

REVIEW ARTICLE

Acute pancreatitis- a clinical update

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Abstract

Acute pancreatitis is an acute inflammatory process of the pancreas that can range from mild interstitial pancreatitis to severe pancreatitis with pancreatic necrosis with variable involvement of regional tissues and remote organ systems. The incidence of pancreatitis varies in different countries and depends on causes e.g, gallstones, alcohol, metabolic factors and viral infections. Gall stones continue to be the leading cause of acute pancreatitis in most series. Alcohol, hypertriglyceridemia and drugs are also a common cause of acute pancreatitis. Gall stone pancreatitis is more common in women than in men. Alcohol is also a common cause of acute pancreatitis. Alcoholic pancreatitis is more common in men, and usually occurs in individuals with long standing alcohol abuse. The increased frequency of acute pancreatitis may be due to the rising incidence of obesity, a risk factor for the development of gallstones and by extension, gallstone pancreatitis. Acute pancreatitis occurs when there is abnormal activation of digestive enzymes within the pancreas. This occurs through inappropriate activation of inactive enzyme precursors called zymogens or proenzymes inside the pancreas, most notably trypsinogen. Acute pancreatitis is typically rapid in onset and most commonly encountered in its mild form. While mild cases are often successfully treated with conservative measures, such as fasting and aggressive intravenous fluid rehydration, severe cases may require admission to the intensive care unit or even surgery to deal with complications of the disease process. Acute pancreatitis may be accompanied by life threatening complications as well as significant morbidity and mortality despite treatment.

Context

Acute pancreatitis is an acute inflammatory process of the pancreas that can range from mild interstitial pancreatitis to severe pancreatitis with pancreatic necrosis with variable involvement of regional tissues and remote organ systems.¹ The incidence of pancreatitis varies in different countries and depends on causes e.g, gallstones, alcohol, metabolic factors and viral infections. The estimated incidence in industrialized countries is 10-20/100,000 per year.² There are many causes of acute pancreatitis, but the mechanisms by which these conditions trigger pancreatic inflammation have not been identified.³ Gall stones continue to be the leading cause of acute pancreatitis in most series.⁴ Gall stone pancreatitis is more common in women than in men. Alcohol is also a common cause of acute pancreatitis.⁵ Alcoholic pancreatitis is more common in men and usually occurs in individuals with long standing alcohol abuse. Hypertriglyceridemia. is the cause of acute pancreatitis in 1.3 to 3.8% of cases.⁶

Approximately 2 to 5% of cases of acute pancreatitis are drug related. Drugs cause pancreatitis either by a hypersensitivity reaction or by the generation of a toxic metabolites.⁷ Acute pancreatitis is typically rapid in onset and most commonly encountered in its mild form. It can have severe complications and high mortality despite treatment. While mild cases are often successfully treated with conservative measures, such as fasting and aggressive intravenous fluid rehydration, severe cases may require admission to the intensive care unit or even surgery to deal with complications of the disease process. The increased frequency of acute pancreatitis may be due to the rising incidence of obesity, a risk factor for the development of gallstones and by extension gallstone pancreatitis. The average length of hospital stay for a patient with acute pancreatitis is approximately 5 to 6 days.⁹ In addition, acute pancreatitis may be accompanied by life threatening complications as well as significant morbidity and mortality. This article reviews the updated diagnosis and management of patients with acute pancreatitis.

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Pathogenesis

Acute pancreatitis occurs when there is abnormal activation of digestive enzymes within the pancreas. This occurs through inappropriate activation of inactive enzyme precursors called zymogens (or proenzymes) inside the pancreas, most notably trypsinogen. Normally, trypsinogen is converted to its active form trypsin in the first part of the small intestine (duodenum), where the enzyme assists in the digestion of proteins. During an episode of acute pancreatitis, trypsinogen comes into contact with lysosomal enzymes (specifically cathepsin), which activate trypsinogen to trypsin. The active form trypsin then leads to further activation of other molecules of trypsinogen. The activation of these digestive enzymes lead to inflammation, edema, vascular injury and even cellular death. The death of pancreatic cells occurs via two main mechanisms: necrosis, which is less organized and more damaging or apoptosis, which is more controlled. The balance between these two mechanisms of cellular death is mediated by caspases which regulate apoptosis and have important anti necrosis functions during pancreatitis: preventing trypsinogen activation, preventing ATP depletion through inhibiting poly ADP ribose polymerase and by inhibiting the inhibitors of apoptosis (IAPs) If, however the caspases are depleted due to either chronic ethanol exposure or through a severe insult then necrosis can predominate. As part of the initial injury there is an extensive inflammatory response due to pancreatic cells synthesizing and secreting inflammatory mediators: primarily TNF-alpha and IL-1.

Aetiology

List of causes are:- Gallstones, alcohol, metabolic disorders: hereditary pancreatitis, hypercalcemia, elevated triglycerides, malnutrition, post ERCP, abdominal trauma, penetrating ulcers, carcinoma of the head of pancreas and other cancer, Drugs: diuretics, gliptins, tetracycline, sulfonamides, estrogens, azathioprine and mercaptopurine, pentamidine, salicylates, steroids, valproic acid; Infections: mumps, viral hepatitis, coxsackie B virus, cytomegalovirus, Mycoplasma pneumoniae, Ascaris; Structural abnormalities: choledochoceles, pancreas divisum, Radiation X ray, Autoimmune pancreatitis. Less common causes are-scorpion venom, Chinese liver fluke, ischemia from bypass surgery, heart valve surgery, fat necrosis or hypertriglyceridemia, pregnancy, repeated marathon running, hyperparathyroidism, cystic fibrosis, anorexia or bulimia, Familial, Long common duct, Codeine phosphate reaction.¹⁰

Clinical features

The most common symptoms and signs include: severe epigastric pain radiating to the back in 50% of cases, nausea, vomiting, loss of appetite, fever with chills, hemodynamic instability, including shock, tachycardia, respiratory distress, peritonitis, hiccup.⁴ Signs that are less common and indicate severe disease, include: Grey-Turner's sign (hemorrhagic discoloration of the flanks), Cullen's sign (hemorrhagic discoloration of the umbilicus), pleural effusions, Grunwald sign (appearance of ecchymosis, large bruise, around the umbilicus due to local toxic lesion of the vessels), Korte's sign (pain or resistance in the zone where the head of pancreas is located, Kamenchik's sign (pain with pressure under the xiphoid process), Mayo-Robson's sign (pain while pressing at the left costovertebral angle, Mayo Robson's point is a point on border of inner 2/3 with the external 1/3 of the line that represents the bisection of the left upper abdominal quadrant, where tenderness on pressure exists in disease of the pancreas. At this point the tail of pancreas is projected on the abdominal wall Other conditions to consider are: pancreatic pseudocyst, pancreatic dysfunction, pancreatic cancer. Although these are common symptoms, they are not always present. Simple abdominal pain may be the sole symptom. Differential diagnosis includes Perforated peptic ulcer, Biliary colic, Acute cholecystitis, Pneumonia, Pleuritic pain, Myocardial infarction.¹¹

Diagnosis

Acute pancreatitis is diagnosed clinically but requires CT evaluation to differentiate mild acute pancreatitis from severe necrotic pancreatitis. Experienced clinicians were able to detect severe pancreatitis in approximately 34-39% of patients who later had imaging and confirmed severe necrotic pancreatitis. Blood studies are used to identify organ failure, offer prognostic information, determine if fluid resuscitation is adequate and if antibiotics are indicated Blood investigations full blood count, renal function tests, liver function, serum calcium, serum amylase and lipase, arterial blood gas, trypsin selective test. Imaging- a triple phase abdominal CT and abdominal ultrasound are together considered the gold standard for the evaluation of acute pancreatitis.¹² Following investigations are the recent advancement in the diagnosis of acute pancreatitis.

Laboratory tests - Elevated serum amylase and lipase levels, in combination with severe abdominal pain, often trigger the initial diagnosis of acute pancreatitis However, they have no role

in assessing disease severity. Serum lipase rises 4 to 8 hours from the onset of symptoms and normalizes within 7 to 14 days after treatment. Serum amylase may be normal (in 10% of cases) for cases of acute or chronic pancreatitis and hypertriglyceridemia. In general, serum lipase is thought to be more sensitive and specific than serum amylase in the diagnosis of acute pancreatitis.¹³ Reasons for false positive elevated serum amylase include salivary gland disease, bowel obstruction, infarction, cholecystitis and a perforated ulcer. If the lipase level is about 2.5 to 3 times that of amylase, it is an indication of pancreatitis due to alcohol, decreased serum calcium and glycosuria.¹⁴

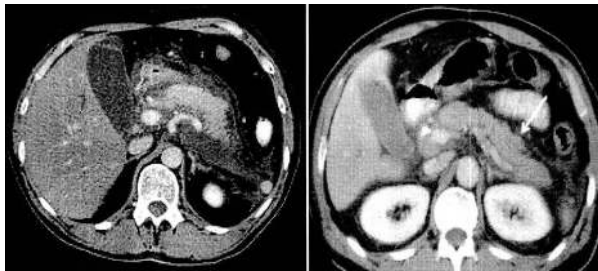


Fig.1 Axial CT in a patient with acute exudative pancreatitis showing extensive fluid collections surrounding the pancreas.

Magnetic resonance imaging- While computed tomography is considered the gold standard in diagnostic imaging for acute pancreatitis, magnetic resonance imaging (MRI) has become increasingly valuable as a tool for the visualization of the pancreas, particularly of pancreatic fluid collections and necrotized debris (Fig. 1).¹⁵ Additional utility of MRI includes its indication for imaging of patients with an allergy to CT's contrast material, and an overall greater sensitivity to hemorrhage, vascular complications, pseudoaneurysms and venous thrombosis. Another advantage of MRI is its utilization of magnetic resonance cholangiopancreatography (MRCP) sequences. MRCP provides useful information regarding the aetiology of acute pancreatitis i.e, the presence of tiny biliary stones (choledocholithiasis or cholelithiasis) and duct anomalies.¹⁶ Clinical trials indicate that MRCP can be as effective a diagnostic tool for acute pancreatitis with biliary etiology as endoscopic retrograde cholangiopancreatography but with the benefits of being less invasive and causing fewer complications.¹⁷

Endoscopic ultrasound- Endoscopic ultrasound is a sensitive means of detecting acute pancreatitis, chronic pancreatitis, pancreatic tumor and distal common bile duct stones. Endoscopic

ultrasonography is as accurate and safer than ERCP for the detection of pancreatic duct stone, common bile duct stone and pancreatic tumor.

Prognosis

Acute pancreatitis patients recover in majority of cases. Some may develop abscess, pseudocyst or duodenal obstruction. In 5 percent cases, it may result in ARDS (acute respiratory distress syndrome), DIC (disseminated intravascular coagulation), etc. Acute pancreatitis can be further divided into mild and severe pancreatitis. Mostly the Ranson Criteria are used to determine severity of acute pancreatitis. In severe pancreatitis serious amounts of necrosis determine the further clinical outcome. About 20% of the acute pancreatitis are severe with a mortality of about 20%. This is an important classification as severe pancreatitis will need intensive care therapy whereas mild pancreatitis can be treated on the common ward. Necrosis will be followed by a systemic inflammatory response syndrome (SIRS) and will determine the immediate clinical course. The further clinical course is then determined by bacterial infection. SIRS is the cause of bacterial (Gram negative) translocation from the patient's colon. In predicting the prognosis, there are several scoring indices that have been used as predictors of survival. Two such scoring systems are the Ranson criteria and APACHE 11 (Acute Physiology and Chronic Health Evaluation) indices. Most but not all studies, report that the Apache score may be more accurate."In the negative study of the APACHE II, the APACHE III 24 hour score was used rather than the 48 hour score.¹⁹ In addition, all patients in the study received an ultrasound twice which may have influenced allocation of co interventions. Regardless, only the APACHE II can be fully calculated upon admission. As the APACHE II is more cumbersome to calculate, presumably patients whose only laboratory abnormality is an elevated lipase or amylase do not need assessment with the APACHE II; however, this approach is not studied.

Management

Initial management of a patient with acute pancreatitis consists of supportive care with fluid resuscitation, pain control and nutritional support.

Fluid replacement- In patients with severe volume depletion that manifests as hypotension and tachycardia, more rapid repletion with 20 mL/Kg of intravenous fluid given over 30 minutes followed by 3 mL/Kg/hour for 8 to 12 hours.²⁰

Fluid requirements should be reassessed at frequent intervals in the first six hours of admission and for the next 24 to 48 hours. The rate of fluid resuscitation should be adjusted based on clinical assessment, hematocrit and blood urea nitrogen (BUN) values. In the initial stages (within the first 12 to 24 hours) of acute pancreatitis, fluid replacement has been associated with a reduction in morbidity and mortality.²¹ There is some evidence that fluid resuscitation with lactated Ringer's solution may reduce the incidence of Systemic Inflammatory Response Syndrome (SIRS) as compared with normal saline.²²

Pain control- Abdominal pain is often the predominant symptom in patients with acute pancreatitis and should be treated with analgesics. Opioids are safe and effective at providing pain control in patients With acute pancreatitis.²³ Meperidine has been historically favored over morphine because of the belief that morphine caused an increase in sphincter of Oddi pressure. However, no clinical studies suggest that morphine can aggravate or cause pancreatitis or cholecystitis.²⁴ In addition, meperidine has a short half life and repeated doses can lead to accumulation of the metabolite normeperidine, which causes neuromuscular side effects and rarely seizures.

Bowel rest- In the management of acute pancreatitis, the treatment is to stop feeding the patient, giving him or her nothing by mouth, giving intravenous fluids to prevent dehydration, and sufficient pain control. Approximately 20% of patients have a relapse of pain during acute pancreatitis. Approximately 75% of relapses occur within 48 hours of oral refeeding. The incidence of relapse after oral refeeding may be reduced by post pyloric enteral rather than parenteral feeding prior to oral refeeding.²⁵ IMRIE scoring is also useful.

Nutritional support- The advantage of enteral feeding is that it is more physiological, prevents gut mucosal atrophy and is free from the side effects of TPN (such as fungemia). Oxygen may be provided in some patients (about 30%) if Pao₂ levels fall below 70mm of Hg.

Antibiotics- Up to 20 percent of patients with acute pancreatitis develop an extrapancreatic infection.²⁶ Extrapancreatic infections are associated with an increase in mortality. When an infection is suspected, antibiotics should be started while the source of the infection is being determined. Prophylactic antibiotics are not recommended in patients with acute pancreatitis,

regardless of the type (interstitial or necrotizing) or disease severity (mild, moderately severe or severe).²⁷

Carbapenems- An early randomized controlled trial of imipenem 0.5 gram intravenously every eight hours for two weeks showed a reduction in pancreatic sepsis from 30% to 12%.²⁸ Another randomized controlled trial with patients who had at least 50% pancreatic necrosis found a benefit from imipenem compared to pefloxacin with a reduction in infected necrosis from 34% to 20%.²⁹ A subsequent randomized controlled trial that used meropenem I gram intravenously every 8 hours for 7 to 21 days stated no benefit; however, 28% of patients in the group subsequently required open antibiotic treatment vs. 46% in the placebo group. In addition, the control group had only 18% incidence of peripancreatic infections and less biliary pancreatitis than the treatment group (44% versus 24%).

ERCP- Early ERCP (endoscopic retrograde cholangiopancreatography) performed within 24 to 72 hours of presentation is known to reduce morbidity and mortality.³⁰ The indications for early ERCP are: Clinical deterioration or lack of improvement after 24 hours, detection of common bile duct stones or dilated intrahepatic or extrahepatic ducts on abdominal CT. The disadvantages of ERCP are: It precipitates pancreatitis and can introduce infection to sterile pancreatitis. The inherent risks of ERCP is bleeding.

Surgery- Surgery is indicated for infected pancreatic necrosis, diagnostic uncertainty and complications. The most common cause of death in acute pancreatitis is secondary infection. Infection is diagnosed on 2 criteria: Gas bubbles on CT scan (present in 20 to 50% of infected necrosis). Positive bacterial culture on FNA (fine needle aspiration, usually CT or US guided) of the pancreas. Surgical options for infected necrosis include: Minimally invasive management (necrosectomy) through small incision in skin (left flank) or abdomen. Conventional management of necrosectomy with simple drainage. Closed management necrosectomy with closed continuous postoperative lavage and open management of necrosectomy with planned staged reoperations at definite intervals (up to 20+ reoperations in some cases)

Complications

Complications can be systemic or local. Systemic complications include: ARDS, multiple organ dysfunction syndrome, DIC, anemia,

hypocalcemia, hyperglycemia, hypertriglyceridemia and insulin dependent diabetes mellitus, hypovolemia and shock, renal failure. Local complications include pancreatic pseudocyst (Most common, occurring in up to 25% of all cases) and phlegmon/abscess formation, splenic artery pseudoaneurysms, gastrointestinal hemorrhage from stress ulceration, hemorrhage from erosions into splenic artery and vein, thrombosis of the splenic vein, superior mesenteric vein and portal veins, duodenal obstruction, common bile duct obstruction, progression to chronic pancreatitis, pancreatic ascites, pleural effusion, pancreatic abscess, sterile/infected pancreatic necrosis, psychosis or encephalopathy, subcutaneous fat necrosis and arthralgia.

Prevention

Risk of new or repeated episodes of pancreatitis can be lowered by taking steps to prevent the medical conditions that can lead to the disease: Aspirin should be avoided when treating a fever in children, especially if they may have a viral illness, to reduce the risk of Reye's syndrome. Avoidance of too much alcohol, vaccination to protect the children against mumps and other childhood illness and treating medical conditions that contribute to hypertriglyceridemia, may reduce the risk of pancreatitis.

Conclusion

The incidence of pancreatitis varies in different countries and depends on causes like gallstones, alcohol, metabolic factors and viral infections. Acute pancreatitis is typically rapid in onset and most commonly encountered in its mild form. While mild cases are often successfully treated with conservative measures, such as fasting and aggressive intravenous fluid rehydration, severe cases may require admission to the intensive care unit or even surgery to deal with complications of the disease process. It may be accompanied by life threatening complications as well as significant morbidity and mortality despite standard treatment.

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