Gallstone Pancreatitis: When Is Endoscopic Retrograde Cholangiopancreatography Truly Necessary?

*Matthias Kraft, MD and Markus M. Lerch, MD, FRCP**

Address
*Department of Medicine B, Westfälische Wilhelms-Universität Münster, Albert-Schweitzer Str. 33, 48129 Münster, Germany.
E-mail: markus.lerch@uni-muenster.de

Current Gastroenterology Reports 2003, **5:**125–132
Current Science Inc. ISSN 1522-8037

Acute pancreatitis is an inflammation of the pancreas that can, in a minority of patients, lead to local complications, multiorgan failure, and death. Gallstones are the most common cause of acute pancreatitis in Western countries. The majority of patients with acute gallstone pancreatitis have mild disease and recover within 3 to 5 days with bed rest and intravenous fluid replacement. In up to 20% of patients, severe pancreatitis develops and can involve pancreatic tissue necrosis and multiorgan failure. Recent advances in the care of patients with gallstone-induced pancreatitis include better severity stratification on hospital admission, more aggressive fluid resuscitation in the early disease course, early use of antibiotics in patients with pancreatic necrosis, a shift from parenteral to enteral feeding regimens, a better defined and less aggressive approach to pancreatic surgery, and the possibility to remove impacted gallstones endoscopically. Urgent endoscopic retrograde cholangiopancreatography and sphincterotomy are recommended in patients with signs of cholangitis or jaundice, ultrasound evidence of dilated common bile duct, or evidence of severe disease.

Introduction

Acute pancreatitis is a disease of significant social impact, with an estimated incidence of approximately 10 cases per 100,000 population per year. The mild form of pancreatitis, which accounts for 75% to 80% of patients, is no longer fatal (mortality < 1%), generally subsides within 3 to 5 days, and benefits from simple symptomatic measures such as initial parenteral fluid supplementation and oral nutrition as early as possible. The severe form is characterized by local and systemic complications, may lead to multiorgan failure, and is burdened with a mortality rate of between 5% and 20%.

Acute pancreatitis can have various causes, of which gallstone disease and excess alcohol consumption account for 80% of patients. In many Western countries biliary pancreatitis is the most frequent disease variety, with reported incidence rates ranging between 16% and 70%. Evidence also suggests that, in a significant proportion of patients who were previously thought to suffer from an idiopathic etiology, microscopic gallstones (microlithiasis or bile crystals) are, in fact, the underlying cause.

In recent years a variety of changes in the management of patients with acute pancreatitis have improved the clinical approach. These improvements include the general availability of contrast-enhanced (dynamic) CT, interventional procedures such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (EST), a better understanding of the underlying pathophysiology of pancreatitis, improved standards of intensive care treatment, and more evidence-based surgical strategies in patients with infected pancreatic necrosis. All of these advances have not, unfortunately, eliminated the mortality of severe pancreatitis (approximately 5%–20%) over the past two decades. According to some multicenter trials, this might be due to the lack of standardized protocols both within and between institutions.

The aim of this article is to outline the principle pathophysiologic mechanisms involved in gallstone-induced pancreatitis, summarize recent developments in the treatment of the disease, and review recent studies that have addressed the question of when endoscopic intervention is required and appropriate.

Etiology and Pathogenesis of Acute Gallstone Pancreatitis

Proposals for a therapeutic approach should, wherever possible, be based on the underlying pathophysiology of a disease. It seems clear today that, in order to cause pancreatitis, gallstones need to migrate through the biliary tract and induce at least a temporary obstruction at the papilla of Vater. By what mechanism an impacted gallstone at the papilla would initiate pancreatitis has long been a matter of debate. In 1856 Bernard [1] discovered that bile is an agent that, when injected into the pancreatic duct of labo-

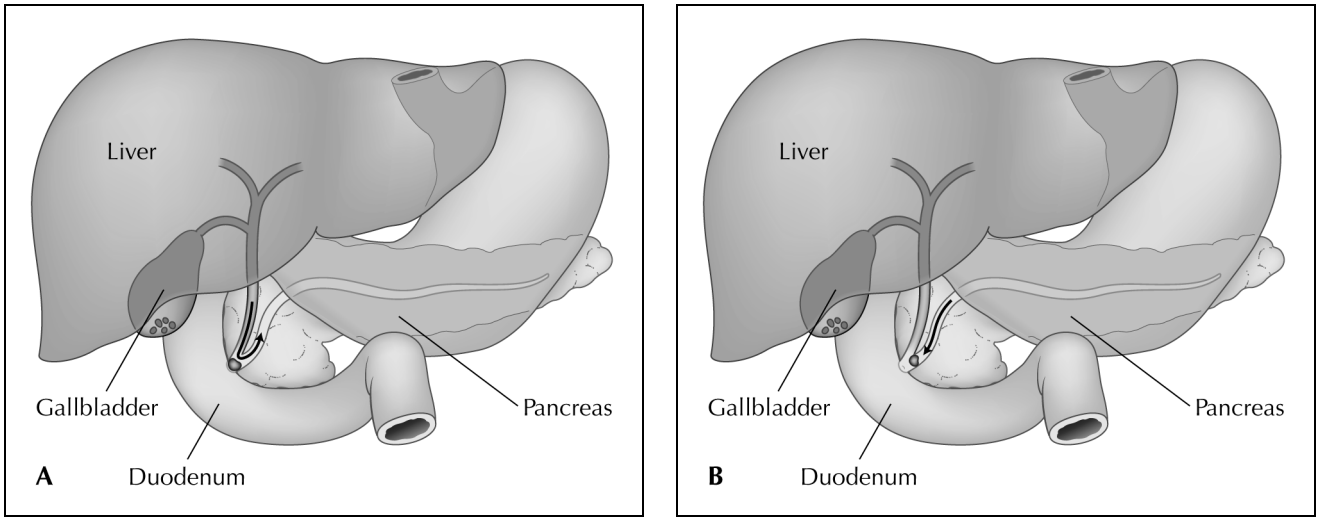

Figure 1. The two "Opie hypotheses" for the pathogenesis of gallstone-induced pancreatitis, both reported in 1901. According to the "common channel" reflux hypothesis (**A**), a gallstone, impacted at the duodenal papilla, creates a communication between the pancreatic duct and the common bile duct. Behind it, bile can flow through this common channel into the pancreatic duct and would trigger the onset of acute pancreatitis. According to the pancreatic duct obstruction hypothesis (**B**), a gallstone on its passage through the biliary tract obstructs the pancreatic duct. The intraductal pressure rises and triggers acinar cell damage that leads to necrosis. Whether the common bile duct is also obstructed is immaterial to the triggering mechanism of pancreatitis but may determine later disease severity. (*Adapted from* Lerch and Adler [50].)

ratory animals, can cause pancreatitis. His experiments represent not only the first systematic attempt at establishing a reproducible animal model of pancreatitis but also have deeply influenced subsequent hypotheses to explain the pathogenesis of the disease. In 1901 Opie [2] postulated that an impaired pancreatic outflow caused by obstruction of the pancreatic duct represents the triggering event of gallstone pancreatitis (Fig. 1). This initial "duct obstruction" hypothesis, however, was rapidly forgotten when Opie published his second "common channel" hypothesis in the same year [3]. This hypothesis predicts that the impacted gallstone would create a communication between the pancreatic duct and the bile duct behind it (the so-called "common channel") through which bile could flow into the pancreas and trigger the onset of pancreatitis. Experimental and clinical evidence, however, appears to be incompatible with these assumptions. Anatomic studies have shown that the communication between the pancreatic duct and the common bile duct is generally much too short (< 6 mm) to permit biliary reflux into the pancreatic duct. An impacted gallstone would therefore be more likely to obstruct both the common bile duct and the pancreatic duct. Even in the event of an existing anatomic communication, pancreatic secretory pressure would still exceed biliary pressure and pancreatic juice would flow into the bile duct rather than bile into the pancreatic duct. Experiments performed on the opossum, an animal model that is anatomically well suited to test the common channel hypothesis, have revealed that neither a common channel nor biliopancreatic reflux is required for the development of acute necrotizing pancreatitis [4]. An alternative hypothesis that can address the inconsistencies of the common channel proposes that reflux of duodenal content into the pancreatic duct through an incompetent sphincter after gallstone passage induces pancreatitis, but this has been conclusively ruled out as the cause of human biliary pancreatitis [5].

In summary, it is now clear that the initial pathophysiologic events during the course of gallstone-induced pancreatitis affect acinar cells [6] and are triggered by obstruction or impairment of flow from the pancreatic duct [7]. Bacterial contamination of bile or reflux of bile into the pancreatic duct is not involved or required for pancreatitis to occur. However, they may represent aggravating factors in the later disease course and could thus determine the severity and prognosis of gallstone pancreatitis.

Diagnostic Procedure for Acute Gallstone Pancreatitis

The diagnosis of acute pancreatitis is based on the cardinal symptoms of abdominal pain in combination with significantly elevated serum amylase (or lipase) activity. The advantages of measuring serum lipase, rather than amylase, are that its activity will remain increased for a longer period and that it is somewhat more specific because no other source of lipase reaches the serum.

The goal of an initial diagnostic workup is to distinguish acute pancreatitis from other life-threatening intra-abdominal conditions that may mimic the clinical symptoms of acute pancreatitis (*eg*, aortic aneurysm, visceral ischemia, or perforated ulcer). A distinction between biliary pancreatitis and other etiologic varieties is more difficult but should be made within 48 to 72 hours after hospital admission to permit effective treatment of the underlying gallstone disease. In patients with a history of recurrent pancreatitis, particularly if

Table 1. Contrast-enhanced CT severity index (CTSI)

CT grade	CT morphology	Score*
A	Normal	0
B	Focal or diffuse gland enlargement; small intrapancreatic fluid collection	1
C	Any of the above plus mild peripancreatic inflammatory changes	2
D	Any of the above plus more prominent peripancreatic fluid collection	3
E	Any of the above plus extensive extrapancreatic fluid collection; pancreatic abscess	4
Add necrosis score to CT score		
Necrosis: none		0
Necrosis: one third		2
Necrosis: one half		4
Necrosis: greater than one half		6
Index	Morbidity, %	Mortality, %
0–3	8	3
4–6	35	6
7–10	92	17

*CTSI = CT grade score + necrosis score (0–10).
Adapted from Balthazar *et al.* [16].

they are under the age of 25 years or have a positive family history of pancreatitis, hereditary pancreatitis associated with trypsinogen mutations must be considered [8••,9,10]. Biochemical findings such as serum amylase or lipase activity three times the upper limit of normal, combined with elevated serum bilirubin and aminotransferase, predict the diagnosis of acute gallstone pancreatitis with an accuracy of about 95 % [11].

An ultrasound examination of the abdomen is probably the most cost-effective and reliable method to detect gallstone disease. Ultrasound is most sensitive for gallbladder stones, but dilation of the common bile duct, the presence of common bile duct stones, or edema and necrosis of the pancreas can also be detected. In addition, such intra-abdominal disorders as aortic aneurysm, appendicitis, and abscess formation can be ruled out by ultrasound. If ultrasound or other imaging techniques deliver equivocal results, ERCP may be required to diagnose bile duct stones, although the utility of ERCP lies in evaluation of the anatomic duct variants or pancreatic and biliary tumors as the underlying cause. In the presence of concomitant ascending cholangitis, ERCP is the therapeutic approach of choice because this group of patients will benefit from rapid bile duct drainage and gallstone clearance. Although ERCP is not required in all patients with pancreatitis, it is the most sensitive method to determine the biliary cause of acute pancreatitis and may detect gallstones in up to 100% of patients when the bile duct is visualized [12]. Bile duct visualization can generally be achieved in 94% to 98% of patients and in 80% of patients with acute pancreatitis [13,14]. Endoscopic cannulation of the pancreatic duct in patients with pancreatitis is not required (unless pancreatic trauma or duct laceration is suspected) but is also not harmful if performed inadvertently.

CT scanning should be performed if the patient is suspected of having pancreatic necrosis [15]. Moreover, a contrast-enhanced (dynamic) CT scan should be done 3 to 10 days from admission in patients suffering from severe acute pancreatitis who do not respond to treatment. Contrast-enhanced CT is the method of choice to detect pancreatic necrosis, peripancreatic or intra-abdominal fluid collections, or infected necrosis. The latter complication, which usually develops between 8 and 20 days after admission, may require rapid surgical intervention [16]. A CT scan without intravenous contrast agent is of so little value in acute pancreatitis that its use cannot be justified.

The role of magnetic resonance cholangiopancreatography (MRCP) in the diagnosis of acute gallstone pancreatitis is not yet defined. With a sensitivity and a positive predictive value of 92% and specificity and negative predictive value of 96%, MRCP has shown accuracy as a diagnostic tool for the detection of gallstones in the common bile duct [17,18]. A more cost-effective alternative for detecting gallstones may be endoscopic ultrasound (EUS) [19]. EUS is discussed further under the heading of Endoscopic Treatment.

Value of Severity Stratification in Acute Gallstone Pancreatitis

Early and accurate severity stratification between patients with mild or severe pancreatitis has shown clinical value for the cost-effective allocation of resources (such as high-dependency and intensive care) as well as for decision making on interventional treatment approaches such as urgent ERCP. Scoring systems have been established using either biochemical parameters or a contrast-enhanced CT-based grading system (Table 1) [16]. Multifactor scoring systems, such as the Ranson or Glasgow score, have predicted severity accurately in 70% to 80% of patients and are comparable with C-reactive protein (CRP) as a prognostic parameter (diagnostic accuracy of 80%) [20,21]. The combination of the Glasgow scoring system with CRP results in better sensitivity and specificity for those patients who develop major clinical complications [22]. Recently, measurement of hematocrit at hospital admission has shown good prognostic value as an indicator of fluid loss and hemoconcentration and is comparable with that of the more complex Ranson and Imrie scores obtained after 48 hours [23••]. The major advantage of this single, easily obtainable, and inexpensive parameter on admission is its high negative predic-

tive value. On the basis of a second study evaluating hematocrit, Lankisch *et al.* [24•] suggest that, in the absence of hemoconcentration, contrast-enhanced CT would be unnecessary on admission and would only be needed if the patient's condition does not improve under therapy.

To assess the severity of the disease and the risk of complication, the Acute Physiology and Chronic Health Evaluation (APACHE II) score has shown utility. Depending on the cut-off level, it will reach a sensitivity of 95% for patients who develop severe complications (cut-off APACHE II score of 6). When the cut-off is raised to 9 points, the APACHE II score will indicate severe attacks with higher specificity, but a significant number of patients who later develop complications will not be detected [25]. If clinical assessment and laboratory markers or severity scores predict a mild clinical course of pancreatitis, imaging studies involving CT scan and magnetic resonance imaging (MRI) are generally not required. Nevertheless, in patients with severe pancreatitis, contrast-enhanced CT may be needed to assess the complications from or the extent of pancreatic necrosis [16].

Conservative Treatment

The standards in conservative treatment of acute gallstone-induced pancreatitis have recently been reviewed in detail [26,27] and are therefore only summarized here. It is now believed that the most critical intervention in the early phase of acute pancreatitis is immediate and aggressive fluid resuscitation. This practice has significantly reduced the number of patients with early organ failure and is also believed (but not yet proven) to prevent progression from mild to severe necrotizing pancreatitis. The requirement for fluid replacement, which is consistently underestimated by emergency physicians, can amount to more than 10 L in 24 hours and is best assessed by measuring central venous pressure or hematocrit (which should ideally be lowered to 35%). The most immediate concern for the patient is often excruciating pain. The most effective strategies for pain control are self-administered analgesics by peridural catheter (which also greatly reduces the incidence of pancreatitis-associated ileus) and systemic opiates. The reluctance to treat patients with pancreatitis using opiates is rationalized by physiologic studies on sphincter of Oddi function but is completely unsubstantiated by clinical evidence, and morphine can be used safely for pancreatitis pain [26]. A paradigm shift has recently occurred in the approach to nutritional support of patients with severe pancreatitis. Enteral feeding by intrajejunal or intragastric feeding tube is more cost-effective (and possibly more clinically beneficial) than intravenous nutrition [26,27]. Antibiotics are not required for patients with mild pancreatitis but are effective in preventing infected necrosis in patients with severe pancreatitis. Whether second-generation cephalosporins, aminoacyl penicillins, carbipenems, or quinolones are more cost-effective has not been determined by comparative studies.

Endoscopic Treatment

Although it is generally accepted that an impacted gallstone at the papilla in a patient with acute pancreatitis should be removed—and is most effectively removed by EST—opinions vary about which patients benefit from the procedure, based on which diagnostic criteria allow them to be identified and how urgently an intervention is needed. In the vast majority of patients with biliary pancreatitis the offending gallstone has already passed into the gut when the patient is admitted to the hospital. Some studies suggest that all patients with pancreatitis in whom clinical, laboratory, or imaging studies suggest an involvement of gallstones in the pathogenesis of pancreatitis should undergo ERCP as soon as possible (preferably within 24 to 72 hours after symptom onset) [28,29]. Although this policy clearly may reduce the morbidity and complication rate from concomitant cholangitis, whether the course of pancreatitis in itself is directly affected remains unclear.

In a prospective, randomized single-center trial by Neoptolemos *et al.* [13] in the UK, 121 patients with suspected biliary acute pancreatitis were enrolled and stratified into groups with mild or severe disease within 48 hours after admission. Patients received ERCP, and, when bile duct stones were found, EST, within 72 hours of admission. No significant difference in the overall mortality and complication rate was found, but in the subgroup of patients with predicted severe pancreatitis a reduction in the complication rate was reported when ERCP was performed. Neoptolemos *et al.* [13] concluded that any evidence for a biliary cause should prompt urgent ERCP in patients with pancreatitis. In a prospective single-center study by Fan *et al.* [28], patients were randomly assigned to receive ERCP within 24 hours after admission irrespective of etiology. In the treatment group, EST was only performed when detectable gallstones were found. In the control group ERCP was not done unless the clinical condition had deteriorated. These authors recommend that ERCP with EST should be performed as an emergency procedure only in patients with severe or complicated acute pancreatitis [28]. In a recent prospective multicenter trial by Fölsch *et al.* [14], 235 patients underwent ERCP and ESP within 72 hours after the onset of abdominal pain. In patients with acute biliary pancreatitis without jaundice (serum bilirubin levels < 5 mg/dL), early ERCP and EST had no benefit. According to these authors, ERCP in combination with EST is only required as an emergency procedure in patients with pancreatitis who have signs of bile duct obstruction. The differences in the results of the German and associated UK trials may be based on their inclusion criteria, which vary in some important details (Table 2). The studies by Neoptolemos *et al.* [13] and Fan *et al.* [28] included patients with biliary complications such as obstructive jaundice and acute cholangitis, whereas this subgroup was excluded from the study by Fölsch *et al.* [14] because they had already been shown to benefit from ERCP and EST. In addition, early intervention by ERCP decreased the incidence

Table 2. Comparison of mortality and complication rates in acute gallstone pancreatitis correlated with performance of ERCP and EST

				Mortality, %			Complications, %		
Study	**Cause**	**Time of ERC/EST**	**Indication for EST**	**Severity**	**Control**	**ERCP**	**Severity**	**Control**	**ERCP**
Neoptolemos *et al.* [13]	Biliary	Within 72 hours of admission	Impacted gallstone	Mild Severe	0 18	0 4	Mild Severe	12 61	12 24
Fan *et al.* [28]	Any	Within 24 hours of admission	Impacted gallstone	Mild Severe	0 3	0 13	Mild Severe	17 54	18 13
Nowac *et al.* [29]	Biliary	Within 24 hours of admission	Always on ERCP	ND	3	13	ND	17	36
Fölsch *et al.* [14]	Biliary	Within 72 hours after onset of pain	Impacted gallstone	ND	6	11	ND	51	46

ERCP—endoscopic retrograde cholangiopancreatography; EST—endoscopic sphincterotomy; ND—not determined.

of biliary complications but had no impact on local or systemic complications of acute pancreatitis in the studies by Fölsch *et al.* [14] and Fan *et al.* [28].

Given the fact that EST is associated with a significant proportion of early (5%–10%) and late complications (5%–25%), depending on the experience of the investigator and the case load of the endoscopy unit, a more restrictive indication for emergency ERCP seems justified [26,27,30–32] and may take individual risk factors of the patient into account [33•]. At our institution we recommend and perform emergency ERCP and EST on patients with acute pancreatitis and gallstone disease who have signs of biliary obstruction based on laboratory or imaging studies or who have signs of severe gallstone pancreatitis. For other patients with biliary pancreatitis, the decision of whether and when to perform ERCP is based on the subsequent clinical course.

Although transcutaneous ultrasound is a sensitive and specific method for detection of gallbladder stones and gross dilation of the common bile duct, the detection rate for small stones at the papilla is poor. EUS, with its much higher resolution, is therefore suggested for imaging in patients with suspected gallstone pancreatitis. A comparison of the specificity, sensitivity, and accuracy of EUS, ERCP, and ultrasound in the detection of common bile duct stones based on results from two recent studies is presented in Table 3. Because of its high diagnostic accuracy, performance of EUS immediately before ERCP has been suggested as a strategy for detecting choledocholithiasis while concomitantly lowering the complication rate [34,35]. In a recent retrospective and prospective analysis by Prat *et al.* [36•] that included 123 patients from nine centers, EST was selectively performed in patients with EUS evidence for intraductal gallstones. In 33 patients, EST was performed immediately after the detection of stones by EUS and in the same endoscopy session. A positive correlation between the presence of common bile duct stones and the occurrence of cholangitis and jaundice was found but, surprisingly, no correlation between disease severity and presence of gallstones could be observed. The timing of EUS and EST (whether performed within 72 hours of admission or later) and the presence or absence of bile duct stones had no effect on the subsequent course of pancreatitis.

In our opinion, the answer to the question of whether to perform EUS before ERC depends on such practical issues as whether the endoscopist called in at night to see a patient with gallstone pancreatitis is equally experienced in both procedures (chances are he or she is not), whether in a patient with laboratory evidence of biliary obstruction the endoscopist would not perform ERCP if EUS does not detect gallstones (we would still perform the ERCP in a jaundiced patient if the EUS were negative), or whether in a patient without laboratory signs of biliary obstruction the endoscopist would consider emergency ERCP in the first place (we would not unless the patient has severe pancreatitis and we have other imaging evidence of bile duct stones).

The indication for EUS before ERC thus depends very much on institutional and personal expertise, and future studies may make this practice more compelling. We recommend emergency ERCP and EST for patients with acute gallstone pancreatitis who have signs of biliary obstruction or cholangitis based on laboratory or imaging studies or in whom clinical, imaging, or laboratory parameters predict a severe course of biliary pancreatitis. When multiple stones cannot be safely removed from the common bile duct after EST, placement of a bile duct stent is an effective alternative treatment of cholangitis that also is preventive against pancreatitis in high-risk patients [37].

Table 3. Comparison of US, ERCP, and EUS detection of choledocholithiasis in patients with acute pancreatitis

			Sensitivity, %			Specifity, %			Overall accuracy, %		
Study*	Patients, *n*	Time of ERCP	US	ERCP	EUS	US	ERCP	EUS	US	ERCP	EUS
Chak *et al*. [35]	36	Within 72 hours of admission	50	92	91	100	97	100	83	89	97
Liu *et al*. [34]	100	Within 24 hours of admission	26	97	97	100	95	98	75	96	98

*The presence of gallbladder stones was confirmed by direct inspection of gallbladder contents whenever cholecystectomy was performed. The presence of choledocholithiasis was assessed by comparing ERCP and EUS.
ERCP—endoscopic retrograde cholangiopancreatography; EUS—endoscopic ultrasound; US—ultrasound.

Surgical Treatment

Because of the high recurrence rate of pancreatitis (up to 45%) in patients who are discharged from the hospital without cholecystectomy after an episode of gallstone pancreatitis, definitive treatment for gallstone disease is highly recommended [27]. Recurrent bile duct calculi have been reported in 2% to 6% of patients after EST. The subsequent clinical course of patients whose gallbladder is left in situ following successful endoscopic removal of stones from the common bile duct remains controversial. Although the number of gallstone carriers who develop pancreatitis is small and ranges from 3% to 8% [38], stones of less than 5 mm in diameter increase the risk of developing acute pancreatitis fourfold [39]. Also, the risk of acute pancreatitis in patients with gallstone disease is reported to be reduced to that of the normal population following cholecystectomy [40]. From the 1960s to the 1980s, early surgical intervention was recommended and found to be associated with a reduced mortality rate [41]. A prospective investigation by Kelly and Wagner [42] in 1988 comparing early and late cholecystectomy in 165 patients with acute gallstone pancreatitis demonstrated decreased morbidity and mortality for delayed surgery, leading to the recommendation that cholecystectomy should be postponed until pancreatitis has subsided. According to the guidelines of the British Society of Gastroenterology, patients with mild gallstone pancreatitis should receive definitive management of their gallstone disease within 2 to 4 weeks after recovery from an episode of acute pancreatitis [43]. Uhl *et al*. [44••] recommend that laparoscopic cholecystectomy should be performed earlier, 5 to 7 days after the onset of mild or edematous acute pancreatitis. These data are congruent with the recommendation by the National Institutes of Health Consensus Conference that cholecystectomy in mild acute gallstone pancreatitis should be performed 5 to 6 days after disease onset. One reason to postpone surgical cholecystectomy in acute gallstone pancreatitis until day 4 or 5 is the observation that severe pancreatitis with pancreatic necrosis is usually fully established after approximately 4 days [45]. Cholecystectomy before day 4, even in mild or edematous pancreatitis, is therefore not recommended, because the rate of complications may still rise. A recently published study by Sargen and Kingsnorth [46] analyzed the effect of deviating from these clinical guidelines and concluded that such deviation would result in high rates of hospital readmission. In patients with severe or necrotizing acute pancreatitis, cholecystectomy should be performed 7 to 21 days after onset, provided that the episode of pancreatitis has subsided (Fig. 2). In elderly high-risk patients with gallstone-induced pancreatitis, EST removal of stones from the common bile duct may be sufficient [47]. Whether placement of a pancreatic duct stent concomitantly with EST, which has been reported to lower post-ERCP pancreatitis rates [48,49], is beneficial for patients who undergo EST for biliary pancreatitis is doubtful and needs further evaluation. An algorithm for the treatment of acute gallstone pancreatitis is presented in Figure 2.

Conclusions

The diagnosis of acute pancreatitis should be established within 48 hours after onset of symptoms or hospital admission. Early identification of a biliary cause is recommended using clinical, laboratory, and imaging studies. In patients with severe pancreatitis, a contrast-enhanced CT scan or MRI may be required to detect complications and the extent of pancreatic necrosis. Signs of biliary obstruction, sepsis, and severe gallstone pancreatitis should prompt urgent ERCP. EST is the treatment of choice in patients with bile duct or papillary stones. For patients with gallstones, cholecystectomy should be performed within 5 to 7 days after onset of mild pancreatitis and within 3 to 4 weeks in patients with severe pancreatitis. Intra-abdominal fluid collection in a patient with signs of sepsis or systemic inflammatory response syndrome should raise the suspicion of an infected necrosis or abscess. This severe complication of pancreatitis may require rapid surgical intervention for necrosectomy and must be ruled out by imaging-guided fine-needle aspiration and gram-stain and bacterial culture.

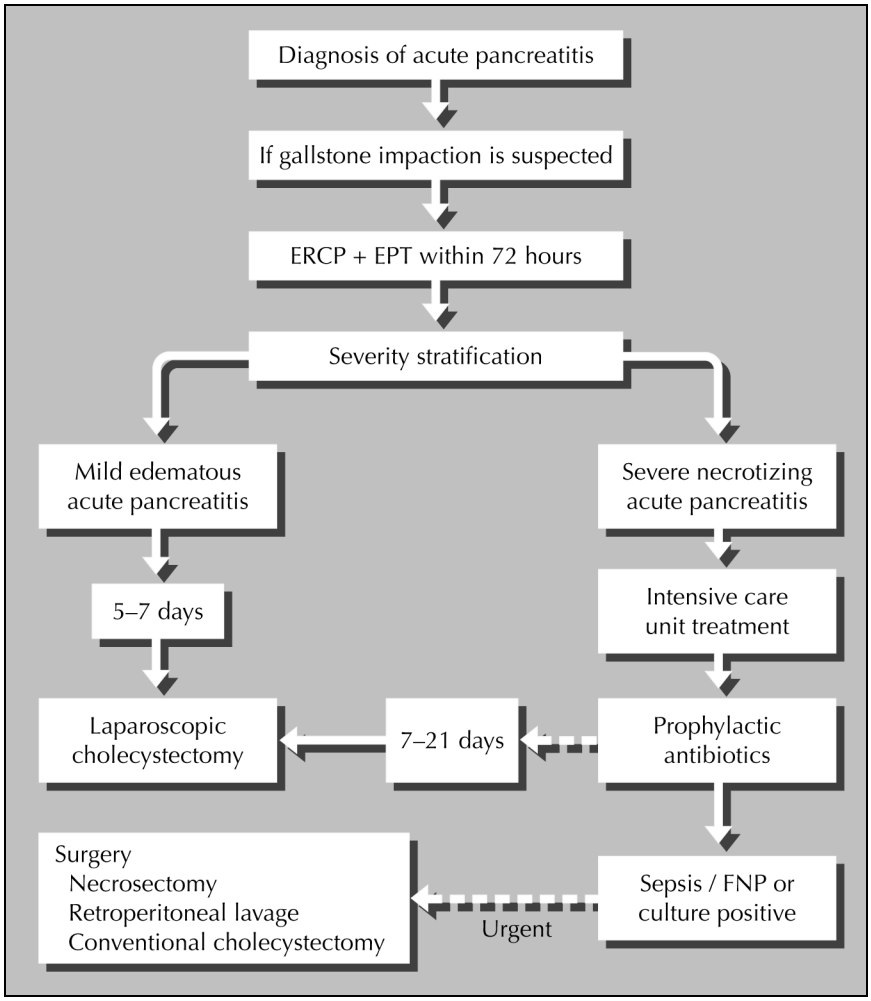

Figure 2. Algorithm for therapeutic approach to acute gallstone pancreatitis. FNP—fine-needle puncture. (*Adapted from* Uhl *et al.* [44••].)

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Bernard C: **Lecons de physiologie experimentale.** *Paris Bailliere* 1856, **2:**758.
2. Opie E: **The relation of cholelithiasis to disease of the pancreas and to fat necrosis.** *Johns Hopkins Hosp Bull* 1901, **12:**19–21.
3. Opie E: **The etiology of acute hemorrhagic pancreatitis.** *Johns Hopkins Hosp Bull* 1901, **12:**182–188.
4. Lerch MM, Saluja AK, Runzi M, *et al.*: **Pancreatic duct obstruction triggers acute necrotizing pancreatitis in the opossum.** *Gastroenterology* 1993, **104:**853–861.
5. Hernandez CA, Lerch MM: **Sphincter stenosis and gallstone migration through the biliary tract.** *Lancet* 1993, **341:**1371–1373.
6. Lerch MM, Saluja AK, Dawra R, *et al.*: **Acute necrotizing pancreatitis in the opossum: earliest morphological changes involve acinar cells.** *Gastroenterology* 1992, **103:**205–213.
7. Lerch MM, Weidenbach H, Hernandez CA, *et al.*: **Pancreatic outflow obstruction as the critical event for human gall stone induced pancreatitis.** *Gut* 1994, **35:**1501–1503.
8. •• Whitcomb DC, Gorry MC, Preston RA, *et al.*: **Post-hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene.** *Nat Genet* 1996, **14:**141–145.

The first report of defined germline mutations (in the cationic trypsinogen gene) associated with hereditary pancreatitis.

9. Simon P, Weiss FU, Sahin-Toth M, *et al.*: **Hereditary pancreatitis caused by a novel PRSS1 mutation (Arg-122 --> Cys) that alters autoactivation and autodegradation of cationic trypsinogen.** *J Biol Chem* 2002, **277:**5404–5410.
10. Simon P, Weiss FU, Rand S, *et al.*: **Spontaneous and sporadic trypsinogen mutations in patients with idiopathic pancreatitis.** *JAMA* 2002, **288:**2122.
11. Steinberg WM, Goldstein SS, Davis ND, *et al.*: **Diagnostic assays in acute pancreatitis: a study of sensitivity and specificity.** *Ann Intern Med* 1985, **102:**576–580.
12. Scholmerich J, Lausen M, Lay L, *et al.*: **Value of endoscopic retrograde cholangiopancreatography in determining the cause but not course of acute pancreatitis.** *Endoscopy* 1992, **24:**244–247.
13. Neoptolemos JP, Carr-Locke DL, London NJ, *et al.*: **Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones.** *Lancet* 1988, **2:**979–983.
14. Fölsch UR, Nitsche R, Ludtke R, *et al.*: **Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis.** *N Engl J Med* 1997, **336:**237–242.
15. Hill MC, Huntington DK: **Computed tomography and acute pancreatitis.** *Gastroenterol Clin North Am* 1990, **19:**811–842.
16. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH: **Acute pancreatitis: value of CT in establishing prognosis.** *Radiology* 1990, **174:**331–6.
17. Albert JG, Riemann JF: **ERCP and MRCP: when and why.** *Best Pract Res Clin Gastroenterol* 2002, **16:**399–419.

18. Brisbois D, Plomteux O, Nchimi A, *et al.*: **Value of MRCP for detection of choledocholithiasis in symptomatic patients: one-year experience with a standardized high resolution breath-hold technique.** *JBR-BTR* 2001, **84:**258–261.
19. Arguedas MR, Dupont AW, Wilcox CM: **Where do ERCP, endoscopic ultrasound, magnetic resonance cholangiopancreatography, and intraoperative cholangiography fit in the management of acute biliary pancreatitis? A decision analysis model.** *Am J Gastroenterol* 2001, **96:**2892–289.
20. Ranson JH, Rifkind KM, Roses DF, *et al.*: **Prognostic signs and the role of operative management in acute pancreatitis.** *Surg Gynecol Obstet* 1974, **139:**69–81.
21. Wilson C, Heads A, Shenkin A, Imrie CW: **C-reactive protein, antiproteases and complement factors as objective markers of severity in acute pancreatitis.** *Br J Surg* 1989, **76:**177–181.
22. Imrie CW: **Prognosis of acute pancreatitis.** *Ann Ital Chir* 1995, **66:**187–189.
23.•• Brown A, Orav J, Banks PA: **Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis.** *Pancreas* 2000, **20:**367–372.

The first study showing the predictive value of a high hematocrit on admission for the clinical course of acute pancreatitis. Failure to rapidly decrease the hematocrit by aggressive fluid replacement had a further negative effect on prognosis.

24.• Lankisch PG, Mahlke R, Blum T, *et al.*: **Hemoconcentration: an early marker of severe and/or necrotizing pancreatitis? A critical appraisal.** *Am J Gastroenterol* 2001, **96:**2081–2085.

This prospective study included 316 patients with a first attack of acute pancreatitis. The authors concluded that the prognostic value of hemoconcentration is comparable to the more complicated Ranson and Imrie scores. Its major value is its high negative predictive value. In the absence of hemoconcentration, contrast-enhanced CT may be unnecessary on admission.

25. Wilson C, Heath DI, Imrie CW: **Prediction of outcome in acute pancreatitis: a comparative study of APACHE II, clinical assessment and multiple factor scoring systems.** *Br J Surg* 1990, **77:**1260–1264.
26. Tham TC, Lichtenstein DR: **Gallstone pancreatitis.** *Curr Treat Opt Gastroenterol* 2002, **5:**355–363.
27. Toouli J, Brooke-Smith M, Bassi C, *et al.*: **Guidelines for the management of acute pancreatitis.** *J Gastroenterol Hepatol* 2002, **17(Suppl):**S15–S39.
28. Fan ST, Lai EC, Mok FP, *et al.*: **Early treatment of acute biliary pancreatitis by endoscopic papillotomy.** *N Engl J Med* 1993, **328:**228–232.
29. Nowak A, Nowakowska-Dulawa E, Marek TA, Rybicka J: **Final results of the prospective, randomized, controlled study of endoscopic versus conventional management in acute biliary pancreatitis [abstract].** *Gastroenterology* 1995, **108:**A380.
30. Freeman ML: **Complications of endoscopic biliary sphincterotomy: a review.** *Endoscopy* 1997, **29:**288–297.
31. Leese T, Neoptolemos JP, Carr-Locke DL: **Successes, failures, early complications and their management following endoscopic sphincterotomy: results in 394 consecutive patients from a single centre.** *Br J Surg* 1985, **72:**215–219.
32. Ell C, Rabenstein T, Schneider HT, *et al.*: **Safety and efficacy of pancreatic sphincterotomy in chronic pancreatitis.** *Gastrointest Endosc* 1998, **48:**244–249.
33.• Freeman ML, DiSario JA, Nelson DB, *et al.*: **Risk factors for post-ERCP pancreatitis: a prospective, multicenter study.** *Gastrointest Endosc* 2001, **54:**425–434.

This comprehensive study concluded that patient-related factors are as important as procedure-related factors for the risk of post-ERCP pancreatitis.

34. Liu CL, Lo CM, Chan JK, *et al.*: **Detection of choledocholithiasis by EUS in acute pancreatitis: a prospective evaluation in 100 consecutive patients.** *Gastrointest Endosc* 2001, **54:**325–330.
35. Chak A, Hawes RH, Cooper GS, *et al.*: **Prospective assessment of the utility of EUS in the evaluation of gallstone pancreatitis.** *Gastrointest Endosc* 1999, **49:**599–604.
36.• Prat F, Edery J, Meduri B, *et al.*: **Early EUS of the bile duct before endoscopic sphincterotomy for acute biliary pancreatitis.** *Gastrointest Endosc* 2001, **54:**724–729.

In this trial EST was selectively performed after EUS detection of bile duct stones in 123 patients. The results show that the mortality and complication rate of EST is low and unrelated to the predicted severity of biliary pancreatitis or the presence of bile duct stones.

37. Chopra KB, Peters RA, O'Toole PA, *et al.*: **Randomised study of endoscopic biliary endoprosthesis versus duct clearance for bileduct stones in high-risk patients.** *Lancet* 1996, **3 48:**791–793.
38. Moreau JA, Zinsmeister AR, Melton LJ III, DiMagno EP: **Gallstone pancreatitis and the effect of cholecystectomy: a population-based cohort study.** *Mayo Clin Proc* 1988, **63:**466–473.
39. Diehl AK, Holleman DR Jr, Chapman JB, *et al.*: **Gallstone size and risk of pancreatitis.** *Arch Intern Med* 1997, **157:**1674–1678.
40. Acosta JM, Rossi R, Galli OM, *et al.*: **Early surgery for acute gallstone pancreatitis: evaluation of a systematic approach.** *Surgery* 1978, **83:**367–370.
41. Frei GJ, Frei VT, Thirlby RC, McClelland RN: **Biliary pancreatitis: clinical presentation and surgical management.** *Am J Surg* 1986, **151:**170–175.
42. Kelly TR, Wagner DS: **Gallstone pancreatitis: a prospective randomized trial of the timing of surgery.** *Surgery* 1988, **4:**600–605.
43. **United Kingdom guidelines for the management of acute pancreatitis. British Society of Gastreoenterology.** *Gut* 1998, **42:**S1–S13.
44.•• Uhl W, Muller CA, Krahenbuhl L, *et al.*: **Acute gallstone pancreatitis: timing of laparoscopic cholecystectomy in mild and severe disease.** *Surg Endosc* 1999, **13:**1070–1076.

Based on this study, laparoscopic cholecystectomy with preoperative endoscopic common bile duct clearance is recommended as definitive treatment for gallstone disease in patients with biliary acute pancreatitis. In mild disease, choleystectomy can be performed safely within 7 days, whereas in severe disease with extended pancreatic necrosis at least 3 weeks should elapse because of an increased risk of infection.

45. Isenmann R, Buchler M, Uhl W, *et al.*: **Pancreatic necrosis: an early finding in severe acute pancreatitis.** *Pancreas* 1993, **8:**358–361.
46. Sargen K, Kingsnorth AN: **Management of gallstone pancreatitis: effects of deviation from clinical guidelines.** *JOP* 2001, **2:**317–322.
47. Boytchev I, Pelletier G, Prat F, *et al.*: **Late biliary complications after endoscopic sphincterotomy for common bile duct stones in patients older than 65 years of age with gallbladder in situ [in French].** *Gastroenterol Clin Biol* 2000, **24:**995–1000.
48. Fogel EL, Eversman D, Jamidar P, *et al.*: **Sphincter of Oddi dysfunction: pancreaticobiliary sphincterotomy with pancreatic stent placement has a lower rate of pancreatitis than biliary sphincterotomy alone.** *Endoscopy* 2002, **34:**280–285.
49. Devereaux BM, Sherman S, Lehman GA: **Sphincter of Oddi (pancreatic) hypertension and recurrent pancreatitis.** *Curr Gastroenterol Rep* 2002, **4:**153–9.
50. Lerch MM, Adler G: **Experimental pancreatitis.** *Curr Opin Gastroenterol* 1993, **9:**752–759.