Pancreatitis – Management Guidelines

Number of Contact Hours – 2

Goals and Objectives

Goals

The goal of this article is to provide evidence-based recommendations for the management of both mild and severe acute pancreatitis as well as the management of complications of acute pancreatitis

Objectives

Describe the molecular pathogenesis of pancreatitis

Discuss the management guidelines for pancreatitis

Identify three management strategies of pancreatitis

Discuss the potential future targets of pancreatitis management

Describe the clinical studies in management of pancreatitis

Introduction

There has been an increase in the incidence of acute pancreatitis reported worldwide. Despite improvements in access to care, imaging and interventional techniques, acute pancreatitis continues to be associated with significant morbidity and mortality. Despite the availability of clinical practice guidelines for the management of acute pancreatitis, recent studies auditing the clinical management of the condition have shown important areas of noncompliance with evidence-based recommendations. This underscores the importance of creating understandable and implementable recommendations for the diagnosis and management of acute pancreatitis. Acute pancreatitis can range from a mild, self-limiting disease that requires no more than supportive measures to severe disease with life-threatening complications. The most common causes of acute pancreatitis are gallstones and binge alcohol consumption. There has been an increase in the incidence of acute pancreatitis reported worldwide. Despite improvements in access to care, imaging and interventional techniques, acute pancreatitis continues to be associated with significant morbidity and mortality. [1, Rank 3]

Molecular Pathogenesis of Pancreatitis

Under physiologic conditions, inactive enzyme precursor secretion from the acinar cell occurs in response to cytosolic calcium. A sustained global elevation of this calcium,

however, can lead to premature activation and secretion of digestive enzymes from the acinar cell, one of the earliest detectable events in pancreatitis. After the initial insult to the pancreatic acinar cell, the disease progression is a multi-phase process that involves local inflammation of the pancreas, followed by a generalized inflammatory response, and the final stage of sepsis involving multi-organ failure in those with severe disease. Following the initial injury, inflammatory cells are often recruited to the pancreas *via* adhesion molecules, which can aggravate the inflammatory response leading to severe acute pancreatitis. One of the key drivers of the inflammatory response in acute pancreatitis is likely circulating cytokines and chemokines. Active digestive enzymes are potent stimulators of macrophages, which subsequently induce the production of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukins.

Cytokine production is governed by a large number of transcription factors, most prominent of which is nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). The various types of cytokines released can cause their effects *via* highly specific cell surface receptors and stimulate enzymes such as cyclooxygenase-2 and inducible nitric oxide synthase (iNOS), which mediate the inflammatory process. Hence inhibition of these enzymes is likely to limit the local and systemic injury induced by pro-inflammatory leukocytes. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) have also been implicated in the pathogenesis of acute pancreatitis. The mechanism by which these agents induce pancreatitis is two-fold. ROS and RNS act directly on biomolecules like lipids, proteins, and nucleic acids and oxidize these components of cell membrane in the pancreas leading to membrane disintegration and necrosis of the pancreatic cells. In addition to the direct detrimental oxidative effects, ROS and RNS can also serve as secondary messengers in intracellular signaling and induce pro-inflammatory cascades.

Preclinical Studies

Anti-secretory Agents

Acute pancreatitis is characterized by pancreatic and peripancreatic fat injury in part mediated by autodigestive enzymes. Excessive stimulation of the exocrine pancreas worsens acute pancreatitis and thus is the rationale for testing anti-secretory agents as potential therapies for acute pancreatitis. Initial animal studies tested glucagon and subsequent studies investigated the use of somatostatin and long-acting somatostatin analogue.

Glucagon increases superior mesenteric artery blood flow and decreases pancreatic exocrine secretion. A study utilizing a dog model of pancreatitis, however, did not find glucagon treatment alone or in combination with volume resuscitation to be better than volume resuscitation alone. In fact in their model, pancreatic hemorrhage was associated with glucagon treatment suggesting possible worsening of the disease. A later study using pigs reported beneficial effects of glucagon but other experimental studies in addition to the

study mentioned above failed to support the use of glucagon therapy in experimental acute pancreatitis.

Somatostatin is an inhibitory hormone with multiple effects on gastrointestinal motility and exocrine pancreas secretions. One preclinical study using a taurocholate-induced rat model of acute pancreatitis, showed that somatostatin was effective in inhibiting basal and hormonal stimulated pancreatic enzyme secretion but did not affect the degree of pancreatic necrosis, pancreatic edema, leukocyte infiltration, or the enzyme content of the pancreas after pancreatitis was induced and did not lead to an overall decrease in mortality. Another study showed that somatostatin stimulates hepatic and splenic reticulo-endothelial function in the rat hence suggesting benefit in the treatment of pancreatitis.

The utility of anti-secretory agents has limitations given that the pancreas not only secretes enzymes, but also secretes bicarbonate and fluids, and animal studies have shown that stimulation of ductal secretion of bicarbonate has a protective effect on the severity of pancreatitis. [2, Rank 3]

Protease Inhibitors

Intrapancreatic activation of digestive enzymes plays an important role in the pathogenesis of acute pancreatitis. For this obvious reason protease inhibitors have been and remain of therapeutic interest in acute pancreatitis. Early studies in dogs with surgically-induced pancreatitis treated with trypsin inhibitors from egg white or soybean, and trasylol (aprotinin), a trypsin-kallikrein inhibitor from cattle were effective in suppressing acute pancreatitis. Several other animal studies, including guinea pig model with taurocholate-induced necrotizing pancreatitis, also showed benefit with using protease inhibitors such as chlorophyll-a. Interestingly however in the choline-deficient DL-ethionine (CDE) supplemented diet model of severe hemorrhagic pancreatitis, neither trasylol nor chlorophyll-a resulted in disease or mortality attenuation. Despite the use of protease inhibitors at the time of CDE acute pancreatitis induction, the difference in rapidity, extent and intracellular protease release as well as the degree of and/or drug tissue penetration associated with the different experimental models might contribute to the observed opposing results

Anti-inflammatory and immunomodulators

Altered products of arachidonic acid metabolism have been detected in experimental acute pancreatitis. In acute pancreatitis thromboxane B levels are elevated whereas levels of prostaglandin E (PGE) are decreased. PGE therapy has been shown to have protective effects on the course of experimental acute pancreatitis in rodent models with taurocholate, CDE diet, or caerulein-induced pancreatitis. Cyclo-oxygenase inhibitors such as indomethacin have been used to treat experimental acute pancreatitis with conflicting results in earlier studies but subsequent studies have supported the beneficial effect of indomethacin particularly when used early or prior to disease induction in rat models with

taurocholate-induced acute pancreatitis. Similar to cyclo-oxygenase, lipoxygenase is downstream of arachidonic acid and studies have shown that its inhibition in rat models with taurocholate-induced acute pancreatitis leads to reduced severity of the disease. Leukotriene receptor antagonism however has shown to either worsen or have no effect on rat acute pancreatitis, indicating the complexity of the pathway and the need for further in depth investigations.

Steroid therapy in acute pancreatitis has been of interest for several decades due to the associated leukocyte activation and release of inflammatory cytokines and chemokines during progression of acute pancreatitis. One experimental study in rat acute pancreatitis caerulein-induced showed that the effectiveness of steroid therapy depended on the severity of illness, with dexamethasone being more effective against pancreatitis with severe inflammation. Another experimental study showed that dexamethasone reduced pancreatic damage when given prophylactically through reduction in intercellular adhesion molecule-1 expression, but was ineffective in preventing leukocyte recruitment into the pancreas when given therapeutically to rats with taurocholate-induced acute pancreatitis. On the other hand, steroids have also been implicated as a cause of acute pancreatitis and some studies show that high-dose hydrocortisone can increase mortality rate and complication rates such as sepsis or infection.

Animal studies have shown that interleukin-10 (IL-10), an anti-inflammatory cytokine, can ameliorate the severity of caerulein-induced acute pancreatitis in rodent models if given before or after the induction of disease. IL-10 plays a protective role in the local and systemic consequences of the disease as IL-10 has been shown to block inflammation leading to improved outcome in experimental models. Lexipafant, an antagonist of the platelet activating factor, induces systemic effects and has been implicated as a mediator in the progression of acute pancreatitis. Treatment of taurodeoxycholate and caerulein-induced rodent models of pancreatitis with lexipafant reduces the severity of pancreatitis-associated complications such as intestinal dysfunction, systemic IL-1 upregulation, and local leukocyte recruitment. Lexipafant reduced acute pancreatitis associated inflammation and improved acute necrotizing pancreatitis. Despite beneficial outcomes with IL-10 and lexipafant in animal studies, their translation into clinical use has proven to be challenging. [3, Rank 5]

Antioxidants

Oxidative stress and injury is implicated in many inflammatory diseases. Oxygen-derived free radicals are generated in experimental acute pancreatitis and there is evidence of decreased blood anti-oxidant levels in patients with severe acute pancreatitis. These observations led to experimental studies that showed a protective effect of exogenously administered anti-oxidants such as selenium through reduction of pancreatic injury. Pre-clinical studies in rodent models of acute pancreatitis induced by a variety of methods, including carrageenan injection into pleural cavity or *L*-arginine hydrochloride, have shown

reduced levels of glutathione and increased levels of oxidized glutathione suggesting a benefit from this intervention. Clinical studies however have not been positive and it may be that anti-oxidants are more useful in prevention and/or as synergistic agents.

Potential Future Promising Targets

One of the major limitations of preclinical studies is the uncertainty and lack of an ideal model that recapitulates all aspects of human disease. In addition preclinical therapies are often given either early or at the time of acute pancreatitis induction, when in reality patients often present with ongoing or late onset acute pancreatitis. Preclinical studies that demonstrate the efficacy of the therapy when administering the drug following disease progression are more likely to yield promising outcomes in clinical trials. With the exception of ERCP-induced acute pancreatitis in which prophylactic therapies can be instituted, it is unlikely that agents that interfere with initiation of acute pancreatitis are going to be effective but rather those that target the subsequent injury, repair or inflammatory pathways are likely to be beneficial in treating acute pancreatitis.

Inducible nitric oxide synthase activity is thought to be increased in experimental acute pancreatitis. Experimental studies in the rat model have shown that agents such as *S*-methylisothiourea, an inducible nitric oxide synthase inhibitor, can decrease the bacterial translocation from gut into pancreatic necrosis thus reducing septic complications and mortality in acute pancreatitis. Treatment with agents such as AR-C102222AA or *L*-N^6-(1-iminoethyl)-lysine, highly selective iNOS inhibitors, early in the course after induction of acute pancreatitis, have also shown to have significant beneficial effects in acute pancreatitis.

Experimental studies with both pentoxifylline and heparin have shown a protective effect in rat models with acute pancreatitis. Studies have shown that pentoxifylline attenuates neutrophil activation, proinflammatory signalling, and systemic inflammation and cytokine levels in experimental acute pancreatitis especially when administered early. Heparin has also been a pharmacologic therapy of recent interest with increasing number of reports suggesting its potential in the treatment of acute pancreatitis. Heparin was initially studied primarily for its ability to improve microcirculation, given that a disruption of the microcirculation contributes to the inflammatory process of acute pancreatitis. The anticoagulation mechanism of heparin is also associated with its anti-inflammatory effect in part secondary to reduced stimulation of macrophages and monocytes. Experimental studies show that addition of heparin results in a decrease of amylase, endothelin-1, and inflammatory cytokines such as TNFα, activation of NF-κB, and improved morphologic changes and vascular flow in the pancreas. Such agents may enhance healing while dampening pro-inflammatory pathways, and may offer benefit in clinical acute pancreatitis.

Up-regulation of hemeoxygenase-1 (HO-1) or treatment with its downstream effectors and heme degradation products, biliverdin and carbon monoxide have protective effects in different rodent models of acute pancreatitis induced by taurocholate, caerulein, or CDE

diet. HO-1 overexpressing macrophages protect against acute pancreatitis. Panhematin, an FDA-approved hemin formulation for acute intermittent porphyria, can prime HO-1 production. Studies have shown that Panhematin if given before development of experimental pancreatitis can upregulate hemin-activated macrophages and lead to less pancreatic injury and if given after the development of acute pancreatitis, can also mitigate the extent of pancreatitis-related injury.

Notably, peripheral blood mononuclear cells from patients with mild acute pancreatitis have reversible HO-1 up-regulation that is associated with clinical recovery supporting therapeutic potential of HO-1 and the heme degradation products in patients with acute pancreatitis. Biliverdin *via* the aryl hydrocarbon receptor up-regulates IL-22. There has been a lot of interest recently on the role of IL-22, a cytokine produced by hematopoietic cells that targets non-immune cells. The pancreas interestingly has the highest expression of IL-22 receptor amongst any other tissue and IL-22 treatment has been shown to ameliorate experimental acute pancreatitis. Thus HO-1 and its downstream effectors are potential targets for clinical acute pancreatitis.

TNFα plays a central role in the pathogenesis of local and distant complications of acute pancreatitis, and its blockade ameliorates experimental acute pancreatitis induced by caerulein, taurocholate, or CDE diet in mice studies. Although there are theoretical increased risk of infectious complications with anti-TNF therapy, there are case reports with positive outcome in acute pancreatitis patients who received anti-TNF due to concomitant medical illness for which the anti-TNF therapy was indicated. Thus with careful patient selection it is likely that anti-TNF therapy will yield beneficial results in clinical trials. [4, Rank 1]

Clinical Studies in Pancreatitis Management

Based on the pathophysiology of acute pancreatitis and the basic science research conducted providing evidence for promising pharmacologic therapy, many clinical studies have been performed assessing the effectiveness of these therapies including anti-secretory agents, protease inhibitors, immunomodulators, anti-inflammatory agents, and anti-oxidants.

<u>Anti-secretory agents</u>

The use of glucagon for acute pancreatitis was first reported in 1971 and since then several subsequent uncontrolled clinical trials have shown a clinical improvement, decrease in pain, and a decline in enzyme activities in acute pancreatitis. However, in a subsequent double-blinded trial of 69 patients glucagon was not found to have a significant impact on the mortality of the patients when compared to placebo. Further clinical trials found no difference in mortality and morbidity such as pain and length of stay.

Atropine was also studied in a randomized clinical trial but did not have a significant effect on the clinical course of patients when compared with no treatment. Infusion of salmon calcitonin was also thought to strongly depress gastric secretions such as gastric acid, pepsin, and gastrin as well as pancreatic enzyme secretions stimulated by various secretagogues without affecting the fluid and electrolyte secretions thus mitigating the pathogenesis of acute pancreatitis. A multicentered randomized double-blinded trial assessing the use of synthetic salmon calcitonin in acute pancreatitis showed that though mortality was not affected, the number of patients without pain and normalized serum amylase was higher in the treated group as compared to the placebo group. Other parameters such as analgesic dose, leukocyte count, and normalization of seven clinical and laboratory criteria showed a positive trend in the treated group but were not clinically significant.

Clinical trials have well studied the use of somatostatin for treatment of acute pancreatitis given that it inhibits pancreatic exocrine secretions, reduces splanchnic blood flow, stimulates the hepatic reticuloendothelial system, and modulates the inflammatory cytokine cascade. However, several randomized clinical trials failed to show a clinically significant benefit with the use of somatostatin. A meta-analysis of seven publications, on the other hand, did show an overall mortality benefit with somatostatin for severe acute pancreatitis (OR = 0.36, 95%CI: 0.2-0.64) but there was no significant decrease in complication rates in patients with acute pancreatitis.

Octreotide, a synthetic analogue of somatostatin, was also tested clinically. While initial small studies did not show any overall mortality benefit, they suggested a decrease in severity of acute pancreatitis, reduced local complications, and earlier return to oral intake. One of the largest clinical trials of 302 patients with moderate to severe pancreatitis however did not show any clinical benefit, but a smaller study of 50 patients with severe acute pancreatitis showed a clinically significant reduction in sepsis (76%-24%), ARDS (56%-28%), hospital stay (33.1-20.6 d), and mortality (8-2 deaths). While an older meta-analysis performed did suggest a mortality benefit for severe acute pancreatitis (OR = 0.57, 95%CI: 0.35-0.88), another more recent meta-analysis that limited their estimate to four higher quality studies did not show any benefits in sepsis, mortality, or complication rates.

Thus clinical studies assessing the use of anti-secretory agents have provided inconclusive evidence on their benefits. There appears to be no benefit with the use of these agents in mild acute pancreatitis, and the benefits are uncertain in severe acute pancreatitis. Hence these agents are not currently recommended in clinical practice.

<u>Protease inhibitors</u>

One of the earliest protease inhibitors studied is aprotinin, and initial studies showed some benefit in mortality though subsequent studies have failed to repeat such results. Studies delivering aprotinin *via* peritoneal lavage have shown less necrosis in the treatment group

with a reduction in complement activation (specifically less C3a and more C1 inhibitor plasma levels) but no overall difference in mortality. Aprotinin may still have a role in treating acute pancreatitis given that it was not given in high enough doses to produce sufficient inhibition of protease activity.

Gabexate mesilate is a smaller protease inhibitor that has been studied in human clinical trials. While early smaller clinical studies suggested a mortality benefit with the administration of this therapy, a larger randomized controlled trial of patients with moderate to severe acute pancreatitis found no clinical benefit. Two other meta-analyses also demonstrate this lack of mortality benefit, though they showed a decreased need for surgery and less complications.

Nafomostat is a newer synthetic protease inhibitor a hundred times more potent than gabexate. Clinical studies assessing the delivery of nafomostat *via* CRAI along with antibiotics have shown greater mortality benefit and lower incidence of necrosis with earlier administration of the drug. Studies have also shown that delivery of the drug *via* CRAI compared to non-CRAI decreases the need for surgery and improves survival.

None of the protease inhibitors mentioned above are currently part of standard clinical care for acute pancreatitis treatment as larger and adequately powered studies are needed prior to their recommendation for clinical use. Nafomostat, however, has the most promise out of the three particularly when given *via*CRAI in combination with antibiotics.

Immunomodulators

Based on the preclinical positive results, Lexipafant was tested in clinical trials in patients with severe acute pancreatitis. The first clinical trial assessing the use of this therapy did not show a difference in mortality but showed a reduction in organ failure. Another study showed significantly less organ failure, a reduction in mortality and SIRS. The largest randomized clinical trial involving this therapy, however, showed no significant reduction in organ failure or local complications leading to the conclusion that lexipafant alone cannot treat severe acute pancreatitis.

Dotrecogin alfa, an analogue of endogenous protein C, has shown some benefit in the treatment of acute pancreatitis. Endogenous protein C is made in the liver and inhibits thrombin formation and facilitates thrombolysis. Given that lower levels of activated protein C are associated with higher mortality in acute pancreatitis, activated protein C was thought to mitigate severe acute pancreatitis by modulating the immune system through regulating leukocyte endothelial interaction and mitogen-activated kinases and improving intestinal microcirculation. Initial case reports showed some benefit in using dotrecogin alfa in acute pancreatitis

Anti-inflammatory agents

Indomethacin, which inhibits phospholipase A2 activity and cyclooxygenase activity thus decreasing neutrophil mediated inflammation, has been clinically studied based on earlier pre-clinical studies. One study assessing this therapy, however, only reported decreased pain and opiate use when given to patients with acute pancreatitis suggesting analgesia but not anti-inflammatory related benefits. So far benefits of indomethacin have been largely limited to post-ERCP pancreatitis.

Steroid therapy is widely used to dampen inflammation in various organ systems. Though steroid therapy has been shown to be beneficial in the treatment of autoimmune pancreatitis, in acute pancreatitis however steroid therapy has been implicated in disease induction. A postmortem study showed histologic evidence of acute pancreatitis or peripancreatic fat necrosis in 16 out of 54 patients treated with steroids. Initial case reports have also linked the use of steroids with acute pancreatitis. Studies have also shown that corticosteroids have no beneficial effect in the prevention of post-ERCP pancreatitis. However, given that some pre-clinical studies suggest that steroids can reduce the inflammatory cascade, leukocyte recruitment, and subsequent pancreatic damage when given prophylactically, further well-designed studies are warranted.

Anti-oxidant agents

Several clinical trials have assessed the benefit of anti-oxidant agents in acute pancreatitis given the role of reactive oxygen species and cellular injury in acute pancreatitis as well as the evidence generated by pre-clinical studies. Anti-oxidant agents studied include n-acetylcysteine, methionine, beta-carotene, selenium, ascorbic acid, and alpha-tocopherol.

A randomized clinical trial assessing treatment with acetylcysteine, selenium, and vitamin C showed increased serum levels of anti-oxidants and decreased markers of oxidative stress but no improvement in organ dysfunction. Another study with patients receiving Vitamin C, n-acetylcysteine, and other anti-oxidants showed no significant difference in complications or length of hospital stay. The third recent clinical study with vitamins A, C, and E also showed no significant difference in organ dysfunction.

Studies assessing the use of glutamine, a more potent anti-oxidant, have been more promising. One study randomizing 80 patients to glutamine showed decreased number of complications, length of stay, need for surgery, and mortality when administered early after hospitalization. A meta-analysis of randomized control trials with glutamine showed a mortality benefit (RR = 0.3, 95%CI: 0.15-0.6) and reduced infectious complications (RR = 0.58, 95%CI: 0.39-0.87), but no difference in length of hospital stay. The benefit with glutamine was observed only in patients receiving total parenteral nutrition. Thus the role of anti-oxidant therapy in acute pancreatitis remains to be determined. [5, Rank 2]

Other Therapies

A variety of other therapies for acute pancreatitis have also been assessed in clinical studies. Antifibrinolytics such as epsilon-aminocaproic acid (EPCA) has been thought to ameliorate the pathogenesis of acute pancreatitis by inhibiting the activation of plasminogen, plasmin, and trypsin, by inhibiting pancreatic kallikrein, and by increasing serum antitrypsin activity. A clinical study assessing the use of EPCA and aprotinin in acute pancreatitis, however, did not have any clinically significant improvement on outcomes such as hospital duration and normalization of laboratory values compared to the conventional treatment group and the aprotinin treated groups.

Fresh frozen plasma (FFP) has also been assessed in the treatment of acute pancreatitis given laboratory studies that showed the inhibitory effect of FFP on proteolytic activity in the serum of patients with acute pancreatitis. While one initial prospective pilot clinical study showed a decrease in mortality with the administration of FFP in patients with acute pancreatitis when administered during the first five days of illness onset, a larger multi-centered controlled clinical trial showed no improved clinical outcome in the group given FFP as opposed to colloids treated group.

Molecular pathways under target development include the kallikrein-kinin and complement system given that severe acute pancreatitis is associated with elevated C3a and sC5b-9 levels. C1 esterase inhibitor blocks a variety of proteolytic enzymes including activated C1 complex and kallikrein, and both experimental studies as well as small human studies have shown that C1 esterase inhibitor has some protective benefit in severe acute pancreatitis. Currently pharmacologic targets of the complement system are used in a variety of other diseases such as hereditary angioedema, paroxysmal nocturnal hemoglobinuria, and hemolytic uremic syndrome that may permit more rapid translation.

Management Guidelines for Pancreatitis

Classification of Severity

Mastery of the management of acute pancreatitis is an art that can challenge experienced clinicians at the best of times. One facet to the art of managing acute pancreatitis is classification of the disease severity so that one can recognize, anticipate, and treat accordingly complications of the disease. The revised Atlanta criteria for classification of the severity of acute pancreatitis are widely accepted. This revised classification defines transient organ failure as organ failure which resolves completely within 48 hours, whereas failure of resolution of organ failure is defined as persistent. The presence of persistent organ failure, usually with one or more local complications, indicates severe acute pancreatitis. On the other hand, the absence of organ failure without any local or systemic complications indicates mild acute pancreatitis. Moderately severe acute pancreatitis, indicated by transient organ failure and/or local or systemic complications in the absence of persistent organ failure, is the new grade of severity between mild and severe that was introduced in the revised classification. Multiple scoring systems for the prediction of the

disease severity and prognostic implications exist. The prognostic features aid the clinician in predicting complications of acute pancreatitis.

The Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system has demonstrated the highest accuracy for predicting severe acute pancreatitis when compared with other scoring systems. The APACHE II score can be repeated daily and its trends correlate well with clinical progress or deterioration. However, there is no significant difference in the prognostic accuracy between the APACHE II and multiple factor scoring systems such as Ranson, computed tomography severity index (CTSI), and the bedside index for severity in acute pancreatitis. [6, Rank 3]

The CRP is a reliable, easily accessible, single marker of assessing severity. It has demonstrated good prognostic accuracy for severe acute pancreatitis, pancreatic necrosis, and in-hospital mortality when measured at 48 hours following hospital admission. Another cheap and easily obtainable parameter indicative of the severity of acute pancreatitis is the hematocrit. An admission hematocrit ≥44% or failure of the hematocrit to decrease at 24 hours following admission is indicative of severe acute pancreatitis in the early stage of the disease. Additionally, some studies have demonstrated that hemoconcentration has been associated with the risk of developing necrotizing pancreatitis and organ failure, while others refute this observation. The absence of hemoconcentration on admission has a high negative predictive value for the development of necrosis. Other markers such as procalcitonin and IL-8, not used routinely in the UK, have been shown to have high predictive accuracy in classifying the severity of necrotizing pancreatitis in the first days of the disease.

The inflammatory response varies between each individual patient. The release of intrapancreatic enzymes triggers the release of proinflammatory mediators and macrophage activation within acinar cells resulting in local complications of acute pancreatitis, which include pancreatic necrosis with or without infection, pancreatic pseudocyst formation, pancreatic duct disruption, and peripancreatic vascular complications. It is unclear why in some patients the local pancreatic inflammation triggers a systemic release of proinflammatory mediators. However, this systemic inflammatory response manifests as organ failure, and its recognition and treatment are important in altering the clinical course of acute pancreatitis.

Imaging

Imaging plays an important role in the diagnosis and management of acute pancreatitis. As 50% of acute pancreatitis cases are gallstone-related, transabdominal ultrasound is the most common initial radiologic investigation of choice. Ultrasonography has the highest sensitivity for detection of gallbladder stones, but a poor sensitivity for choledocholithiasis. The retroperitoneally sited pancreas is usually difficult to visualize in acute pancreatitis during ultrasonography, which can be further compounded by overlying bowel gas, large patient body habitus, and abdominal pain. In the assessment of the presence or absence of

gallstones, it is recommended that at least two good quality ultrasound examinations are obtained. Where the first exam is negative and cannot detect gallstones, the most sensitive test for diagnosis of gallstones that may have been initially missed remains a further ultrasound examination. [7, Rank 1]

In patients with suspected acute pancreatitis, dynamic contrast-enhanced CT (CECT) is the imaging modality of choice. CECT plays a role in establishing the diagnosis, staging the severity of the disease, and assists in the detection of complications. However, it must be borne in mind that the staging of severity and detection of complications depend on the timing of CT scanning. In the first 24–48 hours, the CT findings of necrosis may be equivocal as only 25% of patients with acute pancreatitis develop necrosis. Additionally, pancreatic necrosis may not develop within the first 48 hours. In severe acute pancreatitis, unless the patient is critically ill and in need of emergency intervention, the initial CT scan should ideally be obtained at least 72 hours following symptom onset.

The use of CECT in the localization of site and/or extent of pancreatic necrosis enhances the accuracy in outcome prediction, as evident from the development of the CTSI. High CTSI scores correlate with worsening severity and prognosis, pancreatic infection, and need for intervention. For example, patients with necrosis of the pancreatic head have similar poor outcomes in comparison to patients whose entire pancreas was affected. A modified CTSI has been developed for evaluating the severity of acute pancreatitis, but no significant differences have been observed when compared to the original CTSI. However, both CTSI scoring systems have demonstrated superior accuracy in diagnosing clinically severe acute pancreatitis when compared to the APACHE II severity scoring system.

Magnetic resonance imaging in the form of magnetic resonance cholangiopancreatography (MRCP) has become a popular imaging modality for evaluation of the bile ducts and pancreatic duct. MRCP is reliable in diagnosing choledocholithiasis, and is only superseded by endoscopic ultrasound (EUS) in its sensitivity for detecting choledocholithiasis. The limitations of MRCP include contraindication in patients with pacemakers and other metal objects, long image acquisition times, and difficulty with scanning critically ill patients.

The advent of MRCP and EUS has dramatically reduced the need for ERCP as a diagnostic tool in choledocholithiasis. EUS is the most reliable pretherapeutic diagnostic modality for choledocholithiasis, and when utilized with MRCP, both imaging modalities provide a safer method for investigating choledocholithiasis compared to ERCP, which is itself associated with a risk of postprocedural pancreatitis. EUS is particularly useful in the assessment of microlithiasis, which has been attributed as a cause of recurrent acute pancreatitis in patients with no evidence of choledocholithiasis visible using other imaging modalities. EUS also confers the ability to evaluate ductal abnormalities. [8, Rank 2]

Fluid therapy in acute pancreatitis

The initial management of acute pancreatitis is largely supportive, with fluid replacement and optimization of electrolyte balance, providing adequate caloric support, and preventing or identifying and treating local and systemic complications.

The local and systemic inflammatory response in acute pancreatitis results in fluid depletion in the form of vomiting, reduced oral fluid intake, third-space fluid loss, and increased insensible losses in sweat and respiration. Fluid replacement in acute pancreatitis can be undertaken using crystalloid, colloid, or a combination of both. Ringer's lactate is the preferred crystalloid fluid, but caution should be exercised in hypercalcemic patients. However, to date, there is no clear agreed consensus regarding the ideal fluid type and regimen for fluid resuscitation. The goal of fluid resuscitation is to achieve a urine output of ≥0.5 mL/kg/h and a target heart rate <120/min, and maintain hematocrit between 35% and 44%.Supplemental oxygen should complement fluid resuscitation to maintain arterial oxygen saturations >95%.

Nutrition in acute pancreatitis

Acute pancreatitis results in the rapid metabolism of fat and protein due to the hypercatabolic state. Nutritional support aims to provide adequate caloric intake and modulate the oxidative stress response during the initial phase of acute pancreatitis, thereby counteracting the catabolic effects. Additionally, enteral nutrition maintains intestinal motility, which preserves the gut barrier function and subsequently reduces the risk of secondary infections – it has been hypothesized that the infective complications of acute pancreatitis arise because of bacterial translocation from the gut, a consequence of altered intestinal motility, bacterial overgrowth, and increased intestinal permeability. Enteral nutrition, compared to total parenteral nutrition, in acute pancreatitis is associated with better clinical outcomes.

Immediate oral feeding with the introduction of a soft diet, low-fat solid diet, or a full solid diet is safe in patients with mild acute pancreatitis whose pain is settling. Oral feeding in mild acute pancreatitis has been shown to result in shorter duration of hospitalization with no significant pain relapse noted after initiation of refeeding. However, caution should be exercised in patients whose pain relapses following early oral refeeding, as this has been shown to increase their hospital stay.

In patients with severe acute pancreatitis, there is good evidence that enteral nutrition is preferred over total parenteral nutrition. Total parenteral nutrition is associated with a significant increase in local and systemic infective complications, multiorgan failure, and mortality. Enteral nutrition within 48 hours of admission modulates the inflammatory and sepsis response, which has demonstrated clinically significant reduction in all infections and mortality in one study. However, two randomized clinical trials comparing early enteral feeding vs delayed enteral feeding in acute severe pancreatitis failed to demonstrate superiority of early enteral feeding in reducing complications, organ failure, and mortality in

these patients. Enteral feeding can be administered via the nasogastric and nasojejunal routes. Nasogastric feeding is safe and has comparable outcomes to nasojejunal feeding in severe acute pancreatitis. The UK Working Party on Acute Pancreatitis recommends the use of the enteral route for nutritional support, if tolerated, in patients with severe acute pancreatitis. It also acknowledges that the evidence to support the use of enteral nutrition in all patients with severe acute pancreatitis is not conclusive.

Antibiotic therapy in acute pancreatitis

Secondary infective complications of acute pancreatitis are associated with increased mortality. The widespread use of antimicrobial therapy across all areas of health care has resulted in the need for targeted antimicrobial therapy to achieve better outcomes while simultaneously minimizing the risk of developing antimicrobial resistance. Like the debate surrounding nutrition in acute pancreatitis, there have been controversies with the use of antimicrobials in acute pancreatitis.

The spectrum of microorganisms responsible for infected necrosis is changing. Although Gram-negative aerobic bacteria are commonly yielded in cultures of infected pancreatic necrosis, Gram-positive bacteria, anaerobes, and fungi have also been isolated. Penicillins, first-generation cephalosporins, aminoglycosides, and tetracyclines are ineffective in acute pancreatitis. Antibiotics that are active against Gram-negative bacteria such as imipenem, clindamycin, piperacillin, fluoroquinolones, and metronidazole have adequate tissue penetration and bactericidal properties in infected pancreatic necrosis. Compared with other intravenous antibiotics, carbapenems are associated with a significant reduction in mortality, while use of imipenem significantly reduced the incidence of infected pancreatic necrosis. Caution should be exercised when interpreting results of the meta-analyses as the patient numbers are relatively small.

Studies conducted two decades ago focused on the use of antibiotic prophylaxis in preventing the infective complications in severe acute pancreatitis. Systematic reviews and meta-analysis of these studies demonstrated a reduction in mortality with antibiotic prophylaxis. Two decades later, there is now good evidence to suggest that there is no significant decrease in mortality when patients with acute pancreatitis are treated with prophylactic antibiotics. Furthermore, prophylactic antibiotics are not associated with a significant reduction in infective complications of pancreatic necrosis. [9, Rank 4]

Surgical Intervention

In patients with mild acute gallstone pancreatitis who are fit for cholecystectomy, the guidelines recommend that the procedure should ideally be performed at the index admission, and should not be delayed by >2 weeks. Early laparoscopic cholecystectomy in this cohort of patients can shorten the total hospital stay. On the other hand, studies involving patients with mild acute gallstone pancreatitis who underwent interval (delayed) cholecystectomy observed a high risk of readmission with recurrent biliary events. For

patients who are at high risk or unfit for cholecystectomy, or in centers where in-patient cholecystectomy during the index admission is not a feasible option, ERCP and endoscopic sphincterotomy (ES) alone may be sufficient. ES can reduce the short-term risk of a second attack of pancreatitis by at least 50%.

All patients with acute gallstone pancreatitis should have imaging of the common bile duct to assess for choledocholithiasis. Preoperative imaging utilizes noninvasive methods such as transabdominal ultrasound and/or MRCP, while intraoperative cholangiography provides real-time imaging of the common bile duct. Management of choledocholithiasis is reliant upon availability of local expertise and can be broadly classified into 1) the single-stage approach – laparoscopic or open cholecystectomy with intraoperative cholangiography and common bile duct exploration, or 2) two-stage approach – preoperative ERCP with or without ES followed by laparoscopic or open cholecystectomy. There is no significant difference in the morbidity, mortality, retained stones, and failure rate between the two management approaches for choledocholithiasis.

In centers where the availability of appropriate surgical expertise allows the single-stage definitive management of mild acute gallstone pancreatitis, promising results have been yielded. Low complication and conversion rates have been observed, although the selection of patients with uncomplicated mild acute gallstone pancreatitis may account for this. Postoperative MRCP and/or ERCP are options available to clinicians should there be any concern regarding retained stones or alternative pathologies. The combination of laparoscopic cholecystectomy and preoperative ES has also demonstrated a safe and reliable approach in dealing with choledocholithiasis during acute gallstone pancreatitis.

In patients with severe acute gallstone pancreatitis with choledocholithiasis and/or cholangitis, the evidence suggests that performing ERCP within 72 hours of admission reduces the morbidity and mortality in this group of patients. Furthermore, ERCP reduces the length of hospital stay in patients with acute severe gallstone pancreatitis. To date, there is no evidence for or against early laparoscopic cholecystectomy for patients with severe acute gallstone pancreatitis.

Local complications of acute pancreatitis include pancreatic necrosis with or without infection, pancreatic pseudocyst formation, pancreatic duct disruption, and peripancreatic vascular complications. These local complications can be managed using a combination of endoscopic, radiologic, and surgical techniques, and have been reviewed previously. Open surgical debridement requires multiple laparotomies and is consequently associated with a high postoperative morbidity. However, surgical techniques have evolved to become minimally invasive, which may be associated with better outcomes.

The skunk procedure utilizes imaging to advance catheters (drains) over their guidewires into the infected area within the lesser sac. Closed continuous lavage is then initiated once the catheters are in a satisfactory position. The drainage catheters facilitate a pathway into the lesser sac when performing a video-assisted minimally invasive retroperitoneal

pancreatic necrosectomy. Endoscopic transgastric or transduodenal drainage of infected pancreatic necrosis or pancreatic pseudocysts is another technique associated with lower morbidity than open surgical debridement. The minimally invasive techniques for dealing with complications of acute pancreatitis require a multidisciplinary approach with specialist personnel, skills, and equipment. The procedures should ideally be undertaken in centers where there is readily available expertise to manage any complications. [10, Rank 3]

Prophylactic Antibiotic Administration

Pancreatic and extrapancreatic infections are a determining factor leading to death in severe acute pancreatitis. The mortality rate of patients with infected pancreatic necrosis or sepsis is extremely high, and antibiotic prophylaxis has been recommended to prevent infectious complications in severe acute pancreatitis. A human study investigating pancreatic tissue penetration by antibiotics demonstrated that broad-spectrum antibiotics such as ciprofloxacin, ofloxacin, imipenem, and pefloxacin provided sufficient tissue concentration in the pancreas. Four RCTs (Level 1b) of the prophylactic effect of antibiotics demonstrated that broadspectrum antibiotics with good pancreatic tissue penetration decreased the incidence of infectious complications and the mortality rate. A metaanalysis of those RCTs showed that prophylactic antibiotic administration significantly improved the mortality rate in patients with severe acute pancreatitis (Level 1a). An RCT comparing pefloxacin with imipenem reported that imipenem significantly lowered the incidence of pancreatic infection (Level 1b). An RCT investigating the usefulness of prophylactic imipenem administration within 48h after onset showed that the early administration of imipenem decreased the frequency of surgical intervention and the number of organs that failed (Level 1b). A comparison between meropenem and imipenem showed no difference in the occurrence of pancreatic infection, complications, or mortality rates (Level 1b). On the other hand, a placebo-controlled, double-blind trial of ciprofloxacin + metronidazole in patients with predicted severe acute pancreatitis showed that prophylactic administration of these antibiotics did not prevent pancreatic infection (Level 1b).

Selective digestive decontamination (SDD) has also been reported as a means of antibiotic prophylaxis in severe acute pancreatitis (Level 1b). Although SDD was reported in the 1980s as a method of preventing respiratory tract infection in patients with multiple trauma, only one RCT assessed SDD in severe acute pancreatitis. In that trial, antibiotics were given orally, enterally, and intravenously, as well as being applied topically to the gums and tracheotomy site. SDD significantly reduced the frequency of infectious pancreatic complications compared with that in the control groups, and multivariate analysis with severity assessment demonstrated a reduced mortality rate for SDD. In principle, SDD offers comprehensive infection management, not only by the enteral administration of nonabsorptive agents but also by the prevention of systemic infection through sterilization of the oral cavity, as well as by intravenous antibiotic administration and continuous surveillance cultures of the oral cavity and rectum.

Although the prophylactic application of broadspectrum antibiotics reduces the incidence of infectious complications in severe acute pancreatitis, fungal infection in pancreatic necrosis is increasing. The mortality rate of infected pancreatic necrosis complicated by fungal infection is higher than the mortality rate in the absence of fungal infection (Level 2b). A human study reported that the antifungal agent fluconazole had good penetration into pancreatic tissue (Level 2b), and clinical studies have demonstrated that the prophylactic administration of fluconazole reduced the incidence of fungal infection in patients with severe acute pancreatitis (Level 2b). However, there have been no reliable RCTs of the prophylactic administration of antifungal agents in patients with pancreatic necrosis, and the efficacy of antifungal agents has yet to be investigated in an RCT. [11, Rank 4]

Causes for Acute Pancreatitis

The two major etiological factors responsible for acute pancreatitis are alcohol and cholelithiasis (gallstones). The proportions of pancreatitis attributed to alcohol and gallstones in all cases of acute pancreatitis vary considerably for different countries and regions. In US, the incidence of alcoholic pancreatitis is two and a half times that of gallstone pancreatitis, and the high incidence of acute alcoholic pancreatitis is considered to be associated with high levels of alcohol consumption. In contrast, the incidence of gallstone pancreatitis is much higher than that of alcoholic pancreatitis in Greece, Italy, and Norway. In France, Germany, and Korea, the incidence of acute alcoholic pancreatitis is slightly higher than that for gallstone pancreatitis, whereas the opposite is true in Mexico and Sweden. According to a 1999 national survey done in Japan, the incidence of acute alcoholic pancreatitis was fairly similar to that of gallstone pancreatitis (30% vs. 24%). However, the survey classified as alcoholic pancreatitis those cases in which the consumption of only a small amount of alcohol was identified before the onset of symptoms, so the incidence of alcoholic pancreatitis may have been overestimated. Thus, it remains unknown whether alcoholic pancreatitis or gallstone pancreatitis has a higher incidence. [12, Rank 4]

Gender is strongly associated with the risk of acute pancreatitis: the incidence of alcoholic pancreatitis is higher in men, and the incidence of gallstone pancreatitis is higher in women. A study on acute pancreatitis in five European countries revealed that there were many more cases of alcoholic pancreatitis in men than women (90% vs. 10%).The survey done in Japan also revealed that in women the incidence of gallstone pancreatitis was higher than that of alcoholic pancreatitis (31% vs. 7.2%), whereas in men the incidence of acute alcoholic pancreatitis was twice that of gallstone acute pancreatitis (42% vs. 20%). A similar tendency was observed for severe cases. However, a German study showed that there was no gender difference in the risk of acute pancreatitis after adjusting for alcohol intake.

In a case study, consumption of more than 100 g of alcohol within 24 h before the onset was significantly associated with the risk of acute pancreatitis (odds ratio: 4.4, 95% CI: 1.3–15.5).

Lower lipid intake was also associated with risk of acute pancreatitis; the risk was lower (odds ratio: 0.49) in the one-third of subjects with the highest lipid intake than in the one-third with the lowest lipid intake. Smoking and average sleep duration were not associated with increased risk of acute pancreatitis. [13, Rank 3]

Risk Factors for Developing Pancreatitis

Alcohol

Alcohol is one of the two major etiological factors responsible for acute pancreatitis and several studies have attempted to quantify the risk of acute alcoholic pancreatitis. According to a cohort study, the incidence of acute alcoholic pancreatitis among those with the highest alcohol intake (alcohol consumption ≧60 g/day) was 91.5/100000 per year for men and 81.9/100 000 per year for women. However, even in the highest-risk group, the risk of acute alcoholic pancreatitis during a 25-year period was only 2%–3%. These findings suggest that factors other than alcohol also contribute to the occurrence of acute alcoholic pancreatitis.

Cholelithiasis

Cholelithiasis is another major etiological factor responsible for acute pancreatitis. According to a study done in the United States, 89 (3.4%) of 2583 cholelithiasis patients developed pancreatitis during the follow-up period, and the relative risk (RR) for acute pancreatitis in the cholelithiasis patients was 14/35 for men and 12/25 for women. After adjusting for age and sex, the risk of acute pancreatitis among patients with gallstones was 6.3 to 14.8 per 1000 patient-years. However, the risk dramatically decreased after cholecystectomy to 1.9 per 1000 patient-years for men and 2.0 per 1000 patient-years for women. The RR was decreased to 1/8 in patients who underwent cholecystectomy, and recurrence developed in only 2 of the 58 patients after cholecystectomy (Level 2b).

Endoscopic retrograde cholangiopancreatography/endoscopic sphincterotomy

Acute pancreatitis is one of the major complications of endoscopic retrograde cholangiopancreatography (ERCP). According to reports from the United States and Europe, the incidence of acute pancreatitis after diagnostic ERCP ranged from 0.4% to 1.5% (Level 2c). The incidence of complications resulting from endoscopic sphincterotomy (EST) and therapeutic ERCP was found to be higher than that resulting from diagnostic ERCP (Levels 2b); the incidence of acute pancreatitis after EST and therapeutic ERCP ranged from 1.6% to 5.4%, and the incidence of severe acute pancreatitis ranged from 0.4% to 0.7%.

Researchers conducted a meta-analysis of 15 prospective clinical studies on complications resulting from ERCP and identified risk factors for post-ERCP acute pancreatitis. The relative risk of developing post-ERCP acute pancreatitis for suspected sphincter of Oddi dysfunction was 4.09 (95% CI: 3.37–4.96; $P < 0.001$); for women 2.23 (95% CI: 1.75–2.84, $P < 0.001$); for patients with previous pancreatitis 2.46 (95% CI: 1.93–3.12, $P < 0.001$); for precut sphincterotomy 2.71 (95% CI: 2.02–3.63, $P < 0.001$); and for pancreatic injection 2.2 (95% CI:

1.6–3.01, $P < 0.001$). The following factors have also been enumerated as additional risk factors for acute pancreatitis: absence of cholangiectasis, bile duct diameter of less than 1 cm, older patients, difficulty in cannulation, and performance of pancreatography. Researchers reported that the combined use of ERCP and Oddi manometry markedly increased the risk of acute pancreatitis. The incidence of pancreatitis in patients who underwent sphincter of Oddi manometry alone was significantly lower than that in patients who underwent both manometry and ERCP (9.3% vs. 26.1%, $P < 0.026$). The addition of EST to ERCP, however, had no impact on the risk of post-ERCP acute pancreatitis. There were no consistent findings regarding the association between the use of low-osmolar (nonionic) contrast media and the risk of post-ERCP acute pancreatitis, and the issue is still being debated (Levels 1b–2b).

A few studies have investigated post-ERCP acute pancreatitis in Japan. Researchers analyzed complications after therapeutic ERCP in 25 large medical institutions across Japan. In that survey, EST was performed in 468 patients over a 5-year period; 9 (2%) of them developed pancreatitis, but none died. Another nationwide survey targeted 28 large medical institutions and revealed that of the 14947 patients who underwent diagnostic or therapeutic ERCP between January and December, 166 (1.1%) developed complications. Acute pancreatitis occurred in 89 (0.8%) of the patients who underwent diagnostic ERCP, and the incidence following therapeutic ERCP was 1.9%. The incidence of severe acute pancreatitis among the patients who underwent diagnostic ERCP and therapeutic ERCP was 0.07% and 0.1%, respectively. One patient who underwent therapeutic ERCP died, and the overall mortality was 0.007%. The mortality rate among patients who underwent therapeutic ERCP was 0.02%.

Surgery and medical procedures

The incidence of postoperative pancreatitis is high after surgery conducted near the pancreas, such as biliary tract procedures, gastric surgery, splenectomies, and splenorenal shunts (Level 4). Before the introduction of ERCP and laparoscopic cholecystectomy, the risk of postoperative acute pancreatitis in patients undergoing biliary surgery was reported to be as high as 10%, with a mortality of 30%–80%. Researchers compared the incidence of postoperative pancreatitis after laparoscopic cholecystectomy (LC) and found that the risk of pancreatitis increased after conversion to an open cholecystectomy; the incidence of pancreatitis after completed LC was 0.34%, whereas that after conversion was 0.96% ($P = 0.02$). It was possible to establish a biliary origin for the pancreatitis in 4 (12.5%) of the 32 patients with postoperative pancreatitis, and no evidence was found for a causative role of intraoperative cholangiography or trauma to the pancreas (Level 2c).

There have been many reports of pancreatitis developing after cardiovascular surgery or transplantation (e.g., pancreas, liver, kidney, heart, or bone marrow). Researchers investigated the incidence of postoperative pancreatitis after gynecological and obstetric

surgery and found that it was very low overall, occurring in only 1 of 17000 surgical procedures (Level 2c).

Other reports have shown the occurrence of acute pancreatitis following extracorporeal shock wave lithotripsy (ESWL) for gallbladder stones (2%),following transcatheter arterial embolization (TAE, 33%),following percutaneous biliary drainage (PBD) (24% developed postprocedural hyperamylasemia and 10% developed postoperative acute pancreatitis), following biliary stent insertion (11.5F stent, 3%; 10F stent, none), following intraoperative irradiation (2/98, 2%), and following continuous ambulatory peritoneal dialysis (CAPD) (0.46 per 100 treatment-years).

Drugs

Many studies have suggested associations between the use of drugs and the risk of acute pancreatitis, but direct associations have been demonstrated for only a small number of drugs. The interval between drug administration and the onset of symptoms differs depending on the drug. Certain drugs, such as acetaminophen, can cause pancreatitis after a single dose. Others, such as azathioprine, 6-mercaptopurine, metronidazole, aminosalicylates, and sulfonamides, characteristically can cause pancreatitis within a month after exposure, while still others, such as pentamidine, valproic acid, and didanosine, appear to cause injury weeks or months after exposure, possibly through the accumulation of a toxic metabolite (Level 4). [14, Rank 4]

The drugs reported to be associated with the highest incidence of acute pancreatitis are azathioprine, mercaptopurine, and didanosine. An early study on the risk of acute pancreatitis associated with 6-mercaptopurine reported that 13 (3.3%) of 400 patients with inflammatory bowel disease developed acute pancreatitis. However, a case-control study of 4,90,000 residents showed that the risk of acute pancreatitis in patients under treatment with azathioprine was only 1/659. In that study, the odds ratio for the risk of acute pancreatitis within 90 days after azathioprine administration was 7.5 (95% CI: 2.6–21.6), and after adjusting for cholelithiasis, alcohol, inflammatory intestinal diseases, and steroids, the odds ratio was 8.4 (95% CI: 2.6–21.6). Although many HIV patients treated with didanosine develop acute pancreatitis, the independent risk associated with use of the drug is unknown.

According to a case-control study over a 4-year period, 462 of the 1.4 million registered residents aged between 20 and 85 who did not have a clear etiological factor for their acute pancreatitis were hospitalized on their first attack of acute pancreatitis. A multivariate analysis revealed that H2 blockers, proton pump inhibitors, NSAIDs, and antacids were significantly associated with the risk of acute pancreatitis, but the odd ratios were generally low (1.9–2.4).

Hyperlipidemia

High blood triglyceride levels of more than 1000–2000mg/dl are said to increase the risk of acute pancreatitis. Type V hyperlipidemia, as well as types I and IV, are prominent causes of acute pancreatitis as a result of marked hyperlipidemia (Level 4). Secondary hyperlipidemia is caused by alcohol intake, pregnancy, estrogen therapy, and diabetes mellitus, all of which are risk factors for acute pancreatitis. Genetic polymorphism of lipoprotein lipase and the apolipoprotein C-II defect, which cause hyperlipidemia, are also suggested to cause acute pancreatitis (Level 4). Some recent studies have suggested an association between the risk of acute pancreatitis and marked hypertriglyceridemia related to the administration of protease inhibitors among patients with HIV infection. However, other reports argue that there is no association between the two.

The risk of acute pancreatitis associated with hyperlipidemia has yet to be determined. A large-scale cohort study showed that hyperlipidemia accounts for 12%–38% of all cases of acute pancreatitis, whereas another study suggested that it accounts for only 1.3%–3.8%.

HIV infection

Acute pancreatitis is one of the main complications of acquired immunodeficiency syndrome (4%–22%), and the risk increases with the progression of HIV infection. The risk of acute pancreatitis in HIV-infected populations is 35 to 800 times higher than in populations without infection. Although HIV-infected patients may develop pancreatitis for many reasons, drugs are a common cause of acute pancreatitis. Before the introduction of antiretroviral therapy, the major mechanisms responsible for the development of acute pancreatitis among HIV-infected patients were: (1) pancreatic toxicity resulting from drugs used to treat HIV infection and (2) immunosuppression by the HIV infection itself. When protease inhibitors were released on the market and came to be widely used in the treatment of HIV infection, HIV-infected patients have had a higher incidence of medication-associated hypertriglyceridemia, which is often severe and difficult to treat, and several reports have suggested that hypertriglyceridemia may be involved in the onset of acute pancreatitis.

Researchers investigated whether the release of protease inhibitors onto the market changed the incidence of acute hyperlipidemic pancreatitis in HIV-infected patients. Despite the well-established association between protease inhibitors and hyperlipidemia, there was no significant increase in the prevalence of hyperlipidemic patients in the HIV-infected population: the incidence of acute pancreatitis attributed to hypertriglyceridemia (serum neutral fat level ≧1000mg/dl) was 3.3% before the sale of protease inhibitors (1990–1995) and 3.7% after they came on the market (1996–2001) (P = 0.6). On the other hand, medication-induced pancreatitis was the most common kind in HIV-infected patients: the incidence of medication-induced acute pancreatitis was 46.6% before the release of protease inhibitors and 50.0% after the release (P = 0.6).

Idiopathic

After gallstones and alcohol, the third most common etiology of acute pancreatitis, regardless of country, region, or case series, is idiopathic. Acute idiopathic pancreatitis is defined as acute pancreatitis with a nonspecified etiological factor, but it includes those cases caused by other specific disorders. Two prospective studies of apparently idiopathic pancreatitis have found that two-thirds to three-quarters of the cases had microlithiasis documented by biliary-drainage studies, follow-up sonograms, and ERCP (Level 2b). In the treatment of acute pancreatitis, the diagnosis of acute idiopathic pancreatitis should be minimized by identifying the etiological factors based on clinical symptoms and findings as well as appropriate tests. [15, Rank 5]

Other Factors Associated with Acute Pancreatitis

Other factors associated with acute pancreatitis are inherited conditions, pregnancy, trauma, viral infections (mumps, Coxsackie B, hepatitis B, cytomegalovirus, herpes simplex II, and varicella-zoster), bacterial infections (*Salmonella typhi*, *Leptospira*, and *Legionella*), fungal infection (*Aspergillus*), parasites (*Toxoplasma*, *Cryptosporidium*, *Ascaris lumbricoides*, and *Mycoplasma*), collagen diseases (including systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, and systemic sclerosis), hyperparathyroidism, and end-stage renal failure.

Many studies have suggested the involvement of local predisposing anatomic factors in the etiology of acute pancreatitis. The presence and diameter of a common channel, pancreatic duct reflux, the angle formed between the common bile duct and the pancreatic duct, abnormalities of the Vater's ampulla (edema, hemorrhage, and impacted calculi), patent Santorini's duct, and the position of confluence with the cystic duct have all been suggested to be associated with the development of acute pancreatitis (Levels 2b–3b). Pancreas divisum, a congenital variant of pancreatic ductal anatomy that affects 5%–7% of the general population, has also been suggested to be associated with acute pancreatitis. Some reports have shown a significantly higher incidence of pancreas divisum among patients with acute pancreatitis, including recurrent pancreatitis (Levels 3b–4). However, another study reported no difference in any of these parameters between acute pancreatitis patients and healthy subjects (Level 2b). A randomized controlled clinical trial showed that stenting of the accessory papilla interrupted the cycle of recurrent attacks of pancreatitis in patients with pancreas divisum (Level 1b). Associations between acute pancreatitis and choledochocele (choledochal cyst), peripapillary diverticulum, ectopic pancreas, pancreatitis caused by duodenal duplication, pancreatitis accompanying Caroli's disease, and pancreatitis caused by tumors of the pancreas (cancer of the pancreas, metastatic pancreatic tumors, and carcinoid tumors) have also been reported (Level 4). However, it remains unclear whether the incidence of acute pancreatitis is higher in these patients than in healthy subjects.

Acute pancreatitis in childhood is unusual, and the etiology in children differs from the etiology in adults. Researchers reviewed 5 studies involving a total of 223 children with acute pancreatitis and reported that trauma is the leading cause of acute pancreatitis in children, accounting for 21% of the cases, followed by idiopathic causes (20%), biliary tract disease (17%), drugs (15%), infections (10%), congenital anomalies (6%), and miscellaneous causes (11%). [16, Rank 3]

Supportive Care

Animal studies have shown that aggressive fluid replacement supports pancreatic microcirculation and prevents necrosis. There have been no high-quality trials to test the effectiveness of aggressive fluid resuscitation in patients with acute pancreatitis, and the approach to fluid resuscitation in these patients remains an under-investigated topic. However, poor outcomes, including more deaths and necrosis, have been reported in patients in whom there was hemoconcentration. In an observational study, necrotizing acute pancreatitis developed in all patients who received inadequate fluid replacement as measured by a rise in hematocrit at 24 hours. Further, a recent randomized controlled trial (RCT) compared the use of normal saline versus Ringer's Lactate in goal-directed and standard fluid resuscitation in patients with acute pancreatitis. In this RCT (n = 40), it was found that after 24 hours of resuscitation there was an 84% reduction in the incidence of SIRS in patients resuscitated with Ringer's Lactate (p = 0.035) as well as a significant reduction in CRP from 9905 nmol/L (104 mg/dL) to 5143 nmol/L (54 mg/dL) when Ringer's Lactate was selected over normal saline (p = 0.02).

Pain control is an important part of the supportive management of patients with acute pancreatitis. Therefore, in the absence of any patient-specific contraindications, a multimodal analgesic regimen is recommended, including narcotics, nonsteroidal anti-inflammatories and acetaminophen.

There are no studies assessing the impact of different models of critical care delivery and outcomes in patients with severe acute pancreatitis. However, a systematic review of 26 observational studies showed that critically ill patients cared for by an intensivist or using an intensivist consultant model in a closed intensive care unit (ICU) had a shorter stay in the ICU and lower mortality than similar patients cared for in units without such staffing patterns.

The underlying pathogenesis of acute pancreatitis is the premature activation of proteolytic enzymes resulting in the autodigestion of the pancreas. In the past, it was accepted practice that bowel rest would limit the inflammation associated with this process. Recently, however, a series of RCTs have convincingly shown that early oral/enteral feeding in patients with acute pancreatitis is not associated with adverse effects and may be associated with substantial decreases in pain, opioid usage and food intolerance. Furthermore, researchers demonstrated that oral feeding on admission for mild acute pancreatitis was associated with a significant decrease in length of stay from 6 to 4

days (p = 0.047) compared with withholding oral food and fluids. The major benefits from early feeding appear to be effective only if feeding is commenced within the first 48 hours following admission, and the current recommendation based on a 2010 meta-analysis of 32 RCTs is to commence oral feeding at the time of admission if tolerated or within the first 24 hours. Finally, a low-fat diet was shown to be preferable to clear fluids on admission for mild acute pancreatitis owing to a higher caloric intake with no associated adverse effects. [17, Rank 5]

Conclusion

There is wide variation in the severity of acute pancreatitis. Mild acute pancreatitis tends towards spontaneous remission, but once acute pancreatitis becomes severe, there is a great risk of death from fatal complications, such as circulatory failure, vital organ failure, and infection. To improve prognosis, it is important to assess accurately the severity of the disease in order to select proper initial treatment. Thus, accurate severity assessment and determination of a proper disease management policy are crucial. The severity scoring system most widely used allows sequential scoring of severity and is useful for the selection of proper initial treatment. The scoring system is based on clinical signs, blood test data, and imaging findings, and it is used to decide on the treatment strategy. Because acute pancreatitis that is initially diagnosed as mild or moderate can progress to severe, or become fatal, during treatment, even mild acute pancreatitis should be continuously monitored with the greatest care. Serial assessments of severity should be performed as early as possible to detect signs of a poor outcome. [18, Rank 4]

References

1. Low MJ. Neuroendocrinology. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Williams textbook of endocrinology. 14th ed. Philadelphia: Elsevier/Saunders; 2014

2. Parks JS, Felner EI. Hormones of the hypothalamus and pituitary. In: Kliegman RM, Stanton BF, St Geme JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Elsevier/Saunders; 2014

3. Fenichel GM. Clinical pediatric neurology: a signs and symptoms approach. 4th ed. Philadelphia: W.B. Saunders; 2012.

4. Sheldon CA, Kwon YJ, Liu GT, McCormack SE. An integrated mechanism of pediatric pseudotumor cerebri syndrome: evidence of bioenergetic and hormonal regulation of cerebrospinal fluid dynamics. Pediatr Res. 2014

5. Park E, Abraham MK. Altered mental status and endocrine diseases. Emerg Med Clin North Am. 2014

6. Boveroux P, Bonhomme V, Boly M, Vanhaudenhuyse A, Maquet P, Laureys S. Brain function in physiologically, pharmacologically, and pathologically altered states of consciousness. Int Anesthesiol Clin. 2012

7. Taylor DA, Ashwal S. Impairment of consciousness and coma. In: Swaiman KF, Ashwal S, Ferriero DM, Schor NF, editors. Swaiman's pediatric neurology. 5th ed. [Edinburgh]: Elsevier Saunders; 2012

8. Sharma S, Kochar GS, Sankhyan N, Gulati S. Approach to the child with coma. Indian J Pediatr. 2013

9. Kitabchi AE, Umpierrez GE, Fisher JN, Murphy MB, Stentz FB. Thirty years of personal experience in hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. J Clin Endocrinol Metab. 2015

10. Nyenwe EA, Kitabchi AE. Evidence-based management of hyperglycemic emergencies in diabetes mellitus. Diabetes Res Clin Pract. 2015

11. Zeitler P, Haqq A, Rosenbloom A, Glaser N Drugs and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Hyperglycemic hyperosmolar syndrome in children: pathophysiological considerations and suggested guidelines for treatment. J Pediatr. 2012

12. Papi G, Corsello SM, Pontecorvi A. Clinical concepts on thyroid emergencies. Front Endocrinol (Lausanne) 2014

13. Arsos G. Unexpected diagnosis of thyroid storm in a young child referred for urgent lung perfusion imaging. Clin Nucl Med. 2013

14. Vasconcellos E, Pina-Garza JE, Fakhoury T, Fenichel GM. Pediatric manifestations of Hashimoto's encephalopathy. Pediatr Neurol. 2016

15. Yu HJ, Lee J, Seo DW, Lee M. Clinical manifestations and treatment response of steroid in pediatric Hashimoto encephalopathy. J Child Neurol. 2013

16. Chang JS, Chang TC. Hashimoto's encephalopathy: report of three cases. J Formos Med Assoc. 2014

17. Sharma V, Borah P, Basumatary LJ, Das M, Goswami M, Kayal AK. Myopathies of endocrine disorders: a prospective clinical and biochemical study. Ann Indian Acad Neurol. 2014

18. Rodrigues F, Grenha J, Ortez C, Nascimento A, Morte B, M-Belinchón M, et al. Hypotonic male infant and MCT8 deficiency- a diagnosis to think about. BMC Pediatr. 2014

19. Edvardsson B, Persson S. Subclinical hypothyroidism presenting with gait abnormality. Neurologist. 2012

20. Webb SM, de Andres-Aguayo I, Rojas-Garcia R, Ortega E, Gallardo E, Mestron A, et al. Neuromuscular dysfunction in adult growth hormone deficiency. Clin Endocrinol (Oxf) 2003