Review Article

Current Concepts

ACUTE NECROTIZING PANCREATITIS

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ACUTE pancreatitis may be clinically mild or severe. Severe acute pancreatitis is usually a result of pancreatic glandular necrosis. The morbidity and mortality associated with acute pancreatitis are substantially higher when necrosis is present, especially when the area of necrosis is also infected.[1] It is important to identify patients with pancreatic necrosis so that appropriate management can be undertaken. In recent years, the treatment of these patients has shifted away from early surgical débridement ("necrosectomy") to aggressive intensive medical care, with specific criteria for operative and nonoperative intervention.[2,3] Advances in radiologic imaging and aggressive medical management with emphasis on the prevention of infection have allowed prompt identification of complications and improvement in outcome for these patients.[4] This article reviews recent advances in the diagnosis and treatment of acute necrotizing pancreatitis.

PRESENTATION AND CLASSIFICATION

Acute pancreatitis usually has a rapid onset manifested by upper abdominal pain, vomiting, fever, tachycardia, leukocytosis, and elevated serum levels of pancreatic enzymes. The causes of acute necrotizing pancreatitis are listed in Table 1. Gallstones and alcohol abuse are the most common causes in the United States.

Several severity-of-illness classifications for acute pancreatitis are used to identify patients at risk for complications.[5] Ranson's score is based on 11 clinical signs with prognostic importance; 5 are measured at the time of admission and the other 6 in the first 48 hours after admission (Table 2). The number of Ranson signs is correlated with the incidence of systemic complications and the presence of pancreatic necrosis.[5] The Acute Physiology and Chronic Health Evaluation (APACHE II) score is based on 12 physiologic variables, the patient's age, and any history of severe organ-system insufficiency or immunocompromised state[5] (Table 2). It allows classification of illness severity on admission and may be recalculated daily. Severe acute pancreatitis is diagnosed if three or more of Ranson's criteria are present, if the APACHE II score is 8 or more, or if one or more of the following are present: shock, renal insufficiency, and pulmonary insufficiency.[5]

TABLE 1. CAUSES OF ACUTE NECROTIZING PANCREATITIS.

Most common
Choledocholithiasis
Ethanol abuse
Idiopathic
Less common
Endoscopic retrograde cholangiopancreatography
Hyperlipidemia (types I, IV, and V)
Drugs
Pancreas divisum
Abdominal trauma
Least common
Hereditary (familial)

Acute pancreatitis may be classified histologically as interstitial edematous or as necrotizing according to the inflammatory changes in the pancreatic parenchyma.[6] The International Symposium on Acute Pancreatitis in 1992 defined pancreatic necrosis as the presence of one or more diffuse or focal areas of nonviable pancreatic parenchyma (Fig. 1).[6] Pancreatic glandular necrosis is usually associated with necrosis of peripancreatic fat.[6-8] By definition, pancreatic necrosis represents a severe form of acute pancreatitis.[6] Necrosis is present in approximately 20 to 30 percent of the 185,000 new cases of acute pancreatitis per year in the United States.[9,10]

RECOGNITION OF PANCREATIC NECROSIS

Pancreatic necrosis may be identified pathologically at surgery or autopsy. Pancreatic necrosis is diagnosed radiographically by dynamic intravenous contrast-enhanced computed tomography (CT) of the abdomen.[7] Because the normal pancreatic microcirculation is disrupted during acute necrotizing pancreatitis, affected portions of the pancreas do not show normal contrast enhancement (Fig. 1).[11] The lack of normal contrast enhancement may be better detected

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TABLE 2. IMPORTANT CONCEPTS IN THE MANAGEMENT OF ACUTE PANCREATITIS.*

Recognition of clinically severe acute pancreatitis
Ranson's score ≥3 (Ranson's criteria of severity: at admission — age >55 yr, white-cell count >16,000/mm³, blood glucose >200 mg/dl (11.1 mmol/liter), serum LDH >350 IU/liter, and serum AST >250 IU/liter; during initial 48 hr — absolute decrease in hematocrit >10%, increase in blood urea nitrogen >5 mg/dl (1.8 mmol/liter), serum calcium <8 mg/dl (2 mmol/liter), arterial PaO_2 <60 mm Hg, base deficit >4 mmol/liter, and fluid sequestration >6 liters)
APACHE II score ≥8
Organ failure
Substantial pancreatic necrosis (at least 30% glandular necrosis according to contrast-enhanced CT)
Intensive care unit management for clinically severe acute pancreatitis
Supportive care
Antibiotics for radiographically documented pancreatic necrosis
Strong consideration of endoscopic retrograde cholangiopancreatography for gallstone pancreatitis when jaundice or cholangitis is present
Nutritional support (enteral feeding by nasoenteric tube beyond the ligament of Treitz, in the absence of substantial ileus)
Identification of infected necrosis
CT or sonographically guided fine-needle aspiration
Débridement of infected necrosis
Operative management
Alternative techniques of débridement (percutaneous or endoscopic) in selected centers with expertise

*LDH denotes lactate dehydrogenase, PaO_2 the partial pressure of arterial oxygen, and AST aspartate aminotransferase. Ranson's criteria and the APACHE II scoring system are described by Banks.[5]

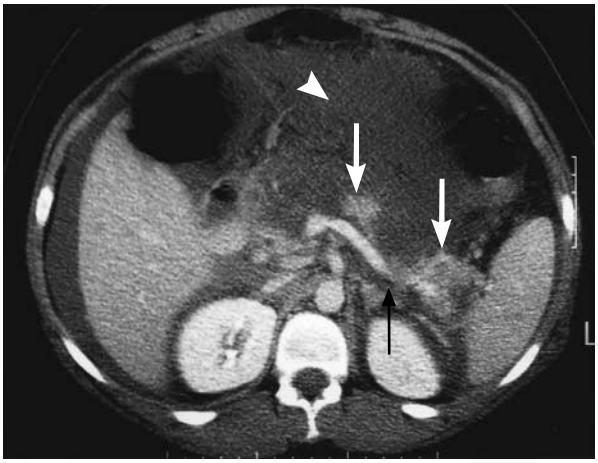

Figure 1. Pancreatic Necrosis.

A dynamic helical contrast-enhanced abdominal CT scan through the pancreas reveals focal low-attenuation areas of pancreatic glandular necrosis in a patient with severe acute gallstone pancreatitis. Residual contrast-enhanced pancreatic tissue (white arrows) is seen anterior to the splenic vein (black arrow). A collection of fluid showing low attenuation extends from the region of the pancreas into the transverse mesocolon (arrowhead).

several days after initial clinical presentation. Contrast-enhanced abdominal CT is the gold standard for the noninvasive diagnosis of pancreatic necrosis, with an accuracy of more than 90 percent when there is more than 30 percent glandular necrosis.[7] The presence of radiographically detected pancreatic necrosis markedly increases the morbidity and mortality associated with acute pancreatitis. In a prospective study, 88 patients with acute pancreatitis underwent contrast-enhanced abdominal CT.[12] Those with pancreatic necrosis had a morbidity of 82 percent and a mortality of 23 percent, whereas those without necrosis had a morbidity of 6 percent and a mortality of 0 percent. As the percentage of glandular necrosis increased, the morbidity increased.

The overall mortality in severe acute pancreatitis is approximately 30 percent.[10] Deaths occur in two phases. Early deaths (those that occur one to two weeks after the onset of pancreatitis) are due to multisystem organ failure caused by the release of inflammatory mediators and cytokines.[1] Late deaths result from local or systemic infection. As long as acute necrotizing pancreatitis remains sterile, the overall mortality is approximately 10 percent. The mortality rate at least triples if there is infected necrosis.[9] In addition, patients with sterile necrosis and high severity-of-illness scores (Ranson's or APACHE II scores) accompanied by multisystem organ failure, shock, or renal insufficiency have significantly higher mortality.[13]

A myriad of systemic and local complications of acute necrotizing pancreatitis may occur. Systemic complications have been described elsewhere[14] and include acute respiratory distress syndrome, acute renal failure, shock, coagulopathy, hyperglycemia, and hypocalcemia. Local complications include gastrointestinal bleeding, infected necrosis, and adjacent bowel necrosis. Late local complications that may require therapy include pancreatic abscesses and pancreatic pseudocysts. Early management of acute necrotizing pancreatitis consists of the combination of intensive medical care and prevention of infection with prophylactic antibiotics. Late management involves treatment of local infectious complications (pancreatic infection) and aggressive débridement. Infected necrosis develops in 30 to 70 percent of patients with acute necrotizing pancreatitis and accounts for more than 80 percent of deaths from acute pancreatitis.[1,3] The risk of infected necrosis increases with the amount of pancreatic glandular necrosis and the time from the onset of acute pancreatitis, peaking at three weeks.[1,3]

MANAGEMENT OF INFECTION

Early studies of antibiotics in patients with acute pancreatitis failed to demonstrate a significant benefit because they included both patients with interstitial edematous acute pancreatitis and patients with acute necrotizing pancreatitis.[14] Since the development of infected necrosis substantially increases mortality among patients with acute necrotizing pancreatitis,[3] prevention of infection is critical. In experimental models of acute necrotizing pancreatitis, pancreatic

infection occurs primarily as a result of bacterial spread from the colon.[15] Several studies in animals have demonstrated a decrease in pancreatic infection and mortality with the use of either oral antibiotics to decontaminate the gut selectively or intravenous antibiotics with high pancreatic-tissue penetration.[15-17] Similarly, studies in humans have shown benefits from both systemic antibiotics and selective gut decontamination.[18-22] In a recent prospective trial, the incidence of gram-negative pancreatic infection and late mortality (deaths more than two weeks after the onset of pancreatitis) were significantly reduced in patients with necrotizing pancreatitis who were treated with selective gut decontamination.[19,20]

Because the antibiotics used for selective gut decontamination must be administered both orally and rectally, this regimen requires substantial nursing time. The use of systemic antibiotics for the prevention of pancreatic infection seems more practical. Early prospective studies showed a significant reduction in the incidence of pancreatic infection in patients receiving intravenous imipenem–cilastatin, although a reduction in mortality was not demonstrated.[21] A recent retrospective study of patients with pancreatic necrosis and severe acute pancreatitis found a significant reduction in the incidence of pancreatic infection, with a trend toward decreasing mortality, among 75 patients who received intravenous imipenem–cilastatin, as compared with historical controls.[22] Theoretically, fluoroquinolones should offer excellent protection against the infection of necrosis. However, in a recent randomized, prospective trial, patients treated with pefloxacin had an incidence of infected necrosis that was significantly higher than that among patients receiving imipenem (34 percent vs. 10 percent).[23] At the present time, intravenous administration of imipenem–cilastatin is recommended. Therapy should begin as soon as the diagnosis of acute necrotizing pancreatitis is made and should continue for at least two to four weeks.

Sterile and infected acute necrotizing pancreatitis can be difficult to distinguish clinically, since both may produce fever, leukocytosis, and severe abdominal pain. The distinction is important, because mortality among patients with infected acute necrotizing pancreatitis without intervention is nearly 100 percent.[9] The bacteriologic status of the pancreas may be determined by CT-guided fine-needle aspiration of pancreatic and peripancreatic tissue or fluid (Fig. 2).[24] This aspiration method is safe and accurate, with a sensitivity of 96 percent and a specificity of 99 percent, and it is recommended for patients with acute necrotizing pancreatitis whose clinical condition deteriorates or fails to improve despite aggressive supportive care.[2] Ultrasound-guided aspiration may have a lower sensitivity and specificity,[25] but it can be performed at the bedside. Surveillance aspiration may be repeated weekly, as clinically indicated.

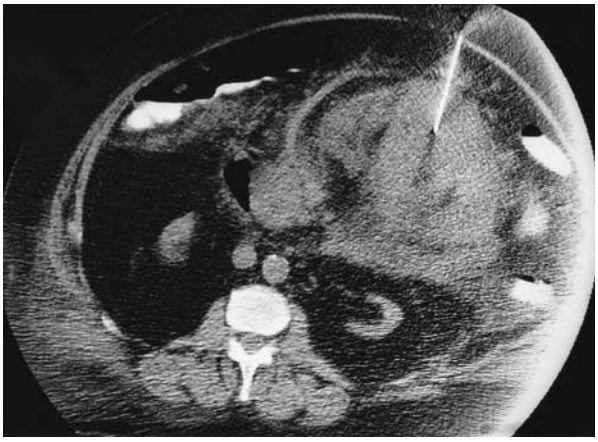

Figure 2. Surveillance for Infection of Pancreatic Necrosis.
An abdominal CT scan obtained without the use of contrast material shows fine-needle aspiration of pancreatic necrosis. The needle is entering the low-attenuation necrotic pancreatic collection in a patient with severe acute necrotizing pancreatitis and suspected infection. The aspirate will be sent for Gram's staining, culture, and antibiotic-sensitivity testing.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Initial studies of urgent endoscopic retrograde cholangiopancreatography (performed within 72 hours of admission) and biliary sphincterotomy in patients with acute gallstone pancreatitis and choledocholithiasis showed an improved outcome only in the group of patients who presented with clinically severe acute pancreatitis.[26] The improvement was attributed to the relief of pancreatic ductal obstruction by an impacted gallstone in the common biliary–pancreatic channel of the ampulla of Vater. More recent studies suggest that the improved outcome after endoscopic retrograde cholangiopancreatography and sphincterotomy in gallstone pancreatitis results from reduced biliary sepsis, rather than representing a true improvement in pancreatitis.[27,28]

In the presence of pancreatic ductal disruption, a frequent occurrence in acute necrotizing pancreatitis,[29] the introduction of infection by incidental pancreatography during endoscopic retrograde cholangiopancreatography may theoretically occur, transforming sterile to infected acute necrotizing pancreatitis. Therefore, endoscopic retrograde cholangiopancreatography must be used judiciously in patients with severe acute gallstone pancreatitis and should be reserved for patients in whom biliary obstruction is suspected on the basis of hyperbilirubinemia and clinical cholangitis.[30] Screening for common-bile-duct stones with magnetic resonance cholangiography or endoscopic ultrasonography may be beneficial in these patients.

NUTRITIONAL SUPPORT

To meet increased metabolic demands and to "rest" the pancreas, total parenteral nutrition administered through a central venous catheter is frequently used in patients with acute necrotizing pancreatitis. This does not hasten the resolution of acute pancreatitis, however.[31] In two recent randomized, prospective studies, patients with severe acute pancreatitis received either total parenteral nutrition or enteral feeding (through a nasoenteric feeding tube radiographically placed beyond the ligament of Treitz) within 48 hours of the onset of illness.[32,33] Enteral feeding was well tolerated, had no adverse clinical effects, and resulted in significantly fewer total and infectious complications. The cost of total parenteral nutrition is significantly greater than that of enteral feeding.[31] It may be up to 15 times greater per day.[33] Acute-phase-response scores and disease-severity scores were significantly improved after enteral nutrition.[33] It appears that total enteral nutrition delivered through a jejunal feeding tube is preferable in patients with acute necrotizing pancreatitis in the absence of substantial ileus.[31]

INTERVENTIONS FOR PANCREATIC NECROSIS

The timing and type of intervention for patients with acute necrotizing pancreatitis are controversial. Since the mortality from sterile acute necrotizing pancreatitis is approximately 10 percent, and surgical intervention has not been shown to lower this figure, most investigators recommend supportive medical therapy in this group.[9] Conversely, infected acute necrotizing pancreatitis is considered uniformly fatal without intervention.[9] Aggressive surgical pancreatic débridement (necrosectomy) remains the standard of care if drainage is undertaken and may require multiple abdominal explorations. Necrosectomy should be undertaken soon after confirmation of infected necrosis.

The benefit of surgery in patients with multisystem organ failure and sterile necrosis remains unproved, although this scenario is frequently cited as an indication for surgical débridement.[34] In addition, the longer surgical intervention can be delayed after the onset of acute necrotizing pancreatitis, the better survival is,[35] probably because of improved demarcation between viable and necrotic tissue at the time of operation. The role of delayed necrosectomy (after the resolution of multisystem organ failure) in patients with sterile acute necrotizing pancreatitis also remains controversial. Some investigators advocate débridement in patients who remain systemically ill four to six weeks after the onset of acute pancreatitis, with fever, weight loss, intractable abdominal pain, inability to eat, and failure to thrive.[2,36,37] Others, however, believe that delayed necrosectomy is unnecessary if the necrotic process remains sterile.[38]

SURGICAL DÉBRIDEMENT

Surgical methods of treating necrosis vary. There are three main types of surgical débridement: conventional drainage, open or semiopen procedures, and closed procedures.[3] Conventional drainage involves necrosectomy with placement of standard surgical drains and reoperation as required (by the presence of fever, leukocytosis, or lack of improvement according to imaging studies). Open or semiopen management involves necrosectomy and either scheduled repeated laparotomies or open packing, which leaves the abdominal wound exposed for frequent changes of dressing. Closed management involves necrosectomy with extensive intraoperative lavage of the pancreatic bed. The abdomen is closed over large-bore drains for continuous high-volume postoperative lavage of the lesser sac. Most surgeons have abandoned the conventional surgical approach to débridement, since inadequately removed necrotic tissue becomes or remains infected, resulting in mortality of approximately 40 percent.[3]

In all procedures except the closed technique, multiple operations are frequently required to remove the necrotic pancreatic and peripancreatic material.[3] Leaving the abdomen open eliminates the need for repeated laparotomy; packing may be changed in the intensive care unit. Repeated débridement and manipulation of the abdominal viscera with the open and semiopen techniques result in a high rate of postoperative local complications, such as pancreatic fistulas, small- and large-bowel complications, and bleeding from the pancreatic bed. Pancreatic or gastrointestinal tract fistulas occur in up to 41 percent of patients after surgical necrosectomy and often require additional surgery for closure.[37,39] The mortality from débridement with open or closed techniques is approximately 20 percent.[3]

ALTERNATIVE METHODS OF DÉBRIDEMENT

Alternative methods of débridement of pancreatic necrotic material have recently been described, but they require considerable technical expertise. As more data become available, the precise role of these techniques in the management of necrotizing pancreatitis will be better defined.

Percutaneous Therapy (Interventional Radiology)

One study has described the successful treatment of infected acute necrotizing pancreatitis by aggressive irrigation and drainage through large-bore percutaneous catheters up to 28 French in diameter.[40] The catheters were inserted into the pancreatic collections of 34 patients with necrotizing pancreatitis and medically uncontrolled sepsis a mean of nine days after hospital admission. An average of three separate catheter sites per patient and four catheter exchanges per patient were necessary for the removal of necrotic

material.[40] Pancreatic surgery was completely avoided in 16 patients (47 percent). In nine patients, sepsis was controlled and elective surgery was later performed to repair external pancreatic fistulas related to catheter placement. Nine patients required immediate surgery when percutaneous therapy failed. Four of the 34 patients (12 percent) died. Many of the 34 patients had multisystem organ failure.

More recently, a select group of hemodynamically stable patients with infected necrosis underwent aggressive percutaneous catheter-directed débridement.[41] With the use of multiple large-bore catheters, high-volume irrigation, and stone-retrieval baskets, solid necrotic pancreatic debris was removed successfully (with a mean of 17 débridements per patient) from 20 patients, in whom there was complete resolution of the necrosis without the need for surgery.[41] These patients underwent intervention a mean of 3.5 weeks after the onset of pancreatitis (range, 1 to 13) (Echenique AM: personal communication).

Endoscopic Therapy

Successful endoscopic drainage of symptomatic sterile or infected pancreatic necrotic material a mean of 6.9 weeks after the onset of severe necrotizing pancreatitis has been reported recently.[42] Several transgastric or transduodenal drainage catheters of 10-French internal diameter and a 7-French nasopancreatic irrigation tube were endoscopically placed into the retroperitoneum through tracts dilated up to 15 mm. With this method, solid debris flows around the catheters through the transenteric tract. Complete resolution of necrosis without the need for surgery was achieved in 25 of 31 patients (81 percent) with this form of late, or "organized," pancreatic necrosis, defined as encapsulation of the necrotic pancreas, fluid, and peripancreatic tissue.[43] In this group of patients, surgical intervention was required more commonly for acute complications of endoscopy (perforation or bleeding) than for true failure of drainage. One patient died from bleeding unrelated to endoscopic therapy. Adjuvant percutaneous drains were required to drain peripheral necrotic collections (those outside the body of the pancreas) in a minority of cases.

To summarize, the drainage options for patients with pancreatic necrosis are expanding. Experience with newer, nonsurgical drainage procedures is limited, and no interdisciplinary comparative data exist. To decide on the timing of treatment or the type of treatment to be employed in these complex cases, the expertise of the local surgeon, the interventional endoscopist, and the interventional radiologist must be considered. Nonsurgical drainage of pancreatic necrosis, whether performed in the first weeks or one month or more after the onset of pancreatitis, should be undertaken only by expert interventional endoscopists or interventional radiologists familiar with the potential complications and time required for successful pancreatic drainage. Improperly drained sterile necrosis may lead to life-threatening infected necrosis. A team approach to planning pancreatic interventions is useful, since some patients may benefit from drainage by a combination of methods. The decision to intervene should be based on infection of the necrosis or, in cases of sterile necrosis, severe clinical symptoms such as gastric-outlet obstruction, intractable abdominal pain, or failure to thrive.[2,36]

LONG-TERM SEQUELAE

Despite the enormous cost of caring for patients with acute necrotizing pancreatitis, the mean quality-of-life outcomes up to two years after treatment are similar to those obtained with coronary-artery bypass grafting.[44] The long-term clinical endocrine and exocrine consequences of acute necrotizing pancreatitis appear to depend on several factors, including the severity of the necrosis, the cause (alcoholic or nonalcoholic), whether the patient continues to use alcohol, and the degree of surgical pancreatic débridement.[45,46] Sophisticated studies of exocrine function show persistent functional insufficiency in the majority of patients up to two years after severe acute pancreatitis.[47] The use of pancreatic enzymes should be restricted to patients with symptoms of steatorrhea and weight loss due to fat malabsorption. Although subtle glucose intolerance is frequent, overt diabetes mellitus is uncommon.[48] Follow-up pancreatography frequently reveals obstructive pancreatic ductal abnormalities that may account for persistent symptoms of abdominal pain or acute recurrent pancreatitis.[49]

FUTURE MEDICAL THERAPIES

Platelet-activating factor, a proinflammatory cytokine, is implicated in the pathophysiology of systemic organ failure in severe acute pancreatitis. Platelet-activating–factor antagonists significantly improve both inflammatory changes and survival in animals.[50] In a recent trial, patients with severe acute pancreatitis who were receiving a platelet-activating–factor antagonist had a significant reduction in the incidence of organ failure at 72 hours.[51] A subsequent report of a larger study by the same authors demonstrated a significant reduction in mortality among patients who received platelet-activating factor within 48 hours after the onset of symptoms.[52] Studies are under way to define better the role of this type of agent in clinical practice.

CONCLUSIONS

Pancreatic necrosis is being increasingly recognized because of physicians' awareness and improved radiologic imaging. The identification of pancreatic necrosis is important, since the morbidity and mortality

associated with acute pancreatitis are markedly increased when necrosis is present. Aggressive medical care with antibiotics is the mainstay of management, with surgery or other types of pancreatic débridement limited to patients with infected necrosis.

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