Introduction

Acute pancreatitis is not an uncommon disease, with high morbidity and mortality. It is an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or other organ systems. A multidisciplinary approach is warranted in patients with severe acute pancreatitis as input from intensivests, gastroenterologists, surgeons, radiologists and others specialists is usually required **(Peery et al., 2012).**

Severe acute pancreatitis is defined as acute pancreatitis associated with other end organ failure and/or local complications such as necrosis, abscess, or pseudocyst **(Gloor et al., 2001).** Causes of severe acute pancreatitis are variable. Gallstones and alcohol are known to be the major causes **(Banks et al., 2006).**

Diagnosis of severe acute pancreatitis depends on clinical picture, laboratory tests, and radiological findings. Specific severity scores as Ranson's criteria, Apache II score, Imrie scoring system and Balthazar Score are used for assessment of severity of the disease **(Neoptolemos et al., 2000).**

The management of patients with acute pancreatitis (AP) is challenging due to late hospitalization after onset of the acute attack and difficulty in distinguishing mild from severe disease in the first 48-72 h. Once the diagnosis is established and the patient is stable, there should be ongoing adequate fluid resuscitation, pain control, early detection and treatment of additional organ failures, and assessment of severity. Choices will have to be made regarding the use of prophylactic antibiotics **(Lankisch and Lerch, 2006),** the route of nutrition, the timing of endoscopic retrograde cholangiopancreatography (ERCP), and the possible benefit of anti-secretory or anti-inflammatory treatment modalities **(Ayub et al., 2004).**

In some patients, the indications and timing of surgical therapy will need to be considered. Surgical intervention is necessary for many patients hospitalized with severe acute pancreatitis (SAP) in an ICU **(Uhl et al., 2002).**

Scoring systems may be helpful early in the clinical course of acute pancreatitis in predicting the prognosis, although their usefulness is diminished as the disease progresses. Generally, renal failure, respiratory failure, multi-organ system failure, fluid collections, necrosis, increased ICU length of stay, and shock are all poor prognostic factors **(Kong et al., 2004).**

Epidemiology

Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract, leading to tremendous emotional, physical, and financial human burden. In the United States, in 2009, AP was the most common gastroenterology discharge diagnosis with a cost of 2.6 billion dollars. Recent studies show that the incidence of AP varies between 4.9 and 73.4 cases per 100,000 worldwide. An increase in the annual incidence for AP has been observed in most studies. Epidemiologic review data from the 1988 to 2003 National Hospital Discharge Survey showed that hospital admissions for AP increased from 40 per 100,000 in 1998 to 70 per 100,000 in 2002 in the United States. Although the case fatality rate for AP has decreased over time, the overall population mortality rate for AP has remained unchanged **(Peery et al., 2012).**

Causes

Gallstones :

Billiary tract stone disease is the most common cause of acute pancreatitis. It accounts for about 30-60% of cases of acute pancreatitis. More women than men are affected and the age of peak incidence is between 50 and 60 years **(Whitcomb, 2006).**

Because the gallbladder and pancreas share a drainage duct; as shown in **Figure 1,** gallstones usually less than one cm that lodge in this duct can prevent the normal flow of pancreatic enzymes leading to high intraductal pressure which could result in ductal disruption with extravasation of activated intraluminal enzymes into the interstitium, where autodigestion of the gland would occur **(Sakorafas and Tsiotou, 2000).**

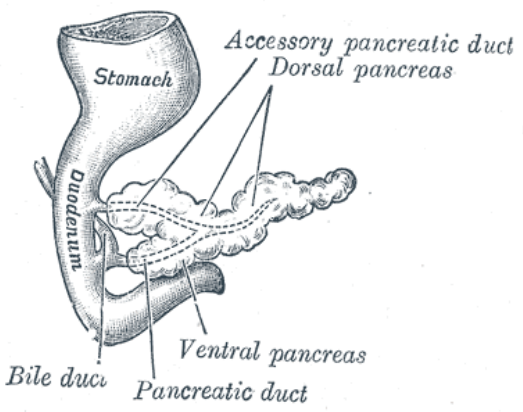

Figure 1: Ductal system of the pancreas (**Sakorafas and Tsiotou, 2000).**

Alcohol:

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. It is responsible for about 30% of all cases of acute pancreatitis. Ethanol is a cellular metabolic poison. It is metabolized in the body to acetaldehyde by the enzyme alcohol dehydrogenase. This occurs primarily in the liver, although there may be limited breakdown in the pancreas as well. It is unclear whether the pancreas contains sufficient alcohol dehydrogenase to account for any direct toxicity, although other toxic metabolic products could be produced **(Matsumoto et al., 1996).**

The mechanism of acetaldehyde toxicity may involve oxygen free radical generation by the enzyme xanthine oxidase. Moreover, alcohol stimulates gastric secretion by direct effect on the mucosa and HCL produced is a potent stimulant for secretin release and could result in an increase in the pancreatic ductal pressure. In addition, ethanol may cause chemical duodenitis and ampullitis, which could partially obstruct the ampulla of Vater (drainage duct of gallbladder and pancreas) and further increase the intraductal pressure in the pancreas which could lead to duct disruption **(Sakorafas and Tsiotou, 2000).**

Many other causes can lead to acute pancreatitis as shown in **Table 1:**

Table (1): Etiology of acute pancreatitis.

Mechanical	Gallstones, biliary sludge, ascariasis, periampullary diverticulum, pancreatic or periampullary cancer, ampullary stenosis, duodenal stricture or obstruction
Toxic	Ethanol, methanol, scorpion venom, organophosphate poisoning
Metabolic	Hyperlipidaemia (types I, IV, V), hypercalcaemia
Drugs	Didanosine, pentamidine, metronidazole, stibogluconate, tetracycline furosemide, thiazides, sulphasalazine, 5-ASA, L-asparaginase, azathioprine, valproic acid, sulindac, salicylates, calcium, estrogen
Infection	Viruses-mumps, coxsackie, hepatitis B, CMV, varicella-zoster, HSV, HIV Bacteria-mycoplasma, Legionella, Leptospira, salmonella Fungi-aspergillus Parasites-toxoplasma, cryptosporidium, Ascaris
Trauma	Blunt or penetrating abdominal injury, iatrogenic injury during surgery or ERCP (sphincterotomy)
Congenital	Cholodochocele type V, pancreas divisum
Vascular	Vascular Ischemia, atheroembolism, vasculitis (polyarteritisnodosa, SLE)
Miscellaneus	Post ERCP, pregnancy, renal transplantation, alpha-1-antitrypsin deficiency
Genetic	CFTR and other genetic mutations

5-ASA: 5-aminosalicylic acid; CMV: cytomegalovirus; HSV: herpes simplex virus; HIV: human immunodeficiency virus; ERCP: endoscopic retrograde cholangiopancreatography; SLE: systemic lupus erythematosus; CFTR: cystic fibrosis transmembrane conductance regulator.

(Badolov et al., 2007).

Pathogenesis of severe acute pancreatitis

The pancreas is a gland located in the upper, posterior abdomen and is responsible for insulin production (endocrine pancreas) and the manufacture and secretion of digestive enzymes (exocrine pancreas) leading to carbohydrate, fat, and protein metabolism. Approximately 80% of the gross weight of the pancreas supports exocrine function, while the remaining 20% is involved with endocrine function **(Barry, 1988).**

The principal of the exocrine pancreas is to make food digesting enzymes. The pancreas, comprising only 0.1% of total body weight, has 13 times the protein producing capacity of the liver and the reticuloendothelial system combined, which make up 4% of total body weight. Enzymes are produced within the pancreatic acinar cells, packaged into storage vesicles called zymogens, and then released via the pancreatic ductal cells into the pancreatic duct, where they are secreted into the small intestine (the medial side of the second portion of the duodenum at the major duodenal papilla) to begin the metabolic process (**PaulYakshe et al., 2008).**

Normal pancreatic function:

In normal pancreatic function, up to 15 different types of digestive enzymes are manufactured in the rough

endoplasmic reticulum, targeted in the golgi apparatus and packaged into zymogens as pro-enzymes. When a meal is ingested, the vagal nerves, secretin, CCK (cholecystokinine), and encephalins stimulate enzymatic release into the pancreatic duct. The pro-enzymes travel to the brush border of the duodenum, where trypsinogen, the pro-enzyme for trypsin, is activated via hydrolysis of an N-terminal hexapeptide fragment by the brush border enzyme enterokinase. Trypsin then facilitates the conversion of the other pro-enzymes to their active forms. Pancreatic enzymes are proteolytic or metabolic enzymes. Proteolytic enzymes are enzymes that specifically break down proteins into amino acids. Digestive enzymes like protease, lipase, amylase, lactase, etc. are produced by the body and released during the digestive process. Their purpose is to help breakdown the food for better absorption **(Brian et al., 2008).**

Mechanism of acute pancreatits:

Premature activation of pancreatic enzymes within the pancreas leads to organ injury and pancreatitis, several mechanisms exist to limit this occurrence. First, proteins are translated into the inactive pro-enzymes. Later, posttranslational modification of the Golgi cells allows their segregation into the unique subcellular zymogen

compartments. The pro-enzymes are packaged in a paracrystalline arrangement with protease inhibitors **(Barry, 1988).**

Zymogen granules have an acidic pH and a low calcium concentration, which are factors that guard against premature activation until after secretion occurs and extracellular factors trigger the activation cascade. Under various conditions, these protective mechanisms are disrupted, resulting in intracellular enzyme activation and pancreatic autodigestion, leading to acute pancreatitis **(Brian et al., 2008).**

Acute pancreatitis may occur when factors involved in maintaining cellular homeostasis are out of balance. The initiating event may be anything that injures the acinar cell and impairs the secretion of zymogen granules, pathophysiologic event triggers the onset of acute pancreatitis. However, it is believed that both extracellular factors (e.g., neural response, vascular response) and intracellular factors (e.g., intracellular digestive enzyme activation, increased calcium signaling, heat shock protein activation) play a role. In addition, acute pancreatitis can develop when ductal cell injury leads to delay or absent enzymatic secretion **(Paul Yakshe et al., 2008).**

Once a cellular injury pattern has been initiated, cellular membrane trafficking becomes chaotic, with the following

deleterious effects: (1) lysosomal and zymogen granule compartments fuse, enabling activation of tryypsinogen to trypsin; (2) intracellular trypsin triggres the entire zymogen activation cascade; and (3) secretory vesicles are extruded across the basolateral membrane into the interstititum, where molecular fragments act as chemo attractants of inflammatory cells. Activated neutrophils then exacerbate the problem by releasing superoxide (the respiratory burst) or proteolytic enzymes (cathepsins B, D, and G; collagenase; and elastase). Finally, macrophages release cytokines that further mediate local (and, in severe cases, systemic) inflammatory responses. The early mediators defined are tumor necrosis factor alpha, interleukin-6, and interleukin-8 **(Brian et al., 2008).**

These mediators of inflammation cause an increased pancreatic vascular permeability, leading to haemorrhage, edema, and eventually pancreatic necrosis. There is a challenging balance between localized tissue damage with pro-inflammatory cytokine production and systemic anti-inflammatory response that restricts the inappropriate movement of pro-inflammatory agents into the circulation. The critical players of this balance include the pro-inflammatory cytokines IL-1beta, TNF-alpha, IL-6, IL-8, and platelet activating factor (PAF). The anti-inflammatory cytokines IL-10, as well as TNF-soluble receptors and IL-1

receptor antagonist, have also been shown to be intimately involved in the inflammatory response of acute pancreatitis **(Granger and Remick, 2005).**

Other compounds implicated in disease pathogenesis in experimental models include complements, bradykinin, nitric oxide, reactive oxygen intermediates, substance P, and higher polyamines. Several of these mediators have been documented to be present at increased concentrations in the plasma of patients with severe acute pancreatitis **(Takeyama et al., 2007).**

Internal fluid losses occur in acute pancreatitis. They are caused by fluid sequestration into areas of inflammation and into the pulmonary parenchyma and soft tissues elsewhere in the body. These latter losses result from the diffuse capillary leak phenomenon that is triggered by pro-inflammatory factors released during pancreatitis **(Barry, 1988).**

About 5–10% of patients develop necrosis of the pancreatic parenchyma, the peripancreatic tissue or both. Necrotising pancreatitis most commonly manifests as necrosis involving both the pancreas and peripancreatic tissues and less commonly as necrosis of only the peripancreatic tissue, and rarely of the pancreatic parenchyma alone (**Isenmann et al., 1993).** The variable pathological features of AP are mentioned in **(Box 1).**

Box (1): Pathological features of AP

Revised definitions of morphological features of acute pancreatitis

1. **Interstitial oedematous pancreatitis**

Acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognisable tissue necrosis

CECT criteria

- Pancreatic parenchyma enhancement by intravenous contrast agent
- No findings of peripancreatic necrosis
- See **figures 4** and **5**

2. **Necrotising pancreatitis**

Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis

CECT criteria

- Lack of pancreatic parenchymal enhancement by intravenous contrast agent and/or
- Presence of findings of peripancreatic necrosis
- See **figures 6, 7,** and **8**

3. **APFC (acute peripancreatic fluid collection)**

Peripancreatic fluid associated with interstitial oedematous pancreatitis with no associated peripancreatic necrosis. This term applies only to areas of peripancreatic fluid seen within the first 4 weeks after onset of interstitial oedematous pancreatitis and without the features of a pseudocyst.

CECT criteria

- Occurs in the setting of interstitial oedematous pancreatitis
- Homogeneous collection with fluid density
- Confined by normal peripancreatic fascial planes
- No definable wall encapsulating the collection
- Adjacent to pancreas (no intrapancreatic extension)
- See **figure 5**

Box (1): Pathological features of AP (Cont.)

4. **Pancreatic pseudocyst**

An encapsulated collection of fluid with a well defined inflammatory wall usually outside the pancreas with minimal or no necrosis. This entity usually occurs more than 4 weeks after onset of interstitial oedematous pancreatitis to mature.

CECT criteria

- Well circumscribed, usually round or oval
- Homogeneous fluid density
- No non-liquid component
- Well defined wall; that is, completely encapsulated
- Maturation usually requires >4 weeks after onset of acute pancreatitis; occurs after interstitial oedematous pancreatitis
- See **figure 9**

5. **ANC (acute necrotic collection)**

A collection containing variable amounts of both fluid and necrosis associated with necrotising pancreatitis; the necrosis can involve the pancreatic parenchyma and/or the peripancreatic tissues

CECT criteria

- Occurs only in the setting of acute necrotizing pancreatitis
- Heterogeneous and non-liquid density of varying degrees in different locations (some appear homogeneous early in their course)
- No definable wall encapsulating the collection
- Location—intrapancreatic and/or extrapancreatic
- See **figures 6–8**

(Van Santvoort et al., 2008)

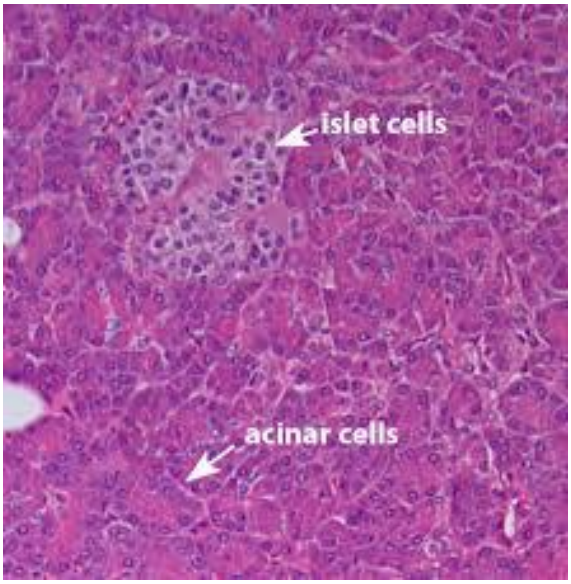

Figure 2: Normal pancreatic cell **(Brian et al., 2008).**

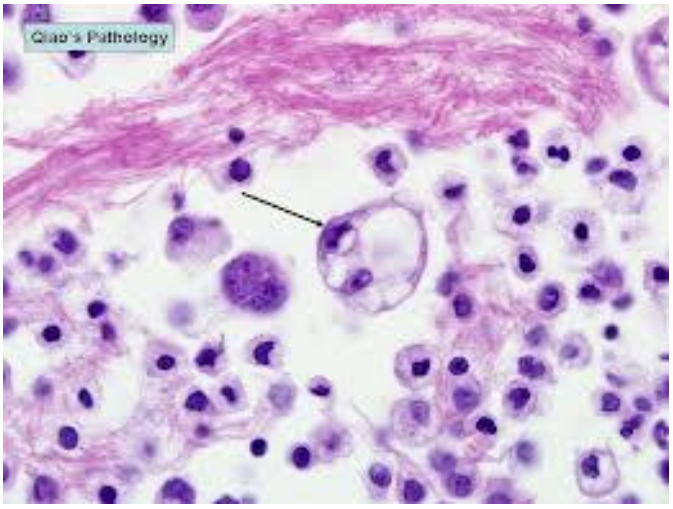

Figure 3: Abnormal pancreatic cell **(Barry, 1988).**

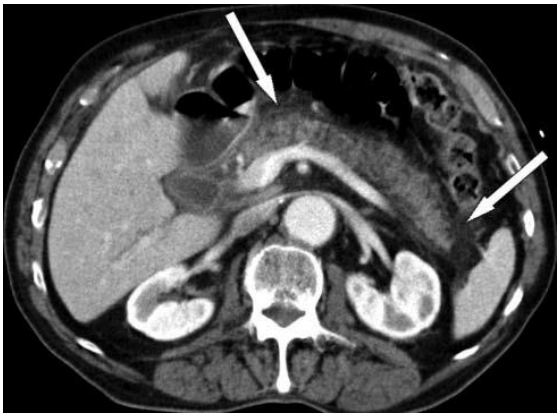

Figure 4: Acute interstitial oedematous pancreatitis on CT. There is peripancreatic fat stranding (arrows) without an acute peripancreatic fluid collection; the pancreas enhances completely but has a heterogeneous appearance due to oedema (**Bharwani et al., 2011).**

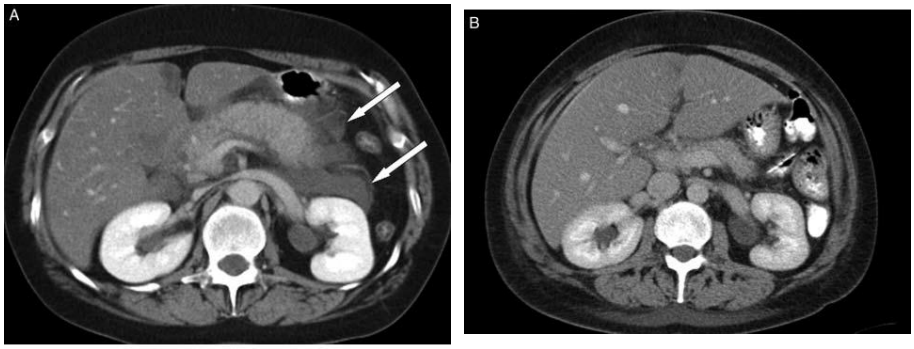

Figure 5: (A) Acute interstitial oedematous pancreatitis and acute peripancreatic fluid collection (APFC) in the left anterior pararenal space on CT (white arrows showing the borders of the (APFC) in a 38-year-old woman. The pancreas enhances completely, is thickened, and has a heterogeneous appearance due to edema. APFC has fluid density without an encapsulating wall. (B) A few weeks later, a follow up CT shows complete resolution of the APFC with minimal residual peripancreatic fat stranding (**Bharwani et al., 2011).**