Acute Pancreatitis and Organ Failure: Pathophysiology, Natural History, and Management Strategies

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Acute pancreatitis is a common condition that carries a significant risk of morbidity and mortality. It is characterized by intra-acinar cell activation of digestive enzymes and a subsequent systemic inflammatory response governed by the release of proinflammatory cytokines. In 80% of patients the disease runs a self-limiting course, but in the rest, pancreatic necrosis and systemic organ failure carry a mortality rate of up to 40%. The key to management is early identification of the patients liable to have a severe attack and require treatment in a high-dependency or critical-care setting by a specialist team. In gallstone-induced pancreatitis, early removal of ductal calculi by endoscopic sphincterotomy is indicated. The use of prophylactic antibiotics to prevent the infection of pancreatic necrosis remains controversial, but once established, infected necrosis must be removed. Although a number of techniques to accomplish this end have been described, minimally invasive techniques are gaining in popularity.

Introduction

Acute pancreatitis is a common condition that is increasing in incidence but still carries a mortality rate of up to 10% to 15% [1••]. The most common causes in Western populations are gallstones and alcohol, but many other factors have been described [2,3], and there is almost certainly an underlying common pathogenetic mechanism. The treatment of severe acute pancreatitis has changed markedly over the past 15 to 20 years, and recent advances have, at last, started to improve the prognosis for patients suffering from this disease.

Pathophysiology

Early events: calcium and enzyme activation

Under physiologic conditions, normal secretion of inactive enzyme precursors from the acinar cell occurs in response to secretagogues, a process associated with local oscillatory calcium signals. Premature activation of digestive enzymes is one of the first detectable events, and is in contrast accompanied by an abnormal sustained global elevation of cytosolic calcium [4•].

Ligation of the main pancreatic duct in rats has been shown to lead to the accumulation of active trypsin and Ca^{2+} within the acinar cell [5]. In fact, an increase in Ca^{2+} is responsible for the activation of digestive enzymes. An abnormal elevation of cytosolic calcium ($[Ca^{2+}]_i$) has been demonstrated after hyperstimulation of acinar cells by a cholecystokinin (CCK) analogue [6•], after ligation of the pancreatic duct in experimental animals [7,8], and after application of bile salts to isolated acinar cells [9]. In these models, suppression of the intracellular Ca^{2+} rise with the Ca^{2+}-chelating agent BAPTA reduced the degree of enzyme activation and ameliorated the systemic effects of acute pancreatitis.

Active digestive enzymes form large intracellular vacuoles by co-localization with lysosomal enzymes such as cathepsin B [10]. A great deal has been written about the mechanism of enzyme co-localization and whether cathepsin B is responsible for the activation of trypsin, but no definitive consensus has been reached. The evidence from studies of hereditary pancreatitis, however, tends to support the primary auto-activation of trypsin [11•]. In this disease, patients suffer from repeated attacks of acute pancreatitis from childhood. A number of point mutations in the gene coding for cationic trypsinogen have been described, all of which are thought to act by rendering activated trypsin resistant to auto-digestion and inactivation [12]. More recently, "loss-of-function" mutations of this gene have been described that appear to protect against the development of acute pancreatitis [13]. These clinical findings are supported by experiments on isolated pancreatic acinar cells using specific fluorescent enzyme substrates in which hyperstimulation led to the initial activation of trypsin and subsequent recruitment of cathepsin B [14].

Although cathepsin B is capable of activating trypsinogen to trypsin, and it has been suggested that activation of trypsin by cathepsin B is the pathologic trigger for acute pancreatitis [15,16], in both of these studies, the first involving a cathepsin B inhibitor and the second cathepsin B knockout mice, the severity of pancreatitis was reduced but not abolished. A separate study has demonstrated that pro-cathepsin B and mature cathepsin B are secreted together with trypsinogen and trypsin into the pancreatic juice under normal circumstances [17]. In this study, the effect of cathepsin B on three of the common hereditary pancreatitis-associated mutant forms of trypsinogen was also studied, and the rate of cathepsin B–induced trypsin activation was no higher with recombinant mutant cationic trypsinogen than with wild type. Thus, trypsin autoactivation appears to be the key initiator rather than the influence of cathepsin B, although the latter may play a role in amplification of the enzyme response.

Cytokines and the systemic response

One of the key features of acute pancreatitis is a severe systemic inflammatory response driven by circulating cytokines [18]. Active digestive enzymes are potent stimulators of macrophages and can induce the production of such proinflammatory cytokines as tumor necrosis factor (TNF)-α and interleukin (IL)-1β in experimental systems [19]. Intraperitoneal injection of active trypsin induced the production of TNF-α within the peritoneum, whereas injection of inactivated, heat-treated trypsin had no effect. Pancreatic acinar cells, too, are capable of producing proinflammatory cytokines [20], and they appear to do so in response to the presence of active digestive enzymes. The ascitic fluid from animals with acute pancreatitis has been shown to contain a wide variety of proinflammatory cytokines in high concentrations [21], and this fluid can induce further cytokine production if administered to other animals [22]. From the peritoneal cavity, cytokines rapidly enter the systemic circulation via the thoracic duct and from there affect many body systems and are responsible for the systemic inflammatory response (SIRS) typical of acute pancreatitis and multiorgan dysfunction syndrome (MODS) [21]. Both the CC and CXC families of cytokines are implicated in the pathogenesis of the local and systemic inflammatory responses, whereas the preprotachykinin-A (PPT-A) gene products, substance P and neurokinin (NK)-A, are involved in mediating lung injury in acute pancreatitis [23–26].

The CC cytokines, which include monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein (MIP)1-α, and regulated upon activation, normal T-cell expressed and secreted (RANTES) primarily activate monocytes, whereas the CXC chemokines, such as IL-8, growth-related oncogene (GRO)-α, and epithelial neutrophil-activating protein (ENA)-78, are potent neutrophil chemoattractants and activators; substance P and NK-A play important roles in neurogenic inflammation [23–26].

Levels of circulating cytokines correlate with disease severity [21,25,27•,28]. Evidence suggests that early inhibition of proinflammatory cytokine activity, such as Met RANTES (a CC chemokine receptor antagonist) [24], and administration of anti-inflammatory cytokines such as IL-10 [29], can decrease the severity of experimental pancreatitis in animals, but these findings have not been replicated in humans.

Cytokine production is governed by a number of transcription factors, prominent among which is NFκB. This transcription factor is activated in the pancreas within 30 minutes of the onset of acute pancreatitis [30] and within distant tissues shortly thereafter [31]. Inhibition of NFκB has been shown to ameliorate experimental acute pancreatitis [23,32,33], which may prove to be a useful approach to prevention of the systemic effects of acute pancreatitis. Inhibition (or genetic deletion) of cyclooxygenase (COX)-2, which is upregulated in response to a variety of proinflammatory stimuli (*eg*, IL-1B, TNF-α, and bacterial lipopolysaccharide), also inhibits local and systemic injury attributable to proinflammatory neutrophils [34].

Natural History

In 80% of patients who develop pancreatitis the disease resolves itself. The other 20% of patients develop severe disease with systemic organ failure and often (but not invariably) extensive pancreatic necrosis, which is associated with a significant risk of mortality. In a prospective study of 86 patients with pancreatitis, 32% developed severe disease. The mortality rate in the severe group was 43% (in 59% the deaths were due to multiorgan failure), and 50% of the deaths occurred within the first week [35]. The course of severe acute pancreatitis can be divided into an early (14 days from symptom onset) and late phase. In the early phase a systemic inflammatory response develops, which can progress to multiorgan dysfunction. During the initial phase, this organ dysfunction is caused by excessive mediator release rather than pancreatic infection [1••]. This response occurs very quickly after the onset of symptoms, as reflected in the high Acute Physiology and Chronic Health Evaluation (APACHE II) scores in these patients upon hospital admission [36–39].

In this phase surgery is rarely indicated unless there are specific indications [1••]. In the late phase, multiorgan failure is usually secondary to sepsis from infected pancreatic necrosis [36,40]. Without surgery, the mortality of these patients approaches 100%, and with surgery this can be reduced to 24% to 39% [36,41,42].

Management

Once a diagnosis of pancreatitis has been established, four important issues need to be addressed: resuscitation and treatment of any organ dysfunction, identification of those who have or will develop severe acute pancreatitis, deter-

mination and treatment of the underlying cause, and prevention and treatment of infected necrosis.

Resuscitation and treatment of organ dysfunction

Patients who present with acute pancreatitis are usually dehydrated due to vomiting and third space losses caused by the pancreatic inflammation. Rapid rehydration should ensue with the appropriate crystalloid solutions. To ensure that adequate resuscitation has taken place, a urinary catheter should be inserted. Depending on the clinical state of the patient, more invasive monitoring, such as central venous lines, might be required. Because it is important to recognize associated organ dysfunction, which can progress to organ failure, full blood count, electrolytes, liver function tests, and arterial blood gases should be performed. Patients who develop organ failure need high-dependency or intensive-care support.

Identification of those who have or will develop severe acute pancreatitis

Early identification of this subgroup of patients allows for alteration in their management, including early endoscopic sphincterotomy (ES) by endoscopic retrograde cholangiopancreatography (ERCP), and permits the most appropriate use of high-dependency or intensive-care resources [1••]. Several clinical, biochemical (inflammatory or pancreatic breakdown products), and radiologic prognostic scoring systems have been proposed to identify this group, but all have their limitations. The most useful is a combination of clinical assessment by an experienced physician and C-reactive protein greater than 150 mg/L at 48 hours, although urinary trypsinogen activation peptide or serum amyloid A may supersede this [38,39]. These clinical and biochemical parameters do not directly predict the extent of necrosis, which is best assessed by contrast-enhanced computed tomography (CECT) [1••,37].

Determination and treatment of the underlying cause

Early ascertainment of the cause of the pancreatitis as gallstones (the most common) may change the approach to clinical management [1••]. Ultrasound is recommended as the initial investigation, although it may be replaced with magnetic resonance cholangiopancreatography (MRCP) as the latter technique improves and becomes more widely available. MRCP provides accurate and noninvasive assessment of the main bile duct, thus selecting those likely to benefit the most from ES, and identifies those with necrosis, an alternative to CECT [43].

Significant controversy has been expressed over the early use of ERCP and ES in patients with severe acute gallstone pancreatitis. A recent review (including the three randomized controlled trials) concluded that early ERCP and ES are indicated in patients with associated cholangitis or increasing jaundice, but in those without evidence of biliary obstruction the role of ES is less conclusive [1••]. In patients with mild acute gallstone pancreatitis, ERCP is not routinely indicated but should be reserved for those with proven choledocholithiasis. In those unfit for subsequent cholecystectomy, ES is an alternative [1••]. Those with mild acute gallstone pancreatitis should undergo cholecystectomy before discharge because of the high incidence of recurrent pancreatitis [1••].

Prevention and treatment of infected pancreatic necrosis

Antibiotics

Whether prophylactic antibiotic treatment should be given routinely remains controversial, although the International Association of Pancreatology recommends antibiotics only for patients with CT-proven necrosis to reduce the rate of infection if not final outcome (survival) [1••]. The choice of antibiotic seems to be imipenem or a quinolone, given the good peripancreatic tissue penetration and broad spectrum of these agents against likely pathogens [44]. Arguments against the use of antibiotics are prompted by concern over the poor quality of randomized trials, with insufficient numbers of patients to provide a definitive answer, and the increasing prevalence of multiresistant organisms and fungal infection, although this is disputed [45]. Recent studies [46,47] have shown increased mortality in patients with fungal infections, but these results have been questioned [44]. Additionally, the development of fungal infection was associated with prolonged courses of antibiotics [47]. Two recent multicenter randomized, controlled trials have found no evidence to support the use of prophylactic antibiotics, and these findings may result in radical rethinking of the problem [48,49].

Riche *et al.* [50] attempted to identify a subgroup of patients with necrosis who were more likely to develop infected necrosis, thus selecting those who might benefit from antibiotics. They found that elevated IL-6 and procalcitonin soon after hospital admission were predictors of infected necrosis and that low levels in both groups had a high negative predictive value of infected necrosis. The role of selective gut decontamination is unknown, and further studies are required. Although this approach has been shown to reduce ventilator-associated pneumonia, this is not manifested in a reduction in mortality [51]. The evidence for a reduction in pancreatic infection is lacking, and concerns over the selection of multiresistant organisms remain.

Nutrition

The traditional approach of "resting the pancreas" after an attack of pancreatitis by restricting oral intake is based on physiologic evidence that the presence of food substances in the foregut stimulates pancreatic secretion, compared with parenteral nutrition [52]. However, this increased secretion of pancreatic enzymes has not been associated with an adverse effect on outcome in patients with severe pancreatitis. Over the past decade, a number of centers have introduced early enteral feeding in patients with severe acute pancreatitis. These results were recently reviewed, leading to the conclusion that nasoenteral feed-

ing is less expensive, safer (reduced septic and electrolyte complications), and more physiologic than parenteral nutrition and that it is tolerated well by 80% of patients [53••]. A randomized trial of 54 patients published in 2002 confirmed these results but raised the issue of the ideal calorific target [54]. In the enterally fed group, only 54% met their estimated nutritional requirements, compared with 88% of those receiving parenteral nutrition. The authors felt that the increased complication rates associated with parenteral nutrition might have been related to the increased rates of hyperglycemia, which has been associated with adverse outcomes in critically ill patients.

Enteral nutrition also plays a role in modulating bacterial translocation [53••,55]. A recent double-blind, randomized, controlled trial comparing lactobacillus and fiber supplementation to early enteral nutrition with fiber in patients with acute pancreatitis found a reduction in pancreatic sepsis in the treatment group. The study had a number of exclusion criteria (including biliary disease), and it was not limited to those with severe pancreatitis. Thus, further studies are required.

Surgery

Indications for surgery in patients with severe acute necrotizing pancreatitis are now well described [1••]. Infected necrosis (proven by CECT-guided fine-needle aspiration of the pancreatic necrosis or extraintestinal gas on CECT) requires surgical debridement, although there are anecdotal reports of successful conservative treatment [56]. Alternatively, sterile necrosis can be managed conservatively in the majority of patients, but a subgroup with extensive necrosis have persisting systemic or local symptoms despite many weeks of maximal conservative treatment. Surgical intervention in this subgroup seems warranted but should be delayed to reduce the mortality risk [1••,42,46].

The mortality rate following surgery for pancreatic necrosis remains high. In the largest reported series, among 340 patients, the overall mortality rate was 39% [36]. The techniques described were transperitoneal, retroperitoneal, minimal access, and percutaneous [36,40,57•,58]. Postoperative regimens varied, with planned repeat laparotomies, open packing, or closed postoperative lavage showing similar results, but there are no randomized trials to indicate which technique is superior. A significant increase in the number of procedures and the duration of postoperative hospital stay has been found with the minimally invasive technique, compared with traditional open necrosectomy, but the need for intensive care is also significantly reduced [37].

Conclusions

The understanding of the pathophysiology and natural history of acute pancreatitis has been greatly improved in the past 15 years, and this knowledge has led to rationally based approaches to therapy. Recent investigation indicates that calcium signaling and trypsinogen activation are the likely basis for acute pancreatitis as well as the mechanism underlying the adverse effects of the systemic inflammatory response syndrome. This understanding is likely to lead to the development of specific drug therapy.

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