without the need for traditional cannulation maneuvers [36]. This results in high rates of BD stone clearance during CCY and is less invasive and costly than sequential CCY followed by ERCP under a second sedative. This combination approach has not been widely accepted since laparoscopic and ERCP expertise usually obligates two physicians, creating a logistical conundrum [37]. For these reasons, EUS and MRCP have been increasingly utilized in these cases of gallstone pancreatitis with question of retained CBD stones [38, 39].

MRCP

MRCP has high sensitivity (81–100%) and specificity (92–100%) for the diagnosis of choledocholithiasis [40]. However, the sensitivity of MRCP is directly related to the size of gallstones, so its diagnostic yield is lowest for small (<5 mm) stones and sludge [41, 42]. This means that a negative MRCP cannot always exclude gallstones as the etiology since small stones are often the cause of AP [16]. In addition, patients must be able to hold their breath for approximately 20 seconds to acquire images of reasonable quality. However, MRCP has the advantage of being noninvasive, more widely available, and less operator dependent than EUS [43].

EUS

Several studies have shown that EUS is highly sensitive (>90%) for detecting choledocholithiasis when conventional imaging is negative [18, 44]. EUS is comparable or superior to cholangiography in detecting biliary stones [45, 46], and its performance is not influenced by stone size or bile duct diameter [21]. In an economic evaluation, an EUS-based approach was superior to ERCP with ES in severe biliary AP (costing C$742 less per patient) and only slightly more expensive in the setting of nonsevere biliary AP; using an EUS-first as opposed to ERCP-first approach was associated with fewer complications (3% fewer cases of post-ERCP pancreatitis) [47]. Moreover, in a meta-analysis comparing EUS to ERCP in patients with acute biliary pancreatitis, EUS avoided unnecessary ERCP in up to 71% of cases (another reminder that most patients with gallstone pancreatitis pass the CBD stone spontaneously) [48]. In the appropriate setting, patients with a moderate suspicion of CBD stones may be consented for EUS and ERCP in the same setting. An EUS should be performed initially, and if a CBD stone is identified, the procedure may be converted to ERCP with ES during the same session (Table 6.2).

Table 6.2 Cross-sectional imaging for gallstone disease.

Modality	Sensitivity/accuracy		Risk profile	Cost
	CBD stones	GB stones		
TUS	+	+++	–	+
CT	++	++	–	++
EUS	++++[a]	++++[b]	+	+++
MRCP	++++	++++[b]	+	+++
ERCP	++++	++	+++	+++

CBD, common bile duct; GB, gallbladder; TUS, transabdominal ultrasound; CT, computed tomography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography.

[a]EUS has a better sensitivity than MRCP and ERCP in detecting small stones (<5 mm) and sludge.

[b]Although the sensitivity of EUS and MRCP is higher than the sensitivity of TUS in identifying gallstones, they are rarely used as a first-line technique due to their cost, availability, and slightly higher risk profile.

In summary, the decision to perform an MRCP, EUS, ERCP, or IOC depends on pretest probability and local expertise. In cases of low to intermediate suspicion, where the probability of a bile duct stone is approximately 30% or less, laparoscopic CCY with IOC first is probably the most expeditious and cost-effective strategy, assuming local surgical expertise. If a stone is identified during IOC and it cannot be extracted or flushed through the sphincter of Oddi during laparoscopy, then ERCP with ES within 24 hours is appropriate. In cases of higher suspicion or known choledocholithiasis preoperatively, EUS with a plan to convert to ERCP during the same session is the preferred approach. In these cases, next-day laparoscopic CCY would result in the shortest hospitalization [49]. MRCP is an excellent and minimally invasive tool to guide management when laparoscopic IOC and EUS expertise are lacking.

For patients with acute gallstone pancreatitis, what is the role for ERCP in the acute setting?

At this point, the clinician has established a diagnosis of gallstone pancreatitis and the probability of choledocholithiasis. In specific cases, early ERCP – typically defined as within 72 hours of clinical presentation – may impact the disease course. In a nutshell, early ERCP reduces the complications of AP when patients have concomitant acute cholangitis or predicted severe AP with biliary obstruction (Figure 6.3). There are a variety of scoring systems to assess disease severity, including Ranson's criteria, APACHE-II score, BISAP score, Balthazar CT severity index, and the systemic inflammatory response syndrome (SIRS) score [50–54]. Due to their simplicity and reasonable predictive value, we prefer to couple clinical judgment with SIRS, serum blood urea nitrogen, and hematocrit at the time of admission and after 24–48 hours to make this determination [55–58].

Ample evidence supports performing early ERCP (<72 hours) with or without ES, in patients with gallstone pancreatitis and concurrent signs or symptoms of cholangitis (typically fever, jaundice, sepsis physiology, and rigors, among others) [59, 60]. In a meta-analysis of seven randomized controlled trials including 757 patients, Tse et al. confirmed a significant reduction in mortality (relative risk (RR) 0.20, 95% CI 0.06–0.68) and local (RR 0.45, 95% CI 0.20–0.99) and systemic complications (RR 0.37, 95% CI 0.18–0.78) using an early ERCP strategy for patients with AP and concomitant acute cholangitis [61]. There were no differences in outcome between individuals undergoing ERCP within 24 or 72 hours. However, in patients with acute cholangitis, we advocate urgent ERCP [6, 55]. Individuals with predicted severe gallstone AP and coexisting biliary obstruction (a conjugated bilirubin level >5 mg/dL) also benefit from early ERCP [3, 62]. This strategy can reduce the frequency of local (RR 0.53, 95% CI 0.26–1.07) and systemic (RR 0.56 95% CI 0.30–1.02) complications [61]. In the absence of cholangitis or biliary obstruction, the role of urgent ERCP remains controversial even in predicted severe AP [60].

Stone removal may not always be accomplished especially in the setting of suppurative acute cholangitis or in cases of large (>1.5 cm) or multiple CBD stones. In these situations, placing a bridging plastic stent is a reasonable temporizing measure in order to achieve short-term biliary drainage [63, 64]. Moreover, stent placement may help by softening or fracturing large CBD stones. Studies have shown that stones are smaller and occasionally even absent several weeks after stent placement [65, 66]. Whenever possible, multiple stents should be placed since the rate of stent occlusion and secondary cholangitis is smaller compared to one stent [67]. Stents with a double pigtail configuration, as opposed to flanged stents, probably have a lower risk of migration below retained stones.

In addition to CBD stone extraction and assuring bile duct drainage, there are limited data suggesting the benefit of early pancreatic duct stent placement to assure pancreatic duct drainage/decompression. In a pilot study of 27 patients, Fejes and colleagues evaluated the feasibility and safety of urgent ERCP with pancreatic stent placement in patients with biliary AP [68]. The authors observed a significantly lower rate of local (pancreatic necrosis, phlegmon, pseudocyst, abdominal fluid collections) and systemic complications (sepsis and shock) and organ failure in those who underwent PD stent placement (7%) than in controls who underwent ERCP with ES alone (25%); mortality rates (0% vs. 7%, respectively) also favored pancreatic stent placement, although this did not reach statistical significance. These data have been supported by two other small studies [69] [70]. However, in all three reports, pancreatic stent placement

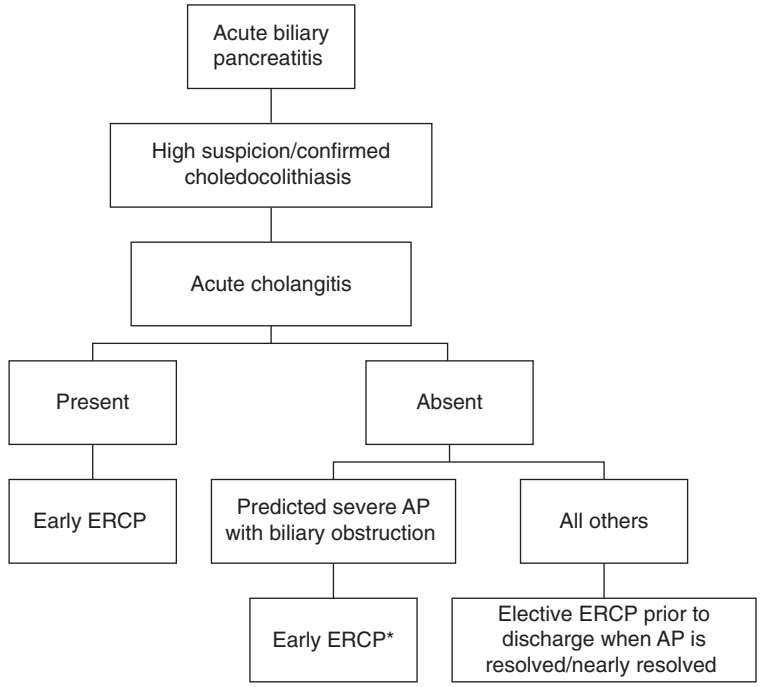

Figure 6.3 Indications and timing of ERCP in acute biliary pancreatitis. *Early ERCP is defined as ERCP within 72 hours of clinical presentation. AP, acute pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography.

was performed only in individuals considered high risk (difficult sphincterotomies) for post-ERCP pancreatitis. The role of urgent PD stent placement as an intervention to attenuate the disease course for patients with gallstone (or other causes) pancreatitis requires further investigation, as there are inherent potential hazards of applying ERCP to this population.

What is the impact of cholecystectomy on the prevention of recurrent gallstone pancreatitis, and when should it be performed?

Once the patient recovers from an episode of mild gallstone pancreatitis, laparoscopic CCY should be performed during the same hospitalization to prevent the recurrence of gallstone-related complications [6, 55, 71]. If the gallbladder is left *in situ*, pancreatitis may recur in 30–50% [72]. The risk is higher in the first month following index gallstone AP [73, 74]. In contrast, when early CCY is performed, the risk can be reduced to <5%; the reasons for recurrence following CCY include inadequate clearance of the CBD at the time of initial presentation and incorrectly attributing gallstones as the underlying etiology for AP [75, 76]. Same-stay CCY is preferred to a postdischarge strategy based on several studies including a systematic review that included 998 patients, which found higher readmission rates (18% vs. 0%, $P<0.0001$) in those who did not undergo same-stay CCY [77]. Additionally, early CCY is associated with reduced length of stay and total hospital charges [78].

Among patients who are good operative candidates, CCY following ERCP with ES is superior to ES alone for the prevention of recurrent gallstone AP [79, 80]. In a cohort of 4682 patients admitted with their first episode of acute gallstone AP, the rate of recurrent AP was significantly lower for those who had ES + CCY (1.2%) as compared to those who underwent CCY alone (4.4%, $P<0.05$) or ES alone (6.7%, $P=0.0001$) [7]. Additionally, while ES significantly decreases the rate of recurrent gallstone AP (compared to medical management), ES alone does not prevent other complications of retained gallbladder stones [77].

In patients with severe gallstone AP and evolving local complications such as fluid collections, laparoscopic CCY during the index admission is technically difficult and has greater morbidity, particularly from postoperative infection [81, 82]. In these cases, CCY should be delayed until peripancreatic fluid collections/necrosis resolve or if they persist at least 6 weeks, at which time CCY can be safely performed as part of the surgical management of organized pancreatic necrosis [55].

What is the benefit of ERCP for patients who are poor candidates for cholecystectomy?

In patients who are poor candidates for CCY, such as those with Child class B or C cirrhosis, ERCP with ES is an acceptable therapeutic alternative to CCY, irrespective of the presence of CBD stones [7, 83]. Hwang et al. found that the probability of developing recurrent attacks of pancreatitis after 1, 2, and 5 years among individuals with gallstone pancreatitis and gallbladder *in situ* was significantly lower in patients who underwent ERCP (5%, 7% and 11%, respectively) compared to those who did not (11%, 16%, and 23%; hazard ratio 0.45 [95% CI, 0.30–0.69]; $P < 0.01$) [84]. However, it is worth reiterating that other complications related to gallstone disease such as cholecystitis and/or biliary pain may still occur [75].

Summary

Gallstones represent one of few etiologies of AP where appropriate and timely intervention may significantly impact the patient's short- and long-term prognosis. While confirming the diagnosis of gallstone pancreatitis is fairly straightforward, it is inappropriate to assume gallstones as the underlying etiology without supporting evidence, since CCY and ES have no proven benefit for individuals with AP secondary to other etiologies. With improvements in laparoscopy, EUS, and MRCP, diagnostic ERCP should be avoided almost without exception. A multidisciplinary approach to patients with known or suspected gallstone AP should include the input of surgeons, gastroenterologists, and radiologists in deciding the need for and appropriate sequence of imaging and interventions. With rare exception, gallstone pancreatitis is now a curable disease.

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