Part III: Gastroenterological Disorders

Chapter 32: Acute Pancreatitis

J Santamaria

Acute pancreatitis remains a relatively common disorder with a significant mortality. It may affect patients of all ages and often becomes a multi-system disorder requiring facilities within Intensive Care Units for optimal management.

Aetiology

Many conditions are known to cause acute pancreatitis (Table 1) but in most studies, these can be divided into four common categories:

1. biliary tract disease;
2. excessive alcohol ingestion over many years;
3. idiopathic; and
4. miscellaneous.

Biliary disease and alcohol count for 70% of cases. Although incidences vary from one location to another, biliary disease is more commonly reported in Britainj while alcohol predominates in American studies. Cases with no discernible cause (idiopathic) may account for up to 30% of some series. Several drugs are known to cause pancreatitis, and many others are implicated but without conclusive evidence.

Pathophysiology

As with many body systems, the pancreas reacts in a limited number of ways to an acute insult. The pancreas is rich in enzymes which have the potential to cause extensive tissue damage. Under normal circumstances, several mechanisms protect the pancreas from damage; they include containment within storage granules, potent enzyme inhibitors, and the production of enzymes in an inactive precursor form (zymogens). Inappropriate activation of these enzymes within the pancreas will lead to extensive damage by "autodigestion".

Although the proteolytic enzymes such as trypsin, chymotrypsin and elastase were initially considered to be the main destructive agents, there is increasing evidence that the lipolytic enzyme, phospholipase A2, may be more important. Furthermore, this enzyme has been implicated in extra-pancreatic complications.

Several mechanisms have been proposed to explain the initial processes by which autodigestion begins.

1. Duodenal Reflux

It is well established in animal models that reflux of duodenal contents into the pancreas will lead to acute pancreatitis but the evidence in humans is inconclusive.

Table 1. Aetiology of Acute Pancreatitis

A. Excess Alcohol Ingestion
B. Biliary Tract Disease
C. Idiopathic
D. Metabolic
    1. Hyperlipaemia
    2. Hyperparathyroidism
    3. Diabetic ketoacidosis
    4. Uraemia
    5. Pregnancy
    6. Post renal transplant
E. Mechanical Disorders
    1. Post traumatis
    2. Post operative
    3. Post endoscopic retrograde cholangiopancreatography (ERCP)
    4. Penetrating Peptic Ulcer
    5. Duodenal Obstruction
F. Infections
    1. Mumps, Epstein-Barr virus, mycoplasma, hepatitis, ascariasis
G. Vascular
    1. Necrotizing vasculitis - Systemic lupus erythematosus (SLE), thrombotic thrombocytopenic purpura (TTP)
    2. Atheroma, shock
H. Drugs
    1. Definite
        a. Azathioprine, thiazides, frusemide, tetracyclines, oestrogens, sulphonamides
    2. Possible
        b. Chlorthalidone, ethacrynic acid, procainamide, L-asparaginase, anticoagulants, propranolol, diazoxide, cimetidine, paracetamol, methyldopa
I. Toxins
    1. Scorpion venom
J. Associations
    1. Hypothermia, histocompatibility antigens, alpha 1 antitrypsin deficiency
    2. Hereditary

2. Bile Reflux

Gallstones have been found in many patients with acute pancreatitis and reflux of biliary contents has been seen on cholangiography. However, impacted stones are rarely seen in autopsies of patients who die from acute pancreatitis.

3. Activation of the Complement System

4. Overstimulation of Secretions

This is an established initiating event in cases of scorpion stings (commonest cause of pancreatitis in the Caribbean) and in hyperparathyroidism.

The coincidental release of vasoactive substances such as bradykinin from the pancreas into the circulation, may explain the increased vascular permeability, hypotension, and organ dysfunction which accompany some episodes of acute pancreatitis.

Classification

The most commonly used classification relies upon a pathological description. Although the pancreas may exhibit a range of changes, two extreme patterns are described.

1. *Acute oedematous pancreatitis* results in a congested and swollen pancreas; this pathology is seen in patients with mild to moderate pancreatitis.

2. *Necrotizing pancreatitis,* on the other hand, causes severe inflammation with necrosis and haemorrhage. Fat necrosis may be seen in adjacent tissues and there is a tendency to suppuration. The whole gland is usually involved and mortality is increased.

Other classifications have attempted to differentiate acute pancreatitis from chronic relapsing pancreatitis. This separation is difficult and remains a retrospective classification with the documentation of chronic pancreatic insufficiency at least 4-6 weeks after the acute episode.

Investigations

1. Serum Amylase

A two or three fold elevation of serum amylase is usually diagnostic of acute pancreatitis but absolute levels do not correlate with severity or mortality. Levels rise within 2-3 hours and return to normal in 3-10 days. Quicker changes are seen in mild oedematous forms and severe necrotizing pancreatitis where enzyme levels diminish because of extensive damage to the gland. Unless levels are done early and frequently, rises in amylase may be missed. Serum levels may also rise in patients with perforated or infarcted bowel and in conditions affecting other organs which secrete amylase (ie, salivary glands and ovaries). Although it is possible to separate the isoenzymes of amylase into pancreatic (P type) and other (S type), these tests are not routinely available.

2. Urinary Amylase

As 25% of the serum amylase is cleared by the kidney, elevated urinary levels are seen in pancreatitis. Such increases occur earlier and last longer than serum elevations. The ration of urinary amylase clearance to creatinine clearance (Cam/Ccr) is normally between 1-

4%, but may be elevated in some patients with acute pancreatitis who exhibit normal serum amylase levels. However, the test is not sufficiently specific nor sensitive for routine usage.

3. Other Enzymes and Fluids

Serum lipase concentrations parallel those of serum amylase, but may remain higher for longer, and are not increased by extra-pancreatic disorders. Amylase levels within pleural or ascitic fluid may be elevated in acute pancreatitis. Plasma trypsin-like immunoreactivity and phospholipase A2 increase, but are not routinely estimated.

4. Haematology

The white cell count is typically raised to 15-20 x 10^3 cells/microL with neutrophilia and left shift. Haemoglobin levels may increase if sufficient haemoconcentration occurs, or may decrease if there is bleeding from the gland.

5. Chemical Pathology

(i) Liver Function Tests

Transient elevations in serum bilirubin are seen in 10% of patients. Levels return to normal within 4 days. Concomitant increases in alkaline phosphatase and transaminases are also observed.

(ii) Glucose

Hyperglycaemia is observed with incidences varying from 25% to 75%. These rises have been attributed to decreased levels of circulating insulin and increased levels of glucagon, catecholamines and steroids.

(iii) Calcium and Magnesium

Serum calcium falls in 25% of patients. The change is usually due to concomitant hypoproteinaemia, although ionized levels of calcium may decrease possibly due to intraperitoneal saponification. Hypocalcaemia may occasionally require treatment. Hypomagnesaemia may also occur and is more common in alcohol induced pancreatitis.

(iv) Methaemalbumin

Methaemalbumin is formed when oxidized heme binds to albumin, and may be found with intraperitoneal haemorrhage, a feature of some patients with necrotizing pancreatitis. It is neither specific nor sensitive for pancreatitis.

6. Electrocardiography

Widespread ST-T wave changes may simulate acute myocardial ischaemia. Arrhythmias have been observed in pericarditis associated with pancreatitis.

7. Imaging

(i) Conventional Radiology

Many changes have been described but are not specific for pancreatitis. These include localized jejunal ileus, generalized small bowel ileus, colon cut-off sign or "sentinel loop" (from isolated peri-pancreatic dilatation) and duodenal distention. A swollen pancreas or associated cyst/pseudocyst may displace the stomach anteriorly or widen the duodenal loop. These changes can be seen when a dye such as gastrograffin is administered prior to plain erect and lateral abdominal radiographs.

(ii) Ultrasound

On abdominal ultrasonography, the pancreas is enlarged with decreased echogenicity. Definition of the gland is more difficult and it is not visualized in up to 40% of patients. Ultrasound is particularly useful in demonstrating collections such as abscesses, cysts or pseudocysts.

(iii) CT Scanning

In acute pancreatitis, the gland is often difficult to see and not visualized in 30%. However, this technique is most useful in demonstrating abscess or cyst formation.

(iv) Chest Radiography

Chest radiography may be abnormal in up to 40% of cases. An elevated left hemidiaphragm with pleural effusion, basal atelectasis or alveolar infiltrates may be noted.

Clinical Presentation

Symptoms

The patient may be any age. Alcoholic pancreatitis usually occurs in patients less than 40 years and males predominate. On the other hand, pancreatitis associated with biliary tract disorders occurs in middle to later life and a female to male ratio of 3:1 is usually described. There may be a history of heavy alcohol intake (usually more than 8 years duration) or previous biliary disorders. It is important to take a detailed drug history.

Pain comes on relatively quickly and is classically central in position radiating to the back and eased by sitting forward. Variations do occur with pain initially confined to the right upper quadrant or felt diffusely over the abdomen; isolated left upper quadrant pain is uncommon. Nausea and vomiting occur in 90% of cases.

Signs

On examination, the patient is usually agitated and restless with tenderness upon palpation of the epigastrium. A fever is often present but usually less than 39 °C. Occasionally, hypothermia may occur. Abnormal respiratory findings of basal wheezes or

pleural effusions are seen in 10-20%. In the severe attack, the patient may be shocked with tachycardia and hypotension or in acute respiratory failure. Erythematous nodules from fat necrosis is evidenced by a gray discolouration in the flanks (Grey Turner sign) or in the umbilicus (Cullen's sign). The abdomen is usually distended due to an associated ileus or the presence of complications.

Acute pancreatitis may simulate other acute abdominal conditions and up to 20% of cases may be first diagnosed at laparotomy. Differential diagnoses include perforated viscus, cholecystis, bowel obstruction, vascular occlusions, renal colic, myocardial infarction, pneumonia and diabetic ketoacidosis.

Complications

Local

Local changes contribute to the mortality of pancreatitis. A phlegmon or swelling of the pancreas may be seen on ultrasound or CT in 30-50% of cases and is palpable in 15-20%. Pancreatic abscesses usually develop after the second week and may lead to septicaemia. Pseudocysts likewise occur after 2-3 weeks and are more commonly seen on scans (ultrasound, CT) than found on palpation. They may cause compression of adjacent structures and may lead to fistula formation, haemorrhage or infection. Spontaneous resolution of pseudocysts may occur. Pancreatic ascites has been described as has involvement of contiguous organs with massive intraperitoneal bleeding, vascular thrombosis and infarction of bowel.

Systemic

As noted above, respiratory complications are frequent and include effusions, atelectasis, pneumonitis and the adult respiratory distress syndrome. Cardiac abnormalities include hypotension, sudden death, ST-T wave changes and pericardial effusions. Renal function may be impaired with acute tubular necrosis progressing to acute renal failure requiring dialysis. Disseminated intravascular coagulation may be noted on coagulation studies. Metabolic complications are common - hyperglycaemia, hypertriglyceridaemia, hypocalcaemia and hypomagnesaemia. Gastrointestinal haemorrhage may be due to acute peptic ulceration, gastritis or erosion of adjacent blood vessels. Many psychic and neurological symptoms have been attributed to acute pancreatitis.

Prognosis

In the majority of cases, acute oedematous pancreatitis is a self-limited disease of 3-7 days duration and with 3-10% mortality. Necrotizing pancreatitis occurs in 20-30% with an estimated mortality of 50%. Abscesses are seen in 5-10% of patients but have a mortality approaching 100% without surgery. Chronic pancreatitis is a rare complication of an isolated episode of acute pancreatitis.

Several attempts have been made to define high risk patients upond admission and during hospital stay. Ranson et al in 100 patients, described 11 early objective findings (Table 2) which correlated with subsequent mortality and morbidity; prospective studies in a further

200 confirmed the initial findings. Additional factors which increase morbidity and mortality include pre-existing cardiovascular disease and diabetes. Failure of major organs (ie, lungs, kidneys or circulation) reduces survival even further.

Table 2. Early Prognostic Signs of Morbidity and Mortality

At Admission

Age greater than 55 years
White cell count greater than 16000 cells/microL
Blood glucose greater than 11 mmol/L
Serum lactate dehydrogenase (LDH) more than twice normal
Serum aspartate transaminase (AST) more than six times normal

During initial 48 hours

Haematocrit (PCV) fall by more than 10%
Rise in urea more than 2.0 mmol/L
Serum calcium less than 2.0 mmol/L
PaO_2 < 7.9 kPa (60 mmHg)
Base deficit greater than 4 mmol/L
Estimated fluid seguestration over 6 litres.

Management

In general terms, acute management consists of medical therapies with surgical intervention reserved for complications. Patients with severe attacks of pancreatitis should be admitted to an ICU where major complications can be detected and treated with minimal delay.

Medical

1. Pain Relief

Adequate analgesia can be achieved by parenteral narcotics in most patients. Morphine should be avoided because it may contract the sphincter of Oddi and reduce drainage of pancreatic secretions. Epidural anaesthesia by intermittent or continuous infusion may be very helpful especially in patients with impaired respiratory function from pain and basal atelectasis.

2. Fluid Replacement

The inflammatory exudate around the pancreas resembles that of an internal burn and huge volumes of fluid may be sequestrated into the retroperitoneal spaces. Rapid fluid loss may occur with deficits of many litres recorded. Blood, plasma expanders and crystalloid should be administered to restore these deficits. The choice of solution is determined by the clinical signs, haemoglobin/PCV results and serum albumin. Volumes and rates of infusion must be adjusted according to central venous pressures, urine output and blood pressure.

Pulmonary artery catheters arew very usefiul in patients with myocardial or respiratory disorders especially if the adult respiratory distress syndrome develops. Overzealous infusions of any fluid will increase the chance of pulmonary oedema especially when vascular permeability mau be abnormal. Low dose dopamine (2 microg/kg/min) may help to maintain or re-establish urine flow.

3. Suppression of Pancreatic Secretion

All patients should be fasted. A nasogastric tube is required if there is gastric distention, vomiting, paralytic ileus or when the patient requires endotracheal intubation. Various drugs (ie, anti-cholinergics, cimetidine and glucagon) have not been shown to be helpful.

4. Metabolic and Electrolyte Balance

Hyperglycaemia usually requires insulin therapy. Under most conditions, insulin infusions provide rapid and better control, but a dextrose infusion should be administered concurrently to prevent inadvertent hypoglycaemia. Calcium gluconate is occasionally required to treat symptomatic hypocalcaemia. Magnesium and phosphate levels should be checked and major deficits corrected.

5. Nutrition

Total parenteral nutrition (TPN) is indicated for nutritional support. Although TPN may reduce pancreatic exocrine production and secretion, the amount of enzyme present in the gland is not reduced.

6. Antibiotics

Antibiotics should not be administered prophylactically. They may be required to treat complications such as abscess or initiating conditions such as cholangitis.

7. Other Therapeutics

Although initially used enthusiastically, aprotinin (Trasylol) is no longer recommended as results of trials have been disappointing. Endoscopic sphincterotomy may be necessary to provide emergency decompression of the biliary tree by an obstructing stone. Ranitidine/cimetidine may help reduce gastric stress erosions.

Surgical

1. Early Intervention

There are very few indications for early surgery in the course of acute pancreatitis. There are reports of increased and decreased mortality with early biliary surgery in patients with gall stone induced pancreatitis. In usual practice, cholecystectomy and/or exploration of the common bile duct are undertaken when the acute episode has settled. Early routine

pancreatic resection or procedures to defunction the pancreas carry a mortality of around 25% and confer no clear benefits and are not recommended.

2. Peritoneal Lavage

Early peritoneal lavage using ordinary peritoneal dialysis catheters has been recommended for patients with moderate and severe pancreatitis. It does not treat the underlying pathology, reduce the incidence of pancreatic collections, nor alter the eventual mortality. Nonetheless, it does result in better haemodynamic stability possibly by removing vasoactive substances within the peritoneal fluid. These substances include proteolytic enzymes, phospholipase A2 and kinins such as bradykinin. Other forms of dialysis such as haemodialysis do not show these benefits, supporting the concept that substances released from the pancreas in ascitic fluid may be absorbed into the bloodstream and contribute to the pathogenesis of the circulatory disturbances. Peritoneal lavage is not necessary in most patients with acute pancreatitis, and should be reserved for those with vascular instability or those at high risk of morbidity and mortality.

3. Management of Complications

Surgery is often necessary for complications which may develop days to weeks after the acute event. Extensive necrosis may require debridement and the placement of large drain tubes within the pancreatic bed. Patients with a pancreatic abscess (sometimes difficult to separate from necrotic tissue) must undergo surgery as mortality is 100% with antibiotics alone and 20-40% with surgery. Attempts to drain these collections by percutaneous catheters placed under CT control have only been moderately successful. Complications such as bleeding, vascular obstruction and fistulae require correction. Pseudocysts may also require drainage which can be undertaken many days after the acute changes have subsided, unless the cyst has become infected.