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Optimising Outcomes in Acute Pancreatitis

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Contents

Abstract

Acute pancreatitis is a common cause for presentation to emergency departments. Common causes in Western societies include biliary pancreatitis and alcohol (the latter in the setting of chronic pancreatitis). Acute pancreatitis also follows endoscopic retrograde pancreatography in 5 to 10% of patients, a group that could potentially benefit from prophylactic treatment.

Although episodes of pancreatitis usually run a relatively benign course, up to 20% of patients have more severe disease, and this group has significant morbidity and mortality. Therefore, attempts have been made to identify, at or soon after presentation, those patients likely to have a poor outcome and to channel resources to this group.

The mainstay of treatment is aggressive support and monitoring of those patients likely to have a poor outcome. Pharmacotherapy for acute pancreatitis (both prophylactic and in the acute setting) has been generally disappointing. Efforts initially focused on protease inhibitors, of which gabexate shows some promise as a prophylactic agent. Agents that suppress pancreatic secretion have produced disappointing results in human studies.

Infection of pancreatic necrosis is associated with high mortality and requires surgical intervention. In view of the seriousness of infected necrosis, the use of prophylactic antibacterials such as carbapenems and quinolones has been advo-

cated in the setting of pancreatic necrosis. Similarly, data are accumulating to support the use of prophylactic antifungal therapy.

Recently, it has become apparent that the intense inflammatory response associated with acute pancreatitis is responsible for much of the local and systemic damage. With this realisation, future efforts in pharmacotherapy are likely to focus on suppression or antagonism of pro-inflammatory cytokines and other inflammatory mediators. Similarly, animal studies have demonstrated the importance of oxidative stress in acute pancreatitis, although to date there is a paucity of information regarding the efficacy of antioxidants.

Although the clinical course for most patients with acute pancreatitis is mild, severe acute pancreatitis continues to be a clinical challenge, requiring a multidisciplinary approach of physician, intensivist and surgeon.

Acute pancreatitis is a common cause for presentation to emergency centres in Western communities. Although attacks usually run a benign course with resolution within 5 days, approximately 20% of patients have severe disease,[1] associated with prolonged hospitalisation and often local and distant complications. This latter group has a significant mortality rate of approximately 10 to 15%.

For the purposes of this review, we adhere to the definition of acute pancreatitis arrived at by a recent consensus meeting in Atlanta, Georgia, USA: 'an acute inflammatory process of the pancreas, with variable involvement of regional tissues and remote organ systems'.[2] Although the pathogenesis of acute pancreatitis remains controversial, there is increasing evidence that triggering of the digestive enzyme cascade is an important early event. Irrespective of the aetiology, episodes are somewhat stereotypic, characterised biochemically by activation of pancreatic digestive enzymes and pathologically by initiation of a local inflammatory response and, if the episode is severe, distant manifestations of an inflammatory response (SIRS; systemic inflammatory response syndrome). Unfortunately, despite the importance of activated digestive enzymes and inflammatory mediators in the pathogenesis of acute pancreatitis, pharmacotherapy aimed at inhibition of digestive enzymes and the inflammatory response has been disappointing. In part, this may be related to the lag-time between initiation of digestive enzyme activation and presentation to hospital. Therefore, optimising outcomes in acute pancreatitis entails early identification of patients at risk of a severe attack, aggressive treatment of local and systemic complications, and identification and correction, if possible, of aetiological factors.

1. Diagnosis

The diagnosis of acute pancreatitis is based upon a suggestive history and clinical findings associated with serum markers of pancreatitis (usually an elevation in amylase and/or lipase levels to at least 3-times the upper limit of normal).

Serum total amylase remains the most widely used blood test for the diagnosis of acute pancreatitis in most hospitals. Although total amylase elevation is relatively nonspecific, when performed in the clinical setting suggestive of acute pancreatitis, it has a sensitivity of 90%.[3] The level of elevation is not prognostic of the severity of the attack. However, modest elevations of amylase may occur for other reasons. In particular, several other causes of acute abdominal pain (e.g. ischaemic/infarcted gut and bowel perforation) may also be associated with elevation of pancreatic amylase. Macroamylasaemia is present in 1 to 3% of the population and results from the binding of amylase to a globulin that is too large to be filtered by the kidney. It is of no pathological consequence but leads to chronic serum amylase elevation. Total serum amylase is the summation of pancreatic (P) and salivary (S) isoforms. The only source of P-amylase is the pancreas, while S-amylase is derived from multiple sources including salivary glands. Sali-

vary amylase is not infrequently elevated in alcoholics. Determination of pancreatic fraction of amylase increases specificity, but is not readily available in the emergency setting. In spite of these limitations, total amylase remains quick, inexpensive and useful in the emergency setting.

The same false-positives are not seen with serum lipase. As with amylase, lipase levels are not prognostic for severity of the attack.

Biliary pancreatitis may be associated with elevation of liver function tests and perhaps transient jaundice. Elevation of aspartate aminotransferase (AST) is the most sensitive liver test of biliary pancreatitis and characteristically elevation is transient, returning to normal within 24 to 48 hours.[4] Elevation of bilirubin and alkaline phosphatase are slightly less sensitive indicators of biliary pancreatitis.

A plain abdominal radiograph may reveal a localised ileus (sentinel loop sign) or pancreatic calcification (indicating acute on chronic pancreatitis). Plain films may also provide evidence of other causes for abdominal pain such as perforated viscus. Increasingly, computed tomography (CT) is used to support the diagnosis with the finding of pancreatic swelling and peri-pancreatic fat stranding as well as to exclude other serious pathologies such as abdominal aortic aneurysm. Contrast-enhanced CT is also the standard technique used to differentiate oedematous (perfused) from necrotising (nonperfused) pancreatitis, and this distinction has major prognostic implications, as discussed in section 2.

2. Prognostic Tests

Given the importance of supportive care in the management of patients with acute pancreatitis, much effort has been placed on determining at presentation those patients who are at high risk of developing severe pancreatitis, and thus identifying those requiring intensive care support. Table I shows the sensitivities and specificities for various assessment scoring systems and blood tests for differentiating mild from severe pancreatitis. Some scoring systems (Ranson[12] and Glasgow[13]) are limited in that full assessment requires 48 hours observation, and therefore are not useful in triaging patients upon first arrival in the emergency department. The Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system does not have this limitation. It is of interest that various markers of the acute inflammatory response (for example, C reactive protein and interleukin 6) are also quite good indicators of severity. This highlights the importance of the inflammatory response in the subsequent development of organ system failure.

Table I. Indicators of severity for acute pancreatitis

Method	Sensitivity (%)	Specificity (%)	Timing
Urinary trypsinogen-2[5]	94	95	Admission
Urinary TAP[6]	100	85	Admission
Clinical assessment[7]	44	95	Admission
Clinical assessment[7]	66	97	48h
Ranson Score[8]	75	77	48h
Glasgow (Imrie) Score[8]	69	84	48h
APACHE-II Score[7]	63	81	Admission
APACHE-II Score[7]	75	92	48h
PMN elastase[9]	90	90	12-24h
Interleukin-6[8]	85	87	24-48h
C Reactive Protein[10]	84	86	2-7 days
Assessment by CT[11]			'Initial assessment'

APACHE = Acute Physiology and Chronic Health Evaluation; **CT** = computerised tomography; **PMN** = polymorphonuclear lymphocytes; **TAP** = trypsin activation peptide.

On the basis of contrast-enhanced CT, pancreatitis can be determined to be either oedematous (interstitial) or necrotising. In oedematous pancreatitis, the pancreas perfuses normally with contrast material, but in necrotising pancreatitis, the necrotic area does not perfuse (fig. 1). Most severe episodes of pancreatitis occur in the setting of necrotising pancreatitis. Furthermore, the area of necrotic pancreas may become infected, and recognition of this serious complication of utmost clinical importance. Whereas complications (10%) and mortality (2%) in patients with interstitial pancreatitis are low, necrotising pancreatitis carries a high rate of organ failure (70%) and mortality (15%).[1] Mortality correlates with both the pres-

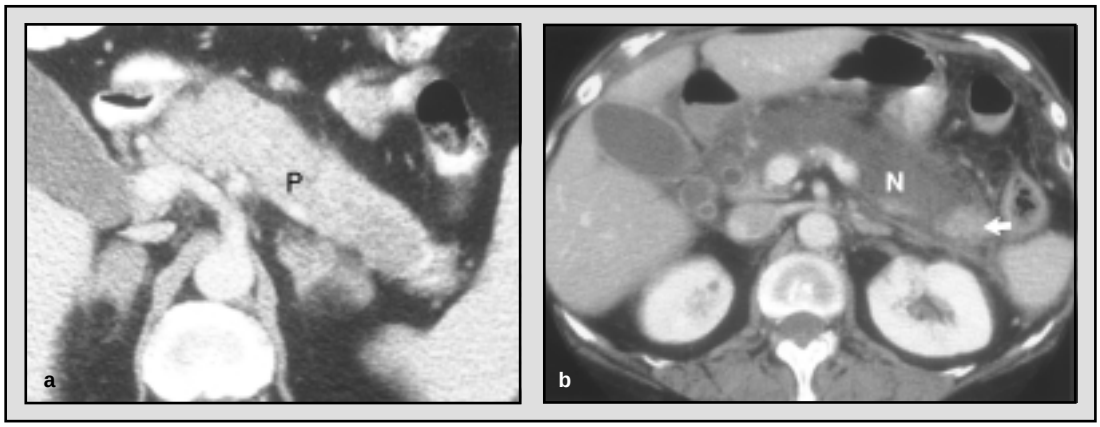

Fig. 1. Contrast enhanced computerised tomography scans demonstrating (**a**) interstitial and (**b**) necrotising pancreatitis. Note that intravenous contrast uniformly distributes throughout the pancreas (P) in interstitial pancreatitis, indicating intact blood flow. However, in (**b**), only a small portion of the tail (arrow) is viable tissue, the remaining being nonperfused necrotic tissue (N).

ence of infection as well as the extent of necrosis.[14] Of patients with pancreatic necrosis, mortality is 10% in the setting of uninfected necrosis, 30% in the setting of infected necrosis,[14] and 50% in the setting of infected necrosis and organ system failure.[1] Contrast enhanced CT is often used in the first week to determine nonperfused (necrotic) areas of the pancreas. A CT-based prognostic index has been developed by Balthazar and co-workers on the basis of peripancreatic inflammation, phlegmon and degree of necrosis.[11] In their study, patients with a high CT severity score had 92% significant morbidity and 17% mortality compared with 2% morbidity and no deaths in the low severity score group.

Recently, haemoconcentration, as measured by haematocrit, has been shown to be a reasonable predictor of the severity of pancreatitis. In a study by Baillargeon et al.,[15] admission haematocrit >47% was predictive of necrotising pancreatitis with sensitivity and specificity of 34% and 91%, respectively. At 24 hours post admission, these figures were and 81% and 88%, respectively.

Trypsin is a major pancreatic proteolytic enzyme. It is secreted from an inactive (zymogen) form, trypsinogen. Proteolytic cleavage of trypsin activation peptide (TAP) from trypsinogen leads to formation of active trypsin. As well as degrading enzymes and structural proteins, trypsin is an activator of other digestive enzyme zymogens. Recently, urinary measurement of trypsinogen-2 (by either assay or rapid dip-stick test) has been shown to have both sensitivity (94%) and specificity (95%) for acute pancreatitis in the emergency department.[5] Further studies are required to confirm these initial promising results. Similarly, urinary TAP level has been shown to be useful in predicting severe pancreatitis at initial presentation to hospital, but it is not useful in determining mild pancreatitis until 24 hours after onset of symptoms and, thus, is of limited usefulness in the initial diagnostic workup.[6]

3. Recognition of Complications

The complications of acute pancreatitis may be local or systemic (see table II). The most important aspect of management of patients with acute severe pancreatitis is the prevention and management of the systemic and local complications. This is reflected in the fact that deaths as a result of acute severe pancreatitis over the first few days illness are now infrequent (not the case 20 years ago).

Most deaths now occur one or more weeks into the course of the illness as a result of multi-organ failure associated with sepsis.[16]

3.1 Hypotension/Azotaemia

Hypovolaemia occurs secondary to massive third space losses associated with inflammation in the pancreatic vascular bed. This is compounded by poor oral intake as well as vasodilatation as a result of the release of inflammatory cytokines into the systemic circulation. Aggressive fluid replacement is essential and in all patients with severe pancreatitis, this mandates central venous pressure monitoring. In haemodynamically unstable patients, especially the elderly or those with a history of cardiac disease, pulmonary arterial (Swann-Ganz) catheterisation should also be considered.

3.2 Respiratory

Respiratory compromise is multifactorial including cardiac failure, pleural effusions and acute respiratory distress syndrome (ARDS). The pathogenesis of ARDS involves a combination of inflammatory cytokines released from the pancreas as well as the action of phospholipase A_2 [17] and other digestive enzymes on the lung. Management is supportive, often requiring endotracheal intubation and ventilation.

Table II. Local and distant complications of acute pancreatitis

Local
Pancreatic ascites
Biliary obstruction
Splenic vein thrombosis/sinistral varices
Pseudocyst formation
Abscess formation
Diabetes mellitus (late)
Distant/Systemic
Hypovolaemia
Pre-renal azotaemia
Hypocalcaemia
Hyperglycaemia
Metastatic fat necrosis
Joint effusions/arthralgias
Acute Respiratory Distress Syndrome (ARDS)

3.3 Sepsis

As outlined in section 2, a major determinant of outcome in necrotising (severe) pancreatitis is the presence or absence of infection in the necrotic pancreatic tissue. Infected necrosis has a 30 to 50% mortality rate; compared with 10% mortality for uninfected necrosis. Thus, differentiation of patients with infected from those with non-infected pancreatic necrosis is of great prognostic and therapeutic importance. Infection should be suspected in the patient with CT demonstrated pancreatic necrosis who, after a week or more, remains systemically unwell with continued pain, fever and leucocytosis. Under these circumstances, fine needle aspiration of pancreatic necrosis under CT guidance for Gram stain and culture is a sensitive technique which can be carried out safely.[18] One study has demonstrated a correlation between the extent of pancreatic necrosis and the rate of local infection.[19]

In most patients, infection of pancreatic necrosis is thought to arise from bacterial translocation from the gut to mesenteric lymph nodes and then via haematogenous spread to the pancreatic phlegmon. This breakdown in the mucosal immune barrier is probably the result of a combination of bacterial overgrowth (associated with ileus) coupled with mucosal ischaemia. Maintenance of hydration and early jejunal tube feeding may help maintain mucosal integrity and reduce bacterial translocation.[16] Between 40 and 80% of infections are monomicrobial.[20-22] Although these usually involve Gram-negative organisms, a significant proportion may also contain staphylococci, enterococci or anaerobes.[20-23]

3.4 Antimicrobial Prophylaxis

Given the importance of infective complications on outcome in acute pancreatitis, much attention has been paid to the potential role for antibacterial prophylaxis, especially in those patients with pancreatic necrosis. Both animal and human studies have addressed the issue of antibacterial penetration into pancreatic tissue and fluid.[24-26] These

studies have indicated that mezlocillin, carbapenems such as imipenem, quinolones and metronidazole all reach tissue levels which are adequate enough to be bactericidal. Penetration into inflamed tissue has been shown to be superior to that of normal tissue,[27] presumably as a result of increased blood flow. Of importance in this regard, data regarding penetration into nonperfused (necrotic) tissue are lacking. Early studies assessing antibacterials in the prevention of infective complications were disappointing.[28,29] However, these studies utilised ampicillin, an agent now known to poorly penetrate pancreatic tissue.[30]

More recently, several studies have addressed newer antibacterial agents. A study by Pederzoli et al.[31] randomised 74 patients with acute necrotising pancreatitis to imipenem/cilastin or placebo. Both pancreatic and nonpancreatic sepsis were reduced in the treatment group (30% to 12% and 48% to 15%, respectively). There was no significant improvement in need for surgery or mortality. A study of 60 patients randomised to cefuroxime versus placebo reported a statistically significant reduction in infectious complications, but only urinary infections were reduced to statistical significance.[32] A recent study comparing imipenem/cilastin to perfloxacin demonstrated reduction in infected necrosis in the imipenem group compared with the perfloxacin group (10% versus 34%). There was no difference in survival. A recent meta-analysis of 8 randomised, controlled trials demonstrated a survival benefit in patients receiving antibacterials ($p = 0.16$) versus those who did not.[33] This improvement became more statistically significant when 4 studies using broad spectrum agents were examined ($p = 0.008$).[31,32,34,35]

Therefore, it appears that antibacterials will reduce local infectious complications in acute necrotising pancreatitis, although these relatively small studies have failed to translate this into a survival benefit. The antibacterial agent of first choice is likely to be imipenem/cilastin, or, in penicillin allergic patients, a quinolone with metronidazole (since quinolones have poor anaerobic cover).

The theory that most infections arise from bacterial translocation from the gut has led to the concept that gut decontamination may be of benefit. In support of this, several animal models of severe pancreatitis have demonstrated improved survival in the setting of gut decontamination.[36,37] The only randomised, controlled study to assess gut decontamination used oral and rectal preparations containing colistin, amphotericin B and norfloxacin. The study demonstrated a statistically significant reduction in pancreatic sepsis (33% versus 8%) and mortality (35% versus 22%). However, the study also used intravenous cefotaxime until the gut was cleared of Gram-negative organisms. Further studies to confirm these results are required.

The role of antifungal medications in acute necrotising pancreatitis is controversial. A study by Buchler and co-workers[38] demonstrated that in the presence of prophylactic broad spectrum antibacterial therapy for pancreatic necrosis (without antifungal therapy), 29% of patients developed a fungal infection in the necrotic tissue. Furthermore, fungal infections have been shown to result in a worse prognosis than bacterial infections.[39] The controversial issue is whether this means that patients receiving antibacterial prophylaxis should also receive antifungal therapy, or whether these data mean that patients should not undergo any prophylaxis (since survival benefit is lacking) and infections should be treated as they arise. Since the meta-analysis of broad spectrum antimicrobial therapy has demonstrated a survival benefit, it seems reasonable to add an antifungal agent to the prophylaxis regimen of patients with pancreatic necrosis. In this regard, fluconazole has been shown to penetrate pancreatic parenchyma in fungicidal levels.[40]

3.4.1 Infectious Complications

Infected pancreatic necrosis should be viewed as a surgical emergency. Surgical necrosectomy, with or without open packing of the pancreatic bed are traditional approaches to this problem. A recent study by Mier et al.[41] demonstrated a survival benefit in patients undergoing intensive supportive therapy with prophylactic antibacterials and planned

necrosectomy after >12 days compared to early necrosectomy. Of particular interest, early cultures of pancreatic tissue demonstrated a significant rate of sub-clinical infection in those patients initially treated conservatively. These data further suggest a role for initial conservative treatment of patients with pancreatic necrosis, even if ultimately they require necrosectomy.

Moreover, there is accumulating uncontrolled evidence suggesting that at least selected patients may be treated with large bore catheter drainage rather than surgery. This management route requires enough time to have elapsed from the initial insult for the necrotic tissue to have partially liquified. Lavage of the pancreatic bed can be achieved either by the percutaneous placement of a drainage catheter radiologically, or the endoscopic placement of a catheter through the duodenal or gastric wall and exteriorised by either a naso-cystic drain or percutaneous endoscopic gastrostomy.[42] Interval imaging with CT and fistulography are necessary to ensure that drainage is maintained and the cavity slowly decreasing in size to a point where the drainage tubes can be removed. Suffice to say that these techniques are new and require considerable expertise that is usually only available in tertiary referral institutions. Whatever the mode of drainage used, these patients are embarking upon a long and complicated medical course, often requiring a team approach of gastroenterologist, radiologist and surgeon.

Pancreatic abscess is a collection of pus in or adjacent to the pancreas. In contrast to infected necrosis, it is a cavity with a well-defined fibrous margin and is generally a later sequel of acute pancreatitis than infected necrosis. In a series of 1300 patients with acute pancreatitis, abscess complicated the clinical course in 2.4% compared with 5.9% who had infected necrosis.[43] Pancreatic abscess is a late complication and in the above study was clinically apparent at a mean of 29 days after onset of pancreatitis, often after recovery from the acute episode. Management requires drainage of the abscess, but since these cavities contain necrotic debris or septation, percutaneous tube drainage may be difficult. In that event surgical debridement is required. Mortality following debridement and lavage was 6.9% in this large German study.[43]

4. Pharmacotherapy

A variety of drugs have been used in the initial phase of acute pancreatitis in an attempt to control the progressive inflammation and damage. Various animal models of acute pancreatitis have shown improved outcome with a variety of agents including protease inhibitors, somatostatin and antioxidants. However, the results of various pharmacotherapies have been generally disappointing in the clinical setting. These conflicting data are probably in large part the result of two factors: firstly, the time delay between onset of inflammation and commencement of therapy in the clinical setting and secondly, statistically under-powered studies because of small patient numbers and/or low rates of severe complications.[44] An exception to this is the prophylactic use of medication prior to endoscopic retrograde cholaniopancreatography (ERCP), a procedure associated with an approximately 5% chance of acute post-procedural pancreatitis (and even higher if pancreatic therapy or manometry is performed). Unfortunately, since there are difficulties in predicting which patients will develop post-ERCP pancreatitis, this strategy requires administration of medication to a large number of patients in order to prevent a few severe attacks of pancreatitis. Hence, the expense involved has prevented this approach from being widely adopted to date.

The drugs investigated for efficacy in acute pancreatitis fall into several categories, those that inhibit the release of pancreatic enzymes, those aimed at decreasing pancreatic secretion and anti-inflammatory agents.

4.1 Protease Inhibitors

An early accompaniment of pancreatic inflammation is the release of active pancreatic enzymes and zymogens into the systemic circulation. Whether this is merely a passive phenomenon as the result of rupturing acinar cells or the active process of exocytosis of zymogen granules across the basolat-

eral membrane is not known. However, it is clear that the release of these enzymes plays a role in the local and distant sequelae of acute pancreatitis.

Active trypsin is found in the local milieu of pancreatitis and in peritoneal fluid, and is thought to be an important factor in the initiation of pancreatic damage. The potential importance of trypsin in the initiation of pancreatitis has been highlighted by the demonstration that trypsin plays a key role in the initiation of pancreatic damage in hereditary pancreatitis. Previous studies with protease inhibitors such as aprotinin have been generally disappointing, with 4 of 5 studies demonstrating no benefit from this drug.[44]

Gabexate (gabexate mesilate) is a low molecular weight protease inhibitor. A recent meta-analysis of trials using this compound demonstrated no improvement in survival, but a decrease in complications.[45] This may have been because of its administration too late in the course of the illness, or because of poor penetration into the ischaemic pancreatic necrotic area. Furthermore, an Italian prospective controlled study using gabexate as a prophylactic agent prior to ERCP demonstrated a decreased incidence of acute pancreatitis and more rapid improvement in those receiving gabexate compared with controls.[46] Whether this approach is reasonable in patients prior to ERCP on cost/benefit grounds is debatable. However, both studies illustrate the potential usefulness of protease inhibitors if given early in the course of the illness, although further prospective, randomised, controlled studies in the setting of early acute pancreatitis are needed.

4.2 Drugs Aimed at Decreasing Pancreatic Secretion

The approach of decreasing pancreatic secretion follows the axiom that a mainstay of treatment for acute pancreatitis is to 'rest the pancreas'. This rationale is perhaps naïve given the fact that the release of proteases from pancreatic acinar cells in acute pancreatitis is unlikely to be controlled via the normal mechanism of apical exocytosis. Furthermore, there is experimental evidence that an early feature of acute pancreatitis is a block in exocytosis and that the gland is therefore in a relatively nonsecretory state.[47] In spite of this, many drugs thought to suppress pancreatic function have been examined in human studies of acute pancreatitis, including anticholinergics,[48] hisitamine H_2-receptor antagonists,[49] calcitonin[50] and somatostatin.[51] None have been found to be of benefit.[44]

Octreotide is a synthetic octapeptide analogue of somatostatin. It is a potent inhibitor of both basal and stimulated pancreatic secretion, but it may increase pressure in the sphincter of Oddi as well as decreasing splanchnic blood flow, effects which could be detrimental in the setting of acute pancreatitis. Many of the studies of octreotide and/or somatostatin were compromised by either poor design (not placebo controlled, small patient numbers), or included patients with mild disease and thus unlikely to derive a benefit. Preliminary data from one prospective study have provided encouraging results supporting the use of octreotide in severe acute pancreatitis.[52] However, the prophylactic use of octreotide has not been useful in preventing post-ERCP pancreatitis.[53,54]

4.3 Anti-Inflammatory Drugs

A prominent feature of the local and systemic manifestations of acute pancreatitis is an acute inflammatory process and studies of various inhibitors of inflammation have been performed.

Corticosteroids have not been helpful in altering the course of acute pancreatitis.

Animal models of acute pancreatitis have demonstrated that platelet activating factor (PAF) is an important cytokine in both the local and pulmonary inflammatory response accompanying acute pancreatitis. PAF receptor antagonists have been shown in animal models to decrease inflammation, improve microcirculation integrity and reduce mortality. At least 2 studies have demonstrated a benefit from the PAR antagonist lexipafant. One study of patients with predicted severe pancreatitis demonstrated a reduced rate of organ failure and a trend toward reduction in mortality in patients given the lexipafant compared with those receiving

placebo.[55] Another British study demonstrated a reduction in mortality when patients were treated within 48 hours of onset.[56] However, a large US and European study randomising 1500 patients to lexipafant or placebo failed to demonstrate a difference in mortality at 28 days. On the basis of this study, an ongoing trial of lexipafant in prophylaxis of ERCP-induced pancreatitis was abandoned.[57] Subsequently, a press release from the company involved (British Biotech) announced suspension of studies assessing the role of lexipafant in pancreatitis.[57]

Under normal circumstances PAF is degraded enzymatically by an acetylhydrolase. Recombinant PAF acetylhydrolase (rPAF-AH) has been shown to reduce pancreatic inflammation in animal models.[58] Clinical studies both as treatment in patients with acute pancreatitis as well as prophylaxis for patients undergoing ERCP are currently underway.

Administration of antioxidants to animals prior to initiation of experimental pancreatitis has clearly been shown to reduce subsequent pancreatic injury.[59] This issue was further addressed in a pilot study on the efficacy of high-dose parenteral antioxidants in patients presenting to an intensive care unit with haemorrhagic pancreatitis involving >50% of the gland mass as measured by CT.[60] In an uncontrolled fashion, 6 patients were administered ascorbic acid, acetylcysteine and selenium, with all participants surviving. Over the same time period, 5 patients who did not receive these supplements died. Given the small numbers and the uncontrolled nature of this study, conclusions cannot be drawn regarding the efficacy of this treatment or the importance of oxidative stress in this setting. However, the data are encouraging and the subject warrants further investigation. Unfortunately, there is no randomised, placebo-controlled trial of antioxidants, either as treatment for acute pancreatitis, or for prophylaxis prior to ERCP.

A novel continuous regional intra-arterial approach to the delivery of pharmacotherapy has been developed by the Japanese. In animal studies continuous infusion of an antibacterial (flomoxef) was shown to improve biochemical indices of inflammation as well as survival.[61] Similarly, in a clinical study, 34 patients with acute necrotising pancreatitis were treated within 72 hours of presentation with an intra-arterial perfusion solution containing imipenem/cilastin and a protease inhibitor (nafamostat). The rate of infection in this group was 2% and mortality was 6%.[62] Clearly, this promising technique requires further study.

5. Conclusions

Acute pancreatitis remains a therapeutic challenge for clinicians. In spite of increases in our understanding of the pathophysiology of acute pancreatic inflammation, these advances are yet to translate into significant therapeutic advances. On the other hand, the ability to predict those patients likely to have a severe attack of pancreatitis, the intensive support measures now widely available, and the management of pancreatic necrosis and infection, do represent significant advances in management. Further improvements in management are likely to be related to the early administration of therapies that control the acute inflammatory response, and which may result in the limitation of local tissue damage and reduction in the incidence of multi-organ failure.

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