46. PANCREATIC INFECTION

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Pancreatic infection occurs most often as a complication of acute pancreatitis. The unique aspects of pancreatic inflammation predispose to secondary bacterial infection, which occurs in approximately 5% of all cases of acute pancreatitis. This review focuses on the pathogenesis, microbiology and surgical management of pancreatic infections, which occur as a complication of acute pancreatitis.

Pathophysiology of Acute Pancreatitis

Acute pancreatic inflammation leads to a spectrum of pathologic conditions ranging from mild edematous pancreatitis which is usually self limited, to severe necrotizing pancreatitis, a fulminant illness associated with mortality rates approaching 50–70%. Clinical and pathological severity of acute pancreatitis correlate with the development of pancreatic and peripancreatic necrosis. The unique predilection of the pancreas to undergo necrosis during acute inflammation is due to the high content of lipolytic and proteolytic enzymes that are contained within this exocrine gland. Although these enzymes are normally stored in an inactivated precursor form, they may become activated following various physiologic stressors such as toxin exposure, direct trauma, viral infection and ischemia.

The two most common causes of acute pancreatitis are alcohol ingestion and biliary tract disease (gallstones). These two etiologies comprise over 90% of cases. The relative frequencies of alcohol and biliary disease vary depending on the population studied. In rural areas of the United States and in Europe, gallstone-pancreatitis predominates, while in large urban areas alcohol is the primary cause of acute pancreatitis [1].

Additional etiologies for acute pancreatitis include the postoperative state (following abdominal or thoracic operations, especially coronary bypass procedures), hypercalcemia, hypertriglyceridemia and drug-associated pancreatitis. Of the latter, azathioprine, sulfonamides, pentamidine and various nucleoside analogues used to treat the Human Immunodeficiency Virus are the most commonly implicated agents. Endoscopic retrograde cholangiopancreatography (ERCP) is the cause of acute pancreatitis in up to 5% of cases. Finally, in 10% of cases, no obvious inciting agent can be identified. However, about two-thirds of idiopathic pancreatitis has been shown to be due to microlithiasis of the biliary tract [2].

Pancreatitis also occurs as a result of ischemia – reperfusion injury in association with pancreas transplantation. The outcome in this situation may be loss of the allograft, as the management of peripancreatic infection in conjunction with immunosuppressive therapy is especially difficult.

The exact mechanisms by which various insults trigger pancreatic inflammation are not known. Regardless, the clinical and pathologic severity seem to be related to the extent of pancreatic enzyme activation and autodigestion which results in pancreatic and peripancreatic necrosis. In addition to local release of pancreatic enzymes and consequent tissue damage, significant systemic release (and toxicity) occurs as reflected by elevated serum levels of amylase,

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TABLE 1. Ranson's early prognostic signs for acute pancreatitis

At admission:
Age older than 55 yrs
WBC > 16,000 cells/mm^3
Blood glucose > 200 mg/dl
Serum LDH > 350 lμ/l
AST > 250 μ/dl
During initial 48 hours:
Hematocrit fall > 10 points
BUN elevation > 5 mg/dl
Serum Ca^{++} fall to < 8 mg/dl
Arterial pO_2 < 60 mmHg
Base deficit > 4 mEq/l
Estimated fluid sequestration > 6 l

WBC, white blood cell, BUN, blood urea nitrogen, LDH, lactate dehydrogenese, AST, asparate amino transferase. (Data from [4]).

lipase and protease [3]. The clinical course in acute pancreatitis is typically not related to the magnitude of serum enzyme elevation, but rather other factors or criteria that may be present on admission to the hospital or develop within the first 48 hours of illness.

The most widely used classification system, initially presented by Ranson *et al.* [4] identified 11 factors that were predictive of poor outcomes for acute pancreatitis. Using the classification as presented in Table 1, patients with 0–2 criteria experienced almost no mortality. Patients with three or four signs had an expected mortality of 15% and approximately 40% require intensive care support. Patients with five or six criteria had mortality rates of approximately 50% and essentially all require intensive care support. Patients with seven or more criteria experienced mortality rates approaching 100%. It is important to recognize that these criteria were published in 1974. Modern day outcomes are expected to be better. Nonetheless, Ranson's criteria are useful because patients can be identified early on for more aggressive management which may include hemodynamic monitoring, frequent computed tomography (CT) scans and prophylactic antibiotics.

Other classification systems have been used in acute pancreatitis. These include the Glasgow (or Imrie) criteria [5], Acute Physiology and Chronic Health Enquiry (APACHE) [6] and the Atlanta Symposium criteria [7]. These criteria and classification systems all have similar predictive value for assessment of acute pancreatitis.

The complications of acute pancreatitis can be divided into two phases: early and late. In both phases the severity of complication is related to the intensity of inflammation and the associated development of pancreatic and peripancreatic necrosis.

Early complications are related to extravascular fluid shifts that are associated with edema in the peripancreatic region and intestinal ileus. Additional fluid shifts may occur in the form of pulmonary edema as the lung serves as a target organ in pancreatic inflammation. Pulmonary capillary dysfunction has been linked to abnormalities of circulating phospholipase A [8] to increased levels of free fatty acids generated from the action of pancreatic lipase [9] and to alteration of pulmonary surfactant [10]. Up to 50% of patients with acute pancreatitis show demonstrable impairment of pulmonary function, usually in the form of hypoxemia. This may be subtle and manifest only as tachypnea or may be dramatic as occurs in adult respiratory distress syndrome (ARDS). Despite advances in critical care medicine, patients with respiratory failure associated with acute pancreatitis experience a high mortality rate [11, 12].

Bacterial translocation and/or alteration of the gut mucosal barrier may be important in the pathophysiology of early organ dysfunction in acute pancreatitis. Endotoxin, a lipopolysaccharide derived from the outer membrane of Gram-negative bacteria and a potent activator of inflammation, can be detected in the serum of patients with severe pancreatitis [13]. Elevated endotoxin levels correlate with the syndrome of multiple organ failure. However, it is not known whether this relationship represents cause or effect.

Patients with severe acute pancreatitis may also experience renal insufficiency. In many

cases this is due in part to hypovolemia. Acute renal failure, which does not respond to fluid replacement, is a grave complication generally associated with overwhelming illness and multiple organ failure. Mortality rates approach 100%.

Late complications of acute pancreatitis occurring after seven days are generally due to the development of secondary infection or pseudocyst formation. Of these, pancreatic infection is associated with much greater morbidity and will be the focus for the remainder of this review.

Pancreatic Infection – Definitions

Secondary pancreatic infections occur in 2% to 5% of all cases of acute pancreatitis and are responsible for more than 80% of the late deaths associated with this disease. The risk of infection is proportional to the severity of illness as determined by Ranson's or other criteria. Three kinds of pancreatic infection occur: pancreatic abscess, infected pancreatic necrosis and infected pancreatic pseudocyst. *Pancreatic abscess* is a discrete, often circumscribed collection of purulent material within or around the pancreas that contains little or no necrotic tissue. *Infected pancreatic necrosis*, on the other hand, is an infection within or around the pancreas that contains nonviable tissue of pancreatic or peripancreatic origin. Most commonly, it is the peripancreatic fat that undergoes necrosis in response to acute pancreatic inflammation. Infected necrosis is by far the most common form of infection accompanying acute pancreatitis, constituting approximately 90% of infections [14]. Pure pancreatic abscess is relatively rare.

Both pancreatic abscess and infected pancreatic necrosis occur as a progression or continuation of pancreatic inflammation and, therefore, develop within 2–4 weeks of the onset of initial illness. *Pancreatic pseudocyst* develops after resolution of the acute illness, usually after four weeks. By definition, pancreatic pseudocyst is a localized collection of pancreatic juice enclosed by a wall of fibrous granulation tissue and, thus, requires time to develop. Most pancreatic pseudocysts are sterile, but they may become secondarily infected either spontaneously or as a consequence of instrumentation.

Pathogenesis of Infection

The pathogenesis of pancreatic infection in acute pancreatitis may be multifaceted, as there are several potential pathways by which microorganisms can reach the pancreas or peripancreas tissue during acute inflammation. The most direct pathway is through the biliary ducts, which contain bacteria in up to 90% of cases of choledocholithiasis [3]. This would seem to be the most likely pathway in gallstone pancreatitis. Another pathway appears to be by way of translocation through the adjacent transverse colon, either through direct spread or via lymphatic channels [15]. Other possible routes include hematogenous [16, 17], via lymphatic channels to the circulation [18, 19], and via ascites to the pancreas [16, 18]. Experimental studies support both direct extension from the colon and transperitoneal migration. Widdison *et al.* demonstrated in a feline model of acute pancreatitis that radioactively labeled intestinal *E. coli* were not recovered from the site of acute necrotizing pancreatitis when the colon was enclosed in an impermeable plastic bag which prohibited direct bacterial translocation [15]. Using a model of caerulein-induced pancreatitis in rats, Medich *et al.* [20] concluded that bacterial translocation leads to transperitoneal infection of the pancreas. These authors suggested that selective decontamination of the gut and peritoneal lavage may prevent secondary pancreatic infection in acute pancreatitis. In contrast, Arendt *et al.*, using the same model of acute pancreatitis, found that bacteria did not spread through the peritoneal route [21].

In humans the mechanism for pancreatic and peripancreatic infection in acute pancreatitis is not known. However, the results of a prospective randomized trial by Luiten *et al.* suggests a prominent role for enteric organisms [22]. These

investigators examined the use of selective gut decontamination in severe acute pancreatitis. Patients were entered into this trial according to clinical or radiographic criteria that placed them at high risk for development of secondary pancreatic infection. The treatment group received oral colistin sulfate 200 mg, amphotericin 500 mg and norfloxacin 50 mg every six hours until the episode of pancreatitis resolved clinically. The control group did not receive any prophylactic antibiotics. The groups were equally matched with respect to severity of pancreatitis as judged by clinical and CT criteria. Secondary pancreatic infection occurred in 20/52 (38%) of the control group vs 9/50 (18%) of the selective decontamination group ($p = 0.03$). Gram-negative infection predominated in the control group (33%) whereas only 8% of patients in the selective decontamination group developed Gram-negative pancreatic infection. Patients in the control group developed more frequent complications such as requirement for bowel resections and fistula formation and trended toward a higher mortality rate (35% vs 22%) although the latter difference did not reach statistical significance ($p = 0.19$). However, when early mortality (due to the initial phase of acute pancreatitis) was excluded, the difference in late mortality was impressive: 10/44 (23%) for control and 3/42 (7%) for selective decontamination. The authors of this study also demonstrated convincingly that Gram-negative pancreatic infection in the control group was preceded by intestinal colonization with the same Gram-negative organisms. The results from this multicenter trial reported by Luiten *et al.* provide strong evidence for the role of gut-derived organisms in the pathogenesis of secondary infection in acute pancreatitis.

The risk of pancreatic infection rises steadily during the course of illness from acute pancreatitis [23–25]. Beger *et al.* reported that 24% of patients undergoing surgery within the first week for severe acute pancreatitis were infected and this figure rose to 46% after the second week and 71% after the third week [23]. Similar rates of infection were reported by Gerzof *et al.* who performed CT-guided percutaneous aspirates [24] and by Bassi *et al.* who examined smears taken intra-operative [25].

TABLE 2. Correlation of the extent of pancreatic necrosis (as determined from contrast enhanced CT scanning) and risk of infection in 226 patients with severe acute pancreatitis

Extent of necrosis	Sterile (n = 155)	Infected (n = 71)
<30%	57	35
30–50%	22	23
>50%	21	42

From [34].

The risk of secondary pancreatic infection in acute pancreatitis is clearly related to the extent of pancreatic and peripancreatic necrosis [26–28]. Using contrast-enhanced CT scanning, Berger *et al.* demonstrated that an increasing percentage of pancreatic necrosis was associated with an increasing risk of infection. Patients with more than 50% necrosis had a 66% incidence of infection, whereas patients with less than 30% necrosis had a 38% incidence of infection (Table 2).

Due to the association between pancreatic and peripancreatic necrosis, one of the therapeutic goals in the management of acute pancreatitis should be to decrease tissue necrosis. A variety of strategies have been tried, including the use of high molecular weight dextran [29], Somatostatin [30, 31] and protease inhibitors such as gabetate mesilate. The latter inhibits phospholipase A2 [32, 33]. Unfortunately, none of these agents have been found to be effective when administered in the clinical setting.

Microbiology of Pancreatic Infection

Pancreatic or peripancreatic infection in the setting of acute pancreatitis is most often caused by Gram-negative enteric bacteria [34–36]. As many as 50% of infections are polymicrobial [37]. Table 3 illustrates the spectrum of bacteria

TABLE 3. Bacteriology in severe acute pancreatitis (n = 87 patients)

Escherichia coli	25%
Staphylococcus aureus	17%
Pseudomonas spp	15%
Klebsiella spp	9%
Proteus spp	9%
Candida	4%
Streptococcus faecalis	3%
Enterobacter spp	3%
Anaerobes	16%
Monomicrobial	76%
Polymicrobial	24%

Adapted from [34].

involved. The most common organism isolated is *E. coli*, which occurs in 25–40% of cases. The next most common organisms tend to be Pseudomonas spp [22, 34], although in some studies Enterobacter spp are more common [35]. Klebsiella spp, Proteus spp, Acinetobacter spp and Citrobacter spp have also been noted [38]. Staphylococcus epidermidis and staphylococcus aureus are the most common Gram-positive organisms isolated. Enterococci are increasingly isolated as are Candida (usually Candida albicans) in more recent reports [22, 35]. Infections with Gram-negative organisms seem to carry a higher mortality rate than infections with Gram-positive organisms [38]. It should be noted that the preponderance of pseudomonas and staph infections in some series may be related to the use of percutaneous drainage catheters.

The use of selective gut decontamination may modify the bacterial flora found in secondary pancreatic infections. When a regimen of colistin, amphotericin and norfloxacin was used, the percentage of gram isolates decreased from 61% to 21% [22]. However, of four Gram-negative infections from 50 patients treated with this combination of antibiotics, three of these involved resistant strains of Pseudomonas aeruginosa or Klebsiella.

Anaerobic species have not been cultured frequently from infections complicating acute pancreatitis. This is perhaps surprising considering the close proximity of the colon and a postulated role for direct extension of organisms. The paucity of anaerobes could be in part related to technical difficulties in culturing anaerobes from intra-abdominal infections [39].

The Role of Prophylactic Antibiotics

The potential role of prophylactic antibiotics in preventing secondary pancreatic infections in acute pancreatitis has been demonstrated in experimental studies [13]. In a rat model of caerulein-induced pancreatitis, Foitzik *et al.* compared several prophylactic regimens: intravenous cefotaxime, intravenous imipenem, selective gut decontamination (with polymyxin E, tobramycin and amphotericin) and full gut decontamination (the same oral antibiotics plus intravenous cefotaxime). None of these regimens affected early mortality, but animals receiving imipenem or full gut decontamination demonstrated decreased bacterial counts in the pancreas relative to controls [40].

Additional studies with the rat caerulein-induced pancreatitis model have examined the prophylactic use of intravenous ciprofloxacin and imipenem [41]. At seven days, 75% of control rats (not receiving antibiotics) had developed pancreatic infection with organisms similar to those found in humans. Both ciprofloxacin and imipenem significantly reduced the incidence of secondary infection in these animals by roughly 50%. However, due to the low numbers of animals surviving, the authors were not able to show a difference in mortality.

In a feline model of pancreatic infection, Widdison *et al.* demonstrated that cefotaxime was effective in reducing bacterial counts in the pancreas when administered 12 hours after induction of pancreatitis [42]. However, this model is clearly different from other experimental models as pancreatitis is induced by ductal infusion of glycodeoxycholic acid and live E. coli. Animals in this study did not develop necrotizing pancreatitis and mortality did not

occur in any of the groups. Therefore, the relevance to human pancreatitis is uncertain.

The efficacy of antibiotic prophylactics in acute pancreatitis is related to the properties of tissue penetration for specific agents. Trudel *et al.* demonstrated that ampicillin does not achieve adequate concentrations in pancreatic tissue in a model of canine pancreatitis [43]. Roberts and Williams also investigated penetration of ampicillin into pancreatic tissue by measuring ampicillin levels in pancreatic ductal fluid at the time of ERCP [44]. In six of seven subjects, ampicillin was undetectable in the fluid.

In contrast, ciprofloxacin and imipenem consistently achieve good penetration into pancreatic tissue. Buchler *et al.* examined pancreatic tissue levels for ten different antibiotics in patients undergoing elective pancreatic surgery [45]. They found that aminoglycosides consistently failed to achieve significant tissue levels in the pancreas. Extended-spectrum penicillins including mezlocillin, piperacillin and third generation cephalosporins such as ceftizoxime and cefotaxime achieved minimum inhibitory concentrations that inhibited most, but not all, of the common infecting organisms. Ciprofloxacin and imipenem achieved bactericidal levels against most organisms.

Acute inflammation may alter the penetration characteristics of antibiotics. Foitzik *et al.* demonstrated in a rat model of acute pancreatitis that cefotaxime tissue levels may vary according to changes in capillary blood flow and pancreatic edema [46]. Interestingly, tissue imipenem levels do not seem to be altered by changes in blood flow or inflammation. It has been shown, in addition, that ofloxacin (from the 4-Quinolone class) achieves bactericidal tissue levels in normal and inflamed pancreas, but, more importantly, in pancreatic necrosis.

In human studies, Drewelow *et al.* have shown that ceftazidime achieved adequate antimicrobial concentrations in both viable and necrotic pancreatic tissue in three human subjects with acute necrotizing pancreatitis [47]. Bassi *et al.* examined penetration of several antibiotics including aminoglycosides, perfloxacin, imipenem, mezlocillin and metronidazole into infected pancreatic necrosis [48]. These samples were collected by CT-guided needle aspiration or at the time of surgical intervention. The authors found that perfloxacin and metronidazole consistently attained levels greater than the MICs for the organisms found in necrotic tissue. Aminoglycoside levels were consistently inadequate. Mezlocillin and imipenem were intermediate, although imipenem tissue levels increased with time.

In summary, the third generation cephalosporins, piperacillin, mezlocillin, 4-quinolones, imipenem and metronidazole achieve adequate pancreatic tissue concentrations when given as prophylactic agents for acute pancreatitis. The aminopenicillins (ampicillin), first generation cephalosporins and aminoglycosides do not achieve effective concentrations in pancreatic tissue. It should be noted, however, that the relevance of pancreatic tissue penetration to clinical efficacy in acute pancreatitis is debatable since, in most cases, secondary infection occurs in peripancreatic necrosis.

Clinical Trials of Antibiotic Prophylaxis

The rationale for prophylactic antibiotic therapy in acute pancreatitis is based on the widely accepted premise that severe acute pancreatitis is commonly associated with pancreatic and peripancreatic necrosis, which is, in turn, susceptible to secondary infection. Thus, prevention of infection should have a measurable impact on clinical outcomes. Unfortunately, it has not been possible to demonstrate unequivocal benefit for the use of prophylactic antibiotics in acute pancreatitis. There are many reasons for this. Many cases of pancreatitis are mild and these patients are not at high risk for secondary infection. Studies which fail to include sufficient numbers of patients with severe pancreatitis as determined by clinical (Ranson, Imrie) or CT criteria may not show a difference in outcome with

antibiotic prophylaxis. Furthermore, if enrollment criteria for antibiotic studies are based on CT criteria that require establishment of pancreatic or peripancreatic necrosis, it may be too late for antibiotics to alter the outcome. The failure of early trials may also have been related to use of ampicillin and similar drugs that do not achieve good tissue penetration. Recent studies provide stronger evidence for a beneficial role of prophylactic antibiotics.

In 1993, Pederzoli *et al.* from Italy reported the results of a multicenter randomized controlled trial [49]. Seventy-four patients with severe pancreatitis as judged by Ranson's criteria and with pancreatic necrosis proven by CT scan, were randomized to receive imipenem 0.5 g intravenously every eight hours for 14 days or to a control group receiving no antibiotics. Pancreatic infection was confirmed by fine needle aspiration or at operation. Imipenem reduced the incidence of secondary pancreatic infection from 30% in control to 12% in treated patients ($p < 0.001$). However, multiple organ failure, need for operative intervention and mortality were not reduced to an equal extent and none of the differences in these outcome measures achieved statistical significance. Of note, there was a trend toward decreased mortality in the imipenem group (7.3% vs 12.1%). Also, the rates of non-pancreatic infection were significantly reduced in the antibiotic treated group (14.6% vs 48.5%). A weakness of this study is the small number of patients overall and a selection bias whereby only two of 16 patients with extensive (>50%) pancreatic necrosis were randomized to the control group. Thus, infection and mortality in the control group were lower than expected making it difficulty to detect a difference between control and treatment arms.

In 1995, Sainio *et al.* from Finland reported a randomized controlled trial evaluating the use of cefuroxime, a second generation cephalosporin, for prophylaxis of pancreatic infection in patients with alcohol-induced severe pancreatitis [50]. Sixty patients were randomized to receive either intravenous cefuroxime 1.5 g three times daily or no antibiotics. Cefuroxime did not reduce the incidence of pancreatic sepsis, but significantly decreased both the number of surgical interventions (8 vs 36, $p = 0.012$) and mortality from 23% in the control group to 3% in the antibiotic group ($p = 0.028$). The reason for this dramatic effect on mortality is not clear, especially in view of the fact that cefuroxime did not alter the incidence of secondary pancreatic infection.

In another small study, Schwarz *et al.* in 1997 reported 26 patients with necrotizing pancreatitis proven by CT scan, randomized to a regimen of ofloxacin plus metronidazole versus no antibiotics [51]. The antibiotic regimen did reduce the number of Gram-negative pancreatic infections (1/13 vs 6/16), but the overall infection rate and mortality were not significantly different.

Several uncontrolled studies support the use of prophylactic antibiotics in severe acute pancreatitis. In the previously cited study [48] a series of 60 patients receiving either prophylactic perfloxacin or imipenem for severe pancreatitis were compared. Although perfloxacin more consistently penetrated pancreatic tissue and exceeded the MICs for commonly isolated organisms, imipenem was more effective at preventing pancreatic infections (10% vs 34%; $p < 0.05$) and lowering mortality (10% vs 24%) although the latter did not reach statistical significance.

A recent retrospective review by Ho and Frey [14] also supports the use of prophylactic antibiotics for severe acute pancreatitis. These authors reviewed 180 patients treated over 14 years and grouped them into three periods. During 1982–1989 (50 patients) no prophylactic antibiotics were used; during 1990–1992 ($n = 55$) patients were given antibiotics in a non-uniform manner. From 1993–1996, 75 patients with severe pancreatitis and APACHE II scores greater than six associated with abnormal CT findings were given a four-week course of intravenous imipenem. A progressive decrease in the incidence of secondary pancreatic infection was noted over the three time periods. During the

most recent period 20 of 75 (27%) patients developed pancreatic infection. Moreover, mortality was progressively lowered from 16% during 1983–1989, to 7% during 1990–1992, to 5% during 1993–1996. Due to the increasing numbers of patients observed during these three time periods and use of the APACHE scoring system which may have included patients with slightly milder forms of pancreatitis, it is difficult to compare the results of this retrospective study to the prospective studies which have been based on Ranson or Imrie criteria. Also, these authors included significant numbers of patients with peripancreatic fluid collections only (without necrosis) whereas most of the randomized trials have included primarily patients with necrosis. Nonetheless, the overall results suggest a beneficial role for prophylactic antibiotics in severe acute pancreatitis.

Finally Golub *et al.* performed a meta-analysis of eight published trials of prophylactic antibiotics in acute pancreatitis [52]. Using an endpoint of death, their analysis revealed a positive benefit for prophylactic antibiotics when limited to cases of severe pancreatitis and using antibiotics that achieve therapeutic pancreatic tissue levels such as the 4-quinolones and imipenem. However, the validity of meta-analysis as used to define the role of prophylactic antibiotics in acute pancreatitis has been questioned [13] as varying antibiotic regimens have been used and the majority of studies have not been sufficiently powered to detect important clinical differences.

In summary, there is substantial evidence, experimental and clinical, to provide a rationale for prophylactic antibiotics in severe acute pancreatitis. The majority of published reports indicate a benefit and, to date, there are no reports to suggest a worse outcome due to infection with resistant strains. By using various clinical and radiographic criteria, it is relatively simple to identify subsets of patients who are at greatest risk for secondary pancreatic infection. It would seem prudent to identify these patients as early as possible and administer prophylactic antibiotics such as imipenem.

Clinical Management of Pancreatic Infections

PRESENTATION

Abdominal pain, tenderness and fever are the most common symptoms and signs of pancreatic infection. Unfortunately, these findings are neither sensitive nor specific. Fever may be absent in up to 35% of patients [53, 54]. Additional findings may include prolonged nausea or vomiting and a palpable mass. In general, patients who do not resolve their symptoms of acute pancreatitis within one week should be suspected of developing pancreatic infection.

DIAGNOSIS

There are no sensitive or specific laboratory markers for pancreatic infection. Leukocytosis to a variable degree is almost uniformly seen, but is certainly not pathopneumonic for infection. Amylase and lipase values may return to normal despite the presence of pancreatic infection. Elevated serum levels of C-reactive protein, phospholipase A_2 and trypsinogen activation peptides have been shown to correlate with the development of pancreatic and peripancreatic necrosis [55–60]. However, none of these assays are specific for infection nor are they readily available in most hospitals. Currently, the diagnosis of pancreatic infection requires radiologic imaging.

Contrast-enhanced computed tomography (CT scanning) has become the gold standard for evaluating the pancreas in acute pancreatitis. The value of CT scanning is greatly enhanced by intravenous injection of contrast. In certain situations there may be hesitancy to use intravenous contrast, but the information gained usually justifies its use. The contrast-enhanced CT scan delineates normal homogeneously perfused pancreatic tissue from under-perfused or

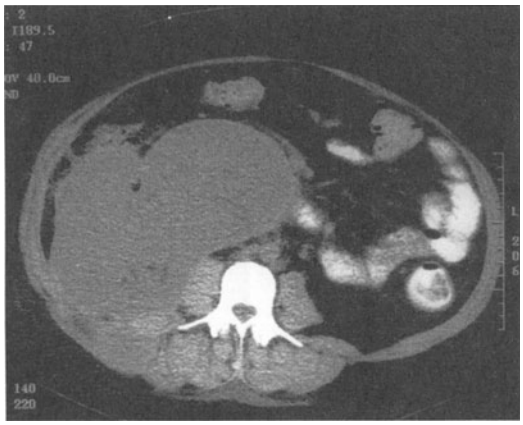

FIGURE 1. CT scan of a patient with severe pancreatitis and a large peripancreatic collection tracking behind the ascending colon. At operation, the collection contained a mixture of fluid and necrotic tissue.

nonviable pancreatic tissue. In addition, extension of inflammation, fluid and necrosis beyond the pancreas into retroperitoneal tissue planes can be appreciated with CT scanning. It is often not possible to distinguish peripancreatic fluid from necrosis and most often there is a combination of both (Figure 1).

Several investigators have developed scoring systems to characterize the CT findings of acute pancreatitis [61]. Balthazar and colleagues have reported a grading system which correlates well with clinical course and has predictive value similar to Ranson's criteria for assessing the risk of infection [62].

Definitive diagnosis of pancreatic infection requires percutaneous CT-guided aspiration or direct operative sampling of tissue or fluid. Blood cultures are often negative or may reflect alternate sites of infection such as pulmonary or central venous lines. Percutaneous CT-guided aspiration of suspicious fluid collections has been found to be safe and accurate for diagnosis but probably not 100% reliable in excluding pancreatic infection [63, 64].

The role of percutaneous CT-guided aspiration in clinical management of pancreatitis continues to be debated. The appearance of peripancreatic fluid collections or necrosis in a patient who is exhibiting recovery from acute pancreatitis does not mandate immediate intervention. Thus, percutaneous aspiration is less useful in this situation. At the other extreme, patients who are failing medical management in association with peripancreatic fluid collections and/or necrosis should probably undergo operation anyway. It is the patient in between the two extremes, with an unresolved illness and positive findings on CT scan, who may benefit from CT-guided aspiration. A positive aspirate mandates surgical intervention while a negative aspirate permits continued close observation. It is important to remember that patients should be re-aspirated if fluid collections or inflammatory masses persist and illness continues.

Gerzof and colleagues have reviewed the role of CT-guided aspiration in diagnosis and management of pancreatic inflammatory masses [65]. They evaluated the outcome of 92 aspirations in the setting of acute pancreatitis. Fifty of these aspirates were sterile. All of these were judged to be true negatives on the basis of cultures obtained at the time or surgery or by resolution of the pancreatic mass or fluid collection without surgery. Forty-two aspirates were judged to have been positive and all of these were confirmed by surgery or catheter drainage. Of these 42, six were initially negative but positive on reaspiration. These were no significant complications related to the procedure. The authors emphasized that CT appearance together with clinical findings cannot distinguish sterile vs. infected inflammatory masses. They also demonstrated that pancreatic infection occurs earlier than previously suspected, with 55% of infections occurring within 14 days of the onset of pancreatitis. Their study and others [66–69] emphasize the useful role of percutaneous aspiration in the evaluation and management of complicated pancreatitis.

MANAGEMENT OF STERILE PANCREATIC NECROSIS

Many patients with sterile pancreatic or peripancreatic necrosis can be managed nonoperatively. However, this assumes a negative CT-guided aspirate and a resolving clinical course. Repeated aspirates may be necessary in order to reduce the possibility of false negative results. Several authors have emphasized the need for operative débridement in selected cases of sterile necrosis [70–72]. There is clearly a subset of patients with sterile necrosis and clinical deterioration who probably benefit from an aggressive surgical approach as outlined in the next section on management of pancreatic infection. There is no role for percutaneous catheter drainage in sterile necrosis as this will serve only to provide a route for secondary bacterial infection.

MANAGEMENT OF INFECTED NECROSIS

The vast majority of secondary pancreatic infections are associated with pancreatic and peripancreatic necrosis. As a result, these infections are not managed adequately using percutaneous techniques. Surgical treatment requires adequate exposure of the pancreas through a generous incision – either midline or bilateral subcostal. Patients with wide costal angles may be easier to explore through subcostal incisions. The incision should be designed to achieve exposure of the pancreas and both paracolic gutters as directed by CT findings. The anterior surface of the pancreas should be visualized by entering the lesser sac, if possible. Also, the base of the transverse mesocolon should be examined as should the paraduodenal area, tail of the pancreas and the retroperitoneal spaces behind the ascending and descending colon. Resection and débridement should be limited to that which is easily performed by digital dissection, using blunt forceps or by gently pinching away necrotic tissue. Extensive resections with concomitant hemorrhage should be avoided. We believe a series of repeated gentle débridements is better tolerated (and more effective) than one or two major operations with heavy blood loss. At the initial operation, one should make a decision regarding number and frequency of re-explorations. Traditional management has consisted of a single extensive débridement and placement of closed-suction drains [70]. However, in recent years there has been increasing consensus about the merits of repeated laparotomies for management of necrotizing pancreatitis [71–75].

The repeated laparotomy approach involves a less extensive initial débridement but multiple re-operations at 24 to 48 hours apart. There are several advantages of this method. Pancreatitis is a unique inflammatory disease, which may persist over a period of several days or weeks. This is fundamentally different from other abdominal inflammatory disorders such as appendicitis, perforated ulcer or diverticulitis. Tissue damage, necrosis and infection evolve over time and may progress slowly. Thus a more prolonged (or repeated) surgical approach may be better suited for the disease process. We believe it is best to débride necrotic tissue gently. This way, bleeding is minimized but, more importantly, débridement is more complete and infection is better controlled. Repeated operations can be tailored according to the patient's physiological condition and complications such as colonic necrosis or intestinal fistula can be recognized as they occur. One disadvantage of the multiple laparotomy approach may be an increased risk of bowel injury associated with gauze packing. This is especially likely with open packing techniques or when gauze remains in contact with the intestine for longer than 48 hours. Our technique at the Medical College of Wisconsin involves repeated gentle débridement with temporary abdominal closure using either a Silastic sheet or a velcro device, the Wittmann Patch™ (Starsurgical, Burlington, WI). The latter is especially useful and well suited to the repeated laparotomy concept. Using either technique, it is possible to keep the abdominal contents enclosed and appropriately moist such that iatrogenic fistulas are avoided. We use gauze packing only at the initial débridement or as

required for bleeding – but we try not to débride extensively such that bleeding occurs. All débridements are performed in the operating room. The numbers of débridements vary but have ranged from 5 to 26. Using the concepts of multiple, gentle débridements and temporary abdominal closure, we achieved excellent results in a series of renal transplant recipients who developed necrotizing pancreatitis [76].

The overall results for surgical management of infected pancreatic necrosis have improved significantly in recent years [70, 72, 75]. With adherence to the above mentioned concept, mortality rates have declined into the 10–20% range.

MANAGEMENT OF PANCREATIC ABSCESS AND INFECTED PANCREATIC PSEUDOCYSTS

Occasionally a pure pancreatic abscess (without necrosis) may present. As an isolated fluid collection this may respond to percutaneous catheter drainage. Infected pseudocysts may also be managed effectively with percutaneous drainage. In either case, a pancreatic fistula may ensue if the fluid collection (or pseudocyst) exhibits a connection to the pancreatic ductal system. This can be determined by performing an ERCP either before or after drainage. In the case of a suspected pancreatic abscess, it should be re-emphasized that the majority of these "fluid collections" are found in fact found to contain substantial amounts of necrotic tissue (as illustrated in Figure 1). Therefore surgical drainage remains the preferred treatment.

Summary

The overall risk of pancreatic infection in acute pancreatitis is approximately 5% but this may rise to 30–50% in cases of severe pancreatitis. Most infections arise from enteric bacteria. There is sufficient evidence for a beneficial effect of prophylactic antibiotics in severe pancreatitis such that patients who meet appropriate criteria should probably receive a course of antibiotic such as imipenem or a quinolone until clinical recovery occurs. The presence of pancreatic or peripancreatic necrosis itself does not mandate surgical intervention, but should prompt a diagnostic percutaneous aspirate to detect early infection, even in patients who are clinically stable. Patients with negative aspirates should undergo repeated aspirates as dictated by clinical progress or surgical intervention if deterioration occurs. Patients with positive aspirates should undergo prompt surgical intervention, as there is no role for medical or percutaneous management of infection in the presence of pancreatic or peripancreatic necrosis. Patients who are admitted to a medical service for management of acute pancreatitis should be seen in consultation by surgeons experienced in the management of pancreatic infection.

References

1. Lillemoe KD, Yeo CJ. Management of Complications of Pancreatitis. Current Problems in Surgery 1:1, 1998.
2. Farion AM, Ricci GL, Sianesi M, *et al.* Physiopathologic role of microlithiasis in gallstone pancreatitis. Surg Gynecol Obstet 164:252, 1987.
3. Klar E, Warshaw AL. Infections of the Pancreas. In Howard RJ, Simmons RL (eds). Surgical Infectious Diseases. Appleton & Lange 41:1059, 1995.
4. Ranson JHC, Rifkind DM, Roses DF, *et al.* Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet 139:69, 1974.
5. Blamey SL, Imrie CW, O'Neill J, Gilmour WH, Carter DC. Prognostic factors in acute pancreatitis. Gut 25:1340, 1984.
6. Knaus WA, Draper EA, Wagner DP, *et al.* APACHE II: a severity of disease classification system. Crit Care Med 13:818, 1985.
7. Bradley EL. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga., 1992. Arch Surg 128:586, 1993.
8. Kellum JM, Demeester TR, Elkins RC, *et al.* Respiratory insufficiency secondary to acute pancreatitis. Ann Surg 175:657, 1972.
9. Kimura T, Toung JK, Margolis S, *et al.* Respira-

tory failure in acute pancreatitis: a possible role for triglycerides. Ann Surg 189:509, 1979.
10. Maciver AG, Metcalfe IL, Possmayer F, *et al.* Altercation of surfactant chemistry in experimental acute pancreatitis. J Surg Res 23:311, 1977.
11. Ranson JHC, Turner JW, Roses DF. Respiratory complications in acute pancreatitis. Ann Surg 179:557, 1974.
12. Jacobs ML, Daggett WM, Cirett JM, *et al.* Acute pancreatitis: analysis of factors influencing survival. Ann Surg 186:43, 1977.
13. Powell JJ, Miles R, Siriwardena AK. Antibiotic prophylaxis in the initial management of severe acute pancreatitis. Br J Surg 85:582, 1998.
14. Ho HS, Frey CF. The role of antibiotic prophylaxis in severe acute pancreatitis. Arch Surg 132:487, 1997.
15. Widdison AL, Karanija ND, Reber HA. Routes of spread of pathogens into the pancreas in a feline model of acute pancreatitis. Gut 35:1306, 1994.
16. Lange JF, van Gool J, Tytgat GN. The protective effect of a reduction in intestinal flora on mortality of acute haemorrhagic pancreatitis in the rat. Hepatogastroenterology 34:28, 1987.
17. Webster MW, Pasculle AW, Myerowitz RL, *et al.* Postinduction bacteremia in experimental acute pancreatitis. Am J Surg 138:419, 1979.
18. Tarpila E, Nystrom PO, Franzen L, *et al.* Bacterial translocation during acute pancreatitis in rats. Eur J Surg 159:109, 1993.
19. Runkel NS, Moody FG, Smith GS, *et al.* The role of the gut in the development of sepsis in acute pancreatitis. J Surg Res 51:18, 1991.
20. Medich DS, Lee TK, Melhem MF, *et al.* Pathogenesis of pancreatic sepsis. Am J Surg 165:46, 1993.
21. Arendt T, Wendt M, Olszewski M, *et al.* Cerulein-induced acute pancreatitis in rats: does bacterial translocation occur via a transperitoneal pathway? Pancreas 15:291, 1997.
22. Luiten EJ, Hop WC, Endtz HP, *et al.* Prognostic importance of Gram-negative intestinal colonization preceding pancreatic infection in severe acute pancreatitis. Results of a controlled clinical trial of selective decontamination. Intensive Care Med 24:438, 1998.
23. Beger HG, Bittner R, Block S, *et al.* Bacterial contamination of pancreatic necrosis. A prospective clinical study. Gastroenterology 91:433, 1986.
24. Gerzof SG, Banks PA, Robbins AH, *et al.* Early diagnosis of pancreatic infection by computed tomography-guided aspiration. Gastroenterology 93:1315, 1987.
25. Bassi C, Falconi M, Girelli R, *et al.* Microbiological findings in severe acute pancreatitis. Surg Res Commun 5:1, 1989.
26. Banks PA. Infected necrosis: morbidity and therapeutic consequences. Hepatogastroenterology 38:116, 1991.
27. Uhl W, Buchler M, Malfertheiner P, *et al.* PMN-elastase in comparison with CRP, antiproteases, and LDH as indicators of necrosis in human acute pancreatitis. Pancreas 6:253, 1991.
28. Schmid SW, Uhl W, Steinle A, *et al.* Human pancreas-specific protein. A diagnostic and prognostic marker in acute pancreatitis and pancreas transplantation. Int J Pancreatol 19:165, 1996.
29. Klar E, Herfarth C, Messmer K. Therapeutic effect of isovolumic hemodilution with dextran 60 on the impairment of pancreatic microcirculation in acute biliary pancreatitis. Ann Surg 211:346, 1990.
30. Choi TK, Mok F, Zahn WH, *et al.* Somatostatin in the treatment of acute pancreatitis: a prospective randomized controlled trial. Gut 30:223, 1989.
31. D'Amico D, Favia G, Biasiato R, *et al.* The use of somatostatin in acute pancreatitis-results of a multicenter trial. Hepatogastroenterology 37:92, 1990.
32. Buchler M, Malfertheiner P, Uhl W, *et al.* Gabexate mesilate in human acute pancreatitis. Gastroenterology 104:1165, 1992.
33. Valderrama R, Perez-Mateo M, Navarro S. Multicenter double-blind trial of gabexate mesilate (FOY) in unselected patients with acute pancreatitis. Digestion 51:65, 1992.
34. Schmid SW, Uhl W, Friess H. The role of infection in acute pancreatitis. Gut 45:311, 1999.
35. Farkas G, Marton J, Mandi Y, Szederkenyi E. Surgical strategy and management of infected pancreatic necrosis. Br J Surg 83:930, 1996.
36. Foitzik T, Fernandez-del Castillo C, Ferraro MG, *et al.* Pathogenesis and prevention of early pancreatic infection in experimental acute necrotizing pancreatitis. Ann Surg 222:179, 1995.
37. Bradley EL III. A fifteen-year experience with open drainage for infected pancreatic necrosis. Surg Gynecol Obstet 177:215, 1993.
38. Luiten EJ, Hop WC, Lange JF, *et al.* Differential prognosis of Gram-negative versus Gram-positive infected and sterile pancreatic necrosis; results of a randomized trial in patients with

severe acute pancreatitis treated with adjuvant selective decontamination. Clin Infect Dis 25:811, 1997.
39. Finegold SM. Anaerobic bacteria. In Surgical Infectious Disease, Howard RJ, Simmons RL (eds). Appleton & Lange 6:81, 1995.
40. Foizik TF, Fernandez-del Castillo C, Ferraro MJ, Mithofer K, Rattner DW, Warshaw AL. Pathogenesis and prevention of early pancreatic infection in experimental acute necrotizing pancreatitis. Ann Surg 222:179, 1995.
41. Mithofer K, Fernandez-del Castillo C, Ferraro MG, Lewandrowski K, Rattner DW, Warshaw AL. Antibiotic treatment improves survival in experimental acute necrotizing pancreatitis. Gastroenterology 110:232, 1996.
42. Widdison A, Karanjia ND, Reber HA. Antimicrobial treatment of pancreatic infection in cats. Br J Surg 81:886, 1994.
43. Trudel JL, Wittnich C, Brown RA. Antibiotics bioavailability in acute experimental pancreatitis. J Am Coll Surg 178:475, 1994.
44. Roberts EA, Williams RJ. Ampicillin concentrations in pancreatic fluid bile obtained at endoscopic retrograde cholangiopancreatography (ECRP). Scand J Gastroenterol 14:669, 1979.
45. Buchler M, Malfertheiner P, Friess H, Isenmann R, Vanek E, Grimm H, *et al.* Human pancreatic tissue concentration of bactericidal antibiotics. Gastroenterology 103:1902, 1992.
46. Foitzik T, Hotz HG, Kinzig M, Sorgel F, Buhr HJ. Influence of changes in pancreatic tissue morphology and capillary blood flow on antibiotic tissue concentrations in the pancreas during the progression of acute pancreatitis. Gut 40:526, 1997.
47. Drewelow B, Koch K, Otto C, Franke A, Reithling AK. Penetration of ceftazidime into human pancreas. Infection 21:229, 1992.
48. Bassi C, Pederzoli P, Vesentini S, Falconi M, Bonora A, Abbas H, *et al.* Behavior of antibiotics during human necrotizing pancreatitis. Antimicrob Agents Chemother 38:830, 1994.
49. Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicentre clinical trial of antibiotic prophylaxis of septic complications in acute pancreatitis with imipenem. Surg Gynecol Obstet 176:480, 1993.
50. Sainio V, Kemppainen E, Puolakkainen P, Taavitsainen M, Kivisaari L, Valtonen V, *et al.* Early antibiotic treatment in acute necrotizing pancreatitis. Lancet 346:663, 1995.
51. Schwartz M, Isenmann R, Meyer H, Beger HG. Antibiotic use in necrotizing pancreatitis. Results of a controlled study. Dtsch Med Wochenschr 122:356, 1997.
52. Golub R, Siddiqi F, Pohl D. Role of antibiotics in acute pancreatitis: A meta-analysis. J Gastrointestinal Surg 2:496, 1998.
53. Warshaw AL, Jin G. Improved survival in 45 patients with pancreatic abscess. Ann Surg 202:408, 1985.
54. Fedorak IJ, Ko TC, Kjuricin G, *et al.* Secondary pancreatic infections: are they distinct clinical entities? Surgery 112:824, 1992.
55. 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 76:177, 1989.
56. Buchler M, Malfertheiner P, Schoetensack C, *et al.* Sensitivity of antiproteases, complement factors and C-reactive protein in detecting pancreatic necrosis. Results of a prospective clinical study. Int J Pancreatol 1:227, 1986.
57. McMahon MJ, Bowen M, Cooper EH, Mayer AD. C reactive protein: an aid to assessment and monitoring of acute pancreatitis. J Clin Pathol 37:207, 1984.
58. Puolakkainen P, Valtonen V, Paananen A, Schroder T. C-reactive protein (CRP) and serum phospholipase A2 in the assessment of the acute pancreatitis. Gut 28:764, 1987.
59. Schmidt J, Fernandez-del Castillo C, Rattner DW, *et al.* Trypsinogen activation peptides in experimental pancreatitis in the rat. Prognostic implications and histopathologic correlates. Gastroenterology 103:1009, 1992.
60. Gudgeon AM, Heath DI, Hurley P, *et al.* Trypsinogen activation peptides assay in the early prediction of severity of acute pancreatitis. Lancet 335:4, 1990.
61. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JHC. Acute pancreatitis: value of CT in establishing prognosis. Radiology 174:331, 1990.
62. Balthazar EJ, Ranson JHC, Naidich DP, *et al.* Acute pancreatitis: prognostic value of CT. Radiology 156:767, 1985.
63. Fink AS, Hiatt JR, Pitt HA, *et al.* Indolent presentation of pancreatic abscess: experience with 100 cases. Arch Surg 123:1067, 1988.
64. Rattner DW, Legemate DA, Mueller PR, Warshaw AL. Early surgical debridement of pancreatic necrosis is beneficial irrespective of infection. Am J Surg 163:105, 1992.
65. Gerzof S, Banks P, Robbins AH, Johnson WC, Spechler SJ, Wetzner SM, Snider JM, Langevin RE, Jay ME. Early diagnosis of pancreatic infec-

tion by computed tomography-guided aspiration. Gastroenterology 93:1315, 1987.
66. Karlson KB, Martin EC, Fankuchen EI, Mattern RF, Schultz RW, Casarella WJ. Percutaneous drainage of pancreatic pseudocysts and abscesses. Radiology 142:619, 1982.
67. Gerzof SG, Johnson WC, Robbins AH, Spechler SJ, Nabseth DC. Percutaneous drainage of infected pancreatic pseudocysts. Arch Surg 119:888, 1984.
68. Barkin JS, Pereiras R, Hill M, Levi J, Isikoff M, Rogers AI. Diagnosis of pancreatic abscess via percutaneous aspiration. Dig Dis Sci 27:1011, 1982.
69. Hill MC, Dach JL, Barkin J, Isikoff MB, Morse B. The role of percutaneous aspiration in the diagnosis of pancreatic abscess. AJR 141:1035, 1983.
70. Warshaw AL, Gongliang J. Improved survival in 45 patients with pancreatic abscess. Ann Surg 202:408, 1985.
71. Stanten R, Frey CF. Comprehensive management of acute necrotizing pancreatitis and pancreatic abscess. Arch Surg 125:1269, 1990.
72. Bradley EL. A fifteen year experience with open drainage for infected pancreatic necrosis. Sur Gynecol Obstet 177:215, 1993.
73. Malangoni MA, Richardson D, Seiler JG, Polk HC. Factors contributing to fatal outcome after treatment of pancreatic abscess. Ann Surg 203:605, 1986.
74. Pemberton JH, Nagorney DM, Becker JM, Ilstrup D, Dozois RR, Remine WH. Controlled open lesser sac drainage for pancreatic abscess. Ann Surg 203:600, 1986.
75. Orlando R, Welch JP, Akbari CM, Bloom GB, Macaulay WP. Techniques and complications of open packing of infected pancreatic necrosis. Surg Gynecol Obstet 177:65, 1993.
76. Slakey DP, Johnson CP, Cziperle DJ, Roza AM, Wittman DH, Gray DWR, Roake JA, Britton J, Morris PJ, Adams MB. Management of severe pancreatitis in renal transplant recipients. Ann Surg 225:217, 1997.