Chapter

Prologue: Biliary System - History and Background

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1. Introduction

Cholecystectomy is one of the most common surgeries performed all around the world; over 600,000 people in the US undergo cholecystectomies each year. It is the treatment of choice for inflammation of the gallbladder (cholecystitis), pain and inflammation related to gall stones (calculus cholecystitis) and pancreatitis caused by gall stones.

Carl Johann August Langenbuch, a 27-year-old director of the Lazarus Hospital in Berlin, first practiced cholecystectomy on a cadaver, and then in the year 1882, he performed a cholecystectomy on a man who had suffered from gallstones for 16 years and cured his painful condition overnight. He was initially frustrated and disturbed that his patients continued to suffer after minor procedures to drain or clean the gallbladder, and then he became determined to give these patients a cure rather than temporary relief, and thus the first open cholecystectomy captured the history books.

By 1897, over 100 cholecystectomies had been performed, and it turned out that the removal of the gallbladder not only would not take life but could in fact provide a pain-free future. Then in 1985, the modern era of cholecystectomies began when the surgeon Erich Mühe of Böblingen, Germany, did the first endoscopic cholecystectomy. Thereafter the pioneers in France and the US surgeons attached a CCD video camera to a laparoscope allowing the surgical team to view the operative field and perform with laparoscopic instruments. A French gynecologic surgeon performed a laparoscopic gallbladder removal in 1987. Soon after that in just 2 years, demand for the laparoscopic approach transformed surgical practice in the US and other countries and subsequently recognized laparoscopic cholecystectomies as the gold standard treatment for gallstone disease. The benefits of the laparoscopic approach were ultimately codified in the new National Institutes of Health (NIH) guidelines in 1992, and they stated that it provided a safe and effective treatment for most patients with symptomatic gallstones.

To date, it is documented that more than 80% of the cholecystectomies are done via laparoscopic approach. The advantages of laparoscopic over open surgeries are quite clear. These advantages include shorter length of hospital stay, very less operative pain, avoiding a big scar over the abdomen, earlier return of bowel function, improved cosmesis, earlier return to normal activities and overall decreased cost. The rates of cholecystectomies have increased subsequently with the introduction of laparoscopic procedures accompanied by evidence of lower clinical thresholds for operative therapy of gallstone diseases.

2. Tips for a safe cholecystectomy

I have personally penned down certain points in my personal experience which can be used as a guide or may be even as a checklist before the young talented surgeons place their hands on cholecystectomies:

1. Selection of initial cases—female thin built patients with short history of biliary colics and especially no history of cholecystitis as there would be adhesions and would be a task to dissect during the initial days.

2. Informed consent including chances of conversion and high risk of various injuries to bile duct or other nearby structures.

3. Proper cleaning and sterilization of instruments.

4. Good quality equipment and instruments.

5. A good first assistant and a qualified and trained surgeon.

6. Formal training in laparoscopic surgeries to have a basic knowledge about the instruments and the technique.

7. 30° telescope.

8. Open technique of first port.

9. Urine to be evacuated just before the surgery.

10. Fundus should be retracted towards the right shoulder.

11. Vascular anatomy and biliary tract anatomies are different and vary from person to person.

12. Consider cystic lymph node of Lund as a guide for the cystic duct.

13. Hydrodissection and suction cannula can be a good instrument for blunt dissection.

14. It is safer to leave a few mm of cystic duct than to shave it off near to the common bile duct.

15. Double clips are always safer on the patient side of the structures.

16. Cystic ducts can be wider, longer, tortuous, double or even very short.

17. Fundus-first techniques can be adopted for difficult cases.

18. Bleeding seen on the screen will usually be less as they are magnified versions.

19. All bleedings will stop with pressure except the physiological menstrual bleed. So in case if there is bleeding, avoid panic, give pressure with gauze piece and control the bleed.

20. Partial cholecystectomies are an option for difficult cases.

21. Do not hesitate to open the abdomen in case of bleeding or difficult anatomy.

22. All stumps should be carefully examined.

23. Bile spillage and stone spillage should be sucked out or removed.

24. Conversions are not failures, and surgeons should not have an ego to finish all cases via a laparoscopic approach.

25. Whatever taken out of the body including all gallbladders should be sent for histopathology.

3. Gallstone pancreatitis

Acute pancreatitis is now the most common reason for hospital admission among all gastrointestinal disorders [1]. Population-based studies indicate that the incidence of acute pancreatitis is rising from 14.8 in 100,000 (1990–1994) to 31.2 in 100,000 (2010–2013) among British males [2]. The most common (about 30–50%) preventable cause of pancreatitis in the United Kingdom is gallstones [3]. Recurrent attacks of gallstone pancreatitis (GSP) carry a mortality rate of 10% and a major morbidity rate of 30–40%. Most of these cases follow a mild course and are self-limited with supportive care, but approximately 20% progress to severe disease, requiring a prolonged hospital stay and intensive care, and are associated with a mortality rate approaching 30%. Three key areas in the management of patients with gallstone pancreatitis are diagnosis, risk stratification with predictors of severity and the type and timing of definitive intervention. In this chapter we have attempted to cover all relevant clinical aspects of gallstone pancreatitis regarding its etiopathogenesis, disease severity and management.

3.1 Etiopathogenesis

Considering all non-malignant gastrointestinal diseases, currently acute pancreatitis has become the most frequent reason for hospital admission. An overall mortality of 4.3% within 90 days and a 1-year mortality of 7.9% make it a lethal disease [2]. Gallstone disease is becoming more common along with heavy alcoholism as the cause of pancreatitis. Population-based studies indicate that the prevalence of gallstones in some Western countries surpasses 20% of the adult population [4].The continuous rise in gallstone prevalence is much more likely to be due to nutritional and life style factors, though genetic predisposition plays an important part in formation of gallstones [5, 6]. When a patient develops pancreatitis due to gallstones, the disease is likely to recur until the migrating bile duct stones are removed or their impaction at the duodenal papilla is prevented. According to a study involving some 5000 patients admitted with first episode of acute gallstone-associated pancreatitis, the recurrence rate was reduced from 30 to 6.7% with endoscopic sphincterotomy done during the first week; an elective interval cholecystectomy reduced it to 4.4%, and it was further reduced to 1.2% by performing endoscopic sphincterotomy combined with elective cholecystectomy during the same hospital admission [7]. The manipulation of the papilla while removing a gallstone or during a sphincterotomy, the consequent swelling can obstruct the pancreatic duct, and triggers pancreatitis in some patients. A way

to address this problem is the transient insertion of small plastic stent into the pancreatic duct, which prevents the prolonged impairment of pancreatic secretion and has been shown to significantly reduce the incidence of ERCP-induced pancreatitis [8].

Taking into account the observations from various clinical and population-based studies:

a. Carrying gallstones increases the risk of developing acute pancreatitis.

b. Only gallstones that are small enough to pass through the biliary tract confer a pancreatitis risk, rather than the ones that remain asymptomatically in the gallbladder.

c. The risk of developing pancreatitis in the first place and the risk of a recurrence of pancreatitis can be reduced by strategies intended to remove the source of migrating gallstone or that prevent their impaction near the duodenal papilla.

d. Preserving the flow from the pancreatic duct is an effective way of preventing ERCP-induced pancreatitis.

3.2 Mechanisms of gallstone-induced pancreatitis

In 1856, Claude Bernard discovered that bile, when injected into the pancreatic duct of laboratory animals, can cause pancreatitis [9]. It is firmly established today that requires the passage of a gallstone from the gallbladder through the biliary tract causes initiation of pancreatitis and not gallstones, which remain in the gallbladder [10]. Eugene Opie, in 1901, postulated that impairment of the pancreatic outflow due to obstruction of the pancreatic duct causes pancreatitis [11]. Later, he modified this theory and published "common channel hypothesis," which predicted that an impacted gallstone at the papilla of Vater creates a communication between the pancreatic and the bile duct (the so-called common channel) through which bile flows into the pancreatic duct and thus causes pancreatitis (**Figure 1**).

There is inadequate experimental and clinical evidence compatible with Opie's assumptions. In fact, anatomical studies have shown that an impacted gallstone would most likely obstruct both common bile duct and pancreatic duct [12], as the communication between the pancreatic duct and the common bile duct is much too short (< 6 mm) to permit biliary reflux into the pancreatic duct [13]. The pancreatic secretory pressure is higher than biliary pressure, and pancreatic juice would flow into the bile duct rather than bile into the pancreatic duct, in the event of an existing anatomical communication between bile and pancreatic ducts [14, 15]. However, when pancreatic necrosis is firmly established, the observation of a bile-stained necrotic pancreas at the time of surgery may explain a biliopancreatic reflux due to a loss of barrier function in the damaged pancreatic duct. But this should not be regarded that biliary reflux initiates the disease process.

The "common channel" hypothesis has its own inconsistencies. In order to overcome that, it was proposed that the passage of a gallstone could damage the duodenal sphincter in a manner to cause sphincter insufficiency. This, in turn, could permit duodenal content, including bile and activated pancreatic juice, to flow through the incompetent sphincter and into the pancreatic duct [16], thus inducing pancreatitis. The perfusion of bile through the pancreatic duct has been shown to be completely harmless [17]. It has been identified that an influx of infected bile, which might occur after prolonged obstruction at the papilla, may represent an aggravating factor, as opposed to an initiating event, for the course of pancreatitis when the pressure gradient between the pancreatic duct (higher) and the bile duct (lower) is reversed [18, 19].

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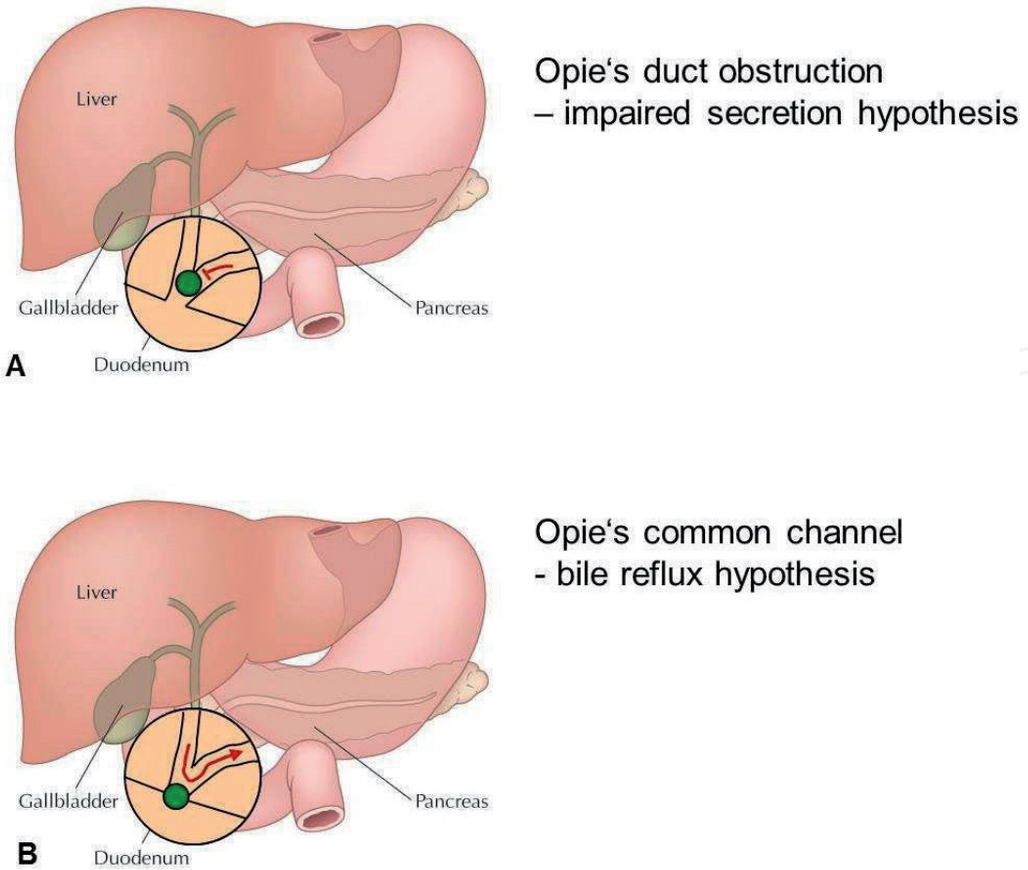

Figure 1.
The two "Opie hypotheses" for the pathogenesis of gallstone induced pancreatitis. (A) A gallstone in the biliary tract obstructs the pancreatic duct to cause an impaired flow from the exocrine pancreas triggering acinar cell or duct cell damage. Obstruction of the common bile duct is immaterial to the triggering mechanism of pancreatitis in this scenario. (B) The duodenal papilla is obstructed by an impacted gallstone, and creates a communication between the pancreatic duct and the common bile duct. This "common channel" allows passage of bile into the pancreatic duct and would trigger the onset of acute pancreatitis. Lerchand Aghdassi [23].

These data rtaken together, it is the acinar cells which are affected by the initial pathophysiological events [20] and are triggered by obstruction or impairment of flow from pancreatic duct, in accordance with Opie's initial hypothesis. Biliary reflux into pancreatic duct, by whichever mechanism, is neither required nor likely to occur during initial course of acute pancreatitis [21].

Intra-acinar pancreatic enzyme activation induces auto digestion of normal pancreatic parenchyma. As a result, acinar cells release proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-1, IL-2 and IL-6, and anti-inflammatory mediators, such as IL-10 and IL-1 receptor antagonist. These mediators propagate the initial injury response locally and systemically so that TNF-α, IL-1 and IL-7, neutrophils and macrophages are recruited into the pancreatic parenchyma and cause the release of more TNF- α, IL-1 and IL-6, reactive oxygen metabolites, prostaglandins, platelet-activating factor and leukotriene. The local inflammatory response increases the permeability and causes damages to the microcirculation of the pancreas further aggravating the pancreatitis. Local hemorrhage and pancreatic necrosis occur in severe cases as a result of local inflammatory response. In addition, neutrophils release some of the inflammatory mediators and aggravate the pancreatic injury by causing pancreatic enzyme activation [22].

The inflammatory cascade is self-limited in approximately 80–90% of patients. However, in the remaining patients, a vicious circle of recurring pancreatic injury and local and systemic inflammatory reaction persist. In a small number of patients, there is a massive release of inflammatory mediators to the systemic circulation.

Active neutrophils mediate acute lung injury and induce the adult respiratory distress syndrome frequently seen in patients with severe pancreatitis. The mortality seen in the early phase of pancreatitis is the result of this persistent inflammatory response.

3.3 Clinical presentation

The patients with gallstone pancreatitis usually present with acute onset of epigastric pain that radiates to back. The pain is unrelenting and accompanied typically by severe nausea and occasional vomiting. In the presence of choledocholithiasis/acute cholangitis, they have high-grade fever with chills, jaundice, acholic stools and dark urine as accompaniments.

3.4 Disease severity

In general, patients with gallstone pancreatitis can be classified into one of the three categories (mild acute pancreatitis, moderately severe acute pancreatitis and severe acute pancreatitis) according to pancreatic morphology, the presence of organ failure and local or systemic complications (**Table 1**). Morphologically as assessed by CECT, acute pancreatitis is defined as interstitial pancreatitis, which is characterized by edematous changes in the pancreatic parenchyma with or without accompanying acute peripancreatic fluid collections (APFC; **Figure 2**) or necrotizing pancreatitis with the presence of nonviable pancreatic parenchyma and, most typically, a surrounding acute necrotic collection (ANC; **Figure 3**) in the peripancreatic tissues. Organ failure in patients with gallstone pancreatitis may be transient (less than 48 h) or persistent (more than 48 h) and usually initially is accompanied by respiratory failure followed by renal failure and, in severe cases, cardiovascular failure. The Modified Marshall scoring system is being used to grade organ dysfunction by the 2012 revised Atlanta classification of acute pancreatitis, but for categorizing and managing patients with gallstone pancreatitis, the presence of transient or persistent single- or multi-organ failure is adequate. Local complications of pancreatitis are defined as an APFC, acute necrotic collection (ANC), pancreatic pseudocyst (PP) or walled-off pancreatic necrosis (WOPN). Briefly, peripancreatic fluid in the presence of interstitial edematous pancreatitis without necrosis is called an APFC, and it often

	Mild acute pancreatitis	**Moderately severe pancreatitis**	**Severe acute pancreatitis**
Morphology	Interstitial/edematous	Necrotizing	Necrotizing
SIRS response	Absent	Transient	Persistent for 1–2 weeks
Organ failure	Absent	<48 h	>48 h
Local complications			
APFC	Occasional	Often	Present initially
ANC	Absent	Occasional	Present
PP	Absent	Rare	Occasionally
WOPN	Absent	Rare	Often
Risk of infection	Nil	Low	Moderate

ANC, acute necrotic collection; APFC, acute peripancreatic fluid collection; PP, pancreatic pseudocyst; SIRS, systemic inflammatory response syndrome; WOPN, walled-off pancreatic necrosis.

Table 1.
Characteristics of the various forms of gallstone pancreatitis (2012 revised Atlanta classification).

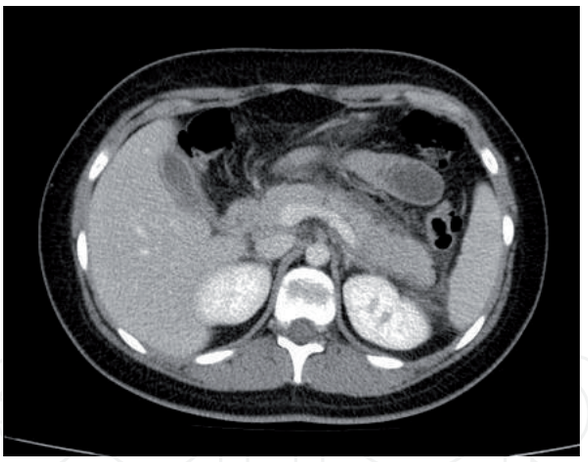

Figure 2.
APFC.

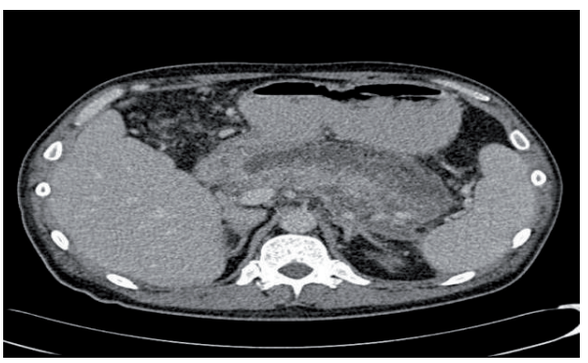

Figure 3.
WOPN.

resolves spontaneously within weeks. An ANC is a collection of fluid and necrosis associated with necrotizing pancreatitis, and it may involve the parenchyma, the peripancreatic tissues alone or both the pancreas and the retroperitoneal tissues. A pancreatic pseudocyst is an encapsulated, homogenous, enzyme-rich fluid collection with a well-defined wall that matures over 4 weeks. Finally, WOPN is a mature encapsulated collection of necrosis that develops over 4 weeks. Systemic complications of pancreatitis represent exacerbations of pre-existing comorbidities, such as coronary artery disease or chronic obstructive pulmonary disease.

3.4.1 Mild acute gallstone pancreatitis

Abdominal pain, nausea or vomiting; an increased serum amylase or lipase concentration; and transient increases in serum bilirubin, alkaline phosphatase or alanine aminotransferase concentrations characterize patients with mild acute gallstone disease. These symptoms and abnormal laboratory findings usually abate within 24–48 h. CECT is not indicated, because an APFC is not present or is not significant clinically. These findings are consistent with a gallstone or sludge which produced a transient obstruction of the pancreatic duct. The presence of gallstones is confirmed by an abdominal ultrasonography.

3.4.2 Moderately severe gallstone pancreatitis

A patient with moderately severe gallstone pancreatitis is complicated by persistent typical abdominal symptoms that may be accompanied by the presence

of a fever, leukocytosis or persistently increased pancreatic- and/or liver-associated enzymes. These symptoms persist for over 48 h and may be accompanied by transient organ failure manifested by increasing oxygen requirements and an abnormally elevated creatinine or blood urine nitrogen (BUN). A CECT is indicated provided the symptoms last for more than 3 days, and that may reveal interstitial, edematous pancreatitis with an APFC or sterile pancreatic necrosis without persistent organ failure. Magnetic resonance cholangiopancreatography (MRCP) is indicated to confirm or exclude the presence of an obstructing stone in patients with continually increased liver-associated enzymes (bilirubin >4) which may have biliary obstruction from gallstones.

3.4.3 Severe acute gallstone pancreatitis

Patients with severe acute gallstone pancreatitis have severe abdominal symptoms and develop persistent single or multiple organ failure. These patients exhibit signs of the systemic inflammatory response syndrome with tachycardia, hypothermia or hyperthermia, leukocytosis and tachypnea. They require admission to the intensive care unit and often require intubation and mechanical ventilation, renal replacement therapy and/or inotropic support due to progressive organ failure. After resuscitation and stabilization, CECT may demonstrate pancreatic necrosis with local complications; however, necrotizing pancreatitis evolves over days and weeks, and early CECT may not demonstrate significant pancreatic or peripancreatic findings. Patients with high suspicion of acute cholangitis require evaluation with MRCP, and perhaps, in these critically ill patients, the most efficient procedure for the relief of biliary obstruction is endoscopic retrograde cholangiopancreatography (ERCP).

3.5 Diagnosis

A definitive diagnosis of acute pancreatitis requires two of the following three criteria:

(1) Abdominal pain that is constant, severe, epigastric and often radiating to the back; accompanied by nausea, vomiting and anorexia; and exacerbated by oral intake; (2) serum lipase (or amylase) level at least three times the upper limit of normal; and (3) characteristic imaging findings, ideally with a contrast-enhanced computed tomography (CT). It is often advisable to delay CT for 72 h, in patients with typical abdominal pain and elevated lipase or amylase, and at that time to perform a dedicated pancreas protocol CT (PPCT) with an early arterial phase and a delayed portal venous phase, ideally calibrated to cardiac output. Important advantages of this 72-hour delay in the PPCT include avoiding excessive radiation and contrast exposure associated with repeat CT imaging, allowing free fluid to begin to coalesce and increasing the ability to distinguish pancreatic necrosis from transiently ischemic areas. In some cases of obviously mild pancreatitis, or frequently recurrent alcoholic pancreatitis, CT may be omitted.

The diagnosis of gallstones as the cause of the pancreatitis is largely a diagnosis of exclusion. Careful history-taking is essential for patients who have acute pancreatitis to help rule out non gallstone causes. In addition, several different laboratory values, such as elevated aminotransferases, bilirubin and alkaline phosphatase, are useful in identifying a biliary origin of pancreatitis. Initial imaging with ultrasound (US) is essential to confirm the presence of gallstones or sludge and to measure the diameter of the common bile duct. Although the US is optimally 95% sensitive in detecting cholelithiasis, in gallstone pancreatitis, the sensitivity may decrease to

	Finding	Points	
Grade	A: Normal pancreas	1	
	B: Pancreatic enlargement	2	
	C: Pancreatic or peripancreatic inflammation	3	
	D: Single peripancreatic fluid collection	4	
	E: Two or more fluid collections or peripancreatic air	5	
Necrosis	<30%	2	
	30–50%	4	
	>50%	6	
CT severity index	**0–3 (%)**	**4–6 (%)**	**7–10 (%)**
Morbidity	8	35	92
Morality	3	6	17

Table 2.
Computer tomography severity index (Balthazar score).

60% from 80% because of the increased bowel gas caused by concomitant ileus. A CECT with pancreatic protocol is indicated in patients with moderate and severe pancreatitis, ideally 48–72 h after diagnosis, and may demonstrate pancreatic necrosis with local complications (**Table 2**).

3.6 Treatment

In acute gallstone pancreatitis, intravenous fluid resuscitation is the mainstay of treatment regardless of disease severity. All patients require frequent serial re-evaluations because even patients with apparently mild disease may go on to rapidly develop severe pancreatitis and require intensive care, which may include mechanical ventilation and cardiovascular support.

3.6.1 Mild-moderate disease

The initial fluid administration should be in boluses followed by titration of infusion based on urine output, heart rate, blood pressure and correction of acidemia. Oral intake may be restricted in these patients on presentation but should begin soon after, as tolerated, typically within 24 h. If nausea and vomiting persist, however, nasogastric tube decompression can protect against vomiting and aspiration. While this treatment is going on, the primary complaint of the patient is to be addressed, which is severe abdominal pain. This is taken care of mainly by intravenous opiates. There is no role for prophylactic antibiotics unless an infection has been identified. However those patients with cholangitis and those who go on to develop extensive necrotizing pancreatitis, intravenous antibiotics may be warranted. Patients with significant cholangitis in addition to gallstone pancreatitis require urgent ERCP. Some people advocate early routine ERCP for all patients, but the latest guidelines limit ERCP and sphincterotomy to those patients with severe disease, to decrease complications.

Patients with moderately severe gallstone pancreatitis have evidence of local complications from pancreatic injury and transient organ failure and thus should be managed in a monitored setting. Because organ failure is transient with this condition, rapid improvement is anticipated, and a prolonged intensive care unit stay should be unnecessary.

However, the duration of hospitalization may be dependent on the local complications related to pancreatic injury. Edematous pancreatitis with an APFC should resolve relatively quickly, whereas sterile necrosis may cause persistent symptoms and limit per oral intake, necessitating institution of enteral nutrition. For patients who have sterile necrosis, follow-up CECT is recommended to ensure resolution of the pancreatic injury without complicating features such as the development of a pancreatic pseudocyst.

Laparoscopic cholecystectomy should be offered to patients with mild GSP during the index hospitalization, generally as soon as the patient is stable with significant resolution of acute symptoms.

3.6.2 Severe disease

Patient with severe disease should be treated aggressively in a higher center with well-equipped intensive care units, endoscopy and operative rooms all of which are staffed by critical care experts, gastroenterologists, interventional radiologists and surgeons. These patients develop a profound SIRS response and often have rapid deterioration requiring intubation and mechanical ventilation, renal replacement therapy and inotropic support. This critical period is driven by cytokine response and may last for 1–2 weeks. Aggressive fluid resuscitation is the cornerstone of initial therapy in severe. The goals of therapy during this period of critical illness include maintenance of oxygen delivery to the central nervous system and viscera by mechanical ventilation, adequate resuscitation with Lactated Ringer's solution, inotropic administration as needed to support blood pressure and decrease heart rate, maintenance of renal function with or without renal replacement therapy and nutritional support. Enteral nutrition should be tried, though less often possible, because of less incidence of infected pancreatic necrosis. Antibiotics are often used to prevent conversion of sterile necrosis to infected necrosis, if the necrosis is <30%.

As the systemic inflammatory response wanes over 1–2 weeks, these patients will develop local complications of necrotizing pancreatitis. An early ERCP plus sphincterotomy along with conservative management can help decrease complications of severe disease. By 4–6 weeks these complications mature and management to be guided according to symptoms. Unlike in mild disease, an early operation should be avoided in severe pancreatitis, whether for cholecystectomy or pancreatic debridement. There are, however, a few notable exceptions, such as abdominal compartment syndrome, refractory hemorrhage and colonic necrosis or perforation, in which case immediate operation is warranted.

An ANC accompanying pancreatic necrosis may be sterile or infected. Sterile necrosis often requires no intervention, and patients recover over time except for the infrequent patient who develops failure-to-thrive syndrome as a result of sterile necrosis. Patients with failure-to-thrive syndrome may require percutaneous drainage or endoscopic or operative debridement for full recovery. Those patients with infected necrosis require drainage and debridement of infected pancreatic tissues with vigorous antibiotic therapy. The mode of drainage or debridement can vary from percutaneous drainage, endoscopic or laparoscopic debridement to dual-modality drainage (combined percutaneous and endoscopic drainage). The open surgical approaches are heterogenous, and some of these approaches are no longer used in contemporary management.

Importantly, before debridement, a CECT should be obtained to ascertain the presence of the disconnected pancreatic duct syndrome. A viable pancreatic remnant in the tail separated by a substantial area of pancreatic necrosis in the neck of the gland should lead to the suspicion of a disconnected pancreas. This warrants the need for distal pancreatectomy and splenectomy accompanied by pancreatic

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debridement as necessary, regardless of the surgical approach. Finally, concomitant with or following pancreatic drainage or debridement, the patient must have a cholecystectomy to prevent further episodes of gallstone-induced pancreatitis. The outcomes of patients with severe acute gallstone pancreatitis are variable depending on the patient's overall condition, the extent of the disease, the type of procedure performed, the expertise of the providers and the institutional experience with such patients.

4. Conclusion

Acute gallstone pancreatitis represents a wide spectrum of disease ranging from mild disease that resolves spontaneously to severe disease with SIRS and necrotizing pancreatitis. These patients are best managed by a multidisciplinary approach to combat complications. Finally they should have a timely cholecystectomy to treat the cause of disease.

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