Endoscopic Management of Acute Biliary Pancreatitis

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KEYWORDS

• Biliary pancreatitis • ERCP • Sphincterotomy • Timing of ERCP
• Pancreatic duct stenting

KEY POINTS

- Acute pancreatitis is considered an endoscopic emergency when a biliary cause is likely and there is suspected cholangitis or ongoing biliary obstruction.
- Elective endoscopic retrograde cholangiopancreatography (ERCP) should be considered when there is jaundice or proven choledocholithiasis by noninvasive imaging or intraoperative cholangiography.
- There remains some debate regarding the role of early ERCP in the setting of acute biliary pancreatitis without evidence of biliary obstruction.
- Further studies should better establish the indicators for ampullary obstruction and predictors for severe attacks.
- Additional prospective endoscopic trials are needed to clarify the optimal timing of biliary intervention, the potential benefit of biliary sphincterotomy in all cases independent of biliary obstruction, and the usefulness of pancreatic stenting.

Videos of the needle-knife precut sphincterotomy and standard sphincterotomy techniques accompany this article at http://www.giendo.theclinics.com/

OBJECTIVES

- Understand the pathophysiology of acute biliary pancreatitis
- Recognize important factors in the clinical evaluation of a patient with acute biliary pancreatitis
- Know the available literature on the role of early endoscopic retrograde cholangiopancreatography (ERCP) versus conservative management for acute biliary pancreatitis

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- Understand the types of endoscopic therapy available for ERCP in acute biliary pancreatitis

INTRODUCTION

Acute pancreatitis represents numerous unique challenges to the practicing digestive disease specialist. Clinical presentations of acute pancreatitis vary from trivial pain to severe acute illness with a significant risk of death. Management goals are 4-fold:

1. Identify patients with a mild attack who initially require only conservative care
2. Early recognition and appropriate treatment of biliary obstruction and potentially severe attacks to reduce morbidity and mortality caused by infection, organ failure, or pancreatic fluid collections
3. Manage complications of severe acute pancreatitis
4. Direct therapy to prevent recurrent attacks

Multidisciplinary collaboration often is required, and the endoscopist plays a central role. At present, urgent endoscopic treatment of acute pancreatitis is only considered when there is causal evidence of biliary pancreatitis.

CLINICAL FEATURES AND SIGNIFICANCE

It is usually not difficult to diagnose acute pancreatitis. It requires at least 2 of 3 criteria: (1) abdominal pain, typically located in the upper abdomen and often radiating to the back; (2) serum amylase and/or lipase increased 3 times greater than the upper limit of normal (lipase is more sensitive, specific, and remains increased longer than amylase); and/or (3) radiographic evidence of pancreatitis.[1] Gallstones are considered the most common single cause of acute pancreatitis, being responsible for at least half of all cases. About 5% of those with symptomatic gallstones develop acute biliary pancreatitis (ABP), and there is a 1% annual incidence of acute pancreatitis among those with gallstones.[2,3] Most ABP attacks are not severe, and full recovery without recurrence can be expected with conservative care and directed therapy to prevent future attacks. However, the overall mortality for an initial attack of ABP is at least 10%.[4,5] Up to 25% of ABP attacks are severe, carrying a significant risk for multiorgan system failure, long-term medical disability, and a mortality up to 30%.[6] Without definitive treatment, the risk of a recurrent attack within the next several months is about 30% to 50%.[7–11] Even after a mild attack, cholecystectomy and/or biliary sphincterotomy must be considered within weeks.[12,13] A large retrospective cohort study of more than 5000 patients with ABP emphasized the importance of early biliary intervention either with cholecystectomy or endoscopic retrograde cholangiopancreatography (ERCP) during index admission. Hospital readmission rates for ABP within 12 months were significantly reduced with cholecystectomy (14.0%–5.6%) or ERCP (13.1% vs 5.1%).[14]

The important questions an endoscopist must consider when caring for a patient with acute pancreatitis are:

- Is the cause of pancreatitis related to gallstones?
- Is there evidence of ongoing biliary obstruction?
- How severe is the attack?
- When should urgent ERCP be considered?
- What endoscopic therapy should be performed during urgent ERCP?
- When should elective ERCP be considered?

To address these questions, it is helpful to review the pathophysiologic factors of ABP and the clinical experiences that have provided historical insight regarding treatment principles.

PATHOPHYSIOLOGY

Pertinent factors related to the pathophysiology of ABP are (1) bile duct stones or crystals, (2) pancreatic duct obstruction, (3) common pancreaticobiliary channel, and (4) nonpatent accessory papilla.

Since the autopsy report in 1901 by Opie[15] of a gallstone impaction at the papilla, numerous surgical series have implicated bile duct stone impaction and/or passage as a cause of pancreatitis. Bile duct stone impaction was found in 26% to 72% of patients who had ABP when surgery was performed soon after an attack compared with less than 10% for patients undergoing elective surgery.[16–18] Out of 19 fatal cases of ABP that underwent autopsy, nearly half had a stone impacted at the papilla.[4] To implicate transpapillary stone passage, 2 studies in the 1970s reported that fecal stones were discovered in about 90% of patients who had suspected ABP compared with only about 10% of controls.[18,19] Biliary crystals or small stones are perhaps more prone to negotiate cystic duct and papillary migration and are considered to be more likely to cause ABP.[17,20–24]

Pancreatic duct obstruction may occur after stone impaction or sphincter of Oddi spasm. Distal bile duct stone impaction may obstruct the pancreatic duct orifice by compressing the pancreaticobiliary septum. Stone impaction at the papillary orifice also may cause pancreatic duct obstruction when there is a common pancreaticobiliary channel. Increased amylase levels were found in biliary T-tube fluid from a patient who had ABP that decreased promptly after sphincterotomy and removal of an impacted stone.[25] In addition, sphincter of Oddi spasm and a common pancreaticobiliary channel may cause functional papillary obstruction in patients with ABP who have passed bile duct stones. Compared with patients who had biliary stones and no history of pancreatitis, increased amylase levels were found in biliary T-tube fluid from patients with ABP who had documented transpapillary stone migration.[26] As an indication of sphincter spasm and a common channel, reflux of contrast into the pancreatic duct is observed in about two-thirds of intraoperative cholangiograms.[17,18,24,27,28] Compared with controls, basal sphincter of Oddi pressures were increased significantly in 30 consecutive patients with mild ABP when measured within 24 hours of admission.[29] Impaired drainage by means of the accessory papilla also contributes to promoting pancreatic ductal obstruction. The accessory papilla is patent in 30% to 70% from normal anatomic studies. Nowak and colleagues[30] reported that only 17% of patients with ABP had a patent accessory papilla compared with 69% of patients for controls.

Experimental studies have provided important information regarding mechanisms and timing of pancreatitis and subsequent organ injury. Pancreatic and biliary duct obstruction in animals causes pancreatitis, whereby the extent of histologic injury is related directly to duration of duct obstruction (up to 5 days), but progression of injury is prevented when duct obstruction is relieved.[31,32] Early pancreatic injury occurs within hours of duct obstruction, and necrotizing acinar injury is observed within 24 hours.[33,34] Data pertaining to the timing of duct obstruction and organ injury also are derived from studies of cytokines, the mediators of systemic inflammation, and distant organ dysfunction.[35,36] Cytokine production begins early and peaks about 24 to 36 hours after onset of symptoms. Inflammatory cytokine levels are increased significantly after severe attacks and organ dysfunction occurs between 36 and 72 hours after symptom onset.

LESSONS FROM SURGICAL EXPERIENCE

Three important principles regarding the treatment of ABP were learned from surgical studies:

1. There is benefit with early relief of ductal obstruction.
2. Benefit only occurs after surgical procedures that promote ductal drainage.
3. Early surgery without augmenting drainage is detrimental.

In the late 1970s, Acosta and colleagues[16] reported a case series of 132 patients who had ABP to compare outcomes for patients treated differently during 2 time periods. From 1964 to 1972, most patients were operated on for biliary tract disease electively or earlier only if there were absolute indications. During 1972 to 1975, patients underwent early surgery (14 of 46 having surgical sphincteroplasty) within 48 hours of symptom onset. There was only 2% mortality for the group that underwent early surgery compared with 16% for those undergoing elective or indicated surgery. The investigators concluded that "treatment given for acute gallstone pancreatitis in hopes of avoiding pancreatic necrosis must relieve obstruction quickly."[16] In a separate report by Acosta and colleagues,[37] the extent of pancreatic damage (interstitial to necrosis) correlated with duration of ampullary obstruction, and relief of obstruction was associated with remission of symptoms. Similar outcomes with an overall 5% mortality for ABP were reported by Stone and colleagues[38] from a randomized controlled trial comparing early (within 72 hours) versus delayed (3 months) surgery. Surgical procedures included sphincteroplasty and septotomy, after which a "sudden gush of clear pancreatic juice"[38] was observed when performed during the early operations.

A later randomized controlled trial concluded that early ($\leq$48 hours) cholecystectomy was associated with increased mortality (15%) compared with when it was performed electively (2%).[39] However, procedures to augment ductal drainage (sphincteroplasty) were not done. A retrospective study also reported increased mortality (31%) in patients undergoing immediate surgery for ABP.[8]

CONCLUSIONS FROM PROSPECTIVE ENDOSCOPIC TRIALS

Although debates regarding the role of early surgery for ABP were escalating, the first endoscopic treatments for ABP were being reported. Van der Spuy[40] performed biliary sphincterotomy to promote spontaneous bile duct stone migration in 10 patients who had gallstone pancreatitis. Safrany and Cotton[41] performed ERCP with biliary sphincterotomy and stone extraction in 11 patients who had severe ABP; 9 patients had endoscopic therapy within 24 hours of hospital admission. Dramatic improvement was observed with respect to laboratory (liver and pancreas chemistries, white blood cell counts) and clinical symptoms. Rosseland and Solhaug[42] reported good outcomes after endoscopic therapy in 15 patients within 48 hours of symptom onset. From these early reports, it was concluded that ERCP was safe and effective in the setting of ABP.

Prospective trials have compared early ERCP with conservative therapy for ABP. However, it is difficult to draw firm conclusions because these studies lack congruency with respect to inclusion criteria, the timing of ERCP after onset of symptoms, and endoscopic intervention. Clinical outcomes for urgent ERCP in ABP may not be different from an elective ERCP strategy when a significant minority of elective ERCP patients undergo clinically indicated ERCP. Studies in which ERCP is not performed early enough may not prove beneficial. Any benefit for early ERCP may be negated unless all patients undergo sphincterotomy to augment ductal drainage. In

addition, no studies have evaluated endoscopic expertise; an important factor because ERCP in the setting of acute pancreatitis can be more difficult. Nevertheless, these studies provide useful data.

An early meta-analysis concluded that early ERCP significantly reduces morbidity (25% vs 38%) and mortality (5% vs 9%) in ABP.[43] Two later meta-analyses evaluated 3 trials that excluded patients with cholangitis.[44,45] They concluded that early ERCP with or without endoscopic sphincterotomy in patients with either mild or severe pancreatitis does not lead to significant reduction in overall risk of complications or mortality. There was a suggestion that it may even lead to higher mortality. The definitions of early ERCP were defined differently in each study; some defined early as within 72 hours of admission and others defined it as within 72 hours of symptom onset. Also, endoscopic sphincterotomy was only performed when common bile duct stones were visualized during ERCP. There were also variation in definitions of overall complications.

The most recent meta-analysis, by Tse and Yuan,[46] evaluated 7 trials that compared early ERCP versus early conservative management for acute gallstone pancreatitis. The general definition of early in the meta-analysis was within 72 hours of admission. Overall, they did not find significant improvement in mortality and local or systemic complications of pancreatitis with early ERCP strategy compared with early conservative management; this conclusion was independent of whether patients had predicted mild or severe pancreatitis. Their results did support the empirical evidence of the benefits of early ERCP in patients with cholangitis.

It is instructive to carefully evaluate some of the individual endoscopic studies and focus on the important details such as whether ERCP was performed early (eg, within 24–48 hours of symptom onset), whether endoscopic therapy with sphincterotomy was performed, and the frequency of crossover endotherapy in conservative groups. **Table 1** summarizes these parameters for each study and more specific details of each study are discussed later.

Neoptolemos and colleagues[47] reported the first endoscopic randomized controlled trial in ABP comparing urgent ERCP (within 72 hours of hospital admission) in ABP with conservative care that only allowed ERCP after 5 days if indicated. Urgent ERCP was performed successfully in 88% of patients, but success was less likely if pancreatitis was severe (80%) versus mild (94%). Biliary sphincterotomy was performed in about one-third of patients (those found to have bile duct stones). Of patients confirmed to have gallstones, bile duct stones were discovered significantly more often in severe (63%) versus mild (25%) attacks. The study design does not strictly compare early versus clinically indicated ERCP, because ERCP was delayed by at least 72 hours in the urgent ERCP group, and ERCP in the conservative group was delayed for 5 days even when there was a need for ERCP. Significant differences were found only in patients predicted to have severe attacks; early ERCP was associated with lower overall complications (24% vs 61%) and a shorter hospital stay (9.5 days vs 17.0 days).

In the randomized trial reported by Fan and colleagues,[48] urgent ERCP was performed earlier, within 24 hours of hospital admission. Similar to the report by Neoptolemos and colleagues, early ERCP was performed successfully in 90% of patients, and biliary sphincterotomy was done only in the 38% of patients found to have ampullary or bile duct stones. Patients in the conservative group underwent selective ERCP at any time there were indications to proceed. Of the patients randomized to initial conservative care, 28% underwent ERCP, and 37% of these had treatment of ampullary or bile duct stones, usually within 3 days of admission when there was evidence of cholangitis, sepsis, shock, or other organ system failure. Further, of the patients in the

Table 1
Summary of prospective endoscopic trials for ERCP and ABP

Study	Trial Design	ERCP Group	Timing of ERCP	Sphincterotomy (%)	Conservative Group ERCPs (%)
Neoptolemos et al,[47] 1988	RCT	59 (34 mild, 25 severe)	≤72 h of admission	19/59 (32)	14/62 (23)
Fan et al,[48] 1993	RCT	97 (56 mild, 41 severe)	≤24 h of admission	37/97 (38)	27/98 (28)
Folsch et al,[49] 1997	RCT	126 (84 mild, 26 severe, 16 undefined)	≤72 h of symptoms	58/126 (46)	22/112 (20)
Zhou et al,[50] 2002	RCT	20 (13 mild, 7 severe)	≤24 h of admission	12/20 (60)	0/25 (0)
Oría et al,[51] 2007	RCT	51 (34 mild, 17 severe)	≤24–48 h of symptoms (46) 48–72 h of symptoms (5)	38/51 (75) —	2/52 (4) —
Van Santvoort et al,[52] 2009	Prospective observational	81 (all severe)	<24 h of symptoms (17) 24–48 h of symptoms (53) 48–72 h of symptoms (11)	69/81 (85) — —	7/72 (10) — —
Chen et al,[53] 2010	RCT	21 (all severe)	<24 h of symptoms (5) 24–48 h symptoms (10) >48 h of symptoms (6)	17/21 (81) — —	0/32 (0) — —

Abbreviation: RCT, randomized controlled trial.

conservative group with a predicted severe attack, almost half (45%) underwent selective ERCP. This study design decreases the ability to show benefit with early ERCP, because the ratio of patients who underwent sphincterotomy and treatment of stones was virtually identical in both groups. A significant minority (35%) of patients was discovered not to have a biliary cause for pancreatitis. Thus, benefit for urgent ERCP was only found in those proved to have gallstones. Compared with selective ERCP, urgent ERCP significantly reduced morbidity (33%–16%) and biliary sepsis (12%–0%), and there was a trend toward lower mortality (8%–2%).

Folsch and colleagues[49] compared early ERCP, defined as within 72 hours of symptom onset, with a conservative approach in a randomized controlled trial for patients who had suspected ABP, but excluded those with bilirubin levels of at least 5 mg/dL. ERCP was successful in 96% of patients in the early group, and biliary sphincterotomy was performed only in the 46% found to have bile duct stones. Selective ERCP was performed within 3 weeks of randomization on 20% of patients in the conservative treatment group if there was evidence of cholangitis or biliary colic. A lower success rate for selective ERCP (86%) was attributed to ampullary edema or periampullary diverticula. Similar overall morbidity and mortality were observed between the two groups.

A small trial by Zhou and colleagues[50] involving 45 patients evaluated the role of ERCP in patients with ABP within 24 hours of admission. Patients were randomly divided into ERCP and supportive treatment groups and then subdivided into mild or severe pancreatitis. Twenty patients in the ERCP group all received ERCP within 24 hours of admission. Twelve of the patients had a sphincterotomy for either stones or stenosis, and the remaining 8 patients had a nasobiliary drain placed for large stones or duodenal edema. None of the patients in the conservative management group underwent ERCP. There was a statistically significant decrease in complications and length of hospitalization in the ERCP group compared with the non-ERCP group only in patients with severe ABP.

Oría and colleagues[51] concluded that early endoscopic intervention failed to reduce systemic and local inflammation in patients with ABP. This randomized controlled trial compared ERCP (with endotherapy if evidence of bile duct stones) to conservative management. Some patients presented nearly 20 hours after onset of symptoms. ERCP was performed within 48 to 72 hours after symptom onset and only about three-fourths of patients in the ERCP group underwent sphincterotomy. Two patients in the conservative arm eventually had ERCP because of cholangitis or progressive jaundice. Measured outcomes included changes in organ failure score and computed tomography (CT) severity index during the first week of admission, incidence of local complications, and overall morbidity and mortality. There were no statistically significant differences between the ERCP and conservative management patient groups in these outcome measures.

Van Santvoort and colleagues[52] conducted a prospective observational multicenter study that evaluated a subset of patients with predicted severe ABP but without evidence of cholangitis. The decision to perform ERCP with or without sphincterotomy was left to the discretion of the treating physician. Patients who had an ERCP within 72 hours of symptom onset were classified as the early ERCP group and almost all (86%) underwent ERCP within 48 hours. Most patients (85%) in the ERCP group underwent therapy that included a biliary sphincterotomy. Patients who did not undergo ERCP or had ERCP later than 72 hours after onset of symptoms were in the conservative treatment group. Seven patients in the conservative group underwent an elective ERCP at a median of 5 days after symptoms (range 4–18 days). In patients with predicted severe ABP and concurrent cholestasis, early ERCP was associated with

significantly fewer complications including pancreatic necrosis. Despite the study not being a randomized controlled trial, it still provides favorable observational data for the role of early ERCP in patients with severe ABP.

Chen and colleagues[53] evaluated the efficacy of early endoscopic intervention without fluoroscopy for severe ABP in the intensive care unit. More than 70% of patients randomized to the endoscopic intervention arm underwent ERCP within 48 hours of symptoms; cannulation was reported to be more difficult when performed later. Biliary sphincterotomy with stone removal was completed in 80%. The remaining patients had suppurative cholangitis and were treated initially with nasobiliary drainage only. No patients in the conservative arm received ERCP. Patients in the endoscopic intervention group had a significant decrease in severity score at day 10; quicker relief of clinical symptoms including temperature, abdominal pain, and peritoneal irritation; and no mortality. There were 2 deaths in the conservative arm.

The available published randomized controlled trials for ABP performed sphincterotomy only if there was evidence of bile duct or ampullary stones. Also, the existing controlled studies do not provide data to compare outcomes of those who did or did not undergo sphincterotomy. Biliary sphincterotomy likely augments pancreatic drainage and bile flow, particularly for patients who have a common pancreaticobiliary channel. An abstract by Nowak and colleagues[54] compared outcomes in a consecutive series of 280 patients with ABP. Duodenoscopy was performed within 24 hours of admission to assess for stone impaction. Seventy-five patients (27%) who had stone impaction underwent urgent treatment with sphincterotomy. The remaining patients with a normal papilla were randomized to urgent sphincterotomy (n = 103) or conservative treatment (n = 102). Patients who underwent urgent sphincterotomy (impacted stones plus randomized patients) had significantly fewer complications (17%) and lower mortality (2%) compared with those treated conservatively (36% and 13%, respectively). Another abstract by Nowak and colleagues[55] reported outcomes after biliary sphincterotomy within 24 hours of admission in 307 consecutive patients who had ABP treated over 10 years. Outcomes were analyzed according to predicted severity and interval between sphincterotomy and onset of pain. The best outcomes (7% complications, 0% mortality) were observed when sphincterotomy was performed before 24 hours elapsed after onset of pain, despite 31% of these patients having a predicted severe attack. For patients who underwent sphincterotomy more than 72 hours after symptom onset, outcomes were worse (20% complications, 13% mortality), even though only 18% had predicted severe attacks.

INITIAL CLINICAL EVALUATION

Clinical evaluation of a patient with ABP (**Box 1**) should be directed to answer the following questions:

1. Is the cause of pancreatitis related to gallstones?
2. Is there evidence of ongoing biliary obstruction?
3. How severe is the attack?

Is the Cause of Pancreatitis Related to Gallstones?

Establishing the cause of acute pancreatitis is important when developing a treatment algorithm. If ABP is not diagnosed in a timely fashion, the potential for benefit with endoscopic therapy may be lost. Further, recurrent pancreatitis may result without appropriate treatment when gallstones are not recognized as the cause of pancreatitis.

Box 1
Important clinical evaluation of patients with suspected acute biliary pancreatitis

Evidence for biliary cause

Female

History of biliary colic

Age greater than 50 years

Alanine aminotransferase greater than or equal to 3 times normal

Dilated bile duct

Evidence of ongoing biliary obstruction

Cholangitis

Unrelenting pain

Laboratory trend of increasing liver tests

Factors associated with severe attack

Age greater than 55 years

Body mass index greater than 30

Organ system dysfunction

Baseline Acute Physiology and Chronic Health Evaluation (APACHE)-II score 8 and/or increasing score during initial 24 hours

Hematocrit greater than or equal to 44% and/or failure to decrease during initial 24 hours

Bedside Index for Severity in Acute Pancreatitis (BISAP) score of greater than or equal to 3 within 24 hours of presentation

Systemic Inflammatory Response Syndrome

Women older than 50 years are more likely to have gallstones as the cause of pancreatitis.[56] A history of antecedent biliary colic may suggest a biliary cause, but laboratory studies and imaging are most helpful to establish the diagnosis of ABP. Serum alanine aminotransferase increase of at least 3 times the upper limit of normal has been shown to have a positive predictive value of 95% for ABP.[57] Serum calcium and triglycerides are additional laboratory tests that should be obtained at admission to exclude other causes of pancreatitis.

Transabdominal ultrasound generally is considered the best initial imaging study to establish a cause for pancreatitis. Ultrasound is highly specific for diagnosing cholelithiasis and has been shown to be about 90% accurate in patients who have gallstone pancreatitis.[58,59] CT of the abdomen with contrast generally has a limited role in the initial evaluation of patients who have acute pancreatitis. However, CT may be helpful to rule out other important causes of abdominal pain and to identify mass and cystic lesions of the pancreas. Magnetic resonance cholangiopancreatography and endoscopic ultrasound may be helpful in some cases to diagnose choledocholithiasis but are of limited benefit for showing gallstones in the absence of choledocholithiasis.

Is there Evidence of Ongoing Biliary Obstruction?

Whether there is ongoing biliary obstruction is of central importance to determine whether ERCP is likely to benefit a patient with acute pancreatitis. As discussed earlier, bile obstruction and pancreatic duct obstruction are paramount to the

pathophysiology and treatment of ABP. Cholangitis with symptoms of abdominal pain, fever, and jaundice is not difficult to recognize. Otherwise, clinical and biochemical trends are most useful for identifying ongoing biliary obstruction. Unrelenting pain and increasing liver function test abnormalities may indicate ongoing obstruction caused by an impacted stone. Acosta and colleagues[60] reported that decreasing severity of abdominal pain, decreasing serum bilirubin, and presence of bile in a nasogastric tube aspirate strongly suggested ampullary stone decompression.

Diagnosis of choledocholithiasis (without ampullary stone impaction) is important but not with respect to the potential need for urgent intervention. Endoscopic ultrasonography has a high sensitivity for diagnosis of bile duct stones.[61,62] Okan and colleagues[63] reported results of magnetic resonance cholangiopancreatography in 81 patients with nonsevere ABP and found a low false-negative rate of 7.4% for diagnosing choledocholithiasis. ERCP should not be considered as a diagnostic test in this setting.

How Severe is the Attack?

Persistent organ dysfunction (circulatory, respiratory, and renal failure) and infected pancreatic necrosis portend increased mortality. However, such events often occur after a missed opportunity to intervene in hopes of preventing them. Baseline patient factors (age older than 55 years and body mass index greater than 30) and early clinical evidence for organ dysfunction have been shown to predict the severity of acute pancreatitis.[64]

Acute pancreatitis generally has a biphasic clinical course. The first phase, within 2 weeks of the attack, is characterized by the patient's clinical course and the inflammatory immune response. The severity of this phase is related to presence of one or more organ system dysfunctions, which can occur in up to 40% of severe cases with a mortality of 30%. The second phase occurs after 2 weeks of symptoms when patients are more susceptible to infectious complications, and the assessment involves a morphologic evaluation of the pancreas. About three-fourths of cases have an edematous pancreas that resolves without serious sequelae. The remaining quarter of cases develop necrosis with mortality related to infection and independent of the extent of necrosis. The most severe complication is infected pancreatic or peripancreatic necrosis, which occurs in about one-third of patients; the remaining two-thirds of patients have sterile necrosis. The greatest risk for infection is about 2 to 4 weeks after presentation.[1]

The Ranson score,[65] the most recognized prognostic method, and the Glasgow modification of the Imrie score,[66] are of limited use, because they require 48 hours of clinical data. A large meta-analysis concluded that the Ranson score is a poor predictor of severity and offers no advantage compared with clinical judgment.[67]

The APACHE-II (Acute Physiology and Chronic Health Evaluation II) and serum hematocrit both remain valid for assessment of severity at presentation.[64] The APACHE-II is calculated easily after entering patient parameters such as age, vital signs, hematocrit, leukocyte count, sodium, potassium, creatinine, cardiopulmonary, and neurologic parameters to generate a composite score. Combining an obesity score with the APACHE-II seems to improve accuracy for prediction of severe or mild acute pancreatitis.[68] Serum hematocrit as an indicator of third spacing and volume depletion has proved to be useful in predicting the clinical course of acute pancreatitis. Hematocrit of at least 44% at presentation and a failure to decrease during the first 24 hours seems to correlate with pancreatic necrosis and development of organ failure.[69,70] Further, hematocrit less than 44% seems to predict a more benign course of acute pancreatitis.[71] None of the prognostic scoring methods are specific for ABP.

Singh and colleagues[72] generated a scoring system to use as a bedside index for severity in acute pancreatitis (BISAP). The BISAP score includes 5 variables: blood urea nitrogen greater than 25 mg/dL, presence or absence of impaired mental status, systemic inflammatory response syndrome, age greater than 60 years, and pleural effusion on imaging. One point is given for each variable and 3 or more points within 24 hours of presentation is associated with a greater mortality, increased risk of organ failure, and pancreatic necrosis.

Another classification for severity of pancreatitis is the Atlanta criteria, which was first instituted in the early 1990s.[73] Numerous pancreas experts convened in Atlanta, Georgia, to establish a clinically based classification system for acute pancreatitis. They came to a consensus for standardized definitions, clinical manifestations, pathologic findings for degrees of pancreatitis, and certain complications such as fluid collections, pancreatic necrosis, pseudocysts, and abscesses. The Atlanta criteria have recently been revised to reflect substantial advances in understanding of acute pancreatitis.[74] Severity is classified into mild, moderate, or severe depending on presence and duration of organ failure and local and/or systemic complications (**Box 2**).

ROLE OF ERCP

Questions regarding the role for ERCP in the setting of ABP are:

- When should urgent ERCP be considered?
- What endoscopic therapy should be performed during urgent ERCP?
- When should elective ERCP be considered?

Suggested indications and timing for ERCP in ABP are shown in **Box 3**.

When Should Urgent ERCP be Considered?

ERCP is indicated in the setting of ABP when there is evidence of acute cholangitis, and when there is evidence of ongoing biliary obstruction. This view is supported by the Tse and Yuan[46] meta-analysis and the International Association of Pancreatology evidence-based guidelines for management of acute biliary pancreatitis.[75]

Existing experimental data and clinical insights from surgical and endoscopic experience all suggest that procedures to augment ductal drainage must be accomplished

Box 2
Classification of acute pancreatitis severity

Mild acute pancreatitis

No organ failure

No local or systemic complications

Moderately severe acute pancreatitis

Organ failure that resolves within 48 hours (transient organ failure) and/or

Local or systemic complications without persistent organ failure

Severe acute pancreatitis

Persistent organ failure greater than 48 hours

From Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:108; with permission.

Box 3
Indications and timing for ERCP in acute biliary pancreatitis

Urgent (within 48 hours of symptom onset)

Cholangitis

Ongoing biliary obstruction

Elective

Jaundice or imaging shows choledocholithiasis

Abnormal intraoperative cholangiography

Biliary sphincterotomy as primary therapy in poor operative candidates

Biliary sphincterotomy as temporary therapy during pregnancy

early in the course of ABP to be of benefit. However, there is no clear definition of what is early. Radiological evidence suggests that pancreatic necrosis occurs within 4 days.[76] Surgeons may discover pancreatic necrosis about 48 hours after onset of symptoms.[37] A case-control study compared extent of pancreatic injury at laparotomy between patients with ongoing ampullary obstruction with those with spontaneous ampullary stone clearance.[77] Pancreatic injury was similar between the two groups if ampullary obstruction was cleared within 48 hours, but more than 80% of patients with ampullary obstruction for more than 48 hours developed pancreatic necrosis. A randomized controlled trial comparing early (24–48 hours) versus delayed (after 48 hours) ERCP and sphincterotomy for ABP and evidence of ampullary obstruction found significantly less morbidity for those treated within 48 hours of symptom onset.[78] Thus, benefit is likely if ductal drainage is achieved within the first 2 days. The clinical situation also dictates whether an early ERCP is indicated. For example, ERCP is indicated whenever there is evidence of symptomatic biliary obstruction, independently of when the attack started. However, there may be limited benefit, if any, even after a severe attack when ERCP is performed several days after onset of significant symptoms. Delay between clinical symptoms and presentation for medical attention is a potential uncontrollable limitation of an urgent ERCP strategy. One prospective study found that only two-thirds of patients present within 24 hours of symptom onset.[79] A retrospective study reported that 70% of patients presented for clinical attention after delay of more than 2 days.[11] Differentiating between milder initial symptoms of biliary colic and more significant pancreatic symptoms may explain this discrepancy.

What Endoscopic Therapy Should be Performed during Urgent ERCP?

There are several arguments that support doing a biliary sphincterotomy in all cases of ABP whenever urgent ERCP is done. First, most studies of ERCP in patients with ABP report that about 50% have bile duct or ampullary stones.[49,80–82] Second, biliary sphincterotomy augments pancreatic drainage in addition to ensuring bile drainage. Third, sphincter of Oddi dysfunction may contribute to the pathophysiology of ABP even after bile duct stone migration. From a retrospective study, ERCP with biliary sphincterotomy was performed in 24 of 35 patients with severe ABP even though 10 (42%) did not have bile duct stones.[82] A significantly lower incidence of pancreatic necrosis (8% vs 64%) and mortality (4% vs 36%) was observed in those who were treated with sphincterotomy compared with those who were not. Fourth, biliary sphincterotomy may protect against further attacks.[12] A retrospective study reported

that patients undergoing sphincterotomy after ABP were significantly less likely to have recurrent pancreatitis independently of whether cholecystectomy was done.[83] Fifth, sphincterotomy may be adequate therapy and may delay, and perhaps obviate, cholecystectomy (discussed later). Any potential for benefit of biliary sphincterotomy must be weighed against the risk of postprocedure complications.

Different techniques in performing a sphincterotomy may be required in the setting of ABP. If there is evidence of ampullary obstruction caused by an impacted stone, a needle-knife precut sphincterotomy may need to be performed before stone extraction (Video 1). Otherwise, standard sphincterotomy techniques can be used (Video 2). Bile duct stenting without sphincterotomy may impair pancreatic drainage further, and this should be avoided unless there is evidence of life-threatening cholangitis in the setting of coagulopathy or other contraindication to sphincterotomy.

There may be some rationale for considering pancreatic drainage procedures in addition to biliary sphincterotomy at the time of urgent ERCP. Pancreatic sphincterotomy and/or stenting might augment pancreatic drainage and favorably affect the course of severe ABP. Two studies reported that main pancreatic duct disruptions are found in 30% to 44% of patients with ABP with pancreatic necrosis when ERCP is performed within 1 week of an attack.[84,85] However, early ERCP (within several days) rarely shows a pancreatic duct disruption even when there is extensive pancreatic necrosis.[84] Therefore, the decision of whether to proceed with pancreatic endotherapy cannot be made based on early pancreatography findings. Also, pancreatic instrumentation and stenting generally introduce bacterial colonization and potentially lead to infection of sterile necrosis.[86]

Recent studies have evaluated the safety of pancreatic duct stents in patients with ABP. None of the studies reported increased infections or complications after temporary pancreatic duct placement. However, the risk is primarily in patients with severe necrotizing pancreatitis, and there were limited numbers of such patients in these studies.

Fejes and colleagues[87] evaluated the feasibility and safety of urgent ERCP, defined as within 48 hours of symptom onset, and pancreatic duct stenting with short ($\leq$5 cm) small-caliber (3 or 4 F) stents as a bridging procedure in ABP. Pancreatic stents were placed if biliary cannulation was difficult or failed and/or if sphincterotomy was contraindicated. Consecutive patients (n = 87) with severe ABP had emergency ERCP; 60 underwent ERCP with sphincterotomy and stone extraction (if necessary) without pancreatic duct stenting. The remaining 27 patients had a small-caliber pancreatic stent placed. In the patients who had a pancreatic stent placed, selective biliary access, sphincterotomy, and stone extraction were difficult but successful in 14 of the 27 patients. Cannulation was unsuccessful despite needle-knife precut in 8 patients. The remaining 5 patients had successful cannulation but no sphincterotomy because of poor blood coagulation status. The stents were removed an average of 10 days after the initial ERCP procedure. Patients who had a pancreatic duct stent had a lower overall complication rate (7.4% vs 25%) and fewer complications in those with predicted severe attacks (13% vs 40%).

Another study also suggested that pancreatic duct stenting can be safe and effective in ABP to reduce the incidence of complications.[88] In a nonrandomized fashion, outcomes after pancreatic duct stenting and biliary sphincterotomy were compared with sphincterotomy alone. Patients had ERCP performed within 72 hours from onset of pain. Half the patients had a pancreatic stent insertion (5 Fr, 3–5 cm), with the main indication being a difficult cannulation. All pancreatic duct stents were removed within 10 days after ERCP. The overall complication rate in the stent group (10%) was significantly lower than in the no-stent group (31%).

Guoqian and colleagues[89] reported results from the study of patients with ABP and difficult biliary sphincterotomy who were randomly assigned to a pancreatic stent group or a no-stent group. The stents had internal flanges and were 3 to 5 Fr, and 5 to 7 cm long. All the stents were removed within 1 to 2 weeks. They reported that pancreatic duct stenting in patients with ABP lowered the overall complication rate (8% vs 32%).

Preliminary data on pancreatic duct stenting in ABP suggest that pancreatic duct placement might lead to a decrease the overall complication rate. However, the patients in these studies who received a pancreatic duct stent also had a difficult or failed biliary cannulation and/or sphincterotomy, and thus there may have been indications for prophylactic pancreatic duct stenting. In addition, the numbers of patients with severe necrotizing pancreatitis who have a high risk of introducing infection by placement of a pancreatic stent were limited. More prospective randomized trials to evaluate pancreatic duct stenting in ABP are needed, ideally in patients without difficult ERCP.

When Should Elective ERCP be Considered?

As mentioned earlier, most patients who have ABP have a mild attack that resolves with conservative care. Thus, whether to proceed with cholecystectomy and a preoperative ERCP become common questions. The important variables to consider are the patient's operative risk, the likelihood for choledocholithiasis, and the success and complication profiles of the endoscopist.

Most patients undergo cholecystectomy after recovering from ABP. Intraoperative cholangiography can be performed to determine whether postoperative ERCP is needed, so, in general, there is a limited role for preoperative ERCP. A randomized controlled trial found that selective postoperative ERCP (after positive intraoperative cholangiogram) was more cost-effective than preoperative ERCP in patients with increased risk for bile duct stones who had recovered from mild to moderate ABP.[90] However, it is reasonable to consider preoperative ERCP when a need for endoscopic therapy is strongly suspected based on clinical criteria or imaging studies. Patients who have jaundice might benefit from ERCP to diagnose and treat choledocholithiasis or other biliary tract disorders such as Mirizzi syndrome or ampullary, bile duct, or pancreatic neoplasia. In patients without jaundice, it is helpful to consider the likelihood for a retained common bile duct stone. Multivariate analysis from a prospective study on patients who had ABP found that abnormal total bilirubin on the second hospital day was the best predictor of choledocholithiasis.[91] Choledocholithiasis is uncommon (20%–30%) following a mild attack of ABP.[92,93] A decision analysis compared strategies of intraoperative cholangiography, endoscopic ultrasound, magnetic resonance cholangiopancreatography, and ERCP in patients who had mild ABP.[94] Simple observation and elective cholecystectomy with intraoperative cholangiography was the least expensive option when the probability of choledocholithiasis was less than 15%. EUS was cost-effective for an intermediate probability of choledocholithiasis, whereas ERCP was cost-effective when the probability of choledocholithiasis was greater than 45%.

Cholecystectomy after recovery from ABP remains the standard of care for patients who are good candidates for surgery. However, common sense and existing literature support the practice of sphincterotomy as primary therapy in elderly patients and those who are otherwise unfit to undergo cholecystectomy.[95–97] Outcomes after ERCP with sphincterotomy from case series of patients with ABP are notable for most patients remaining symptom free without the need for cholecystectomy.[80,98,99] A recent large retrospective study compared outcomes for patients treated with

cholecystectomy with or without ERCP versus those treated with ERCP alone. The risk of recurrent pancreatitis after long-term follow-up (6%) was similar for both groups but mean age was 20 years older in the ERCP-alone group. The investigators concluded that ERCP with endoscopic therapy was an appropriate alternative to cholecystectomy in elderly (>75 years old) and in those unfit for surgery.[100]

There are scenarios in which it might be reasonable to consider elective ERCP with endopancreatic therapy in the setting of ABP.[101] Refractory symptoms or smoldering pancreatitis characterized by pain or inability to advance diet may indicate impaired pancreatic ductal drainage caused by duct disruption and/or sphincter of Oddi dysfunction. Imaging studies can be used to diagnose symptomatic acute pancreatic fluid collections or other conditions that may indicate a pancreatic duct disruption such as pleural effusion or pancreatic ascites. There is some promise for secretin-stimulated magnetic resonance cholangiopancreatography for diagnosis of pancreatic duct disruptions.[102] Transpapillary techniques have been used successfully to treat acute pancreatic duct disruptions.[103] However, pancreatic stenting to treat duct disruptions from acute pancreatitis is successful in less than 50% of cases, and may lead to infection of otherwise sterile necrosis in patients with necrotizing pancreatitis.[104]

SUMMARY

Acute pancreatitis is considered an endoscopic emergency when a biliary cause is likely and there is acute cholangitis or ongoing biliary obstruction. Biliary sphincterotomy should be considered in all patients who undergo urgent ERCP for severe ABP, preferably within 48 hours of symptom onset. Elective ERCP should be considered when there is jaundice or proven choledocholithiasis by noninvasive imaging or intraoperative cholangiography. There remains some debate regarding the role of early ERCP in the setting of ABP without evidence of biliary obstruction. Further studies should better establish the indicators for ampullary obstruction and predictors for severe attacks. Additional prospective endoscopic trials are still needed to clarify the optimal timing of biliary intervention, the potential benefit of biliary sphincterotomy in all cases independent of biliary obstruction, and the usefulness of pancreatic stenting.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.giec.2013.06.002.

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