

Classic diseases revisited

Acute pancreatitis: assessment and management

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Summary

In the 1920s Moynihan described acute pancreatitis as “..the most terrible of all intra-abdominal calamities”. He established a practice of immediate surgical intervention to remove the toxic products accumulating in the peritoneal cavity, and this treatment was endorsed by most centres, remaining the standard therapy for the next 20 years. In the 1940s, the mortality of patients treated surgically was shown to be far higher than those treated conservatively, and a more conservative line of management was recommended, comprising nasogastric stomach decompression, intravenous fluid therapy, opiate analgesia, and the administration of atropine. Despite half a century passing, a clinician would not be criticised for adopting such a regime today, which in part reflects the lack of understanding of this condition and the failure of seemingly appropriate therapy. Reduction in mortality is a consequence of advances in intensive care preventing the high early mortality of organ failure, but the area of specific therapy remains elusive. While this is so, the mortality rates for these patients will remain static, while the doctor continues to feel clinically impotent.

Keywords: pancreatitis

Pathophysiology

Although in the 1920s surgical intervention was the established treatment for acute pancreatitis,¹ this practice was amended in the mid 1940s when Fallis reported a mortality of 46% in surgically treated patients compared to one of only 6% in those treated conservatively.²

From the diverse number of aetiologies, the acute pancreatitis syndrome remains a homogeneous disease, varying in severity which is largely unrelated to its aetiology. The link between aetiology and pathogenesis, however, remains poorly understood, and for this reason the basis of treatment remains supportive and expectant. The key to relevant treatment depends upon finding the ‘final common pathway’ which links all these aetiologies.

It is apparent on observation of the clinical course of the disease that it may be considered to consist of two phases, an initial cellular injury caused by the various triggering factors, followed by a subsequent systemic inflammatory response.

INITIAL CELLULAR INJURY

Over the last five years, great interest has been shown in the acinar cell as possibly providing the key to this initiating event. The acinar cell is the most active protein-synthesizing cell in the body and more than 90% of this protein is in the form of digestive enzymes.³ These digestive enzymes, together with lysosomal hydrolases, are synthesized in the rough endoplasmic reticulum within the acinar cell. Within membrane-enclosed compartments these newly synthesized proteins migrate to the Golgi complex, where they are differentiated by phosphorylation of those proteins destined to become lysosomal.⁴ The digestive proteins are packaged in condensing vacuoles which mature to zymogen granules, while the lysosomal hydrolases become separately packaged into lysosomes. The final point in the cell for the zymogen granules is at the apex, where fusion occurs at the luminal surface to allow discharge of enzyme precursor into the pancreatic duct (figure 1).

It has been noted in several studies that luminal enzyme secretion is in fact reduced in acute pancreatitis, while protein production by the rough endoplasmic reticulum, processing in the Golgi, and amino acid synthesis remain normal. Thus, there is seen to be an increase in intracellular zymogen granules as a consequence of diminished apical exocytosis of enzyme precursor in the face of continued zymogen synthesis and intracellular transport.⁵ This accumulation cannot continue indefinitely and eventually fusion of the zymogen granule and lysosomal membranes occur, with subsequent discharge of precursor enzyme into the lysosomal compartment – a process known as crinophagy. This colocalisation of the two compartments is usually a physiological process in which excess stored secretory products are broken down and removed.

Cathepsin B is a lysosomal enzyme capable of activating trypsinogen to trypsin which is then able to convert other pro-enzymes within the zymogen to their active form (chymotrypsin, elastase and phospholipase A2). Rupture or release of these activated digestive enzymes into the interstitium results in autodigestive damage to the gland and adjacent tissues. This results in the activation of a host of inflammatory mediators which serves to amplify the local response. The resulting oedema, haemorrhage and local necrosis spreads along pancreatic and peri-pancreatic planes. The overlying peritoneum becomes involved in the inflammation and pours a protein-rich fluid into the peritoneal cavity, along with enzymes and inflammatory mediators from the inflamed pancreas. This is, in fact, akin to an intraperitoneal burn.

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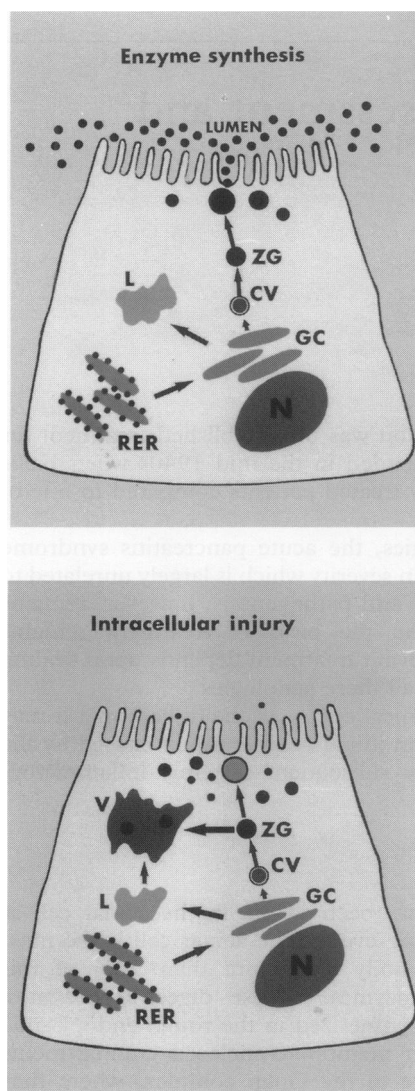


Figure 1 Schematic representation of intracellular injury. Note in the lower illustration that colocalisation has occurred between zymogen granule and lysosome resulting in inappropriate intracellular activation of enzyme precursors. RER=rough endoplasmic reticulum; ZG=zymogen granule; GC=Golgi complex; CV=condensing vacuole; L=lysosome; V=vacuole; N=nucleus

PATHOGENESIS OF SYSTEMIC EFFECTS

If we consider the activation of trypsinogen at the level of the acinar cell as the starting point of the acute pancreatitis syndrome, then it is clear that the ability of trypsin to activate its own precursor and other pancreatic enzymes has the potential to cause a cascade of activation. It is this cascade that is implicated in the systemic manifestations of the syndrome. Enzyme systems involved in this systemic inflammatory response are shown in box 1.

Many effects of acute pancreatitis are the result, directly or indirectly, of circulating active proteases. In mild pancreatic inflammation, these proteases are combined with α 1-antitrypsin (an acute phase protein) to cause inactivation. The proteases are then transferred to α 2-macroglobulin (the principal protease inhibitor) which is rapidly consumed by circulating monocytes and macrophages, by which they are phagocytosed (figure 2).^{6,7} In severe pancreatitis, however, this system becomes overwhelmed with the excess circulating protease, α 2-macroglobulin is reduced by consumption, and the reticulo-endothelial function depressed. It is in this situation that free proteases may circulate and cause significant damage by the activation of other enzyme systems.

Recent evidence suggests that mediators produced and released by activated inflammatory cells may contribute considerably to the recognised complications of pancreatitis, ie, multi-organ failure, pancreatic necrosis and sepsis.

In the early stages of localised inflammation, chemotactic factors (notably complement) activate polymorphonuclear cells initially and later circulating monocytes. At the site of inflammation these cells release biologically active products – proteolytic enzymes, reactive oxygen metabolites, vasoactive substances and cytokines (tumour necrosis factor (TNF)- α , IL-1, IL-6, and IL-8).⁸

It has been shown that neutrophil activation is a significant event in human pancreatitis.⁹ The mechanism by which they induce injury directly is by the production of elastase¹⁰ and superoxide ions¹¹ which are capable of causing considerable endothelial damage (figure 3).

A further cytokine which has stimulated a lot of research interest is platelet-activating factor (PAF), which plays a major role in pancreatic inflammation. In experimental models of pancreatitis, its pancreatic tissue levels are said to be raised nine-fold.¹² It is known to be pro-adhesive for granulocytes and is expressed by a number of cells including endothelial cells. PAF is released from neutrophils when activated by TNF.

Prediction of severity

Prediction of severity is of great benefit to the clinician if it can be assessed accurately early in the disease process by allowing institution of optimal medical care at an early stage, while giving a guide to the development of the well recognised complications and ultimate prognosis.

Systems of scoring severity have been available for many years. Their purpose is to identify those patients with severe attacks of pancreatitis with high sensitivity, so that appropriately aggressive therapy can be instituted. Equally, specificity (ie, the proportion of mild attacks correctly predicted compared with the total number of mild attacks) should be high, so that valuable intensive therapy unit beds are not wasted. Finally, to be of use in practice, predictive criteria for acute pancreatitis should be readily available for stratifying patients into various risk groups at the time of admission.

Ranson's 11 objective measurements is a well-established scoring system. Five values are measured on admission, four of which reflect the intensity of the

Enzyme systems involved in systemic inflammatory response	
● Kallikrein:	activation results in the formation of bradykinin, causing increase in capillary permeability and vasodilatation
● Complement:	activation leads to leukocyte chemotaxis; has a profound influence on the development of subsequent damage to a variety of structures
● Thrombin:	activation may result in the development of disseminated intravascular coagulation
● Phospholipase A2:	activation leads to destruction of cell membranes and lung surfactant
● Elastase:	leads to the destruction of blood vessels
● Chymotrypsin:	results in synthesis of damaging oxygen-derived free radicals

Box 1

Figure 2 The process of protease inactivation in acute pancreatitis

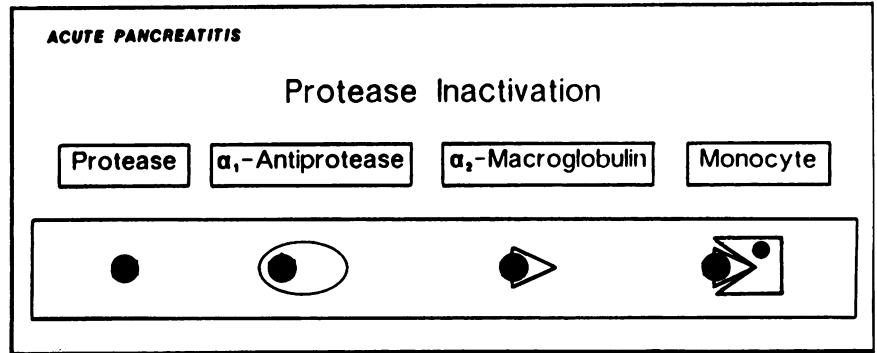
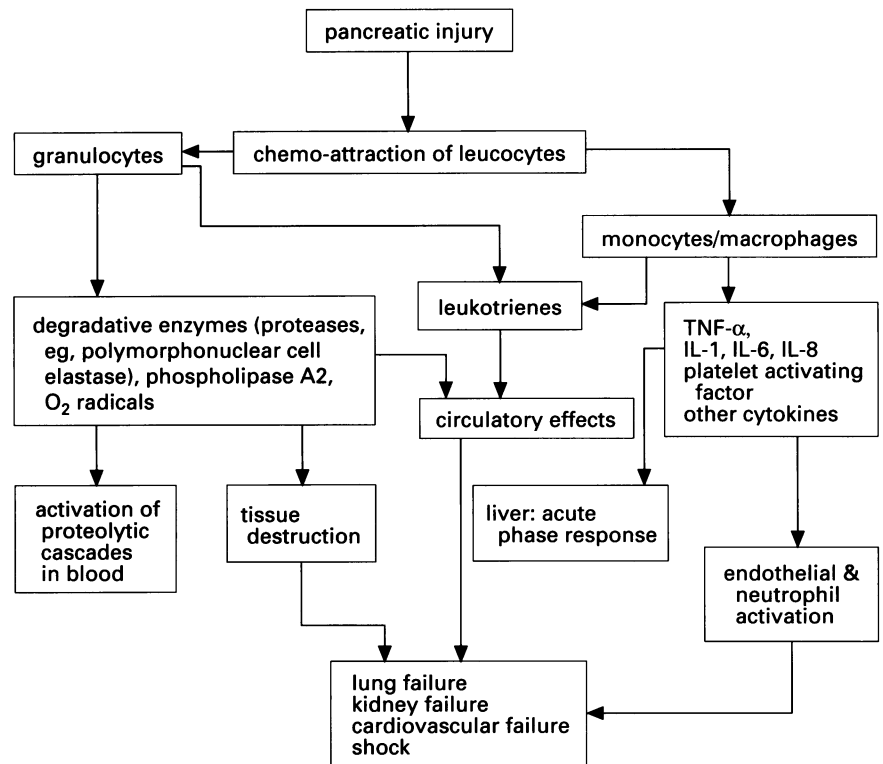


Figure 3 Pathophysiological mechanisms in acute pancreatitis



inflammatory process. The remaining six measurements are completed after 48 h and measure systemic complications and fluid sequestration (box 2). This scoring system has rationalised the basis of supportive treatment in acute pancreatitis by providing some objective comparison of severity. However, its very structure makes it an unsuitable system to use as a basis for the initiation of early appropriate treatment. Its limitations include the fact that laboratory investigations may take 48 h to be processed, so an opportunity for appropriate therapy may be lost, and also that all 11 parameters are necessary for the best prediction, which is often difficult in a clinical setting. Further, the system is only a predictor of severity within the initial 48 h of hospitalisation, ie, it is a single snapshot in a whole feature-length film. Therefore, while it may be reasonably sensitive for major organ failure, it is a poor predictor for later pancreatic necrosis. However, it remains a reliable yardstick by which other scoring systems and alternative indicators of inflammation may be gauged. Imrie's prognostic score, which possesses the same benefits and limitations, correlates well with Ranson's system.

More recently, systems for quantifying acute illness have been developed and adopted for use in assessing acute pancreatitis, the most promising of which is the APACHE II scoring system (Acute Physiology and Chronic Health Evaluation),¹³ a multivariate scoring system, again measuring objective parameters (vital signs and biochemical analysis), while taking into account the patient's pre-morbid state and age. This has the effect of assessing the severity of disease, while considering the individual's reserve for recovery. Here it has been shown to be both specific and sensitive, not only for initial assessment of severity, but also in sequential scoring for subsequent organ failure and pancreatic necrosis.

Ranson's scoring system	
<i>On admission:</i>	
●	age > 55 years
●	white cell count > 16 000
●	lactate dehydrogenase > 600 U/l
●	aspartate transaminase > 120 U/l
●	glucose > 10 mmol
<i>Within 48 h:</i>	
●	haematocrit fall > 10%
●	urea rise > 0.9 mmol/l
●	calcium < 2 mmol
●	pO ₂ < 60 mmHg
●	base deficit > 4
●	fluid sequestration > 6000 ml

Box 2

Serum markers

To date, the gold standard for diagnosis of acute pancreatitis has been a raised serum amylase due mainly to its high sensitivity. Various other inflammatory markers in acute pancreatitis have been assessed and their relation to the clinical course examined, both as a guide to treatment to supplement the established scoring systems, and also to predict later complications of pancreatic necrosis. The following are of particular interest:

C-Reactive protein is an acute phase protein which has been extensively investigated in relation to time course, severity of acute pancreatitis, and clinical outcome. Production of C-reactive protein is a non-specific response to inflammation, and has been extensively used in conditions such as ulcerative colitis as an indicator of inflammatory activity. In acute pancreatitis it has been shown that serum C-reactive protein concentrations are higher in patients with a severe outcome compared to those who run a milder course. Also, C-reactive protein can identify severe acute pancreatitis which may not be obvious at the outset.¹⁴

Polymorphonuclear elastase has been shown to be a sensitive marker for the early identification of acute inflammation, activation of granulocytes and subsequent identification of inflammatory complications.¹⁵ It has been shown to be a most useful marker of severity of disease due to its high sensitivity and specificity. Its peak value occurs early in the disease and therefore, by implication, it is most useful for predicting complications.

α 2-Macroglobulin has, as mentioned previously, a protective role in 'collecting' activated proteases, which are cleared from the circulation, and complexing with them by the action of the reticulo-endothelial system. In this case, the consumptive depletion of α 2-macroglobulin is shown to correlate with the disease severity¹⁶ and ultimate prognosis.

Phospholipase A2 concentrations rise to high values in severe acute pancreatitis, especially in those who develop complications such as necrosis, respiratory failure, shock or sepsis.

The complexity of acute pancreatitis is such that any single criterion listed above cannot accurately predict prognosis, unlike the continuous day-to-day monitoring, which can be achieved using the APACHE-II critical care scoring system.

Mild acute pancreatitis has histologically been demonstrated to consist of interstitial oedema, whereas the most severe forms consist of areas of necrosis due to activation of protease enzyme precursors which subsequently produce a digestive form of necrosis.¹⁷ It is now possible to quantify this protease activation directly, so removing the need to rely on surrogate markers which merely reflect the severity of inflammation and correlating this with subsequent necrosis.

When trypsinogen is activated, it has a five amino-acid sequence cleaved from the N-terminal end of the enzyme precursor. A recent immunoassay has been developed using antibodies directed at the C-terminal portion of this amino acid sequence known as trypsinogen activation peptides. Raised concentrations of trypsinogen activation peptides measured in peritoneal fluid from patients with acute pancreatitis have been shown to correlate with pancreatic necrosis with a sensitivity of 89% and a specificity of 85%, which is comparable to contrast-enhanced, computed tomography (CT), at present the best method of detection.

Imaging

Using conventional ultrasonography the pancreas can be visualised in only 45% of cases due in part to the ileus that often overlies it. CT of the abdomen provides the best means of visualising the pancreas where it is very accurate in diagnosing pancreatitis and its local complications (figure 4). Over 90% of CT scans are abnormal in patients with acute pancreatitis, and these changes persist for seven days in around 85% of cases.¹⁸

Severity of pancreatitis can be inferred by CT, based on the extent of pancreatic enlargement, presence of peripancreatic inflammatory changes and the number and location of fluid collections. By grading this inflammation, a clear relationship has been demonstrated between early CT findings and the clinical course of acute pancreatitis using contrast-enhanced dynamic

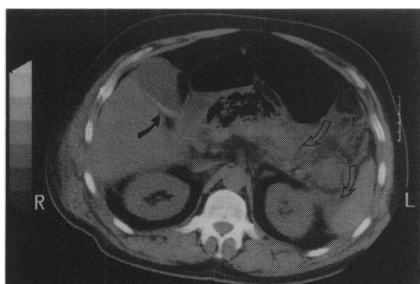


Figure 4 CT scan demonstrating pancreatic and peripancreatic oedema including the pararenal space (hollow arrows). Note also the presence of a gallstone (black arrow). With assistance from Dr CJ Garvey, Royal Liverpool University Hospital

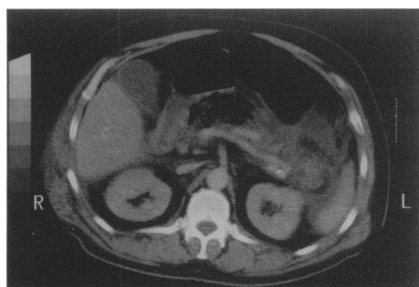


Figure 5 Post-contrast CT scan. Pancreatic necrosis demonstrated by poor enhancement of the pancreas, with the further complication of gas within the body of the pancreas caused by infecting organisms. With assistance from Dr CJ Garvey, Royal Liverpool University Hospital

Grading system for pancreatitis¹⁹

- Grade A: normal pancreas
- Grade B: pancreatic enlargement, focal or diffuse
- Grade C: pancreatic enlargement with mild peripancreatic inflammation
- Grade D: enlarged pancreas associated with fluid in the anterior pararenal space
- Grade E: enlarged pancreas with fluid collections in at least two areas.

Box 3

tomography where, after a rapid bolus of intravenous contrast, areas of the pancreas with reduced perfusion can be readily identified (figure 5).^{19,20} Balthazar and colleagues have provided such a grading system (box 3).¹⁹

In the early phase of inflammation, mild pancreatitis is seen as a homogenous enlargement, and recovery follows within a week or two. In more severe inflammation a pancreatic phlegmon can be seen, which reflects the presence of severe retroperitoneal inflammation and presents a continuum with pancreatic necrosis and subsequent sepsis, secondary to bacterial contamination. It is this series of events that has aroused most interest in identifying areas of necrosis, or danger of necrosis, which is the prerequisite of pancreatic infection. These areas can now be identified with great accuracy, and certainly more accurately than any serum markers. From the information CT provides therefore, we can see the severity of local inflammation, identify areas of necrosis and hence those individuals in danger of infection.

Who, then, needs a CT scan? Biochemical and general clinical observations correlated in a scoring system can aid the clinician in treatment and likely prognosis, while inflammatory markers may add sensitivity. In the later inflammatory stages, CT remains the most valuable investigation, when areas of necrosis are well established and further evolution of the disease process is less likely.²¹

Therapeutic trials

In acute pancreatitis, 80% of patients will follow an uncomplicated course. For these patients a supportive regime of resting the gut, maintaining hydration with intravenous fluids, appropriate parenteral analgesia, and careful observation of their clinical course and biochemical trends is sufficient to ensure recovery from the acute phase of the illness.

The remaining 20% will experience a more turbulent course due to the severity of the pancreatic inflammation and proteolytic damage resulting in gross systemic upset. For these patients more intensive care is necessary to manage the organ failure that often ensues. No specific treatment has been found to prevent the occurrence of these life-threatening sequelae, despite the fact that at-risk patients can be identified at an early stage. Attempts to develop such a treatment have been formulated by looking at the pathogenesis and the ways in which to antagonise, remove or inhibit these inflammatory mediators. Accepting that injury within the cell precedes injury to the organ and subsequently the system, therapeutic efforts have concentrated on the site of initiation. Enzymatic damage of pancreatic acinar cells by activated proteases has promoted the use of specific anti-protease treatment. Trasylol (aprotinin), a protease inhibitor developed 30 years ago, was demonstrated to be of no benefit (MRC trial 1974-78).²² Its lack of efficacy was related to an inability to enter the acinus to exert its effect. Subsequent trials have been conducted with a lower molecular weight agent, gabexate mesilate, which inhibits proteases as well as phospholipase A2.²³ This again was shown to confer no benefit in terms of morbidity and mortality, although administration prior to induction of pancreatitis was shown to be effective in mice.²⁴ In Japan, however, this medication is accepted to be of value in acute pancreatitis, to the point that it is deemed unethical not to use it.²⁵

It is apparent that an effective treatment for acute pancreatitis must be therapeutic when administered some time after the onset of the disease, when the patients present themselves to the doctor. It is appropriate that management should therefore address the propagating factors rather than the initiating events.

The analogue of somatostatin, octreotide, has been used as a specific treatment based on the knowledge that it both inhibits the hormone responsible for stimulation of pancreatic enzyme precursor production and its release into the ductal system. This would have a dual effect of reducing any ductal hypertension while inhibiting the release of potentially damaging hormone precursors. However, as stated above, apical exocytosis is known to be deficient in the face of continuing zymogen production. Basolateral transport of zymogen content has been shown to occur into the pancreatic interstitium where activation will result in proteolytic damage. It has also been demonstrated that octreotide further reduces pancreatic blood flow. Accordingly, octreotide has been shown to confer no benefit in this situation.²⁶ Perhaps further attempts to maintain pancreatic secretion will prove more fruitful.

Similarly, atropine has been used as a standard treatment since the 1940s. It is known to reduce the resting pressure of the sphincter of Oddi, and to assist in reduction of intraductal pressure, while its antispasmodic effects reduce gastric acid secretion and thus secretin-mediated pancreatic stimulation. It was only as

recently as the late 1970s that it was clinically evaluated and found to confer no benefit over other non-specific conservative measures.²⁷

Moving on to circulating proteases, a further therapeutic possibility would be to inhibit these in the peritoneal exudate and later in the blood. In the pathogenesis of the systemic sequelae, circulating proteases overwhelm the endogenous protease-binding proteins, notably α 2-macroglobulin. Replenishment of these by intravenous or intraperitoneal infusion of fresh frozen plasma has been shown to be effective in rats,²⁸ although little impact has been demonstrated in human studies.

Peritoneal lavage has been advocated as a treatment in the early stages of acute pancreatitis since the peritoneal cavity forms a reservoir of pancreatic enzymes, and lavage at an early stage may reduce the systemic absorption of these damaging compounds. This has shown a reduction in early mortality in some studies.²⁹

PAF, a biologically active phospholipid, is a potent inflammatory mediator and largely responsible for the cascade of inflammatory events by way of neutrophil priming. The term 'systemic inflammatory response syndrome' has been introduced to describe the exaggerated inflammatory reaction involved in severe acute pancreatitis. PAF-receptor antagonists have been developed and are now undergoing phase III clinical trials with promising results. More recently still, the enzyme PAF-acetylhydrolase has been isolated and its recombinant product shown to block 80% of its pro-inflammatory effects.³⁰ These promising therapeutic advances are aimed at damping down the inappropriate inflammatory response rather than tackling the initiating factors.

Looking historically at the management of acute pancreatitis, some of the treatments have clearly failed due to a mistaken understanding of the pathogenesis of the disease. Others have failed although the direction of treatment is appropriate to the pathogenesis. Resolution of the problem can be helped by carefully conducted clinical trials of therapeutic agents, while studying their effects in good, reproducible animal models of acute pancreatitis.

Surgical intervention

It is recognised that 4–8% of patients with gallstones will develop acute pancreatitis, and the mortality resulting from this is in the order of 10%. Once pancreatitis has occurred in this situation, there is greater than 50% chance that a second episode of acute pancreatitis will occur within six months of the first attack.³¹ While this is rare if cholecystectomy and clearance of the common bile duct of stones has been undertaken, patients who have stones retained in the common bile duct frequently develop a recurrent episode.

It is accepted that biliary pancreatitis is initiated by an obstruction, albeit transient, of the ampulla of Vater by a migrating stone. It is not possible to predict which stones will pass and which will obstruct the ampulla. A further sequel to this scenario is the development of ascending cholangitis, which is in itself an indication for intervention, while persistent pancreatic duct obstruction has been implicated in the observed increase in pancreatic necrosis. For these reasons, some authors recommend early duct exploration to determine the presence of any stones and remove those found.³² This would appear to address two issues: (a) removal of obstruction, so reducing the risk of cholangitis while reducing pancreatic duct pressure to reduce the theoretical risk of subsequent pancreatic necrosis, and (b) prophylaxis.

It is equally apparent that biliary pancreatitis may be devastating even in the absence of retained gallstones. The age-old method of dealing with gallstone-induced pancreatitis was to allow the pancreatic inflammation to subside and then re-admit the patient for cholecystectomy and exploration of the common bile duct. This obviously runs the risk of recurrent pancreatitis, especially if there are stones within the common bile duct.

Early surgical intervention involving open cholecystectomy (within 48 h of admission) or later surgery (after 48 h) on the same admission have been compared to see if patients would benefit from prompt treatment of their cholelithiasis. This study produced conflicting results until disease stratification was allowed for,³³ which showed that while there was no difference observed in terms of morbidity or mortality for mild disease, patients having more than three of Ransons' criteria showed a substantial increase in mortality. Hence, in treating the milder end of the spectrum in this way, one would only be addressing the problem of prophylaxis. How then can intervention affect the outcome of severe acute pancreatitis?

In a study conducted by Neoptolemos³⁴ there was prospective random allocation of patients to early endoscopic retrograde cholangiopancreatography

(ERCP) and endoscopic sphincterotomy or noninterventional treatment, with patients stratified according to the modified Glasgow scale into mild and severe. It was shown that the morbidity was significantly reduced (17% vs 34%) in the severe group with no significant difference in mortality. It is reasonable to assume that those benefitting from this procedure had impaction of gallstones, and so the identification of these patients could be further aided by ERCP, or a blood profile suggestive of biliary obstruction.

Laparoscopic surgery is now increasingly advocated for the management of cholelithiasis, although its application to cholecystectomy following gallstone pancreatitis has not been clearly defined. Bearing in mind that the need for common bile duct exploration is said to be 70% at the time of hospital admission, 20% after four days and 14% at one week,³⁵ then if surgery is to be undertaken within the same admission, one must be prepared to visualise the common bile duct. This is undertaken laparoscopically by way of the cystic duct, which allows removal of small stones only. Laparoscopic choledochotomy is a much more hazardous procedure, but it is only a matter of time before technological advances make this a safer approach while retaining the evident advantages of minimal access surgery.

Conclusion

From a vast array of aetiologies acting through different mechanisms to reach an unknown 'common pathway', we now know that acute pancreatitis produces a predictable series of events governed by a cascade system, starting with protease-induced inflammation through to activation of diverse inflammatory systems. Some advances have been made in quantifying the disease process in the individual, while therapeutic advances have allowed us to address the individual components responsible for the disease process. It has become apparent that prevention of protease activation in established pancreatitis is too late to be of any benefit and that future efforts should be in the direction of a damage-limitation exercise, aimed at the local and systemic responses.

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