Acute Pancreatitis – Etiology, Pathogenesis, Pathophysiology and The Current Trend in Its Management and Prevention

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ABSTRACT

Acute pancreatitis is an episode of cellular injury and inflammation of the pancreas parenchyma triggered by autodigestion of pancreatic parenchyma by abnormally activated pancreatic enzymes, its manifestations ranges from mild, moderate-severe and severe pancreatitis. Most episode of acute pancreatitis resolved completely while some develop recurrent acute pancreatitis and in turn progressing to chronic pancreatitis and its sequelae. While many etiologies known may cause acute pancreatitis, current theories propose three mechanism that may be involved in the pathogenesis of acute pancreatitis i.e. duct obstruction, direct acinar injury and defective intracellular transport. Recommendations from current guidelines are very useful to treat acute pancreatitis, few groundbreaking changes from the previously dated guidelines on treating acute pancreatitis are also made, providing us dated evidence-based approach to treat acute pancreatitis. Judicious and aggressive treatment are needed to minimize the damaged area of involved pancreatic parenchyma. Holistic prevention is needed to minimize the incidence of acute pancreatitis, pushing down the numbers of recurrent acute pancreatitis and ultimately may decrease the incidence of chronic pancreatitis and its sequelae.

Keywords: *pancreatitis, pathophysiology, autodigestion, parenchyma, obstruction*

ABSTRAK

Pankreatitis akut merupakan suatu episode jejas seluler dan radang dari parenkim pankreas yang dicetuskan oleh autodigesti dari parenkim pankreas oleh enzim pankreas yang teraktivasi secara tidak normal, manifestasi dari pankreatitis akut dapat berupa pankreatitis akut ringan, sedang-berat dan pankreatitis akut berat. Kebanyakan episode pankreatitis akut sembuh sempurna sedangkan sisanya dapat mengalami pankreatitis akut berulang dan menyebabkan pankreatitis kronik dan sekuelenya. Banyak etiologi yang diketahui dapat menyebabkan pankreatitis akut, teori yang kita ketahui saat ini menyebutkan tiga mekanisma yang diduga terlibat dalam pathogenesis dari pankreatitis akut yaitu obstruksi duktal, jejas asiner pankreas secara langsung dan transpor intraseluler yang defektif. Rekomendasi-rekomendasi dari pedoman tatalaksana pankreatitis akut sangat berguna dalam menangani kasus pankreatitis akut, beberapa perubahan yang drastis dapat ditemui berbeda dari pedoman-pedoman di periode sebelumnya, pedoman tatalaksana yang sekarang memberikan rekomendasi tatalaksana yang terbaru dan berbasis bukti klinis dalam menangani kasus pankreatitis akut. Penanganan yang teliti dan agresif dibutuhkan untuk meminimalisir daerah yang rusak oleh radang pada parenkim pankreas. Pencegahan secara holistic dibutuhkan untuk meminimalisir insidensi dari pankreatitis akut, menekan angka pankreatitis akut berulang dan pada akhirnya dapat mengurangi insidensi pankreatitis kronik dan sekuelenya.

Kata kunci: *pankreatitis, patofisiologi, autodigesti, parenkim, obstruksi*

INTRODUCTION

Acute pancreatitis, which is a discrete episode of cellular injury and inflammation in the pancreas, is triggered by the release of activated digestive enzymes into the pancreas and peripancreatic tissues. With repeated episodes, there can be a shift from acute inflammation, necrosis, and apoptosis to a milieu of chronic inflammation, the activation of pancreatic stellate cells, continued tissue destruction, and ultimately the fibrosis characteristic of chronic pancreatitis.[1] About 21% of patients with acute pancreatitis will have recurrence, and about 8% will develop chronic pancreatitis.[2]

Acute pancreatitis, which is the most common cause of hospitalization for a gastrointestinal condition in the United States, accounts for approximately 275,000 hospitalizations annually. The incidence of acute pancreatitis is increasing in the United States and in many other countries.[1] Pathologically, acute pancreatitis varies from interstitial pancreatitis (pancreas blood supply maintained), which is generally self-limited to necrotizing pancreatitis (pancreas blood supply interrupted), in which the extent of necrosis may correlate with the severity of the attack and its systemic complications.[3]

Post pancreatitis diabetes mellitus (PPDM), exocrine pancreatic insufficiency (EPI) and osteoporosis may occur as the sequelae of chronic pancreatitis. As mentioned earlier, repeated episodes of acute pancreatitis may cause chronic pancreatitis, judicious management and holistic prevention are required to prevent recurrent acute pancreatitis thus may decrease the occurrence of chronic pancreatitis. In general healthy population, primary prevention is required to reduce acute pancreatitis incidence.

ETIOLOGY OF ACUTE PANCREATITIS

They are many etiologies of acute pancreatitis, but the mechanism by which these conditions trigger pancreatic inflammation have not been fully elucidated. Gallstones continue to be the leading cause of acute pancreatitis in most series (30-60%). Alcohol is the second most common cause, responsible for 15-30% of cases in the United States. Acute pancreatitis occurs in 5-10% of patients following endoscopic retrograde cholangiopancreatography (ERCP). Hypertriglyceridemia is the cause of acute pancreatitis in 1.3-3.8% of cases; serum triglyceride levels are usually >1000 mg/dL (>11.3 mmol/L). Other common causes of acute pancreatitis include drugs (azathioprine, 6-mercaptopurine, sulfonamides, estrogens, tetracycline, valproic acid, anti-HIV medications, 5-aminosalicylic acid [5-ASA], Trauma and postoperative pancreatitis. [3]

PATHOGENESIS OF ACUTE PANCREATITIS

Both acute and chronic pancreatitis are initiated by injuries that lead to autodigestion of the pancreas by its own enzymes. Under normal circumstances, the following mechanisms protect the pancreas from self-digestion by its secreted enzymes: (1) Most digestive enzymes are synthesized as inactive proenzymes (zymogens), which are packaged within secretory granules; (2) Most proenzymes are activated by trypsin, which itself is activated by duodenal enteropeptidase (enterokinase) in the small bowel; thus, intrapancreatic activation of proenzymes is normally minimal; (3) Acinar and ductal cells secrete trypsin inhibitors, including serine protease inhibitor Kazal type 1 (SPINK1), which further limit intrapancreatic trypsin activity. Pancreatitis occurs when these protective mechanisms are deranged or overwhelmed.[4]

Pancreatic enzymes, as we discussed, including trypsin, are synthesized in an inactive proenzyme form. Inappropriate intrapancreatic activation of trypsin can in turn cause the activation of other proenzymes such as prophospholipase and proelastase, which then degrade fat cells and damage the elastic fibers of blood vessels, respectively. Trypsin also converts prekalikrein to its activated form, thus brining into play the kinin system and, by activation of coagulation factor XII, the clotting and complement systems as well. The resulting inflammation and small-vessel thrombosis (which may lead to congestion and rupture of already weakened vessels) damage acinar cells, further amplifying intrapancreatic activation of digestive enzymes.[4]

How inappropriate activation of pancreatic enzymes occurs in sporadic forms of acute pancreatitis as mentioned above, is not entirely clear, but there is evidence for at least three major initiating events:

Pancreatic duct obstruction. Whatever the cause, obstruction raises intrapancreatic ductal pressure and leads to the accumulation of enzyme-rich fluid in the interstitium. Although most pancreatic enzymes are secreted as inactive zymogens, lipase is produced in an active form and has the potential to cause local fat necrosis. The death of adipocytes is hypothesized to produce “danger” signals locally that stimulate peri-acinar myofibroblasts and leukocytes to release proinflammatory

cytokines and other inflammatory mediators that initiate local inflammation and promote the development of interstitial edema through a leaky microvasculature. Edema may further compromise local blood flow, causing vascular insufficiency and ischemic injury to acinar cells.

Primary acinar cell injury. Leading to release of digestive enzymes, inflammation and autodigestions of pancreatic tissues, inflammation, and autodigestion of pancreatic tissues. Oxidative stress may generate free radicals in acinar cells, leading to membrane lipid oxidation and the activation of transcription factors, including AP1 and NF-κB, which in turn induce the expression of chemokines that attract mononuclear cells. Increased calcium flux appears to be another important trigger for inappropriate activation of digestive enzymes. When calcium levels are low, trypsin tends to cleave and inactivate itself, but when calcium levels are high autoinhibition is abrogated and activation of trypsinogen by trypsin is favored. It is suspected that any factor that causes calcium levels to rise in acinar cells may trigger excessive activation of trypsin, including certain inherited abnormalities that affect calcium levels.

Defective intracellular transport of proenzymes into intracellular compartment containing lysosomes hydrolases within injured acinar cells. Proenzymes are then activated, the lysosomes are disrupted, and the activated enzymes are released. The role of this mechanism in human acute pancreatitis is not clear.[4]

Cytokines and other inflammatory mediators such as tumor necrosis factor (TNF), interleukins (especially IL-1, IL-6, and IL-8), platelet activating factor (PAF), and endotoxin are released rapidly and predictably from inflammatory cells. The degree of TNF-induced inflammation correlates with the severity of pancreatitis. Cytokines rapidly enter the systemic circulation from peritoneal cavity via the thoracic duct and may affect many body systems and can produce the systemic inflammatory response syndrome (SIRS) and the multiorgan dysfunction syndrome typical of severe acute pancreatitis.[5]

PATHOPHYSOLOGY OF ACUTE PANCREATITIS

Abdominal pain is nearly universal and a hallmark presentation of acute pancreatitis. The pain of acute pancreatitis is thought to derive in part from stretching

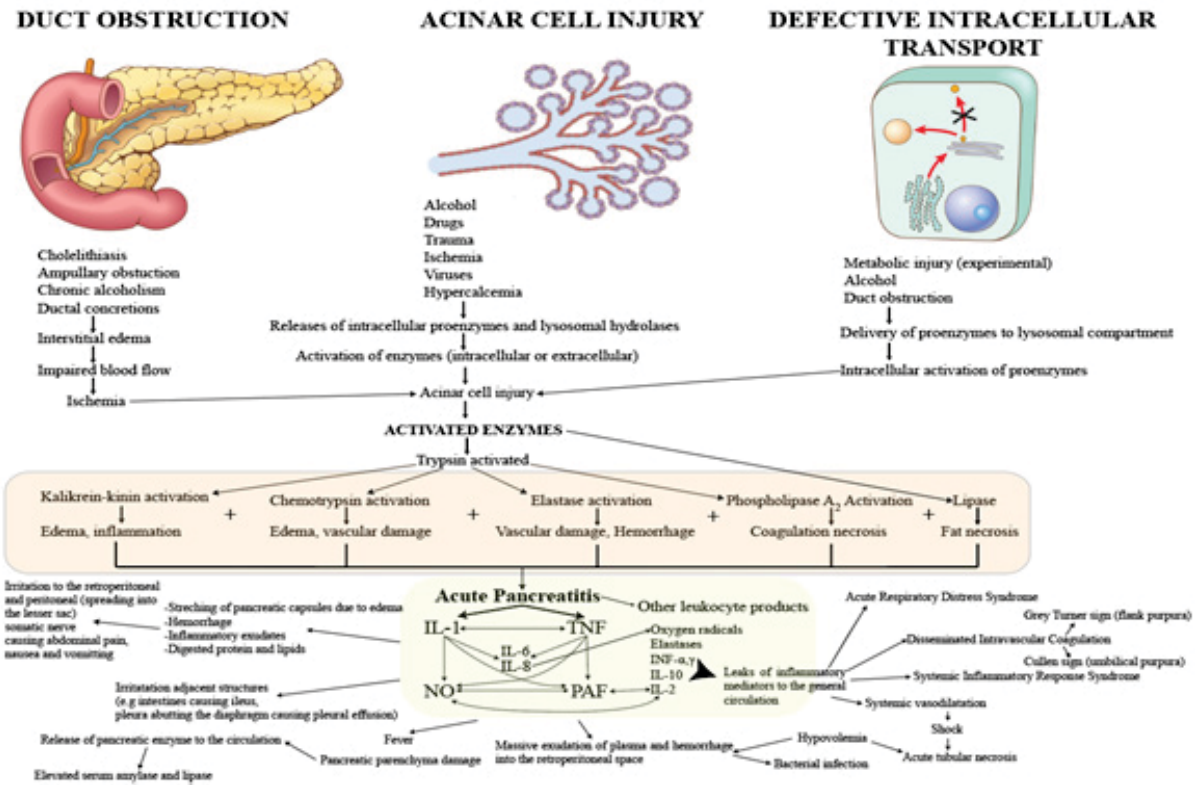

Figure 1. Proposed mechanism causing acute pancreatitis and its pathophysiology[4,5,6,7]

of the pancreatic capsule by distended ductules and parenchymal edema, inflammatory exudate, digested proteins and lipids, and hemorrhage. In addition, these materials may seep out of the parenchyma into the retroperitoneum and lesser sac, where they irritate retroperitoneal and peritoneal sensory nerve endings and produce intense back and flank pain.[5]

Stretching of the pancreatic capsule may also produce nausea and vomiting. Increasing abdominal pain, peritoneal irritation, and electrolyte imbalance (especially hypokalemia) may cause a paralytic ileus with marked abdominal distention. If gastric motility is inhibited and the gastroesophageal sphincter is relaxed, they may be emesis. Both small and large bowel often dilate during an acute attack. Sometimes only a localized segment of bowel dilates.[5]

Almost two-thirds of patients with acute pancreatitis develop fever. The pathophysiologic mechanism responsible for fever involves the extensive tissue injury, inflammation, and necrosis and release of endogenous pyrogens, principally IL-1, from polymorphonuclear leukocytes into the circulation. In most cases of acute pancreatitis, fever does not indicate a bacterial infection. However, persistent fever beyond the fourth and fifth day of illness – or spiking temperatures to 40°C or more –may signify development of infectious complications such as infected peripancreatic fluid collections, infected pancreatic necrosis, or ascending cholangitis.[5]

Shock may occur in severe acute pancreatitis as a result of several interrelated factors. Hypovolemia results from massive exudation of plasma and hemorrhage into the retroperitoneal space and from accumulation of fluid in the gut as a result of ileus. Hypotension and shock may also result from release of kinins into the general circulations. For example, activation during acute inflammation of the proteolytic enzyme kallikrein results in peripheral vasodilation via liberation of the vasoactive peptides, bradykinin and kallidin. Cytokines like PAF, a very potent vasodilator and leukocyte activator, have been implicated in the development of shock and other manifestations of the SIRS. The contracted intravascular volume combined with the hypotension may lead to myocardial and cerebral ischemia, respiratory failure, metabolic acidosis, and decreases urinary output or renal failure as a result of acute tubular necrosis.[5]

Tissue factor release and expression during proteolysis may cause activation of the plasma coagulation cascade and may lead to disseminated intravascular coagulation (DIC). In other cases, hypercoagulability of the blood is thought to be due to elevated concentrations of several coagulation factors, including factor VIII, fibrinogen, and perhaps factor V. Clinically affected patients may present with hemorrhagic discoloration (purpura) in the subcutaneous tissues around the umbilicus (Cullen sign) or in the flanks (Grey Turner sign).[5]

Pulmonary complications are a dreaded manifestation of severe acute pancreatitis and occur in 15-50% of patients. The severity of pulmonary complications can vary from mild hypoxia to respiratory failure (acute respiratory distress syndrome [ARDS]. It is estimated that 50% of early deaths in patients with severe acute pancreatitis are associate with respiratory failure due to profound acute lung injury. The pathophysiology of this acute lung injury appears to involve an increase in permeability of the alveolar-capillary membrane. The endothelial cell destruction in the alveolar capillaries may be mediated by circulating activated pancreatic enzymes including elastases and phospholipase A_2. Pulmonary surfactant, another important alveolar barrier, appears to be destroyed by phospholipase A_2.[5]

Acute pancreatitis may be accompanied by a small (usually left-sided) pleural effusion. The effusion may be reactive and hence secondary to a direct effect of the inflamed, swollen pancreas on the pleura abutting the diaphragm (typically transudative). Alternatively, in cases of severe acute pancreatitis, an effusion can be due to the tracking of exudative fluid from the pancreatic bed retroperitoneally into the pleural cavity through defects in the diaphragm. Characteristically, the pleural fluid in this latter circumstance is an exudate with high levels of protein, lactate dehydrogenase, and amylase. The effusion may contribute to segmental atelectasis of the lower lobes, leading to ventilation-perfusion mismatch and hypoxia.[5]

With increasing extent of pancreatic parenchymal damage due to recurrent inflammation and fibrosis, both exocrine and endocrine function of the pancreas are affected. Post pancreatitis diabetes mellitus may occur due to damage of endocrine parenchyma of pancreas and exocrine pancreatic insufficiency (EPI) may occur due to the damage of exocrine parenchyma of the pancreas. EPI can lead to maldigestion and malabsorption, five of nine studies in the systematic review noted an association between pancreatic enzyme insufficiency and osteoporosis. One consequence of malabsorption is deficiency of vitamin D, which has an important role in bone health and in turn, may cause osteoporosis.[2]

THE CURRENT TREND IN MANAGEMENT OF ACUTE PANCREATITIS

Risk Assessment

Most episodes of acute pancreatitis are mild and self-limiting, needing only brief hospitalization. Mild acute pancreatitis is defined by the absence of organ failure and/or pancreatic necrosis. By 48 hours after admission, these patients typically would have substantially improved and begun refeeding. In patients with severe disease, two phases of acute pancreatitis are recognized: early (within the first week) and late. Local complications include peripancreatic fluid collections and pancreatic and peripancreatic necrosis (sterile or infected). Most patients with severe disease present to the emergency room with no organ failure or pancreatic necrosis; unfortunately, this has led to many errors in clinical management of this disease. These errors include failure to provide adequate hydration, failure to diagnose and treat cholangitis, and failure to treat early organ failure. For this reason, it is critical for the clinician to recognize the importance of not falsely labeling a patient with mild disease within the first 48 h of admission for acute pancreatitis. Severe acute pancreatitis occurs in 15-20% of patients.[8]

Severe acute pancreatitis is defined by the presence of persistent (fails to resolve within 48 h) organ failure and/or death. Local complications (including pancreatic necrosis with or without transient organ failure) define moderately severe acute pancreatitis (see Table 1). Moderately severe acute pancreatitis is characterized by the presence of transient organ failure or local or systemic complications in the absence of persistent organ failure. If persistent organ failure develops in a patient with necrotizing pancreatitis, it is then considered severe disease.[8]

Organ failure had previously been defined as shock (systolic blood pressure < 90 mm Hg), pulmonary insufficiency (PaO2 < 60 mm Hg), renal failure (creatinine > 2 mg/dL after rehydration), and/or gastro intestinal bleeding (> 500 mL of blood loss/24 h). The Revised Atlanta Criteria now define organ failure as a score of 2 or more for one of these organ systems using the modified Marshall scoring system.[8]

Pancreatic necrosis is defined as diffuse or focal areas of nonviable pancreatic parenchyma > 3 cm in size or > 30% of the pancreas. Pancreatic necrosis can be sterile or infected (discussed below). Both patients with sterile necrosis and infected necrosis may develop organ failure. The presence of infection within the necrosis probably does not increase the likelihood of present or future organ failure. Patients with sterile necrosis can suffer from organ failure and appear as ill clinically as those patients with infected necrosis. Persistent organ failure is now defined by a Modified Marshall Score.[8]

Isolated extra-pancreatic necrosis is also included under the term necrotizing pancreatitis. This entity, initially thought to be a non-specific anatomic finding with no clinical significance, has become better characterized and is associated with adverse outcomes, such as organ failure and persistent organ failure, but these outcomes are less frequent. Extra-pancreatic necrosis is more often appreciated during surgery than being identified on imaging studies. Although most radiologists can easily identify pancreatic parenchymal necrosis, in the absence of surgical intervention, extra pancreatic necrosis is appreciated less often.[8]

Table 1. Definitions of severity in acute pancreatitis: comparison of Atlanta and recent revision[8]

Atlanta Criteria (1993)	Atlanta Revision (2013)
Mild acute pancreatitis Absence of organ failure Absence of local complications	**Mild acute pancreatitis** Absence of organ failure Absence of local complications
Severe acute pancreatitis	Moderately severe acute pancreatitis
1. Local complication and/or 2. Organ failure: Gastrointestinal bleeding (>500cc/24h) Shock- systolic blood Pressure ≤ 90mmHg PaO_2 ≤ 60% Creatinine ≥ 2 mg/dL	1. Local complication and/or 2. Transient organ failure (< 48 h) Severe acute pancreatitis Persistent organ failure > 48 h (defined by a Modified Marshal Score)

Predicting Severe Acute Pancreatitis

Clinicians have been largely unable to predict which patients with acute pancreatitis will develop severe disease. In general, acute pancreatitis-specific scoring systems have a limited value, as they provide little additional information to the clinician in the evaluation of patients and may delay appropriate management.[8]

Although laboratory testing such as the hematocrit and blood urea nitrogen (BUN) can assist clinicians, no laboratory test is practically available or consistently accurate to predict severity in patients with acute pancreatitis. Even the acute-phase reactant C-reactive protein (CRP), the most widely studied inflammatory marker in acute pancreatitis, is not practical as it takes 72 h to become accurate. CT and/or MRI imaging also cannot reliably determine severity early in the course of acute pancreatitis, as necrosis usually is not present on admission and may develop after 24– 48 hour. Thus, in the absence of any available test to determine severity, close examination to assess early fluid losses,

hypovolemic shock, and symptoms suggestive of organ dysfunction is crucial.[8]

Rather than depending on a scoring system to predict severity of acute pancreatitis, clinicians need to be aware of intrinsic patient-related risk factors, including laboratory and imaging risk factors, for the development of severe disease. These include: a patient's age, comorbid health problems, body mass index, the presence of SIRS, signs of hypovolemia such as an elevated BUN and an elevated hematocrit, presence of pleural effusions and/ or infiltrates, altered mental status, and other factors (Table 1).[8]

During the early phase of the disease (within the first week), death occurs as a result of the development, persistence, and progressive nature of organ dysfunction related to SIRS. Although the presence of SIRS during the initial 24 h has a high sensitivity for predicting organ failure and mortality, the presence of SIRS lacks specificity for severe disease (41%). For this reason, patients with persistent SIRS, particularly those who are tachypneic and/or tachycardic, should be admitted to an intensive care unit or similar unit for aggressive intravenous hydration and close monitoring.[8]

Non-Surgical Management of Acute Pancreatitis

Intravenous Fluids

Adequate prompt fluid resuscitation is crucial in the prevention of systemic complications. There is some evidence that early oxygen supplementation and fluid resuscitation may be associated with resolution of organ failure, and early resolution of organ failure is associated with very low mortality, so it is appropriate to ensure that all patients with acute pancreatitis receive adequate oxygen and fluids until it is clear that the danger of organ failure has passed. Oxygen saturation should be measured continuously and supplemental oxygen should be administered to maintain an arterial saturation greater than 95%.[8]

In acute pancreatitis, 3 guidelines are instructive. Recommendations were weak or strong for lactated Ringer's solution as the preferred type of fluid, with different rates and levels of evidence: 5-10 mL/kg/h (moderate quality evidence), 250-500 mL/h during the first 12-24 hours using frequent clinical assessments to decrease BUN (moderate quality evidence), and 150-600 mL/h (low quality evidence).[9]

Although there are limited prospective data that aggressive intravenous hydration can be monitored and/or guided by laboratory markers, the use of hematocrit, BUN, and creatinine as surrogate markers for successful hydration has been widely recommended. Although no firm recommendations regarding absolute numbers can be made at this time, the goal to decrease hematocrit (demonstrating hemodilution) and BUN (increasing renal perfusion) and maintain a normal creatinine during the first day of hospitalization cannot be overemphasized.[9]

In a well-designed prospective randomized trial, hydration with lactated Ringer's solution appears to be more beneficial, resulting in fewer patients developing SIRS as compared with patients receiving normal (0.9 %) saline. The benefit of using lactated Ringer's solution in large-volume resuscitation has been shown in other disease states to lead to better electrolyte balance and improved outcomes. In acute pancreatitis, there are additional theoretical benefits to using the more pH-balanced lactated Ringer's solution for fluid resuscitation compared with normal saline. Low pH activates the trypsinogen, makes the acinar cells more susceptible to injury and increases the severity of established acute pancreatitis in experimental studies.[8]

By contrast, the presence of lactate Ringer, but not NS, resulted in significantly reduced activation of macrophages when cultured in the presence of IFN-γ + LPS. It prevented the switch to the inflammatory phenotype, characterized by the induction of inflammatory cytokines and inhibition of MRC1. Accordingly, it also inhibits the activation of $NF\text{-}_kB$, the main transcription factor involved in inflammatory processes. This inhibition is related to the effect of lactate since the addition of Ringer's solution without lactate to cell cultures resulted in a loss of this inhibitory effect. It is known that short-chain fatty acids as butyrate, propionate and lactate down-regulate the Toll-like receptor (TLR)-induced inflammatory response and promote the alternative anti-inflammatory polarization of macrophages. The effect of lactate in suppressing innate immunity has also been observed in experimental models of pancreatitis. Consequently, it could be argued that the more robust anti-inflammatory response observed when using LR is probably related to the inhibitory effect of lactate on the activation of macrophages.[10]

It is important to recognize that aggressive early hydration will require caution for certain groups of patients, such as the elderly, or those with a history of cardiac and/or renal disease in order to avoid complications such as volume overload, pulmonary edema, and abdominal compartment syndrome. Measurement of the central venous pressure via a

centrally placed catheter is most commonly used to determine volume status in this setting. Patients not responding to intravenous hydration early (within 6-12 hours) may not benefit from continued aggressive hydration.[8]

Nutrition in Mild Acute Pancreatitis

Historically, the focus of nutrition and feeding during acute pancreatitis aimed to "rest the pancreas," mainly by providing Nil Per OS (NPO), and removing the food induced stimulation of exocrine pancreatic secretion, which presumably reduces enzyme-driven inflammation and promotes earlier recovery, and/or to address intolerance to feeding by mouth, namely by fasting or by administering total parenteral nutrition (TPN). More recently, the focus has shifted toward protecting the gut mucosal barrier by initiating enteral feeding, either orally or by enteral tube.[9]

Clinical use of TPN declined further with accumulation of evidence that enteral feeding had a beneficial trophic effect on the gut mucosal barrier, thereby reducing bacterial translocation from the lumen into the bloodstream and reducing the risks of infection of (peri) pancreatic necrosis (infected necrosis) and severe outcomes in necrotizing acute pancreatitis. Thus, the concept of "gut rousing not gut resting" was introduced.[9]

Recent guidelines have recommended early oral feeding in mild (interstitial) acute pancreatitis. In mild acute pancreatitis, oral intake is usually restored quickly and no nutritional intervention is needed. Although the timing of refeeding remains controversial, recent studies have shown that immediate oral feeding in patients with mild acute pancreatitis appears safe. In addition, a low-fat solid diet has been shown to be safe compared with clear liquids, providing more calories.[8] Early refeeding also appears to result in a shorter hospital stay. Based on these studies, oral feedings introduced in mild acute pancreatitis do not need to begin with clear liquids and increase in a stepwise manner, but may begin as a low-residue, low-fat, soft diet when the patient appears to be improving. Few studies have compared nasogastric (NG) feeding to nasojejunal (NJ) (nasoduodenal in some) feeding in predicted severe or necrotizing acute pancreatitis because NG tubes can be placed at the bedside, making it simple and cheap. No differences between the 2 routes of feeding have been noted, although many methodologic problems with these studies preclude a definitive conclusion.[9]

Antibiotics

Infectious complications, both pancreatic (infected necrosis) and extra-pancreatic (pneumonia, cholangitis, bacteremia, urinary tract infections, and so on), are a major cause of morbidity and mortality in patients with acute pancreatitis. When an infection is suspected, antibiotics should be given while the source of the infection is being investigated. However, once blood and other cultures are found to be negative and no source of infection is identified, antibiotics should be discontinued.[8]

Preventing the Infection of Sterile Necrosis

The paradigm shift and controversy over using antibiotics in acute pancreatitis has centered on pancreatic necrosis. When compared with patients with sterile necrosis, patients with infected pancreatic necrosis have a higher mortality rate (mean 30 %, range 14–69%). For this reason, preventing infection of pancreatic necrosis is important. Although it was previously believed that infectious complications occur late in the course of the disease, a recent review found that 27 % of all cases of infected necrosis occur within the first 14 days; in another study, nearly half of all infections appear to occur within 7 days of admission. Because of the consistency of pancreatic necrosis, few antibiotics penetrate when given intravenously. The antibiotics shown to penetrate and used in clinical trials include carbapenems, quinolones, metronidazole, and high-dose cephalosporins. It remains uncertain if a subgroup of patients with severe acute pancreatitis (such as extensive necrosis with organ failure) may benefit from antibiotics, but large studies required to determine whether any benefit exists will be difficult to perform. Based on the current literature, use of prophylactic antibiotics to prevent infection in patients with sterile necrosis (even predicted as having severe disease) is not recommended.[8,9]

Prevention of fungal infections in these patients is also not recommended. Although it was suggested that fungal infection may be a more common cause of mortality in acute pancreatitis, further study has not confirmed this finding. Finally, probiotics should not be given in severe acute pancreatitis. Although earlier trials suggested a benefit, a very well-conducted, randomized controlled clinical trial demonstrated increased mortality. This lack of benefit has also been shown in a recent meta-analysis.[8]

Infected Necrosis

Rather than preventing infection, the role of antibiotics in patients with necrotizing acute pancreatitis is now to treat established infected necrosis. The concept that infected pancreatic necrosis requires prompt surgical debridement has also been challenged by multiple reports and case series showing that antibiotics alone can lead to resolution of infection and, in select patients, avoid surgery altogether. Garg et al reported 47/80 patients with infected necrosis over a 10-year period who were successfully treated conservatively with antibiotics alone. The mortality in the conservative group was 23% as compared with 54 % in the surgical group. The same group published a meta-analysis of 8 studies involving 409 patients with infected necrosis of whom 324 were successfully treated with antibiotics alone. Overall, 64% of the patients with infected necrosis in this meta-analysis could be managed by conservative antibiotic treatment with 12% mortality, and only 26% underwent surgery. Thus, a select group of relatively stable patients with infected pancreatic necrosis could be managed by antibiotics alone without requiring percutaneous drainage. However, it should be cautioned that these patients require close supervision and percutaneous or endoscopic or necrosectomy should be considered if the patient fails to improve or deteriorates clinically.[8]

Surgical Management in Acute Pancreatitis

The Role of Endoscopic Retrograde Cholangiopancreatography (ERCP)

The role of ERCP in acute pancreatitis is related to the management of choledocholithiasis. Although ERCP can be used to identify pancreatic ductal disruption in patients with severe acute pancreatitis, possibly leading to interventions for the so-called dislocated duct syndrome, a consensus has never emerged that ERCP should be performed routinely for this purpose.[8]

Fortunately, most gallstones that cause acute pancreatitis readily pass to the duodenum and are lost in the stool. However, in a minority of patients, persistent choledocholithiasis can lead to ongoing pancreatic duct and/or biliary tree obstruction, leading to severe acute pancreatitis and/or cholangitis. Removal of obstructing gallstones from the biliary tree in patients with acute pancreatitis should reduce the risk of developing these complications.[8]

There have been several clinical trials performed to answer the question: does early ERCP (within 24–72 hours of onset) in acute biliary pancreatitis reduces the risk of progression of acute pancreatitis to severe disease (organ failure and /or necrosis)? Neoptolemos et al studied 121 patients with probable acute biliary pancreatitis, stratified for severity according to the modified Glasgow criteria. The trial was performed in a single center in the United Kingdom. Patients with predicted severe acute pancreatitis had fewer complications if they underwent ERCP within 72 h of admission (24% vs. 61%, $p < 0.05$). When patients with concurrent acute cholangitis (who would obviously benefit from early ERCP) were excluded, the difference remained significant (15% vs. 61%, $p = 0.003$). Mortality was not significantly different in the two groups. Fan et al reported a study of 195 patients with suspected biliary pancreatitis stratified for severity according to Ranson's criteria. Patients in the study group underwent ERCP within 24 h of admission and those in the control group were offered conservative management. The control group was offered ERCP if acute cholangitis developed. Those who underwent early ERCP had fewer complications (13% vs. 54%, $p = 0.002$).[8]

More recent studies have confirmed that early ERCP within 24 h of admission decreases morbidity and mortality in patients with acute pancreatitis complicated by biliary sepsis. A dilated biliary tree in the absence of an elevated bilirubin and other signs of sepsis should not be confused with cholangitis, but may indicate the presence of a common bile duct stone. In patients with biliary pancreatitis who have mild disease, and in patients who improve, ERCP before cholecystectomy has been shown to be of limited value and may be harmful. Noninvasive imaging studies are the preferred diagnostic modalities in these patients (Endoscopic Ultrasonography [EUS] and/or magnetic resonance cholangiopancreatography [MRCP]). However, it is not clear if any testing needs to be performed in patients who improve.[8]

Cholecystectomy

In patients with mild gallstone pancreatitis, cholecystectomy should be performed during the index hospitalization. The current literature, which includes 8 cohort studies and one randomized trial describing 998 patients who had and who had not undergone cholecystectomy for biliary pancreatitis, 95 (18%) were readmitted for recurrent biliary events within 90 days of discharge (0% vs. 18%, $p < 0.0001$), including recurrent biliary pancreatitis (n = 43.8%). Some of the cases were found to be severe.

Based on this experience, there is a need for early cholecystectomy during the same hospitalization, if the attack is mild. Patients who have severe acute pancreatitis, especially with pancreatic necrosis, will require complex decision making between the surgeon and gastroenterologist. In these patients, cholecystectomy is typically delayed until: (1) A later time in the typically prolonged hospitalization; (2) As part of the management of the pancreatic necrosis if present; or (3) After discharge. Earlier guidelines recommended a cholecystectomy after 2 attacks of acute pancreatitis, with a presumption that many such cases might be because of microlithiasis. However, a population-based study found that cholecystectomy performed for recurrent attacks of acute pancreatitis with no stones/ sludge on ultrasound and no significant elevation of liver tests during the attack of acute pancreatitis was associated with a > 50% recurrence of acute pancreatitis.[8]

In the majority of patients with gallstone pancreatitis, the common bile duct stone passes to the duodenum. Routine ERCP is not appropriate unless there is a high suspicion of a persistent common bile duct stone, manifested by an elevation in the bilirubin. Patients with mild acute pancreatitis, with normal bilirubin, can undergo laparoscopic cholecystectomy with intraoperative cholangiography, and any remaining bile duct stones can be dealt with by postoperative or intraoperative ERCP. In patients with low to moderate risk, MRCP or EUS can be used preoperatively, but routine use of MRCP is unnecessary. In patients with mild acute pancreatitis who cannot undergo surgery, such as the frail elderly and/or those with severe comorbid disease, biliary sphincterotomy alone may be an effective way to reduce further attacks of acute pancreatitis, although attacks of cholecystitis may still occur.[8]

Debridement of Necrosis

Early open debridement for sterile pancreatic necrosis was abandoned. However, debridement for sterile necrosis is recommended if associated with gastric outlet obstruction and/or bile duct obstruction. In patients with infected necrosis, it was falsely believed that mortality of infected necrosis was nearly 100% if debridement was not performed urgently. In a retrospective review of 53 patients with infected necrosis treated operatively (median time to surgery of 28 days) mortality fell to 22% when necrosectomy necrosis was delayed. After reviewing 11 studies that included 1,136 patients, the authors found that postponing necrosectomy in stable patients treated with antibiotics alone until 30 days after initial hospital admission is associated with a decreased mortality.[8]

Although unstable patients with infected necrosis should undergo urgent debridement, current consensus is that the initial management of infected necrosis for patients who are clinically stable should be a course of antibiotics before intervention to allow the inflammatory reaction to become better organized. If the patient remains ill and the infected necrosis has not resolved, minimally invasive necrosectomy by endoscopic, radiologic, video-assisted retroperitoneal, laparoscopic approach, or combination thereof, or open surgery is recommended once the necrosis is walled-off.[8]

Minimally Invasive Management of Pancreatic Necrosis

Minimally invasive approaches to pancreatic necrosectomy including laparoscopic surgery either from an anterior or retroperitoneal approach, percutaneous, radiologic catheter drainage or debridement, video-assisted or small incision-based left retroperitoneal debridement, and endoscopy are increasingly becoming the standard of care. Percutaneous drainage without necrosectomy may be the most frequently used minimally invasive method for managing fluid collections complicating necrotizing acute pancreatitis. The overall success appears to be ~ 50% in avoiding open surgery. In addition, endoscopic drainage of necrotic collections and/or direct endoscopic necrosectomy has been reported in several large series to be equally successful. Sometimes these modalities can be combined at the same time or sequentially, for example, combined percutaneous and endoscopic methods. Recently, a well-designed study from the Netherlands using a step-up approach (percutaneous catheter drainage followed by video-assisted retroperitoneal debridement) demonstrated the superiority of the step-up approach as reflected by lower morbidity (less multiple organ failure and surgical complications) and lower costs compared with open surgical necrosectomy.[8]

Currently, a multidisciplinary consensus favors minimally invasive methods over open surgery for the management of pancreatic necrosis. A recent randomized controlled trial clearly demonstrated the superiority of endoscopic debridement over surgery. The management of patients with pancreatic necrosis should be individualized, requiring consideration of all the available data (clinical, radiologic, laboratory)

and using available expertise. Early referral to a center of excellence is of paramount importance, as delaying intervention with maximal supportive care and using a minimally invasive approach have both been shown to reduce morbidity and mortality.[8]

PREVENTION

The epidemiological burden of pancreatitis and its sequelae underscores the need for a comprehensive approach to its prevention. Prevention approaches are classically categorized as primary, secondary and tertiary in terms of the intervention time point and target population. In primary prevention, intervention is applied to the general population who do not have a disease of interest. These strategies typically aim to reduce disease incidence. Secondary prevention involved early identification of individuals with an existing disease of interest. The purpose of secondary prevention is to apply effective intervention early and reduce morbidity. Tertiary prevention is applied after a disease of interest is established, aiming at minimizing its sequelae and resulting burden.[2]

Primary Prevention.

A comprehensive systematic review of general population-based studies evaluated more than 30 factors associated with diseases of the exocrine pancreas. This study estimated that more than half of pancreatitis cases could have been prevented if all people in the general population were non-smokers, nearly one-fourth of cases if all individuals in the general population were a normal weight (BMI 18-25 kg/m^2), and nearly one-fifth of cases if they had limited alcohol consumption. The review also emphasized that consumption of vegetables and fruits is associated with a nearly 30% reduced risk of all diseases of the exocrine pancreas. Specifically, vegetable consumption was associated with a statistically significantly reduced risk of acute pancreatitis (OR = 0.64; 95% CI: 0.50-0.82).[2]

The form of acute pancreatitis particularly amenable to primary prevention by gastroenterologists is pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP). Avoidance of futile ERCP and the appropriate choice of sedation for ERCP, rectal administration of non-steroidal anti-inflammatory drugs and optimization of cannulation technique in patients at high-risk (for example, in those with clinical suspicion of sphincter of Oddi dysfunction, pancreatic sphincterotomy, precut sphincterotomy or ampullectomy) have proven to be beneficial.[2]

Secondary Prevention

The emerging aspect of secondary prevention of acute pancreatitis is epitomized in the concept of "gut rousing", which has replaced the "pancreas rest" concept that dominated the field in the 20th century. The new concept has been developed to prevent progression of acute pancreatitis severity by optimizing the use of the three mainstays of early management: opiates, fluids and nutrition. The concept postulates that the presence of gut dysfunction worsens the outcomes of patients with acute pancreatitis, and the key factors that affect gut function are both pathogenic and iatrogenic (specifically, liberal administration of opiates and fluids). The concept also recognizes that in acute pancreatitis the gastrointestinal tract should be afforded the same considerations as the other vital systems (respiratory, cardiovascular and renal), and it should be targeted by appropriate therapies. In particular, timely administration of apposite feed into the lumen stimulates (rouses) the gut, mitigates gut dysfunction and restores normal gut function. Neglecting the gut (for example by resting the pancreas) or administering feed at wrong time leads to worsen outcomes.[2]

Tertiary Prevention

Two large studies investigated factors associated with PPDM. A study by Ho et al, included a total of 12,284 patients with first attack acute pancreatitis. Alcohol related acute pancreatitis, more recurrences of acute pancreatitis, male sex and age $\geq$ 64 years were associated with diabetes after acute pancreatitis in multivariable analyses. Conversely, severity of acute pancreatitis, Charlson comorbidity score and monthly income were not associated with diabetes after acute pancreatitis. A multi-center study by Bellin et al included a total of 1,171 patients with chronic pancreatitis. Overweight or obesity, EPI, pancreatic calcifications, prior pancreas surgery, family history of diabetes, male sex, age and duration of pancreatitis were associated with the presence of diabetes in patients with chronic pancreatitis in multivariable analyses, whereas heavy alcohol intake and smoking were not associated with the presence of diabetes. However, the studies by Ho et al and Bellin et al did not investigate the relative weights of risk factors. This aspect was addressed in the derivation of the Prediabetes self-assessment screening Score after acute pancreatitis (PERSEUS), which is the first screening instrument to identify patients after and episode of acute pancreatitis who are at high risk of developing prediabetes (and ultimately diabetes). The score is

intended for use by patients after hospital discharge to self-assess their probability of having impaired glucose homeostasis. Importantly, all variables included in the score are readily available to individuals and do not require laboratory testing. Two variables – tobacco smoking and abdominal adiposity – are modifiable risk factors that are worth targeting with a view to reducing the incidence of PPDM.[2]

CONCLUSION

Understanding the pathophysiology of acute pancreatitis provides better and rational management of acute pancreatitis episode. Adherence of the current guidelines of acute pancreatitis may help to lessen the burden of acute pancreatitis, and the prevention of recurrent acute pancreatitis may help to lessen the occurrence of chronic pancreatitis and its sequelae.

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