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Ability Of Bisap Score In Assessing Acute Pancreatitis But I Could Not Upload Through The Site.

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Acute pancreatitis is a relatively common and a potentially life threatening disease. It is defined as "an inflammatory process of pancreas with possible peripancreatic tissue involvement and multi organ dysfunction syndrome with increasing mortality rate[1]"
Estimates of incidence are often inaccurate, because mild cases are often unreported, and deaths may occur in severe forms even before a diagnosis is made.
Severe acute pancreatitis accounts for about 20 % of the cases, and it is associated with one or more of the following:
Pancreatic necrosis, distant organ failure, and development of local complications like haemorrhage, pancreatic necrosis, pseudocyst etc.
Mortality in severe acute pancreatitis is 15-30 % and is only 0-1 % in case of mild acute pancreatitis[2].
The exact mechanism of pathophysiology of acute pancreatitis is not clearly known, but has been attributed to abnormal activation of pancreatic enzymes within the acinar cells. Co-localization of zymogen granules and lysosomes occur resulting in activation of the enzymes, which results in autodigestion of pancreas. In response to initial insult, acinar cells release proinflammatory cytokines, such as TNF a, IL-1, 2 and 6, and antiinflammatory mediators such as IL-10 and IL-1 receptor antagonist[3].

I. Introduction

These mediators then propagate the response systemically as well as locally. The local response increases the permeability and alters the microcirculation and worsens the disease process. However the inflammatory response is selflimited in most of the patients, but a vicious cycle of pancreatic injury and local and systemic inflammation persists in severe forms.

Acute pancreatitis can be classified as mild and severe form. Mild acutepancreatitis is characterised by interstitial edema of the gland and is usually a selflimiting disease. Whereas in the severe form, there is pancreatic necrosis, sever systemic inflammatory response and multi – organ failure which can lead to death. Hence it is prudent to identify risk stratification tools for the disease, which help in the management.

Various criterial of severity stratification have been developed to define the severity of the disease in the past. The earliest of which was developed by Ranson and colleagues in 1974.[4] It predicts the severity of the disease, which is based on 11parameters that are obtained at the time of admission and after 48 hours. Ransons's score has a low positive predictive value (50%) and a high negative predictive value (90%). Hence its main use is to rule out acute pancreatitis and also predicts a severe attack[5]. The major disadvantage Ranson's and as well as older Glasgow criteria being, many of the parameters which are components of this scoring, are not collected at admission, on a routine basis. Also, it does not predict the severity of the disease at admission, as six of the parameters are assessed only after 48 hours. Hence an early therapeutic window is missed.

The APACHE II, which is the most common scoring used worldwide, was originally developed as a risk stratification tool in intensive care setting. But it takes into account a huge list of parameters, some of which may not be related to the severity.

Hence, an accurate, and relatively simple bedside scoring system BISAP was developed. This scoring system identifies patients with high morbidity as well as risk of mortality, before organ failure sets in. Data for this scoring system is collected within 24 hours of hospitalization, which helps in identifying patients who are risk of developing a severe disease very early, and helps in managing the same effectively, thus decreasing the mortality and morbidity.

AIMS AND OBJECTIVES

- To evaluate the ability of BISAP score to predict mortality in acute pancreatitis patients from our institution
- To assess the ability of the BISAP score to predict which patients are at risk for intermediate markers of severity including the development of organ failure, persistent organ failure and pancreatic necrosis.
- To correlate the outcome of the study with the scores observed, in terms of disease severity and mortality.

II. Review Of Literature

HISTORY

The pancreas was generally ignored in antiquity, both as an organ and as a seat of disease.
The pancreas was ***first discovered by Herophilus***, a Greek anatomist cum surgeon, born in 336 BC on the Asiatic side of the Bosporus in Chalcedon[6].
The word pancreas first mentioned in the writings of Eristratos (310- 250B.C.). The Four hundred years later, ***Rufus,*** (1st or 2nd Century AD), an anatomist cum surgeon of Ephesus, **gave the name "pancreas".** Written in Greek language, the word meant **"pan: all, kreas: flesh"**
Galen (Claudius Galenus 138-201 AD), "Physician to the Gladiators" of Rome& the Roman Emperor, taught that the pancreas serves as a cushion to protect the large blood vessels lying behind it[7].
In March 2, 1642, a German émigré, Johann Georg Wirsung, discovered the pancreatic duct at San Francisco Monastery in Padua, Italy.
But it was named by his colleague as "The Duct of Wirsüng"[8].
Whereas papilla, the enlargement of that duct at its junction with the common bile duct (CBD) which projects into the second part of duodenum, were first described by Vater in 1720.
Santorini, in 1734, described the accessory duct that bears his name .In 1869, Paul Langerhans ("Junior"), a student of the famous Berlin

Institute of Pathology, headed by the eminent Professor Rudolph Virchow, described the islets of the pancreas that was subsequently known as the
"islets of Langerhans", an endocrine system which lies within the pancreas.
This was the first good histologic description of the pancreas.
In 1893, Laguesse suggested that the islet cells produce a hormone. In 1909 Jean de Meyer suggested the name 'insulin' for this hormone.
Eugene Lindsay Opie (1873-1971) was able to show the association between diabetes and failure of the islet cells and in 1901, proposed his "common channel" hypothesis[9].

GROSS ANATOMY

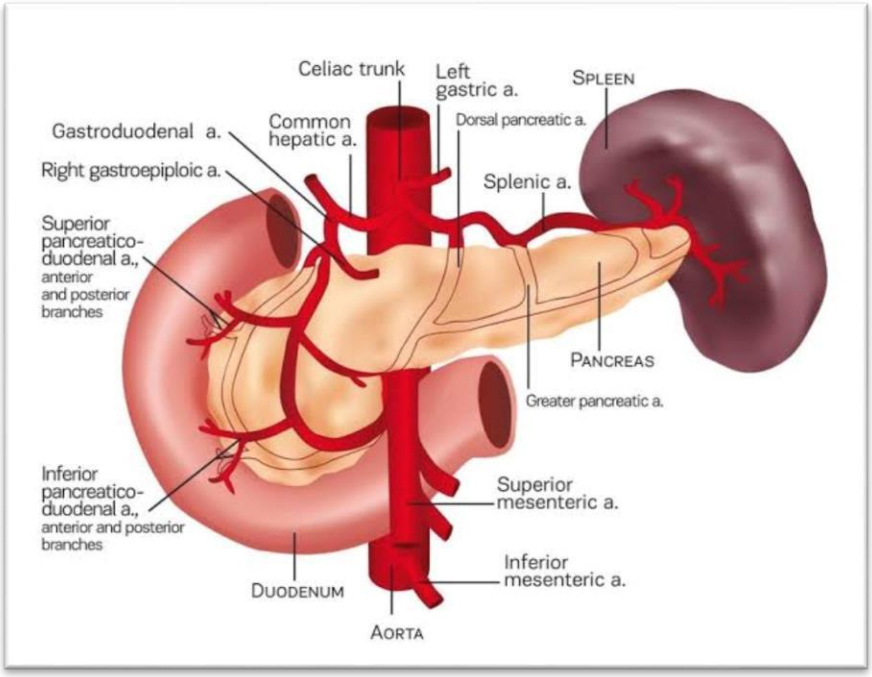
The term "Pancreas" is derived from the Greek word Pan Kreas, meaning "all flesh"[6]. The fascinating embryological development of the Pancreas has intrigued the biologists. It is an endodermally derived organ, consisting of two morphologically different parts, the exocrine and the endocrine tissue[10]. It has also been described as "two organs in one", in view of the distinct function of the gland.
It is a posteriorly situated retroperitoneal organ, lying posterior to the stomach, sloping upward from the C-loop of the duodenum to the splenic hilum at the level of L1.The fact that the pancreas is situated so deeply in the abdomen, and is sealed in the retroperitoneum explains the poorly localized and sometimes ill-defined nature with which pancreatic pathology presents.
It consists of head, neck, body and tail, with one accessory lobe or the "uncinateprocess".The pancreas is 15-20 cm in length, with a mean weight of 91.8 g (range, 40.9 to 182 g).
The head of the pancreas lies to the right of midline, within the C loop of the duodenum, posterior to transverse mesocolon, and immediately anterior to the inferior vena cava at the confluence of the renal veins.
The uncinate process extends from the head of the pancreas, behind the superior mesenteric vein and terminates near the superior mesenteric artery.
The neck lies directly over the portal vein and vertebral bodies L1 and L2, where the splenic and superior mesenteric veins unite to form the portal vein. The inferior mesenteric vein may join the superior mesenteric vein or merge with the superior mesenteric-portal venous junction to form a trifurcation. The superior mesenteric artery lies parallel to, and just to the left of superior mesenteric vein.
The body and tail of the pancreas then extend across the midline, anterior to splenic artery and vein, and anterior to Gerota's fascia and slightly cephalad, terminating within the splenic hilum.
The capsule of the pancreas is loosely attached to its surface and is contiguous with the anterior layer of mesocolon, and it can be dissected in continuity.

BLOOD SUPPLY

ARTERIAL SUPPLY

The major blood supply of the pancreas comes from, multiple branches of the celiac trunk and superior mesenteric arteries, which form arterial arcades within the body and tail of the pancreas. The splenic and common hepatic arteries arise from the celiac trunk. The dorsal and greater pancreatic arteries branch from the splenic artery, whereas the gastroduodenal artery branches from the common hepatic artery, then dividing around the head of the pancreas into anterior and posterior superior pancreaticoduodenalbranches that anastomose with the anterior and posterior branches of the inferior pancreaticoduodenal artery, which are branches of the superior mesenteric artery.

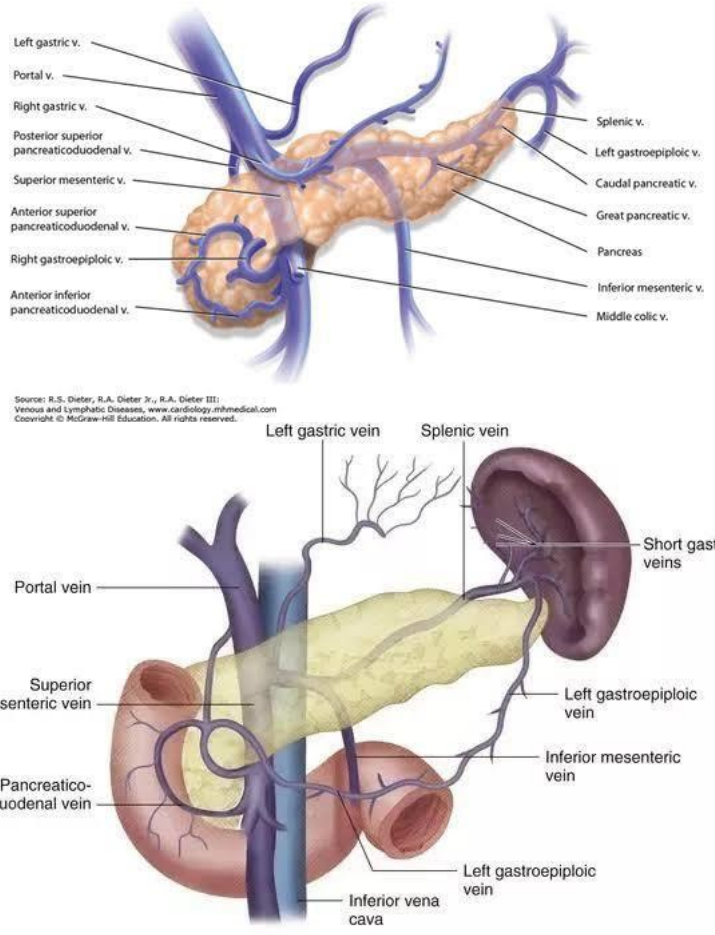
ARTERIAL SUPPLY



The head of the pancreas and its uncinate process are supplied by the pancreatico-duodenal arteries. The neck, body, and tail receive blood supply from the splenic artery. Many small branches arise from the length of the splenic artery, supplying arterial blood flow to the superior part of the organ. The splenic artery, branches to give the dorsal pancreatic artery, which courses posterior to the body of the pancreas, to become the inferior pancreatic artery. The inferior pancreatic artery then runs along the lower border of the pancreas, terminating at the tail.

VENOUS DRAINAGE

Venous drainage of the pancreas is mainly into the portal system, with the head and neck draining primarily through the superior and inferior pancreaticoduodenal veins, and the body and tail drain into the splenic vein.



Venous drainage of the pancreas mimics its arterial supply. Head of the pancreas drains into the anterior and posterior pancreatico-duodenal veins. The posterior-superior pancreatico-duodenal vein enters the superior mesenteric vein, laterally at the superior border of neck of the pancreas. The anterior and posteroinferiorpancreatico-duodenal veins enter the superior mesenteric vein, along the inferior border of the uncinate process.

Body and tail of pancreas are drained via the splenic venous system.

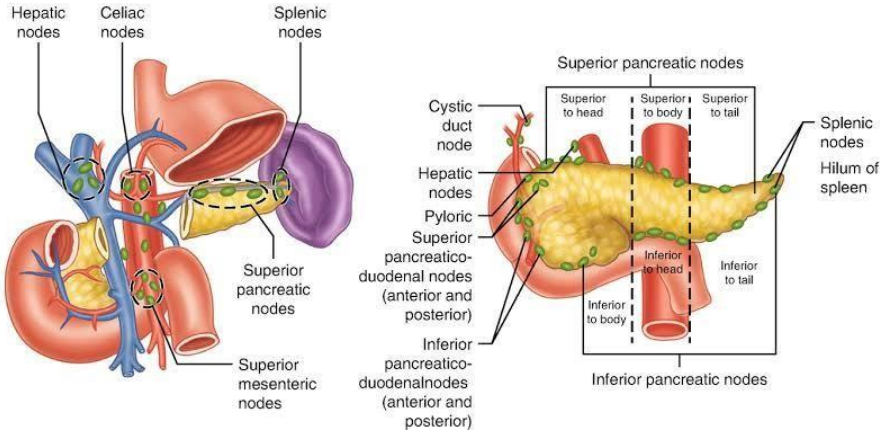
LYMPHATIC DRAINAGE

Lymphatic Drainage

The lymphatic drainage from the pancreas is diffuse and widespread. The lymphatics of pancreas, in general, drain the surface network of lymph toward regional lymph nodes and are formed near the larger blood vessels[11].The superior lymphatics, run along the superior border of the pancreas closely with the splenic blood vessels. Those on the left side of the body and tail of pancreas, empty into lymph nodes in the hilum of spleen. Those on the right side of the body and the neck of pancreas, empty into lymph nodes near the superior border of the head.

They also receive tributaries from the anterior and posterior surfaces of the pancreas. The inferior lymphatics along inferior pancreatic artery. Those that drain the left lower side of the body and tail of the pancreas, drain towards the lymph nodes in the splenic hilum. The remaining areas of the neck and body of the pancreas drain towards the right. The profuse network of lymphatic vessels and lymph nodes draining the pancreas provide egress to tumour cells arising from the pancreas. This diffuse lymphatic drainage contributes to the fact that pancreatic cancer often presents with positive lymph nodes and a high incidence of local recurrence after resection.

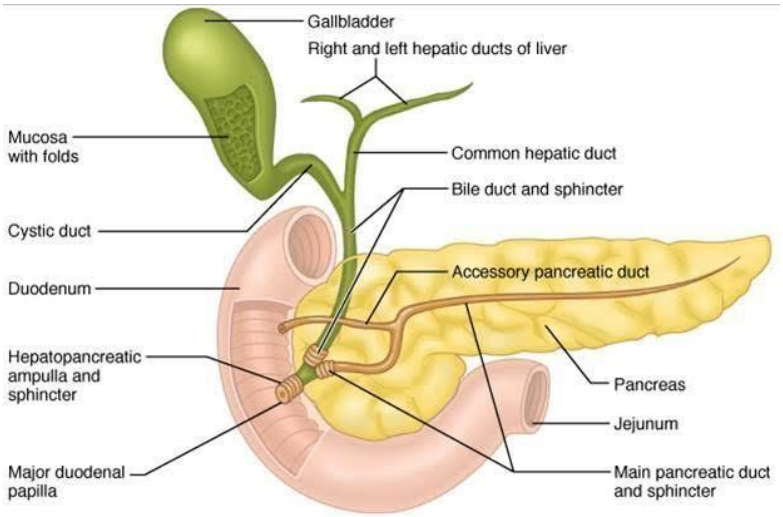
Lymph nodes can be palpated along the posterior aspect of the head of the pancreas in the pancreaticoduodenal groove, where themesenteric vein passes below the neck of the pancreas, along the inferior border of the body, along the hepatic artery ascending into the portahepatis, and along the splenic artery and vein. The pancreatic lymphatics also communicate with lymph nodes in the transverse mesocolon and mesentery of the proximal jejunum.



DUCTAL ANATOMY OF PANCREAS

The main pancreatic duct or the duct of Wirsung, beginning in the distal tail of pancreas as a confluence of small anastomosing ductules draining the lobules of the gland. The duct runs through the body of pancreas to the head, midway between the superior and inferior border of the gland and slightly posterior, where it usually passes downward and backward in close juxtaposition to the common bile duct.

Ductal Anatomy



In the head of the pancreas, the pancreatic duct turns inferiorly at the genu of the pancreatic duct and joins the common bile duct, draining into the duodenum at the ampulla of Vater, 7 to 10 cm distal to the pylorus. The main pancreatic duct is widest at the head of the pancreas (5mm), and the duct gradually tapers as it progresses to the body (4mm) and tail (3mm).

At the level of the ampulla of Vater, the pancreatic duct is anterior and inferior to the common bile duct. There are over 20 secondary branches of the duct of Wirsung throughout the pancreas, which drain the acinar units. The main pancreatic duct is 2 to 4 mm in diameter and has a ductal pressure of approximately 15 to 30 mm Hg. This is higher than the pressure in the common bile duct, 7 to 17 mm Hg, thereby preventing reflux of bile into the pancreatic ductal system.

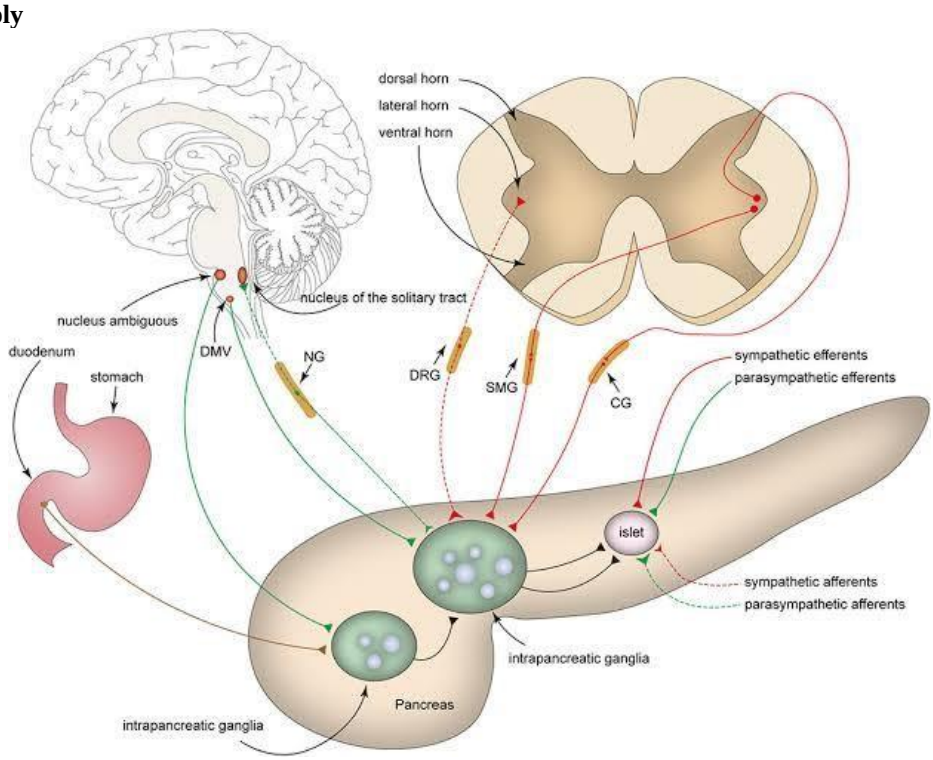
At the level of the major papilla, the duct turns horizontally to join, in most cases with the bile duct. This short common segment is the ampulla of the bile duct, which terminates at the duodenal papilla.

The papilla of Vater at the termination of the common bile duct is a small, nipple like structure that protrudes into the duodenal lumen and is marked by a longitudinal fold of duodenal mucosa. Approximately 70% of the general population have a patent accessory duct (of Santorini), which is also known as the *"minor duct".*

The accessory pancreatic duct, or duct of Santorini, is more variable than the main pancreatic duct. It typically drains the uncinate process and inferior portion of the pancreatic head into the duodenum at the minor papilla, proximal to the ampulla of Vater fold of duodenal mucosa. The accessory pancreatic duct lies anterior to the bile duct, and drains into the minor papilla, which lies proximal to the ampulla of Vater, but is also located in the second part of the duodenum.

NERVE SUPPLY

Nerve Supply



The visceral efferent innervation of the pancreas is through the vagi and the splanchnic nerves by way of the hepatic and celiac plexuses. The efferent fibers of the vagi, pass through these plexuses without synapsing, and they terminate in parasympathetic ganglia in the interlobular septa of the pancreas.

The postganglionic fibers innervate acini, islets, and the ducts. The acinar cells which are responsible for exocrine secretion, the islet cells which are responsible for endocrine secretion, and the islet vasculature, are innervated by both the systems.

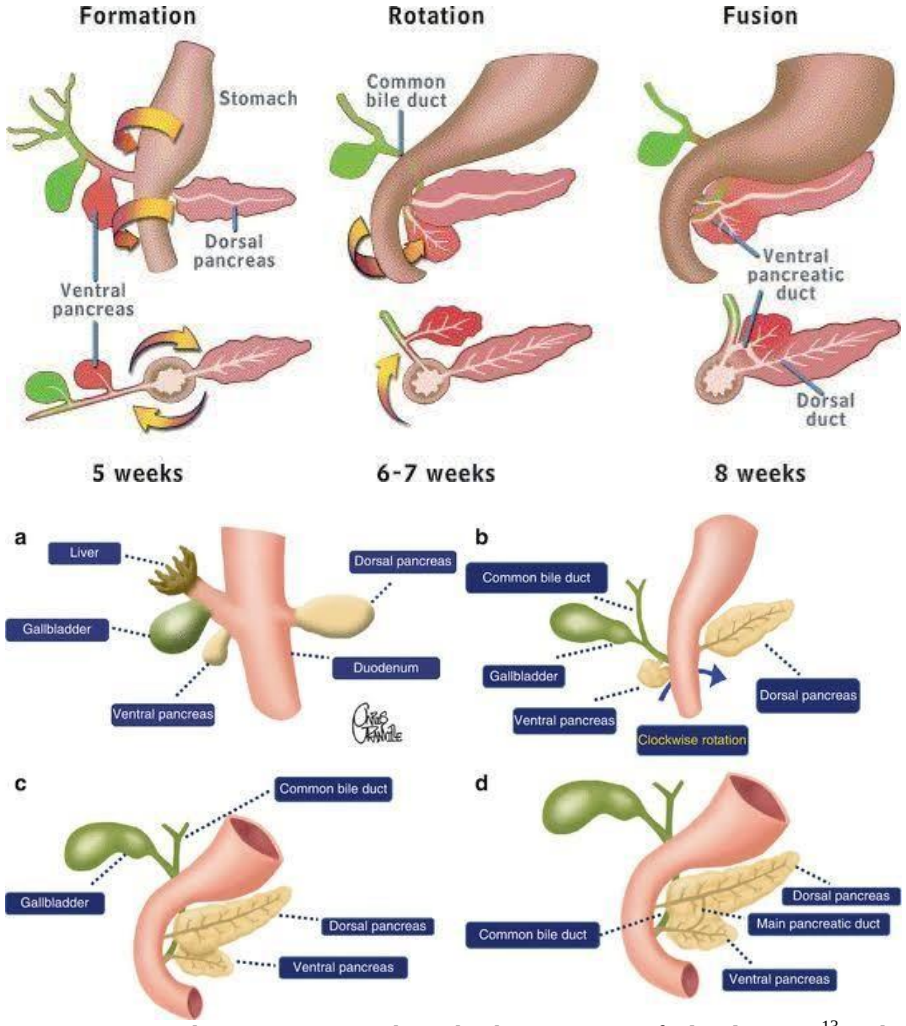
The bodies of the preganglionic neurons of these sympathetic efferent neurons, originate in the lateral gray matter of the thoracic and the lumbar spinal cord. The bodies of the postganglionic sympathetic neurons are located in the great plexuses of the abdomen. Their postganglionic fibers innervate only the blood vessels. The autonomic fibers, are located near the blood vessels of the pancreas.

The parasympathetic system stimulates endocrine and exocrine secretion, and the sympathetic system inhibits secretions. The pancreas is also innervated by neurons which secrete amines and peptides, such as somatostatin, vasoactive intestinal peptide, calcitonin gene-related peptide and galanin. The exact role of these neurons in pancreatic physiology is not clear.

The pancreas also has a rich supply of afferent sensory fibers, which are responsible for the intense pain associated with advanced pancreatic cancer, as well as acute and chronic pancreatitis[12].These somatic fibers travel to the celiac ganglion.

EMBRYOLOGY

Embryology



The embryonic pancreas is known to pass through three stages of development[13] .The first is the undifferentiated stage, in which the endoderm evaginates to initiate pancreatic morphogenesis, with only insulin and glucagon genes being expressed. The second stage, involves epithelial branching with formation of primitive ducts. The final stage begins with formation of acinar cells at the apex of the ductal structures, with development of zymogen granules which contain enzymes.

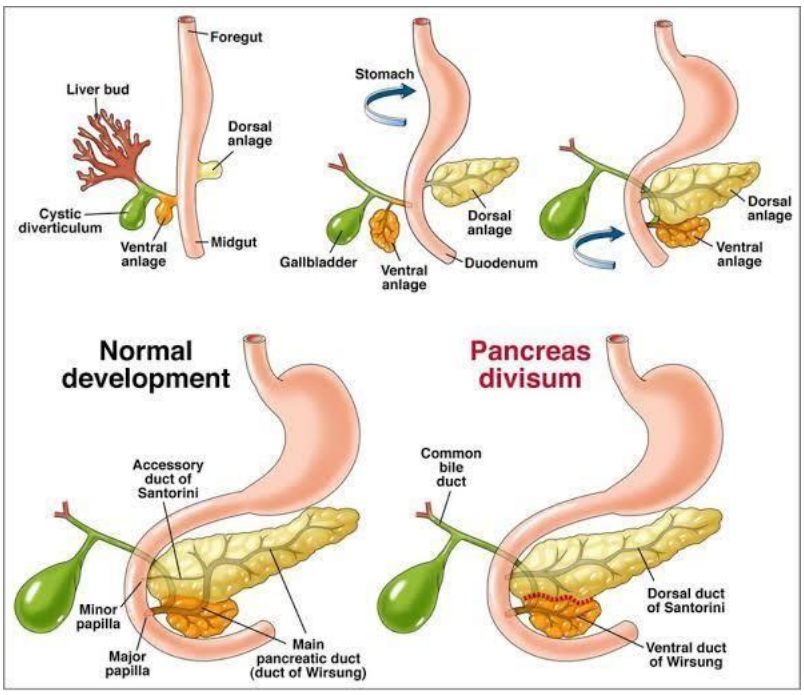
Acinar cells usually begin enzyme secretion only shortly after birth. The pancreas arises from the posterior foregut endoderm. Initially two dorsal and one ventral, and then migrate towards one another, and fuse to form a single unit. After about one month of gestation, the foregut evaginates into a condensation of the overlying mesenchyme to form the first morphologic dorsal bud.

About one week later, one ventral bud forms. Both buds undergo elongation of a stalk and branching. At 37 to 42 days of gestation, ventral pancreas rotates around the duodenum, and fuses with dorsal pancreas.

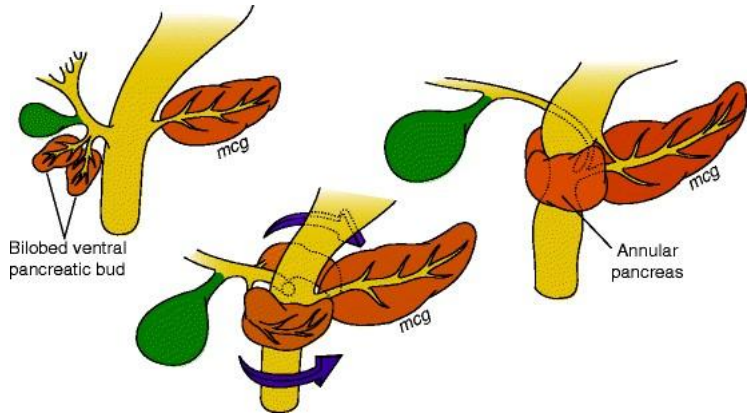
The dorsal pancreas forms the body, tail, and the superior part of the pancreatic head, along with the distal part of the main pancreatic duct (of Wirsung),and the entire minor accessory pancreatic duct (of Santorini). The ventral pancreas forms the uncinate process, and the inferior part of the head of the pancreas. It also forms the proximal part of the main pancreatic duct. The two duct systems corresponding to the ventral and dorsal buds, fail to fuse in to 10% of the general population. This leads to a condition called *pancreas divisum*, in which the accessory pancreatic duct, functions as the main route for drainage and enters the duodenum via major papilla, whereas a dorsal pancreatic duct enters through a minor papilla, which is slightly proximal.

As most of the pancreatic exocrine secretions exit via the dorsal duct, pancreas divisum can lead to partial obstruction caused by a small minor papilla, resulting in chronic backpressure within the duct.

This can leadto acuteon chronic pancreatitis.



Failure of the ventral pancreas to fully rotate around the duodenum leads to a condition called *annular pancreas*, which leads to circumferential or nearcircumferential pancreatic tissue surrounding the second part of the duodenum.

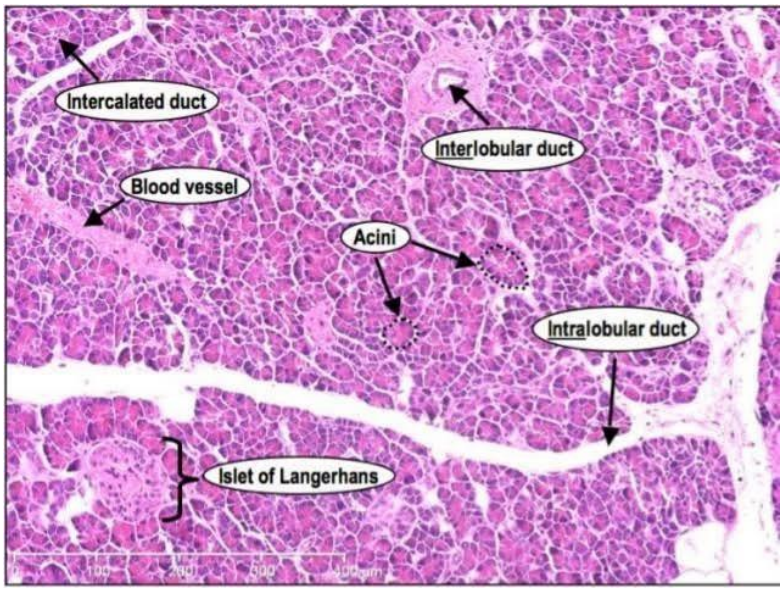


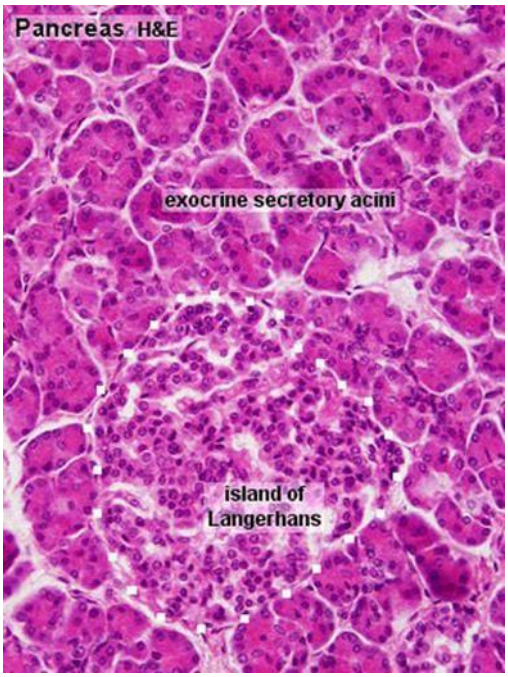
HISTOLOGY

The pancreas is a compound, finely nodular gland. The lobules are visible on gross examination, and are connected by connective tissue septa which contain the ducts, blood vessels, lymphatics, and the nerves. The basic subunit of the exocrine part is the acinus, which is at its base a spherical mass of secretory cells called *acinar cells.* The spherical acinusconnects to a goblet-shaped neck that consists of tubular cells called *duct cells.* The inner lumen of the acinus forms the terminal portion of the secretory duct.

The pancreatic ductal system is lined by columnar epithelium. Goblet cells and occasional argentaffin cells are also present. The larger ducts are thick walled, consisting of connective tissue and elastic fibers. The endocrine part consists of the islets of Langerhans cell. In the resting state, numerous eosinophilic zymogen granules fill the apical part of the cell. The basal part of the cells contain 1 or 2 centrally located, spherical nuclei and basophilic.

Histology





PANCREATIC SECRETIONS

EXOCRINE

The functional unit of the exocrine pancreas is composed of an acinus and its draining ductile. The acini are designed to produce, store, and secrete digestive enzymes. There are receptors for hormones and neurotrasmitters which stimulate release of enzymes, located at the basolateral aspect of acinar cell membrane.

COMPOSITION OF EXOCRINE SECRETIONS

The pancreas secretes approximately 500 to 800 mL per day of colorless, odorless, alkaline, isosmotic pancreatic juice. Pancreatic juice is a combination of acinar and ductal secretions. The acinar cells secrete amylase, proteases, and lipases, which are responsible for digestion of carbohydrates, proteins, and fat.

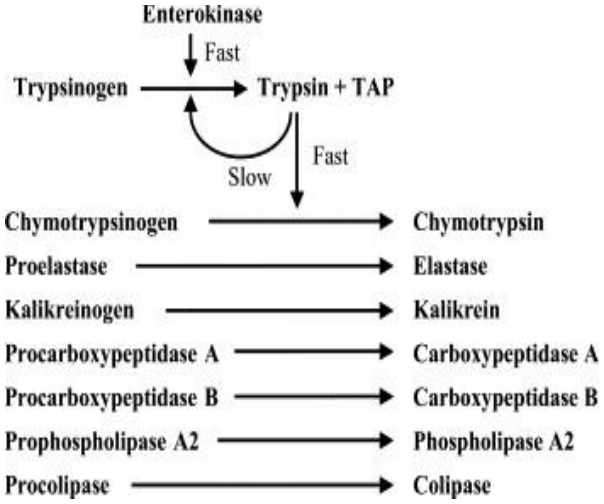
The predominant inorganic components of pancreatic exocrine secretions will include, water, sodium, potassium, chloride, and bicarbonate. Water and ion secretions deliver digestive enzymes to the intestinal lumen help to neutralize gastric acid which is emptied into the duodenum.

Pancreatic juice which is released on stimulation with secretinis "clear, colourless, alkaline, and isotonic with plasma". The flow rate increases from an average of 0.2 or 0.3 mL/min in the resting state to 4.0 mL/min during post prandial stimulation. A volume of 2.5 L is secreted per day.

Secretin stimulates secretion by binding to its receptor on the basolateral membrane of the duct cell, thus activating adenylatecyclase and increasing cyclic adenosine monophosphate (cAMP); acetylcholine does so by binding to its receptor and raising intracellular calcium concentrations.

ORGANIC CONSTITUENTS

The human pancreas has a large capacity for synthesizing protein (mostly digestive enzymes).



Amylases digest the carbohydrates (starch and glycogen) by hydrolyzing 14-glycoside linkages at every other junction between carbon 1 and oxygen. The products of amylase digestion are maltose and maltotriose and α-dextrins. The brush border enzymes of the enterocyte complete hydrolysis of these to glucose.

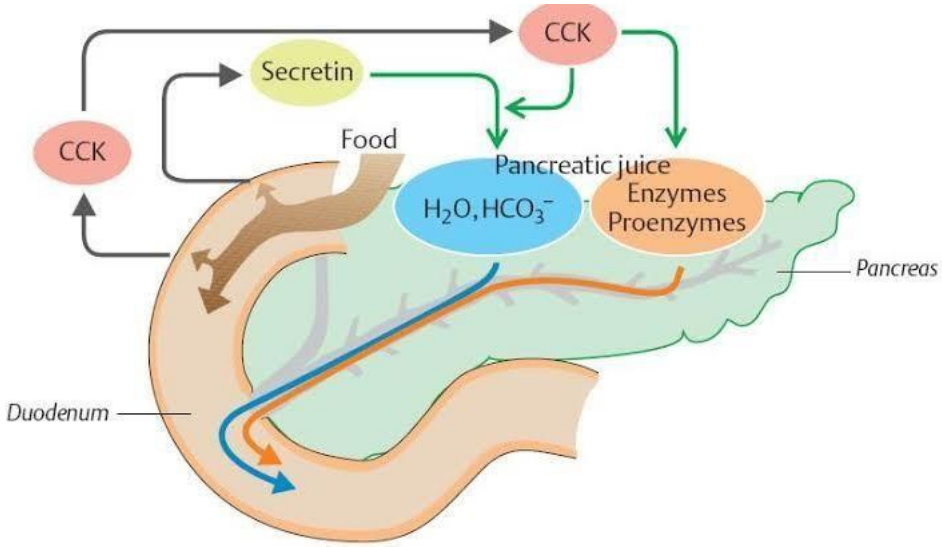
The pancreas secretes three lipases:

1. Lipase (or TG lipase)
2. Phospholipase A2,
3. Carboxylesterase21

Pancreatic lipase hydrolyzes a TG molecule to 2 fatty acid molecules released from carbons 1 and 3 and a monoglyceride with a fatty acid esterified to glycerol at carbon 2. Colipase is believed to form a complex with lipase and bile salts.

Proteases: Trypsin converts the pro-enzymes secreted by the pancreas to an active form, in the duodenum. Trypsinogen is converted to its active form, trypsin, by enterokinase, which is secreted by the duodenal mucosal cells. Failure to express trypsinogen inhibitor, pancreatic secretory trypsin inhibitor (PSTI) or *SPINK1*, is a cause of ***familial pancreatitis***. Trypsinogen is expressed in several isoforms, and a missense mutation on the cationic trypsinogen, or *PRSS1*, results in premature and intrapancreatic activation of trypsinogen causing hereditary pancreatitis. Trypsin, chymotrypsin, and elastase are endopeptidases that cleave specific peptide bonds adjacent to specific amino acids. The combined actions of gastric pepsin and the pancreatic proteases result in the formation of oligopeptides and free amino acids. The oligopeptides can be further digested by enterocyte brush-border enzymes

Pancreatic Secretion



PHYSIOLOGY

Exocrine secretion of the pancreas occurs during the fasting state and after ingestion of a meal. The inter-digestive pattern of secretion begins with the clearance of food from the upper gastrointestinal tract.

The inter-digestive phase of pancreatic secretion is in a cyclical fashion, and follows the pattern of the "migrating myoelectric complex" or

MMC.

The pattern repeats once in 1-2 hours, with periods of increased secretion of enzymes, during periods of increased motor activity in the stomach and the duodenum.

Exocrine pancreatic secretion with ingestion of food is divided into 3 phases:

1. Cephalic
2. Gastric
3. Intestinal

CEPHALIC PHASE

Cephalic phase of pancreatic secretion is vagallymediated. Cephalic stimulation increases acinar secretion within the pancreas, and a decreased pH in the duodenum increases acinar secretion and bicarbonate production by the duct.

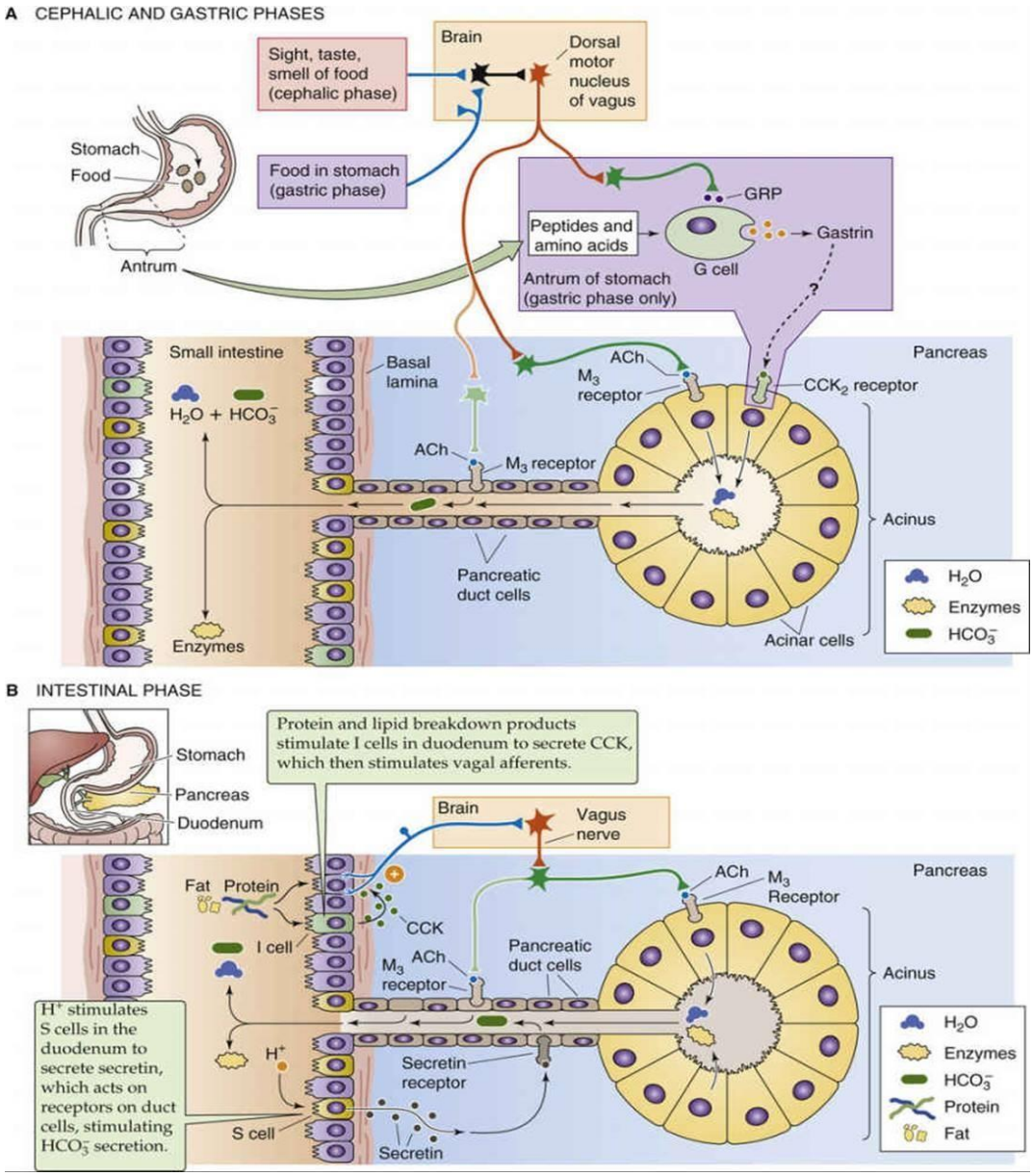
GASTRIC PHASE

The *gastric phase is due to a* meal in the stomach. Distension of stomach is an important stimulus, which results in predominant enzyme secretion with minimal secretion of water and bicarbonates.

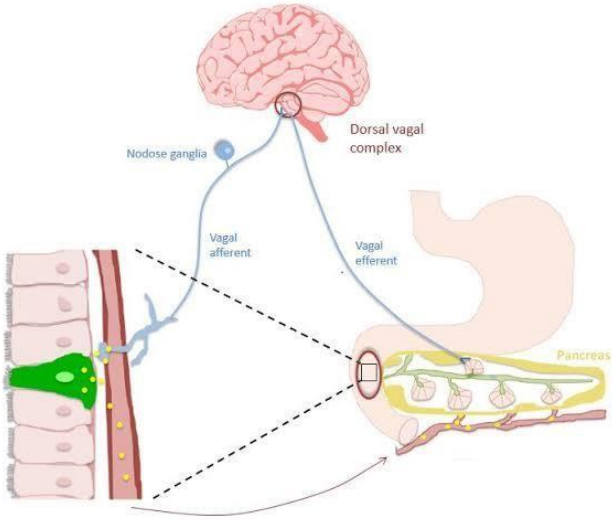
INTESTINAL PHASE

It is mediated by hormones and entero-pancreatic vagovagal reflexes. In contrast to the cephalic and gastric phases, there is significant ductal secretion during the intestinal phase. Ductal secretion is initiated by hydrogen ions in the intestinal lumen. Secretin is released from enteroendocrine S cells in the duodenal mucosa when the pH of the lumen is less than 4.5[14]. The amount of secretin that is secreted as well as the volume of pancreatic secretion is based on the load of "titratable acid" delivered to the duodenum. The mediators of the enzyme secretory response from intestinal stimuli are neural and humoral.

Cholecystokinin is the most important humoral mediator of enzyme secretion during the intestinal phase. Level of CCK usually increases following a meal. The amount of bicarbonate secreted varies with pancreatic secretory rate, greater concentrations of bicarbonate being secreted in high pancreatic secretory rates. Secretion of chloride varies inversely with bicarbonate secretion, and the sum of these two remains constant. However, sodium and potassium concentrations are constant in all secretory rates .



Regulation of Secretion



ENDOCRINE SECRETIONS

There are over a million islets of Langerhans in the adult pancreas. They vary in size from 40 to 900 nm. Larger ones are located near major arterioles, and smaller ones are embedded more deeply within the parenchyma of the gland. Most islets contain, 5 cell types

Alpha Cells: Secrete glucagon, Opposite effects of insulin; increased hepatic glycogenolysis and gluconeogenesis.

Beta Cells: Secrete insulin, Decreased gluconeogenesis, glycogenolysis, fatty acid breakdown, and ketogenesis, Increased glycogenesis, protein synthesis.

Delta Cell: Secrete Somatostatin, Inhibits GI secretion, secretion and action of all GI endocrine peptides, Inhibits cell growth.

Epsilon Cells: Secrete ghrelin, Decreases insulin release and insulin action

PP Cells: Secrete Pancreatic Polypeptide, Inhibits pancreatic exocrine secretion and section of insulin, facilitates hepatic effect of insulin .

ACUTE PANCREATITIS

DEFINITION

Pancreatitis is an "inflammation of glandular parenchyma lead to injury or destruction of acinar components associated with little or no fibrosis of the pancreas". Acute pancreatitis is best diagnosed clinically in a patient presenting with 2 of the 3 following criteria[15].

(1) Symptoms consistent with pancreatitis,

(2) Serum lipase or amylase levels more than 3 times the laboratory's upper range of normal, and

(3) Radiologic features suggestive of pancreatitis, usually using CECT

Usually, the first two criteria are present, and CECT is not required for diagnosis.

The most common cause of acute pancreatitis is gallstones, in approximately 50% of the patients, followed by alcohol in 20%[16]. In a study done in New Delhi, India, gall stones and alcoholism were found to be the cause in 49% and 23.6% cases, respectively[14].

The remaining 10% form a rather large group of other causes of acute pancreatitis. These include hypercalcemia, hypertriglyceridemia, medications, hereditary causes, sphincter of Oddi dysfunction, pancreatic neoplasms, pancreas divisum and others.

ETIOLOGY

GALL STONES

Obstructive cause of acute pancreatitis is most frequently due to gallstones. However, only 3% to 7% of patients who have gallstones, will develop an attack of acute pancreatitis in their lifetime. Gallstone pancreatitis is more common in women than men because gallstones are more frequent in women[17]. Acute pancreatitis occurs more commonly when a patient harbours a smaller stone, less than a diameter of 5mm, as they are more likely large stones to traverse down the cystic duct to go on to obstruct the ampulla. Intermittent and continuous obstruction of the ampullary orifice due to a gallstone or edema induced by stone passage is the inciting factor in the pathogenesis of gallstone-induced pancreatitis.

Microlithiasis refers to "aggregates <5 mm in diameter, of cholesterol mono hydrate crystals or calcium bilirubinate granules detected as "sludge" within the gallbladder" on ultrasonography or on examination of bile obtained during ERCP. An etiologic role for microlithiasis in acute pancreatitis remains unproved. However, cholecystectomy or endoscopic sphincterotomy can reduce the risk of recurrent acute pancreatitis in patients with microlithiasis.

ALCOHOL

Excessive ethanol consumption is the next commonest cause of acute pancreatitis worldwide. It is more is more prevalent in young men (30 to 45 years of age) than in women[18]. However, only 5% to 10% of patients who drink alcohol develop acute pancreatitis. Heavy ethanol abuse (>100 g/day for at least 5 years), smoking, and genetic predisposition, contribute to acute pancreatitis. As compared with non-smokers, the relative risk of alcohol-induced pancreatitis in smokers is 4.9[19].The nature of alcohol consumed is less important than a daily consumption of between 100 and 150 g of ethanol. In a patient with a history consumption on alcohol, with absence of other causes of pancreatitis, the initial attack of acute pancreatitis is deemed to be due to alcohol.

The **"secretion with blockage"** mechanism shows that ethanol consumption causes increased tone of sphincter of Oddi, and, it is a metabolic toxin to pancreatic acinar cells, where it can disrupt enzyme synthesis and secretion. Ethanol causes a brief secretary increase, followed by inhibition. This causes enzyme proteins to precipitate within the duct. Calcium then precipitate within the protein matrix, resulting in multiple ductal obstructions. Ethanol also increases ductal permeability.

SLUDGE

Sludge within the gallbladder, is a suspension in the bile that may contain stones smaller than 3 mm diameter. Because small stones can be obscured by a sludge, the 2 are commonly referred to together as "*biliary sludge and microlithiasis"*.Components of this include of cholesterol monohydrate crystals or calcium bilirubinate granules Patients who harbour these are usually not symptomatic. On USG, this sludge causes a "mobile, low amplitude echo" which does not produce an acoustic shadow.

It usually is visualised in the dependant part of the gallbladder.

TUMOURS

Tumours, by possibly causing obstruction of the pancreatic duct, can cause in repeated episodes of acute pancreatitis, particularly in persons more than 40 years of age. The commonest neoplasm which presents in this manner is intraductal papillary mucinous neoplasm (IPMN) [20]. Acute pancreatitis may be the initial presentation in patients with adenocarcinoma of the pancreas.

Metastases from other cancers (lung, breast) to the pancreas have also caused pancreatitis. Sometimes and adenoma from the papilla can also cause obstruction and subsequent acute attack of pancreatitis.

MEDICATIONS

Drugs though not a very common cause, form an important etiology of acute pancreatitis. Drug- induced pancreatitis probably account for <1 % of cases. Drug-induced pancreatitis tends to occur within 4 to 8 weeks of beginning a drug. It usually does not manifest as an adverse drug reaction prior to onset of an attack of pancreatitis.

Class I (Definite Association)	Class II (Probable Association)	Class III (Possible Association)	
5-Aminosalicylic acid	Acetaminophen	Aldesleukin	Indomethacin
Asparaginase	Carbamazepine	Amiodarone	Infliximab
Azathioprine	Cisplatin	Atorvastatin	Ketoprofen
Corticosteroids	Erythromycin	Bortezomib	Ketorolac
Cytarabine	Hydrochlorothiazide	Asparaginase	Lipid emulsion
Didanosine	Ifosfamide	Calcium	Lisinopril
Enalapril	Interferon α_{2b}	Capecitabine	Mefenamic acid
Estrogens	Lamivudine	Celecoxib	Metformin
Furosemide	Octreotide	Clozapine	Methyldopa
Mercaptopurine	Sitagliptin	Cholestyramine	Metolazone
Opiates		Cimetidine	Metronidazole
Pentamidine		Ciprofloxacin	Nitrofurantoin
Pentavalent antimonials		Clarithromycin	Omeprazole
Sulfasalazine		Clonidine	Ondansetron
Sulfamethoxazole and trimethoprim		Cyclosporine	Paclitaxel
Sulindac		Danazol	Pravastatin
Tamoxifen		Diazoxide	Propofol
Tetracycline		Etanercept	Propoxyphene
Valproic acid/salts		Ethacrynic acid	Rifampin
		Exenatide	Sertraline
		Famciclovir	Zalcitabine
		Glyburide	
		Gold therapy	
		Granisetron	
		Ibuprofen	
		Indinavir	

From references 18, 25, 29–32.

There are many possible mechanisms of drug-induced pancreatitis.

The most common mechanism is a "hypersensitivity reaction". This usually occurs between the 4th and 8th week of starting on the medication, and does not depend on the dosage. On challenging the patient with the drug, recurrent attack results with an earlier onset, in a few days or even within a few hours of the dose.

Aminosalicylates, metronidazole, and tetracycline group of drugs, act by this mechanism. The second mechanism is thought to be due to accumulation of a metabolite of the drug which is toxic, and typically presents after months. Sodium valproate and didanosine (DDI) belong to this category. Drugs causing hypertriglyceridemia like thiazide diuretics, isotretinoin, tamoxifen also belong to this category.

Few drugs are intrinsically toxic, and an excessive dosage of these can result in pancreatitis (erythromycin, acetaminophen).

In general, drug-induced pancreatitis is mild and self limited. The diagnosis should only be entertained after alcohol, gallstones, hypertriglyceridemia, hypercalcemia, and tumors (in appropriate-aged patients) have been ruled out.

METABOLIC DISORDERS

HYPERTRIGLYCERIDEMIA

Hypertriglyceridemia is probably the third most common cause of pancreatitis, accounting for 2% to 5% of cases. Serum triglyceride levels more than 1000 mg/dL can result in attacks of acute pancreatitis. However, recent studies suggest that the serum TGs may have to be even higher to precipitate acute pancreatitis, perhaps above2000 mg/dL, and with obvious lactescent (milky) serum due to increased concentrations of chylomicrons[19]. The mechanism of hypertriglyceridemia causing acute pancreatitis is not clear, but the release of free fatty acids by lipase may damage pancreatic acinar cells or endothelial cells. The hydrolysis of TGs by pancreatic lipase and release of free fatty acids that induce free radical damage can directly injure cell membranes. Disorders of lipoprotein metabolism are conventionally divided into primary (genetic) and secondary causes, including diabetes mellitus, hypothyroidism, and obesity/metabolic syndrome.

HYPERCALCEMIA

Hypercalcemia due to any cause is associated with acute pancreatitis very rarely. Proposed mechanisms include deposition of calcium salts in the pancreatic duct and calcium activation of trypsinogen within the pancreatic parenchyma[21].

Primary hyperparathyroidism causes less than 0.5% of all cases of acute pancreatitis. Hyperparathyroidism attributes to a minority of cases of acute pancreatitis.

Pancreatitis can also be due to other causes of hypercalcemia, like metastatic bone disease, TPN, sarcoidosis, vitamin D toxicity, and infusion of calcium in high doses peri-operatively during cardiopulmonary bypass.

INFECTIONS

The diagnosis of acute pancreatitis caused by an infection requires evidence of acute pancreatitis, evidence of an active infection, and the absence of a more likely cause of acute pancreatitis.

Acute pancreatitis has been implicated to be caused by viruses (mumps, coxsackievirus, hepatitis A, B, and C, and several herpesviruses, including cytomegalovirus, varicella-zoster, herpes simplex, and Epstein Barr virus), MMR vaccine, bacteria (*Mycoplasma*, *Legionella*, *Leptospira*, *Salmonella*, TB, and brucellosis); fungi *(Aspergillus*, *Candida);* and parasites *(Toxoplasma*, *Cryptosporidia*, *Ascarislumbricoides*, *Clonorchissinensis)*. *C. sinensis* and *A. lumbricoides* cause pancreatitis by obstructing the duct of Wirsung.

VASCULAR DISEASES

Ischaemia to the pancreas has been rarely associated with acute pancreatitis. In most cases, it is mild, however a severe necrotizing pancreatitis can occur. Vasculitis like SLE and polyarteritisnodosa can cause vasculitis. Atheromatous embolization of cholesterol plaques after trans-abdominal angiography, intra-operative hypotension, hemorrhagic shock, ergotamine overdose, and trans catheter arterial embolization for hepatocellular carcinoma.

TRAUMA

Both penetrating and blunt trauma can result in acute pancreatitis. Other intra-abdominal organs are also usually involved. Laparotomy is mandatory in all every case of penetrating injury for the assessment of injuries and to manage them accordingly. Blunt injury to the abdomen causes pancreatic injury by compression of pancreas against the spine.

IATROGENIC

Iatrogenic pancreatitis is mainly due to ERCP, which can cause significant morbidity. Asymptomatic hyperamylasemia occurs after 35% to 70% of ERCPs[22]. Post-ERCP pancreatitis is believed to be multifactorial, involving a combination of chemical, hydrostatic, enzymatic, mechanical, and thermal factors acute pancreatitis occurs in 5% of diagnostic ERCPs, 7% of therapeutic ERCPs, and up to 25% in those with suspected SOD or in those with a history of post-ERCP pancreatitis[23].

POST-OPERATIVE STATE

Pancreatitis can be secondary to surgeries of the alimentary tract or thoracic cavity. Pancreatitis occurs after 0.4% to 7.6% of cardiopulmonary bypass operations. 27% of patients undergoing cardio vascular surgery develops hyperamylasemia, and 1% develops necrotizing pancreatitis. Pancreatitis can occur following liver transplantations. Postoperative pancreatitis is associated with higher morbidity as compared to other causes.

SPHINCTER OF ODDI DYSFUNCTION

Sphicter of Oddi dysfunction has an unclear associated with acute pancreatitis. The main argument in favour of this entity as a cause of acute pancreatitis is the many observational series that report that endoscopic pancreatic sphincterotomy or surgical sphincteroplasty reduces recurrent attacks of pancreatitis[24].

PANCREAS DIVISUM

Pancreas divisum is the commonest congenital maldevelopment of pancreas, the vast majority of whom never develop pancreatitis. Obstruction of the minor papilla is thought to the causative factor in these cases. Genetic factor has a possible role to play in patients suffering from pancreatitis, who have pancreas divisum.

MISCELLANEOUS

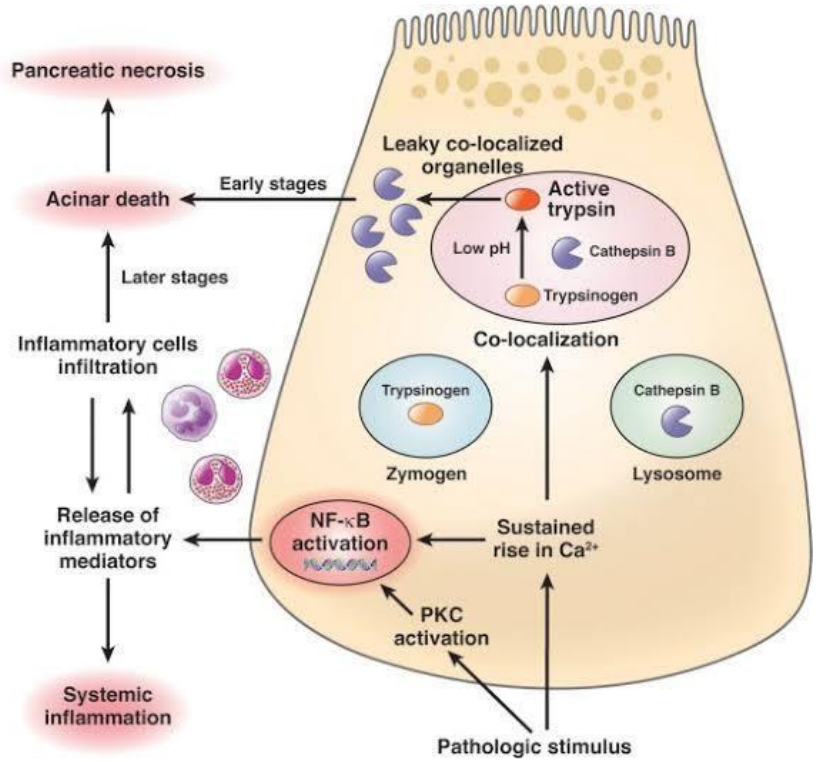
Crohn's disease has been associated with the development of acute pancreatitis. Celiac disease has an uncertain association. Hyper amylasemia in these patients have been thought to be due to disruption of small bowel mucosal barrier. Pancreatitis has been seen in patients after severe burns. Smoking has been suggestive to be causative in acute pancreatitis.

Acute pancreatitis resulting from autoimmune pancreatitis is rare, seen in type II disease, and is associated with granulocyte epithelial lesions.

PATHOPHYSIOLOGY

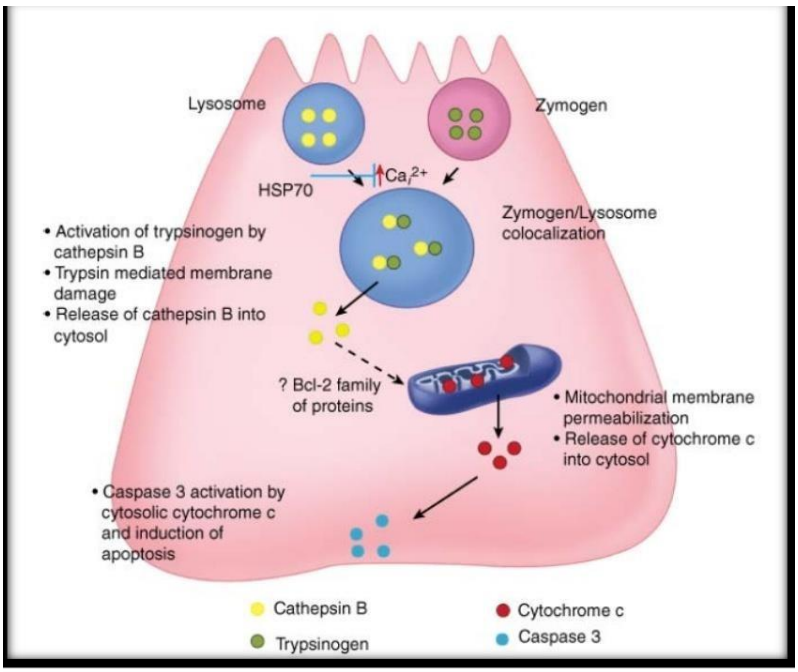
Acute pancreatitis occurs in varying degrees of severity, the determinants of which are multifactorial. The generally belief is that, pancreatitis begins with activation of digestive enzymes within the acinar cells, which results in acinar cell injury. The fact that zymogen and lysosome co-localization occurs before elevation of amylase level, pancreatic edema, and other markers of pancreatitis are evident, suggests that co-localization is an early step in the pathophysiology of pancreatitis.

CO-LOCALIZATION HYPOTHESIS



The initiating factor in the pathogenesis of acute pancreatitis is activation of trypsinogen inside the acinar cells in large quantities. Trypsin, activates other proenzymes, such precursors of elastase, phospholipase A2 (PLA2), and carboxypeptidase, to active forms. It also activates the complement and kinin systems. Active enzymes auto-digest the pancreas, causing a vicious cycle releasing further active enzymes.

Very early in the development of the disease (shortly after the onset, but before morphologic or biochemical changes are apparent), digestive enzymes are localized in cytoplasmic vacuoles that also contain the lysosomal hydrolase cathepsin B, which is known to activate trypsinogen.



Small amounts of active trypsin which are normally produced within the pancreas, are usually inactivated by trypsin inhibitors. Because exocrine pancreas produces several enzymes that are potentially injurious to it, it prevents autodigestion by intracellularly assembling the inactive precursors of these enzymes, called *proenzymes*or *zymogens*, which are then transported and secreted outside of the gland. Their activation occurs safely in the duodenum, where the brush-border enzyme enteropeptidase (or enterokinase) activates the trypsinogen, and the resulting trypsin then activates the other zymogens in a cascade reaction.

To further protect the pancreas from these potentially harmful digestive enzymes, they are segregated from the cytoplasmic space within acinar cells by being enclosed within membrane-bound organelles, referred to as *zymogen granules*.

Another layer of protection is provided by the synthesis of trypsin inhibitors, which are transported and stored along with the digestive enzyme zymogens. These are available to inhibit small amounts of prematurely activated trypsinogen within pancreatic acinar cells. It is generally theorized that acute pancreatitis occurs when this process goes awry and the gland is injured by the erroneously activated enzymes that it produces.

There are three reasons for this theory:

a) The pancreas is digestible by the activated enzymes of the duodenum;

b) Activated digestive enzymes are found within the pancreas during pancreatitis

c) The histology of pancreatitis is suggestive of a coagulative necrosis

Intra-acinar pancreatic enzyme activation causes auto digestion of the normal pancreatic parenchyma.

In response to this initial insult, acinar cells release proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukins (IL)-1, -2, and -6, and IL-1and 10, which are antiinflammatory.

Blockage of secretion of ezymes of the pancreas, with on-going secretion disrupts the acinar cell barrier.

This results in exudation of enzymes from acinar cells, and ductal secretion into interstitial spaces. This may explain the rapid development of interstitial edema and the increase in the concentration of pancreatic enzymes in the serum[24].

The mechanism of gallstone induced pancreatitis is not clearly known. Bile reflux into the pancreatic duct, or ductal obstruction at the ampullary level due to stone or edema due to passing of stone have been proposed to cause pancreatitis. Stone impacted at the distal CBD mechanism of gallstone pancreatitis is that an impacted gallstone in the distal bile duct obstructs the pancreatic duct, causing increased pressure within it, thereby resulting in damage of acini and ductal epithelial cells.

The patho-physiology of acute pancreatitis begins with injury of acinar cells, which may progress to cause local inflammatory complications, SIRS and sepsis.

Mechanisms of injury are microcirculatory injury, leukocyte chemoattraction, release of pro and anti inflammatory cytokines, oxidative stress, extravasation of pancreatic enzymes, and translocation of bacteria into systemic circulation.

The release of pancreatic enzymes damages the vascular endothelium, the interstitium, and acinar cells[26]. Injury to acinar cells results in expression of endothelial cell adhesion molecules like VCAM, which further worsens the inflammatory response.

These abnormalities increase vascular permeability and cause edema of the gland causing "interstitial pancreatitis".

Vascular injury can result in micro-circulatory failure and exacerbation of injury to the pancreas.

Reperfusion of the pancreas which is already damaged can worsen the injury by release of free radicals and inflammatory mediators. Activation of the complement pathway and release of C5a play an important role recruiting of macrophages and leukocytes. These inflammatory cells will release proinflammatory cytokines, like TNF, IL1, IL-6, and IL-8, and platelet-activating factor (PAF) in response to transcription factors such as nuclear factor κB.

Very early in the development of the disease (shortly after the onset, but before morphologic or biochemical changes are apparent), digestive enzymes are localized in cytoplasmic vacuoles that also contain the lysosomal hydrolase cathepsin B, which is known to activate trypsinogen

Some cases of acute pancreatitis progress to develop systemic complications, fever, (ARDS), pleural effusion, renal shutdown, shock, myocardial depression, and metabolic complications.

Systemic inflammatory response syndrome is frequently seen in acute pancreatitis, which is probably mediated by activated enzymes of the pancreas andcytokines which are released into the portal circulation from the inflamed pancreas.

Cytokines reach the liver and Kupffer cells, which, in turn, causes increased and secretion of cytokines into the systemic circulation. These cause acute phase protein synthesis (C-reactive protein [CRP], IL-6) and may cause SIRS and organ damage leading on to MODS and death.

ARDS can be induced by active phospholipase-A, which cleaves lecithin, an important constituent of pulmonary surfactant.

Acute renal failure may be the result of hypotension and decreased intra vascular volume.

Depression of myocardium and shock may be due to release of vasoactive peptides and a myocardial-depressant factor.

Metabolic complications will include hyperlipidemia, hypocalcemia, hyperglycemia with or without ketosis, and hypoglycemia.

The cause of hypocalcemia is multiple, and includes hypoalbuminemia, hypomagnesemia, calcium-soap formation, hormonal imbalance.

Combination of genetic mutations in CFTR, in the pancreatic duct may predispose patients with pancreas divisum, to develop acute pancreatitis.

FACTORS DETERMINING SEVERITY OF THE DISEASE

Severity of pancreas varies widely. Some patients may experience a mild form of disease which is self-limiting, while others suffer a severe form and sometimes a lethal attack.

Factors which determine the severity of pancreatitisare multifactorial, but identification of these is of considerable therapeutic importance, because manipulation of these factors may lower the morbidity and mortality associated with this disease.

The ultimate severity of the disease depends on the extent of the systemic inflammatory response, and several cytokines and chemokines and their receptors that play an important role in the activation and migration of these inflammatory cells to the affected site.

The list of factors associated with pancreatitis and associated lung injury, include tumour necrosis factor alpha, monocyte chemotactic protein-1, Mob1, interleukin-1 (IL-1), platelet activating factor (PAF), substance P, adhesion molecules [intercellular adhesion molecule-1
(ICAM-1) and selectins], IL-6, IL-8, IL-10, C5a, the CCR1 receptor , granulocyte macrophage colony-stimulating factor, macrophage migration inhibitory factor, COX-2, prostaglandin E1, nitric oxide, and reactive oxygen species.

CLINICAL FEATURES

Diagnosing an acute pancreatitis by clinical history and examination is quite challenging, as it clinically mimics other causes of acute abdomen The diagnosis of acute pancreatitis is based on two or more of the following criteria:

1) Severe abdominal pain
2) Serum amylase or lipase more than three times higher than the
institution's upper limit
3) Contrast enhanced computed tomography (CECT) findings of acute pancreatitis.
4) Usually, if the first two criteria are present, and CECT is not required for diagnosis
5) Other upper abdominal conditions that can be confused with acute pancreatitis will include perforated peptic ulcer, gangrenous small bowel obstruction, and acute cholecystitis. Because these pathologies often have

a fatal outcome without surgery, urgent intervention is required in the small number of cases in which doubt persists.

ABDOMINAL PAIN

Abdominal pain is the usual presenting complaint in cases of acute pancreatitis. Biliary colic may persist and further develop into pancreatitis.

Pain is usually felt diffusely over the abdomen. However, it may be only in the epigastrium, right hypochondrium, or, rarely, localised to the left upper quadrant of abdomen.

Lower abdominal pain may be due to tracking of extravasation of pancreatic secretion to the left paracolic gutter. It has been described as "knifing" or "boring through" to the back, and can be relieved by the patient leaning forward.

Onset of pain is rapid, reaching its maximum intensity within 10-20 minutes.

In some cases, pain is gradual in onset and progression, taking hours to reach its peak intensity. Pain is steady, moderate to very severe. Bandlike radiation of the pain, to the back occurs in half the patients.

Pain lasting for only a few hours suggests other intra abdominal pathology. Pain is absent in 5% to 10% of attacks, and a painless presentation may be a feature of serious fatal disease[27].

Pain often precedes onset of nausea and vomiting, with retching often persisting even after the stomach has emptied.

Nausea and vomiting is present in 90% of individuals affected with acute pancreatitis. Patient also has associated retching, and pain does not subside on vomiting. Vomiting is either because of intractable pain or secondary to inflammation of the posterior wall of stomach.

PHYSICAL FINDINGS

Examination findings depend on the severity of the attack. Patients with mild disease, may not appear sick.

On examination, the patient may have tachycardia, tachypnea, hypotension, and hyperthermia. The temperature is usually mildly elevated in uncomplicated pancreatitis.

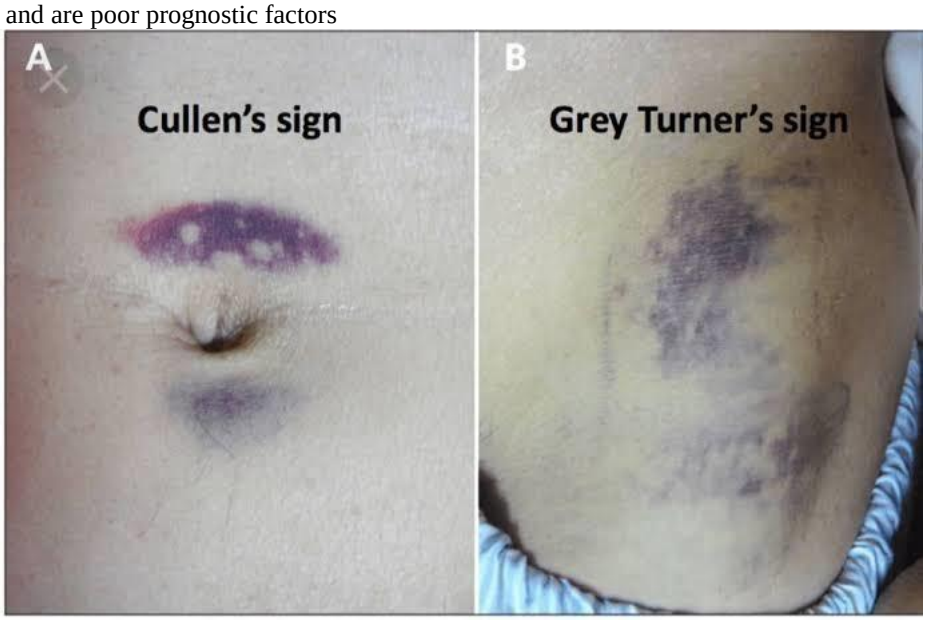
Pulse rate is usually in the range of 100 to 150 /minute. Hyper or hypotension may be present secondary to third space fluid loss and decreased circulatory volume.

The temperature may be normal, but within 1to 3 days it may increase to 101°F to 103°F due to severe retro-peritoneal inflammation.

Tachypnoea, with painful shallow breathing may be due to exudates below the diaphragm. Dyspnea may be due to pleural effusion, atelectasis, ARDS, or congestive cardiac failure. Tenderness may be mild without guarding in mild acute pancreatitis. In severe pancreatitis, patients may appear sick, and may present with distension of abdomen, more so in the epigastrium, secondary to ileus

Epigastric guarding may be present. Tenderness and guarding can be. Rigidity is not a common feature, and when present, other causes of diffuse peritonitis should be ruled out. Bowel sounds are either decreased or not heard

Other findings in the abdomen, include ecchymosis over the flanks “Grey Turner’s sign” or in the peri-umbilical area “Cullen’s sign”, due to extravasion of secretions which are hemorrhagic. These findings are not often present and are poor prognostic factors



Pleural effusion secondary to pancreatitis can cause a dull note on percussion, and decreased breath sounds on auscultation.

Dullness to percussion and decreased breathing sounds in the left or, less commonly, in the right hemithorax suggest pleural effusion secondary to acute pancreatitis

Patients may be disoriented and agitated or in coma, may hallucinate, which may be due to alcohol withdrawal, hypotension, electrolyte imbalances like hyponatremia, hypoxia, fever, or toxic effects of pancreatic enzymes on the central nervous system

Uncommon findings in acute pancreatitis include panniculitis with subcutaneous nodular fat necrosis that may be accompanied by polyarthritis.

Subcutaneous fat necroses are 0.5- to 2-cm tender red nodules that usually appear over the distal extremities but may occur over the scalp, trunk, or buttocks. They occasionally precede abdominal pain or occur without abdominal pain, but usually they appear during a clinical episode and disappear with clinical improvement.

Some physical findings point to a specific cause of acute pancreatitis.

Enlarged liver, spider angioma, and Dupuyten's contracture point towards ethanol induced pancreatitis. Tendon xanthoma and lipemia-retinalis point towards hyperlipidemia as the cause of pancreatitis.

Band keratopathy is seen in hypercalcemic patients.

DIAGNOSIS

PANCREATIC ENZYMES

In general, the diagnosis of acute pancreatitis relies on at least a 3fold elevation of serum amylase or lipase in the blood[27].

SERUM AMYLASE

Pancreatic diseases cause elevated pancreatic isozyme of amylase, and specifically measuring this isozyme improves the accuracy of diagnosis. But this is not routinely used.

Total amylase is measured routinely since it cheaper and easier. It increases 6 to 12 hours after the disease onset and is cleared from the blood rapidly with a half life of 10 hrs

Renal clearance is less than 25 %. This enzymes raises from the first day of disease onset, persisting for about 3-5 days.

Serum amylase is neither very sensitive nor specific. Sensitivity is about 85%.It may be within normal limits or only mildly raised in severe pancreatitis, or in chronic pancreatitis due to very little remnant of acinar tissue. Hypertriglyceridemia induced pancreatitis may be associated with normal level of amylase.

Upto 50% of patients with elevated amylase levels may infact have no evidence of pancreatic disease. Elevated amylase levels is suggestive, rather than diagnostic of pancreatitis. Hyperamylasemia may be present in asymptomatic patients

SERUM LIPASE

The sensitivity of serum lipase for the diagnosis of acute pancreatitis is similar to that of serum amylase and is above 85%[29]. However, Lipase has higher specificity in diagnosing acute pancreatitis as it is not affected by other causes of hyper amylasemia. Serum lipase level is almost always raised on the first day of the disease, and it remains increased for longer, thus providing a higher sensitivity. Combining amylase and lipase does not improve diagnostic accuracy and increases cost.

ROUTINE BLOOD INVESTIGATIONS

The polymorphonucleocyte count is markedly elevated in severe disease, and is not related to a presence of infection

The blood glucose also may be high and associated with high levels of serum glucagon.

Liver enymes (AST, ALT and ALP) and bilirubin may also be elevated in pancreatitis induced by gallstones.

It should be stressed that the decrease in serum calcium seen in patients with acute pancreatitis is mainly related to the decreased serum albumin.

MCV shows some variation in ethanol and non-ethanol related causes of acute pancreatitis. Alcoholic patients tend to have higher MCV due to the toxic effects of alcohol on erythrocytosis in the marrow.

TRYPSINOGEN AND TRYPSINOGEN ACTIVATED PEPTIDE

Urinary concentrations of trypsinogen activated peptide, have been shown to correlate well with the severity of acute pancreatitis at admission, but its measurement by a manual enzyme immunoassay, combined with the limited stability of the TAP assay, restricts its usage as an emergency room test.

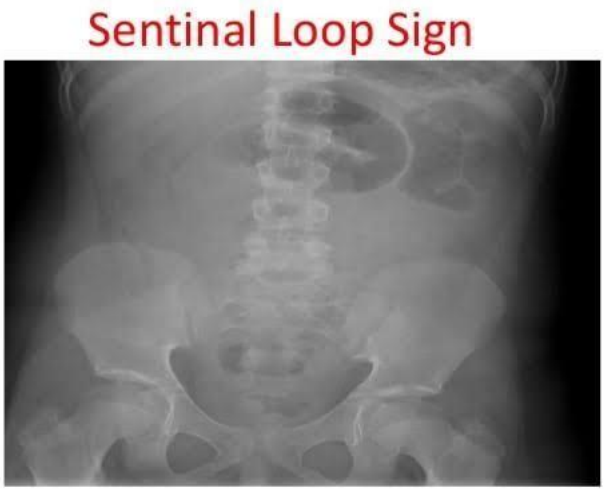
Higher positive likelihood ratio for the urinary trypsinogen-2 test strip than for CRP at 24 hours after admission, was confirmed in a multicenter trial led by Glasgow Johnson et al

TAP is cleaved from the amino-terminal end of trypsinogen when trypsin is activated. TAP is the most studied activation peptide in acute pancreatitis. Unfortunately, the TAP test kit is not commercially available, and therefore the TAP measurement is not a routine clinical measurement

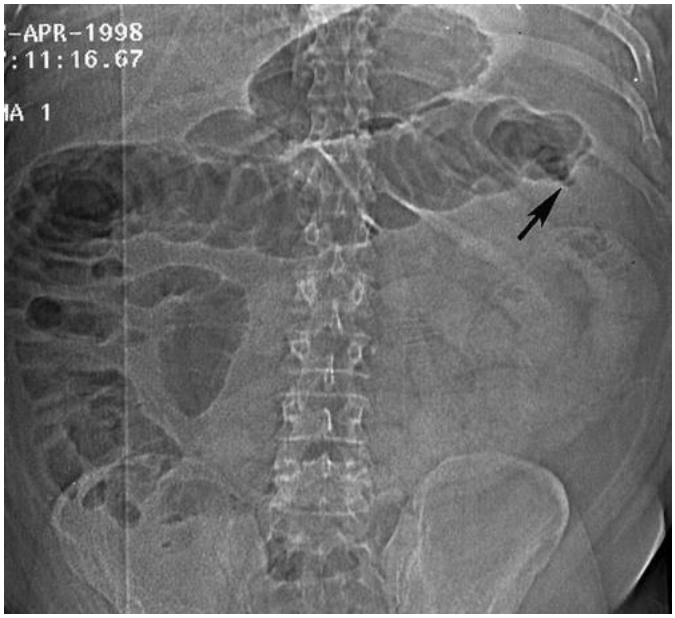
IMAGING

PLAIN X- RAY

Findings on a plain abdominal radiograph, can vary from no specific finding in mild disease to focal ileus of a segment of small bowel ("sentinel loop") or the "colon cut-off sign in severe disease.



A **sentinel loop** is a short segment of adynamic ileus close to an intra-abdominal inflammatory process. The sentinel loop sign may aid in localizing the source of inflammation. For example, a sentinel loop in the upper abdomen may indicate pancreatitis, while one in the right lower quadrant may be due to appendicitis.



Also, X-ray abdomen helps to exclude other acute abdominal pathologies, which may require immediate intervention.

Appearance of hollow viscus depends on the location as well as spread of pancreatic exudates. Gastric abnormalities are due to exudate in the lesser sac, causing forward displacement of the stomach, with separation of contour of the stomach from transverse colon.

Small bowel abnormalities are due to inflammation in near the small bowel mesentery, and include ileus of one or more loops of jejunum (the sentinel loop), of the distal ileum or cecum or the duodenum. Generalized ileus can occur in severe disease.

Spread of the exudate to specific areas of the colon, may produce spasm of that area of the colon with no air distal to the spasm (the colon cut-off sign), or dilated colon proximal to the spasm.

ULTRASOUND ABDOMEN

Abdominal ultrasound is useful in the initial 24 hours of admission, to identify gallstones, CBD dilatation due to choledocholithiasis, and ascites.

Ascites is commonly seen in patients with moderate to severe pancreatitis, as protein rich fluid extravasates from the intravascular compartment to peritoneal cavity.

Pancreas is uniformly enlarged and hypoechoic, and obscured by bowel gas. Ultrasound is used to serially monitor the size of pseudocyst.

CECT ABDOMEN

CECT is the most important mode of imaging in diagnosing acute pancreatitis as well as its intra abdominal complications.

The 3 main indications for a CT in acute pancreatitis are

1) To rule out other causes of acute abdomen
2) To stage the severity the disease
3) To identify complications of acute pancreatitis

Helical CT is the most common imaging used. CT taken after oral followed by intravenous contrast helps in identifying necrosis of pancreas.

If there is a normal perfusion of the pancreas, it could be due to interstitial pancreatitis and defects in perfusion is due to necrosis of pancreas.

A CECT abdomen has to be performed in patients who do not improve after the first week of symptoms

Pancreatic necrosis, may not be apparent on CT upto 48-72 hours after the onset of the disease.

The presence of air bubbles on CT denotes infected necrosis or pancreatic abscess

BALTHAZAR GRADING OF CT SEVERITY OF ACUTE PANCREATITIS

CTSI

Grading of pancreatitis

- A: normal pancreas: 0
- B: enlargement of pancreas: 1
- C: inflammatory changes in pancreas and peripancreatic fat: 2
- D: ill-defined single fluid collection: 3
- E: two or more poorly defined fluid collections: 4

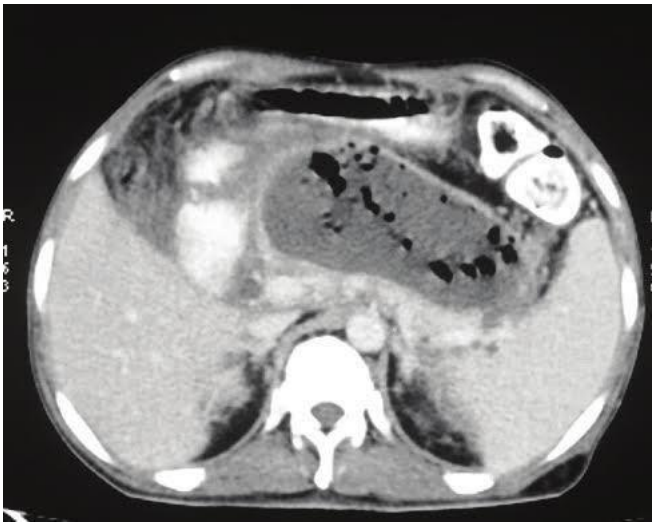
Pancreatic necrosis

- None: 0
- Less than/equal to 30%: 2
- > 30–50%: 4
- > 50%: 6

Early CT often fails to detect an evolving necrosis, which becomes well demarcated after about 48-72 hours after the onset of symptoms. CT is not very useful in diagnosing necrosis or in predicting the severity within 24 hours of onset of symptoms of illness.

The sensitivity of identifying pancreatic necrosis using CECT scan approaches 100%, 96 hours diagnosis.

CT scans also been useful as a diagnostic and therapeutic modality in infected pancreatic necrosis. Image guided aspiration of necrosis can be done, when the patient is not improving clinically or in patients who experience clinical decline.



MRI

MRI abdomen provides similar information CT, in identifying the severity of the disease. MRI is as good as CT in identifying necrosis and fluid collections. MRI is better than CT, and equal to EUS and ERCP in detecting choledocholithiasis. The use of IV secretin, before MRCP helps in better delineation of the pancreatic duct. This is particularly useful in the evaluation of patients with idiopathic and recurrent pancreatitis[30].

ENDOSCOPIC ULTRASOUND AND ERCP

EUS is not very useful early in acute pancreatitis. EUS during an attack of acute pancreatitis and weeks following an episode, shows signals indistinguishable from chronic pancreatitis and malignancy. However, after a month, particularly in patients with idiopathic interstitial pancreatitis, EUS may be helpful in identifying the presence of small tumours, pancreas divisum, and CBD stones. EUS is equivalent to MRCP and ERCP but far more sensitive than either abdominal ultrasound or CT in detecting common duct stones[31] . ERCPappears to be safe in acute pancreatitis if needed, such as in the setting of biliary pancreatitis, with raising serum bilirubin and biliary sepsis.

CLASSIFICATION OF SEVERITY

Various classification systems have been devised in the past

Feature	Acute Pancreatitis	Chronic Pancreatitis
Clinical characteristics	Clinically defined as an acute illness owing to inflammatory pancreatic disease that typically presents with abdominal pain and usually is associated with an increase in pancreatic enzymes in blood or urine Mild pancreatitis: if no multisystem failure occurs and no complications in recovery are seen Severe pancreatitis: if multisystem failure occurs or early or late local or systemic complications occur	Defined as a continuing inflammatory disease of the pancreas; typically presents with abdominal pain or features of pancreatic insufficiency; also can remain painless Only sign of an inflammatory process may be fibrosis, indicating earlier pancreatic inflammation
Morphologic characteristics	Early: subcellular changes Later: fat necrosis or pancreatic tissue necrosis, which may be associated with hemorrhage Complications Phlegmon: an inflamatory mass in or around the pancreas Pseudocyst: a localized collection of fluid containing high concentrations of pancreatic enzymes within, adjacent to, or remote from the pancreas Abscess: pus in or around the pancreas	Not clearly defined; characterized by "irreversible morphologic changes"; classification is based on results of imaging studies
Course	Acute pancreatitis may recur	Many patients may have acute exacerbations of pain

Modified from Sarner M, Cotton PB, 1984: Classification of pancreatitis. Gut 25:756-759.

Table 3. Types of fluid collections (Revised Atlanta Classification) [4].

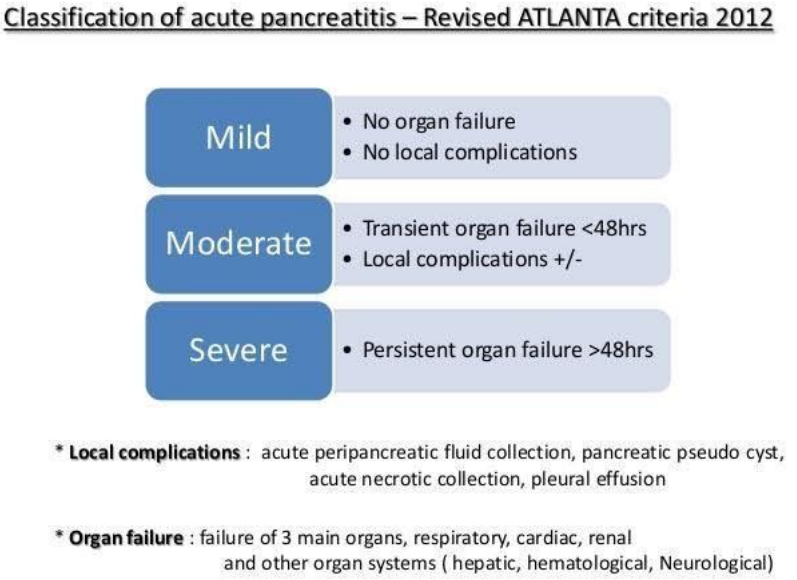
Type of Collection	Type of Pancreatitis	Description	CECT Criteria
Acute peripancreatic fluid collection (APFC)	Acute interstitial edematous pancreatitis	Areas of peripancreatic fluid seen within the first 4 weeks after onset. No associated necrosis	Homogeneous fluid density collection Confined by normal peripancreatic fascial planes. No definable wall encapsulating. Adjacent to pancreas (no intrapancreatic extension)
Pancreatic Pseudocyst	Acute interstitial edematous pancreatitis	Usually occurs more than 4 weeks after onset	Well circumscribed, usually round or oval Homogeneous fluid density. No non-liquid component Well defined wall; completely encapsulated
Acute Necrotic collection (ANC)	Acute necrotizing pancreatitis	Usually occurs less than 4 weeks after onset	Heterogeneous, non-liquid density of varying degrees (some appear homogeneous early in the course). No definable wall encapsulating the collection Location: Intrapancreatic and/ or extrapancreatic
Walled off-necrosis (WON)	Acute necrotizing pancreatitis	Usually occurs more than 4 weeks after onset	Heterogeneous, liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous). Well defined wall; completely encapsulated. Location: Intrapancreatic and/or extrapancreatic

The most widely accepted classification system for severity in acute pancreatitis, the Atlanta classification, was reported in 1992. Atlanta 1992 classification, divides acute pancreatitis into two groups: mild and severe.
Severe disease is defined by the presence of organ failure, local pancreatic complications on imaging (acute fluid collection, pancreatic necrosis, pseudocyst and pancreatic abscess), and/or poor prognostic scores

(Ranson's ≥3 and/or 54 APACHE-II≥8). Atlanta 1992 has offered a universally applicable classification system, that successfully served clinical studies and helped in the comparison of data from different centers for over 20 years.

Due to limitations in the 1992 Atlanta classification of acute pancreatitis, and improved understanding of the pathogenesis of acute pancreatitis, the 1992 classification has been updated.

The revised of the Atlanta classification (Atlanta 2012) divides acute pancreatitis severity into three groups: **mild, moderate, and severe.**



Mild acute pancreatitis which is characterized by absence of organ failure and local or systemic complications.

Moderately severe acute pancreatitis which is characterized by transient organ failure (resolves within 48 hours) and/or local or systemic complications without persistent organ failure (> 48 hours).

Severe acute pancreatitis which is characterized by persistent organ failure that may involve one or multiple organs.

In the early phase, this is based on clinical parameters, whereas in the following weeks, this subdivision is based on a combination of clinical parameters and morphologic complications, either requiring an active intervention (surgical, endoscopic, radiologic) or other supportive measures (like need for vasopressors, ventilatory support, or renal dialysis).

Necrotizing pancreatitis is defined as the "The presence of parenchymal necrosis and/or necrosis of peripancreatic fat."

The updated Atlanta classification, includes patients with peripancreatic necrosis only (that is, without necrosis of pancreatic parenchyma) in the category of Necrotizing Pancreatitis.

Edematous interstitial pancreatitis usually runs a mild course, but a small subset of patients suffer a fulminant attack and die within 2 to 5 days; these patients have severe disease, but do not meet criteria of necrotizing pancreatitis.

EARLY AND LATE ORGAN FAILURE

Acute pancreatitis runs a biphasic course. The first phase, is characterized by a systemic inflammatory response syndrome (SIRS) which lasts for about 2 weeks. The second phase, is characterized by a counter-active anti-inflammatory response syndrome (CARS), which is characterized by a state of immune suppression. Organ failure in the SIRS phase is considered not to be due to infection, but rather due to severe systemic inflammation. Organ failure in the CARS phase, is related to secondary infections, like infected pancreatic necrosis. Infections do occur in the SIRS phase, but bacteremia and (ventilator-associated) pneumonia are common. Organ failure can affect any organ system, but the 56 pulmonary and the cardiovascular systems are predominantly affected. Organ failure in the SIRS phase, is diagnosed at a median of 2 days after admission, but can be present even at admission. Half the patients who die from acute pancreatitis, suffer from organ failure but not from infected pancreatic necrosis. 3 typical scenarios in which organ failure presents, include the following:

1) Early-onset organ failure (week 1), intensive care admission, followed by improvement with supportive care and intensive care treatment (weeks 2 through 3). In the weeks to follow (weeks 3 through 5), clinical deterioration occurs. This sequence of events is highly indicative of infected necrosis.

2) Without early organ failure, clinical stability is suddenly complicated by deterioration in 3rd to 4th week of admission. Again, the chances of infected necrosis as the cause of clinical deterioration are high.

3) Early-onset organ failure does not improve, even after 2 to 3 weeks of supportive therapy, in the intensive care unit. In this case, a fineneedle aspiration (FNA) of one of the collections is done to differentiate between persistent SIRS or infected necrosis and to determine the need for intervention. If, however, gas bubbles are seen on CECT scan, no further diagnostic procedure is required, and an intervention to treat the source of infection needs to be planned.

SCORING SYSTEMS

1) RANSON'S SCORING SYSTEM

The earliest scoring system designed to evaluate the severity of acute pancreatitis was introduced by Ranson and colleagues in 1974[32]. It predicts the severity of the disease based on 11 parameters, which are obtained at the time of admission and or 48 hours later. The mortality rate of acute pancreatitis, directly correlates with the number of parameters positive. Severe pancreatitis is diagnosed, if three or more criteria are fulfilled. The original criteria was analyzed in patients who primarily suffered from alcoholic pancreatitis, which was modified 8 years later, for those patients with gallstone pancreatitis. Higher Ranson's scores predicts a more severe disease.

Ranson's criteria
At admission or diagnosis
Age over 55 years
White blood count over 16,000/cu mm
Blood glucose over 200 mg/dl
Serum Lactic dehydrogenase (LDH) over 350 U/l
Serum glutamic oxaloacetic transaminase (AST) over 250 U/l
During initial 48 h
Hematocrit fall greater than 10% points
Blood Urea nitrogen rise more than 5 mg/dl
Arterial Po_2 below 60 mm Hg
Serum calcium below 8 mg/dl
Base deficit >4 meq/l
Estimated fluid sequestration more than 6000 ml

Mortality rate in mild pancreatitis (scores 3) it is 62%.

The incidence of local and complications of acute pancreatitis correlates with Ranson's score. This criteria is still widely used in the United States and Europe.

The Ranson criteria has several setbacks, which include

1. The criteria is complicated
2. There are two different lists based on the etiology
3. It takes 48 hours to fully calculate the criteria
4. Validation beyond 48 hours has not been studied
5. Some of the parameters in the criteria are not widely used routinely

The overall sensitivity of the Ranson criteria is only 40% to 88%, and the specificity is only 43% to 90%. The positive predictive value is approximately 50%, and the negative predictive value around 90%.

2) IMRIE'S PROGNOSTIC CRITERIA:

During initial 48 hours ,
WBC count > 15000/mm3 Blood sugar > 10 mmol/L
Serum urea > 16 mmol/L (no response to IV fluids)
Po2 level < 60 mm Hg
Serum ca2+ level < 2 mmol/L
Lactic dehydrogenase> 600 IU/L
AST / ALT>200µm/l
Serum albumin level < 32 g/L

Ranson's and Imrie's scores indicate the severity at the time of admission and are not intended for monitoring the clinical course[33].

3) MODIFIED GLASGOW CRITERIA:

This one was useful in both alcoholic and biliary pancreatitis 27. The score ≥ 3 means severe disease requires ICU care.

P - PaO2 < 60 mmhg
A - Age more than 55 years old
N - Neutrophilia with WBC count>15x109/L

C - Ca2+< 8 mg/dl
R - Renal function, Urea >16mmol/L or > 45 mg/dl
E – Enzymes:- serum LDH >600 IU/L; AST>200 IU/L
A – Albumin
S sugar 10mmol/L or >180 mg/dl

4) AGA GUIDELINES

1. The American Gastroenterological Association (AGA) has issued guidelines for assessing the severity of pancreatitis.

A. Prediction of severe disease be performed using the APACHE II system (using a cutoff of ≥ 8) (calculator 1).

B. Those with actual or predicted severe disease and those with other severe comorbid conditions should be considered for triage to an ICU or intermediate medical care unit.

C. In patients with predicted severe disease (APACHE II score of ≥8) and those with evidence of organ failure during the initial 72 hours, rapid-60 bolus CT should be performed after 72 hours of illness to assess the degree of pancreatic necrosis. CT should be used selectively based upon clinical features in patients who do not meet these criteria.

2. Laboratory tests can be used as an adjunct to clinical judgment and the APACHE II score. A serum CRP >150 mg/L at 48 hours is preferred.

5) APACHE II SCORING

It is abbreviated as Acute Physiology and Chronic Health Evaluation (APACHE II) score.
It is probably the most widely studied scoring system in acute pancreatitis. It has good negative predictive value and modest positive predictive value, in predicting severity of acute pancreatitis and can be performed daily. Decreasing values during the first 48 hours will suggest a mild attack, whereas increasing values suggest a severe attack. Studies suggest that mortality is less than 4% with a score < 8 and is 11 to 18% with a score > 8.
APACHE II provides a general measure of the severity of disease, based on the patient's age, previous health status, and 12 routine physiologic measurements. An APACHE II score of 8 or more, defines severe pancreatitis. It has the advantage of be used on a daily basis and has similar positive and negative predictive values as the Ranson score at 48 hours after admission.
The major advantage of the APACHE II scoring system, when compared to the other systems, is that, it can be used in monitoring patient's response to therapy. However, Ranson and the Glasgow scales are mainly meant to assess the severity at presentation.
The APACHE-II system assigns points for 12 physiologic variables, for age, and for chronic health status, in generating a total point score. The 12 variables are

1. Temperature
2. Heart rate
3. Respiratory rate
4. Mean arterial blood pressure
5. Oxygenation
6. Arterial pH
7. Serum potassium,
8. Serum sodium
9. Serum creatinine
10. Hematocrit
11. WBC count
12. Glasgow Coma Scale

Because age and severe chronic health problems reflect a diminished physiological reserve, they have been directly incorporated into APACHE
II.
The laboratory tests which are required are simple, routine and readily available.
APACHE-II scores on admission and within 48 hours help distinguish mild from severe pancreatitis and to predict death. Most patients survive if APACHE-II scores are 9 or less during the first 48 hours. Patients with APACHE-II scores of 13 or more have a high likelihood of dying.
It takes into account all the major risk factors that influence the outcome from the disease including the acute physiological derangements, as well as the patient's ability to recover which may be diminished by advancing age or chronic disease.
The range of the APACHE II score is wide, providing a better spread between the mild and severe attacks because varying weights are assigned to increasingly abnormal values, rather than all or no judgements.

At admission, sensitivity is 34% to 70%, and specificity is 76% to 98%. At 48 hours, sensitivity remains less than 50%, but specificity is close to 90% to a Score of ≥ 2 indicates presence of organ failure. These scores were calculated within 72 hours of hospitalisation. The organ failure was classified as[34]:
Transient (less than 48 hrs.)
Persistent (more than 48 hrs.)

6) BISAP (The Bedside Index for Severity in Acute Pancreatitis):

This new scoring system has been developed recently for early detection of patients with risk of in hospital mortality.
The BISAP score has been developed and validated retrospectively on a large population based study, done by Cardinal Health Clinical Outcomes Research Database, Marlborough, USA[35].
This score was published recently for clinical and research purpose, for its accuracy and reliability in patient stratification.
The BISAP includes:

1. Blood urea nitrogen (BUN) >25 mg / dl.
2. Impaired mental status (GCS < 15).
3. SIRS.
4. Age >60 years.
5. Pleural effusion

SIRS was defined by presence of two or more of the following criteria:

1. Pulse rate > 90/min.
2. Respiratory rate > 20/min or PaCO 2 < 32 mm Hg.
3. Temperature >100.4 F or < 96.8 F / < 36 or > 38 ° C.
4. WBC count >12,000 or < 4,000 cells/mm3, or presence of more than 10% immature blasts.

(SIRS - Systemic Inflammatory Response Syndrome) One point will be given for each variable present for a total of 5, score ranges from 0 to 5. The presence of a pleural effusion was determined by a CT scan, chest X ray or abdominal ultrasound obtained within 24 h of presentation. Imaging obtained within 24 h of presentation at the hospital of origin for transferred patients was also collected and reviewed.
A BISAP score of three or more has been found to have high mortality and have predicted the necrosis and organ failure very well39.

ADVANTAGES:

Simple and easy to calculate, usually done at the time of admission or within 24 hrs of hospitalization. The scores prediction ability was tested across 390 hospitals among large number (36,248) of populations, in contrast to other studies which were based on small number patients.

COMMONLY USED PREDICTIVE LABORATORY SCORING SYSTEMS AND THEIR CUTOFF FOR PREDICTED SEVERE PANCREATITIS

Predictive Score	Cutoff
APACHE II	≥8 in first 24 hours
BISAP	≥3 in first 24 hours
Modified Glasgow (or Imrie)	≥3 in first 48 hours
Ranson	≥3 in first 48 hours
Urea at admission	>60 mmol/L
C-reactive protein	>150 U/L in first 72 hours

MANAGEMENT OF ACUTE PANCREATITIS

GENERAL CONSIDERATIONS

Patients with acute pancreatitis need early and aggressive IV hydration to maintain hemodynamic stability and to adequately perfuse the kidneys and pancreas.
These patients need adequate analgesia to eliminate or significantly reduce the pain. The patient is usually kept nil per oral until any nausea and vomiting have subsided. Abdominal pain can be treated with opiate analgesics, often by a patient-controlled- anesthesia pump. Opiate dosage is monitored carefully and adjusted on according to on-going needs. Although morphine has been studied to increase the tone of sphincter of Oddi, and serum amylase, its use in treating the pain in acute pancreatitis has not been shown to affect outcome adversely[33].
Nasogastric intubation is not routinely used, because it has not been shown to be beneficial in mild pancreatitis. It is only used to treat gastric ileus or intractable nausea and vomiting. Similarly, routine use of proton pump inhibitors or H2 receptor blockers have not been shown to be very beneficial.

The patient should be monitored carefully for signs of early organ failure like hypotension, pulmonary failure, or renal failure by closely monitoring vital signs and urinary output. Tachypnea should not be assumed to be due to abdominal pain. Monitoring oxygen saturation and, if needed, arterial blood gas measurement is advised, and also oxygen supplementation is mandatory in case of hypoxemia. Patients who exhibit signs of early organ dysfunction should be transferred immediately to an ICU, as clinical deterioration can be rapid and fatal.

FLUID RESUSCITATION

Recommendations regarding aggressive volume replacement are based on expert opinion, laboratory experiments, and retrospective as well as prospective clinical trials[36-39]. As the inflammatory process progresses early in the course of acute pancreatitis, there is extravasation of protein rich intravascular fluid, into the general peritoneal cavity as well as retroperitoneum, resulting in hemoconcentration and reduced renal perfusion with associated elevation of blood urea nitrogen. Subsequently, the reduced perfusion pressure into the pancreas results in microcirculatory changes which cause pancreatic necrosis. Hence, an admission hematocrit greater than 44% and a failure of initial hematocrit to decrease at 24 hours, have been shown to be predictors of necrotizing pancreatitis.

An elevated or rising blood urea nitrogen is associated with increased mortality. Early vigorous IV fluid repletion to restore intravascular volume replacement is of foremost importance. The goal is to provide adequate intravascular volume to reduce the hematocrit and blood urea nitrogen, thus increasing pancreatic perfusion.

Ringer lactate may be the preferred solution for initial hydration. Due to its bicarbonate content and stable pH, this isotonic solution, may prevent the development of metabolic acidosis.

It is important to recognize that aggressive early volume repletion, will require caution in certain groups of patients (such as elderly patients or those with a history of cardiac and/or renal disease) to avoid complications, like volume overload, pulmonary edema, and abdominal compartment syndrome.

RESPIRATORY CARE

Hypoxemia (oxygen saturation <90%) requires oxygen supplementation, ideally by nasal prongs or by face mask if required. If nasal oxygen fails to correct hypoxia, or if there is respiratory fatigue and borderline respiratory reserve, early endotracheal intubation and assisted ventilation are required. It is important to use a Swan-Ganz catheter to identify if hypoxemia is due to congestive heart failure or due to primary pulmonary damage.

Acute respiratory distress syndrome (ARDS), is the most serious respiratory complication of acute pancreatitis. ARDS is associated with severe dyspnea, progressive hypoxia, and results in increased mortality. It usually occurs between the second and seventh day of onset of disease (but can be present at admission) and consists of increased pulmonary alveolar capillary permeability resulting in interstitial edema. Treatment for this condition is endotracheal intubation with positive end-expiratory pressure ventilation, with low tidal volumes to protect the lungs from volu-trauma.

ANTIBIOTICS

Antibiotics are not routinely indicated in mild acute pancreatitis. However, antibiotics would be appropriate in pancreatic sepsis (e.g., infected necrosis and, less often, abscess) and non pancreatic sepsis (e.g., line sepsis, urosepsis, or pneumonia).

A recent updated metaanalysis clearly demonstrated no beneficial effect in the routine use of systemic antibiotic prophylaxis[40].

NUTRITION

In severe acute pancreatitis, especially with pancreatic necrosis, 4 to 6 weeks of artificial nutritional support may be necessary. Formerly, TPN was the standard method of refeeding patients with severe acute pancreatitis. Enteral nutrition is cheaper as well as safer, and is preferred. Enteral nutrition is hypothesized to decrease small bowel bacterial overgrowth, and to improve intestinal mucosal barrier function, thus reducing bacterial translocation and resultant infectious complications. The optimal route for the administration of enteral feeding, either through a nasojejunal or a nasogastric tube is yet to be established.

ENDOSCOPY

The question of early removal of a possibly impacted gallstone in improving the outcome of gallstone pancreatitis remains a controversial issue.

SURGICAL THERAPY

Cholecystectomy is routinely performed in patients with gallstone pancreatitis, and a consensus conference suggested that in mild or severe gallstone pancreatitis, cholecystectomy should be performed as soon as the patient has recovered and the acute inflammatory process has subsided[41].

A second potential role for surgery in pancreatitis is to debride pancreatic necrosis (necrosectomy) or drain a pancreatic abscess.

Sterile necrosis from infected necrosis by FNA of the pancreas. Sterile necrosis can be managed non-operatively because the mortality of this condition without surgery is less than 5%. However, surgical therapy of infected pancreatic necrosis carries a substantial mortality of 15% to 73% The types of necrosectomy

operations that have been recommended include necrosectomy with closed continuous irrigation via indwelling catheters, necrosectomy with closed drainage without irrigation, or necrosectomy and open packing.

BILIARY PANCREATITIS

Gallstones are the commonest cause of acute pancreatitis all over the globe. Most patients will pass off the offending stone during early hours of acute pancreatitis, but they have additional stones which are capable of inducing episodes. The issue of when to intervene is controversial. General consensus favours either urgent intervention (cholecystectomy) within the first 48 to 72hours of admission, or a delayed intervention after 72 hours, during the same admission. Cholecystectomy and operative common duct clearance is possibly the best treatment for an otherwise healthy patient with obstructive pancreatitis. However, patients who are at a high risk for surgical intervention are treated by endoscopic sphincterotomy, with clearance of stones by ERCP.

In case of acute biliary pancreatitis, in which obstruction persists after 24 hours of observation, emergency endoscopic sphincterotomy and stone extraction is indicated. Routine ERCP for examination of the bile duct is not encouraged in cases of biliary pancreatitis, as the possibility of finding residual stones is low, and also the risk of ERCP-induced pancreatitis is high. Patients who are suspected of harboring an impacted stone in the distal common bile duct or ampulla should have a confirmation by radiologic imaging (CT, magnetic resonance cholangiopancreatography, or endoscopic ultrasonography) before intervention is planned.

TABLE 88-2 Treatment of Acute Pancreatitis in Various Clinical Scenarios

Clinical Situation	Advice	Exception
	WEEKS 1-2	
Predicted severe pancreatitis	Fluid supplementation based on urine production, enteral nutrition, adequate pain control. Not useful: routine antibiotic prophylaxis antioxidants, and oral probiotics.	
Abdominal compartment syndrome	Decompression laparotomy without accessing the retroperitoneum	Large amounts of intraabdominal fluid. In these cases percutaneous catheter drainage may be used but should lead to immediate clinical improvement.
Sterile necrosis (collections) and multiple organ failure	Treat organ failure. No evidence that necrosectomy and/or drainage of collections will improve outcome. There is evidence that drainage will increase the risk of infection.	Abdominal compartment syndrome, bowel ischemia, bleeding
	WEEK 3 AND THEREAFTER	
Infected necrosis (collections) without or with only partial encapsulation	If possible, postpone intervention using antibiotics	Rapid deterioration without treatable cause
Infected walled-off necrosis (collections)	Intervention according to the "step-up" approach, starting with (retroperitoneal) catheter drainage. If needed, followed by (minimally invasive) necrosectomy.	Lack of experience; if so, transfer the patient to a more experienced center

COMPLICATIONS

Complications are divided into local and systemic

LOCAL

- Fluid collections
- Pancreatic ascites/pleural effusion
- Pancreaticpseudocyst
- Pancreatic necrosis
- Infected pancreatic abscess
- Hemorrhage/pseudo aneurysm

SYSTEMIC A. PULMONARY

1. Pneumonitis, basal atelectasis
2. ARDS
3. Pleural effusion (L)

B. CARDIOVASCULAR

1. Hypotension
2. Hypovolemia
3. Sudden arrest &death
4. Nonspecific ECG (ST-T wave) changes
5. Pericardial effusion

C.HEMATOLOGIC

1. Hemoconcentration
2. Disseminated intravascular coagulopathy

D. GI hemorrhage
1. Acid peptic disease
2. Gastric erosion
3. Portal/splenic vein thrombosis with variceal bleed

E. RENAL
1. Oliguria
2. Azotemia
3. Renal vessel thrombosis

F. METABOLIC
1. Hyperglycemic state
2. Hypocalcemic state
3. Hyperlipidemia (triglyceridemia)
4. Metabolic encephalopathy
5. Sudden loss of vision (Purtscher's retinopathy)

G. CENTRAL NERVOUS SYSTEM
1. Acute psychosis
2. Fat embolism occlusion
3. Alcohol withdrawal syndrome (AWS)

H. FAT NECROSIS
1. Intra-abdominal saponification
2. Subcutaneous tissue necrosis

TABLE 2.

Possible Complications of Acute Pancreatitis

Local complications	Systemic complications
Edema	Shock
Fat necrosis	Pulmonary edema
Phlegmon	Pleural effusions
Pancreatic necrosis (sterile or infected)	Acute kidney injury or failure
Pancreatic abscess	Multiorgan system failure
Hemorrhage	Vascular leak syndrome
Thrombosis of adjacent blood vessels	Hemoconcentration
Fluid collections	Coagulopathy
Pseudocysts	Infection (bacteremia or sepsis)
Pancreatic duct rupture	Hypocalcemia
Pancreatic duct stricture	Hyperglycemia
Extension to nearby organs	Hypermetabolic state
Ileus	Splenic artery pseudoaneurysm

MATERIALS AND METHODS

Study design: Prospective study
Setting: Department of General Surgery, Tertiary Care Hospital,
The study was conducted after obtaining the Institutional Ethical Committee approval.

INCLUSION CRITERIA
Acute pancreatitis is defined as 2 or more of the following

- Characteristic abdominal pain.
- Increased levels of Serum amylase and/or lipase 3 times the normal value.
- Ultrasonography of the abdomen demonstrating changes consistent with acute pancreatitis.

Individual components of the BISAP scoring system

- BUN > 25 mg/dl

- Impaired mental status (Glasgow Coma Scale Score < 15) □S IRS-SIRS is defined as two or more of the following:

(1) Temperature of < 36 or > 38 ° C
(2) Respiratory rate > 20 breaths/min or PaCO2 < 32 mm Hg
(3) Pulse > 90 beats/min
(4) WBC < 4,000 or >12,000 cells/mm3 or >10% immature bands

- Age > 60 years
- Pleural effusion detected on imaging

BISAP, bedside index for severity in acute pancreatitis; SIRS, systemic inflammatory response syndrome.
One point is assigned for each variable within 24 hrs of presentation.
A CT or MRI or USG of the abdomen, obtained at any time in the first 7 days of hospitalization, is required to differentiate necrotizing from interstitial pancreatitis
Organ failure is defined as a score of ≥ 2 in one or more of the three (respiratory, renal, and cardiovascular) out of the five organ systems initially described in the Marshall score[42].
Organ failure scores were calculated for all patients during the first 72 hours of hospitalization based on the most extreme laboratory value or clinical measurement during each 24hrs period.
Duration of organ failure was defined as transient (≤ 48 hrs) or persistent (>48 hrs) from the time of presentation.

	SCORE				
SYSTEM	0	1	2	3	4
Respiration (PaO2/Fio2)	>400	301-400	201-300	101-200	<100
Renal (creatinine mg/dl)	<1.5	1.5-1.9	1.9-3.5	3.5-5	>5
CVS (systolic BP)	>90	<90, fluid responsive	<90, fluid unresponsive	<90 pH <7.3	<90 pH <7.2

For non ventilated patients, Fio2 can be calculated by

Supplemental oxygen (L/min)	Fio2
Room air	21%
2-3	25%
4-5	30%
6-8	40%
9-10	50%

EXCLUSION CRITERIA

- Proven cases of chronic pancreatitis.
- Hereditary pancreatitis.
- Acute pancreatitis patients with organ failure at or within 24hrs of Presentation

Period of Study : january2021 –october2021
Type of Study : Prospective study
METHODS
25 patients attending the general surgery department with clinical features of Acute Pancreatitis are evaluated clinically and subjected to laboratory and radiological investigations as per the designed proforma.
Data pertinent to the scoring systems will be recorded within 24 h of admission to the hospital.
Once diagnosis is established the patient disease severity will be assessed by BISAP scoring system
Sample Size :25Patients
Source of Study: Patients diagnosed as acute pancreatitis in department of General Surgery, Guru Gobind Singh Government Hospital. 25 of them are to be selected on the basis of non probability (purposive) sampling method

- 25 patients attending the General Surgery Department with clinical features of Acute Pancreatitis are evaluated clinically and subjected to laboratory and radiological investigations as per the designed proforma. Data pertinent to the scoring systems will be recorded within 24 h of admission to the hospital.
- Once diagnosis is established the patient disease severity will be assessed by BISAP Scoring system

Statistical Analysis: Appropriate statistical tools.

For each of 25 patients included in the study, BISAP scores were calculated by the Cardinal Health Data base system for BISAP scoring. Patients were classified to have mild or severe acute pancreatitis according to the definitions set by the Atlanta Classification guidelines (1992)[44]

Severe attack--Criteria for severity included:

1) presence of one or more local complications
- Pancreatic necrosis
- Pancreatic abscess
- Pancreatic pseudocyst

2) Presence of one or more organ failures:
- Shock (systolic BP< 90 mmHg).
- Pulmonary insufficiency (PaO2< 60 mm Hg on room air).
- Renal failure (Sr. creatinine> 2mg/dl after fluid replacement).
- Gastrointestinal bleeding (> 500 ml estimated loss of blood within 24 hrs.).
- DIC (thrombocytopenia and hypo fibrinogenemia and fibrin split products).
- Severe hypocalcemia (<8mg/dl).

Survivors were defined as patients discharged alive from the hospital and non-survivors were those who died from pancreatitis or its complications during hospitalization.

Biliary Pancreatitis was presence of gall stones/biliary sludge in the gall bladder or bile duct, which was documented by any radiological methods. Alcoholic Pancreatitis was considered, when the patient found to have regular high intake of alcohol daily, or if there was binge of alcohol consumption prior to the onset of illness and has no signs of other etiologies present. Idiopathic pancreatitis was the one with no identifiable etiological factor based on the history, or after initial investigations.

Patients were observed prospectively until discharge or death.

PROFORMA

Name:	MRD No.:
Age / Sex:	Date of admission:
Residence:	Date of Surgery:
Occupation:	Date of discharge:

CHIEF COMPLAINTS

A) ABDOMEN PAIN Mode of onset:
Site:
Character:
Duration:
Radiation:
Shift:
Aggravating factors:
Relieving factors:
B) NAUSEA
C) VOMITING Onset:
Frequency:
Content:
Color:
D) BOWEL HABITS Constipation:
Diarrhoea:
Blood in stool:
E) MICTURITION

F) HEMATEMESIS/MELENA
G) APPETITE
H) FEVER
I) LOSS OF WEIGHT
J) OTHER COMPLAINS, IF ANY AND THEIR CHARACTERISTICS **PAST HISTORY:**
Similar complaints in the past
Tuberculosis/diabetes/hypertension/jaundice/IHD
Or any chronic illness
Drug history
Bleeding disorder/blood transfusion/BTR
Any previous surgery
FAMILY HISTORY
PERSONAL HISTORY
Diet
Sleep
Appetite-normal/decreased
Bowel Habits-regular
Altered-constipation/diarrhea/tenesmus
Bladder habits
Addiction
OBSTETRIC HISTORY
MENSTRUAL HISTORY- LMP/menstrual complaints
Cycle-regular/irregular
EXAMINATION FINDINGS:
A. General examination Consciousness and orientation:
Nourishment:
Pallor:

Icterus:
Cyanosis:
Clubbing :
Lymphadenopathy:
Pedal edema:
Bone / Joint / Spine:
VITAL DATA:
T-
P- BP- RR- SPO2-
GCS-
SYSTEMIC EXAMINATION (A) PER ABDOMEN EXAMINATION:
1. Inspection:
Contour and shape:
Bilateral symmetry:
Umbilicus:
Veins/Arteries:
Peristalsis:
Respiratory movements:
Any visible fullness/swelling:
2. Palpation:
Temperature:
Tenderness:
Rigidity/guarding:
Lump-
Organomegaly - liver/spleen/kidney Ascites- Hernia site-
Distension-
Any other significant finding-
3. Percussion:
Shifting dullness
Fluid thrill
Liver dullness
4. Auscultation:

Bowel Sounds or any abnormal sound

(B) Rectal Examination

Per rectal examination
Proctoscopy examination

INVESTIGATIONS:

A) BLOOD INVESTIGATIONS:

- HB:
- TLC:
- ESR:
- S.Creat:
- Blood urea:
- Random blood sugar:
- RVD;
- HBsAg/HCV:
- Liver function test

Bilirubin
Direct- Indirect-
SGPT
SGOT
Alkaline phosphatase

- Serum amylase
- Serum lipase
- Coagulation profile
- Serum protein(albumin/globulin/A/G Ratio)
- Blood urea nitrogen

B) IMAGING STUDY/RADIOLOGICAL EXAMINATION

X RAYS ABDOMEN(STANDING/LYING)
X RAY CHEST(PA VIEW)
ULTRASONOGRAPHY ABDOMEN AND CHEST CECT SCAN ABDOMEN

OBSERVATION AND RESULTS

This study was conducted in the Department of General Surgery, Tertiary Care Hospital for a period of 10 months. The 25 persons with features of acute pancreatitis who fulfilled the inclusion criteria were enrolled in this study after obtaining an informed consent

TABLE : 1 AGE DISTRIBUTION

AGE RANGE(YEARS)	NO.OF PATIENTS	PERCENTAGE(%)
1-10	1	4
11-20	1	4
21-30	9	36
31-40	3	12
41-50	3	12
51-60	3	12
61-70	3	12
71-80	2	8
Total	**25**	**100**

The peak incidence of the disease was noted in the 3rd decade of life

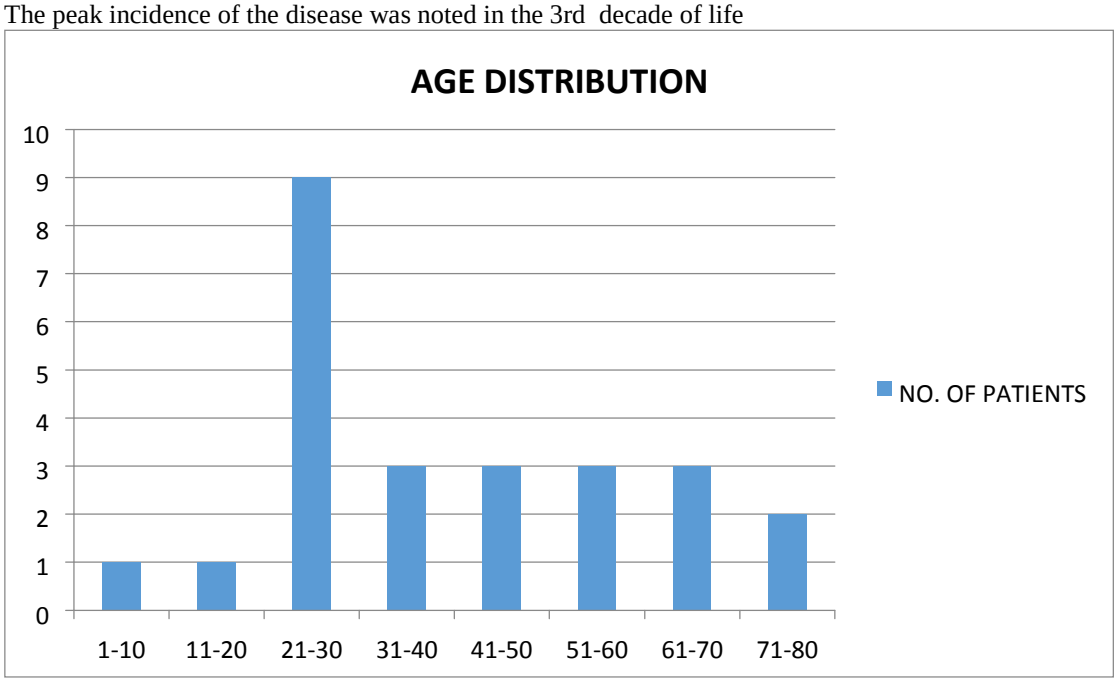


TABLE : 2 GENDER DISTRIBUTION

SEX	NP.OF PATIENTS	PERCENTAGE(%)
MALE	**21**	**84**
FEMALE	**4**	**16**
TOTAL	**25**	**100**

Out of 25 patients enrolled in this study there 21 male and 4 female patients
MALE:FEMALE :: 5:1

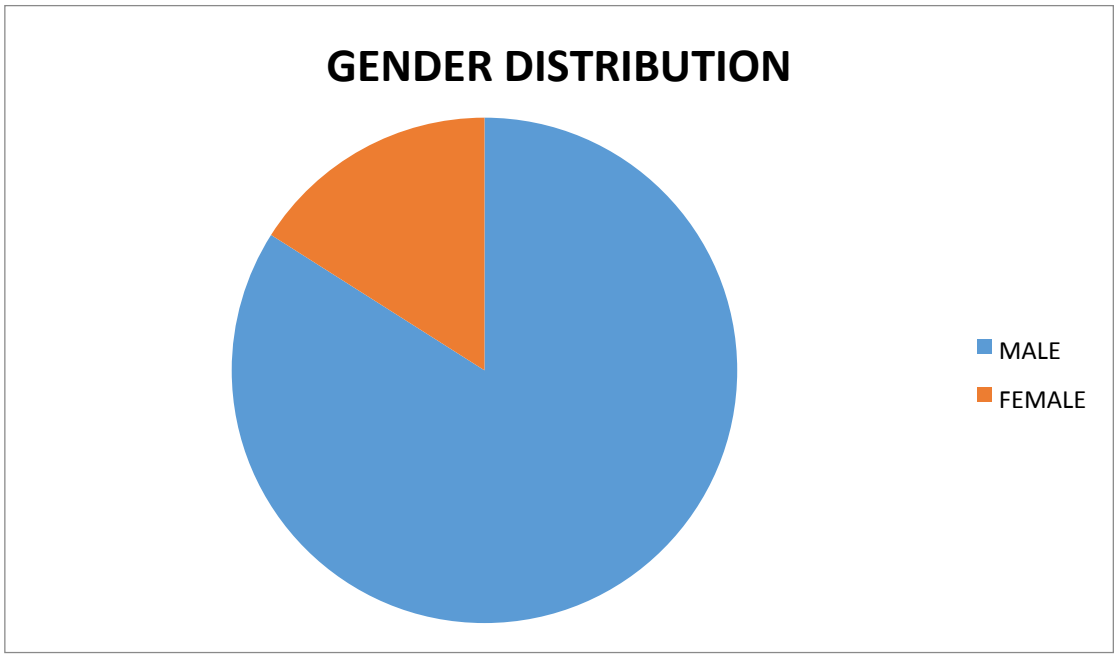


TABLE: 3 LENGTH OF HOPSITAL STAY

DAYS IN HOSPITAL	NO OF PATIENTS	PERCENTAGE%
1 DAY- 5 DAYS	1	4
5 DAYS- 10 DAYS	14	56
11 DAYS – 15 DAYS	9	36
15 DAYS-20 DAYS	1	4
TOTAL	**25**	**100**

The length of hospital stay ranges from 1 day to 20 days . The mean length of hospital stay was 9.2 days

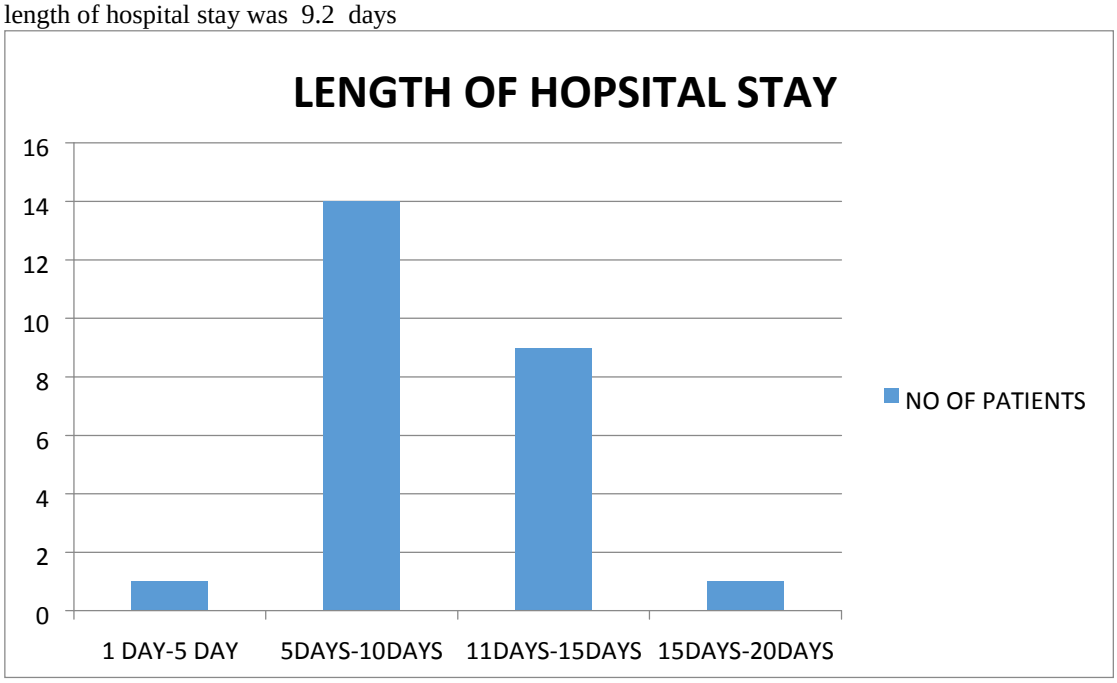


TABLE : 4 CLINICAL FEATURES

SYMPTOMS	NO. OF PATIENTS	PERCENTAGE(%)
PAIN IN ABDOMEN	25	100
FEVER	10	40
VOMITING	20	80
JAUNDICE	5	20

On clinical presentation,100% of patients were presented with the abdominal pain as chief complaint.

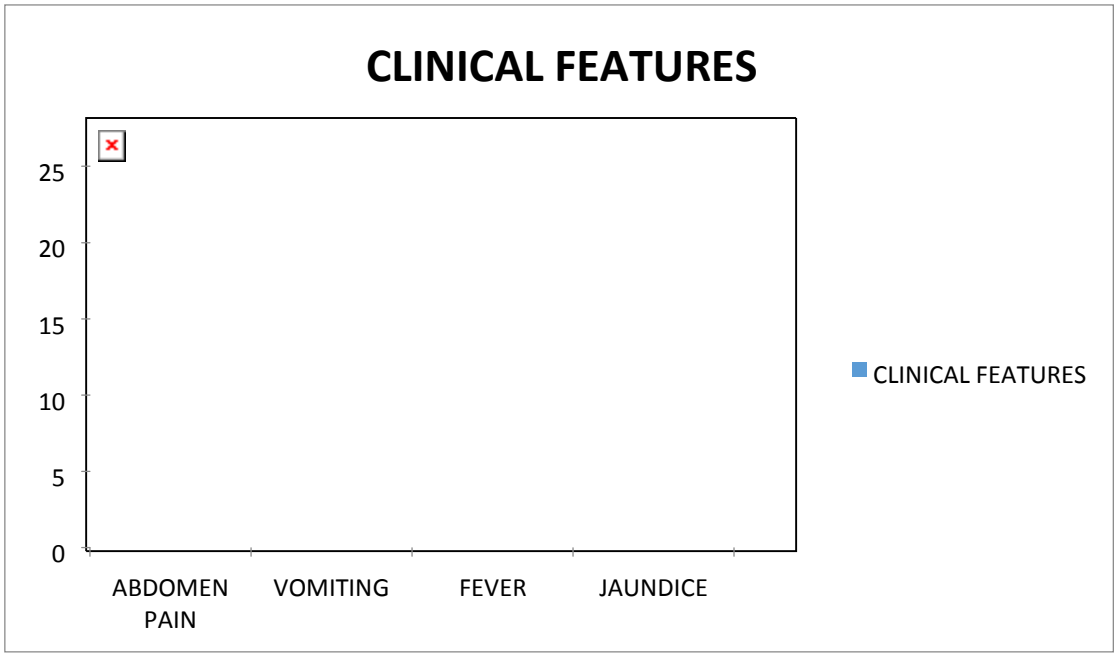
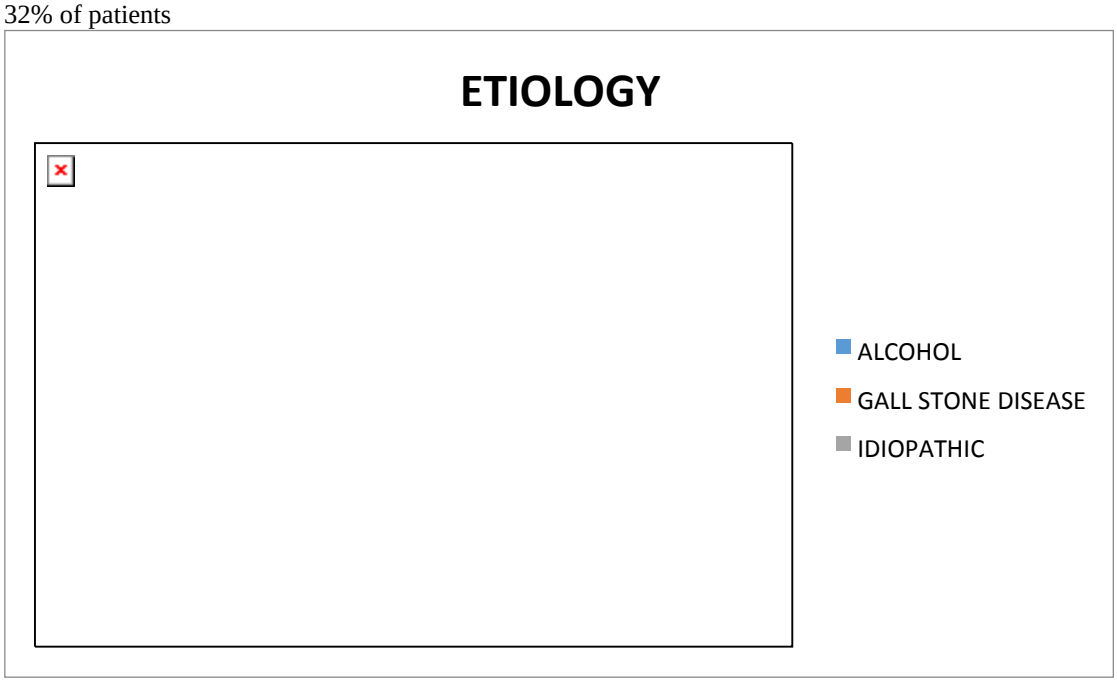


TABLE : 5 ETIOLOGY

ETIOLOGY	NO OF PATIENTS	PERCENTAGE(%)
ALCOHOL	12	48
GALLSTONE DISEASE	5	20
IDIOPATHIC	8	32

History of consumption of alcohol and the possibility of it being the etiology factor were found in 48% of patients. Gall stone disease was attributed in 20% of patients . No cause could be attributed in rest of the 32% of patients



SENSITIVITY AND SPECIFICITY OF BISHOP SCORING

TABLE : 6 - OUTCOMES

BISHOP	NO OF PATIENTS	ORGAN FAILURE	PANCREATIC NECROSIS	MORTALITY
<3	19	1	1	0
≥3	6	3	3	2

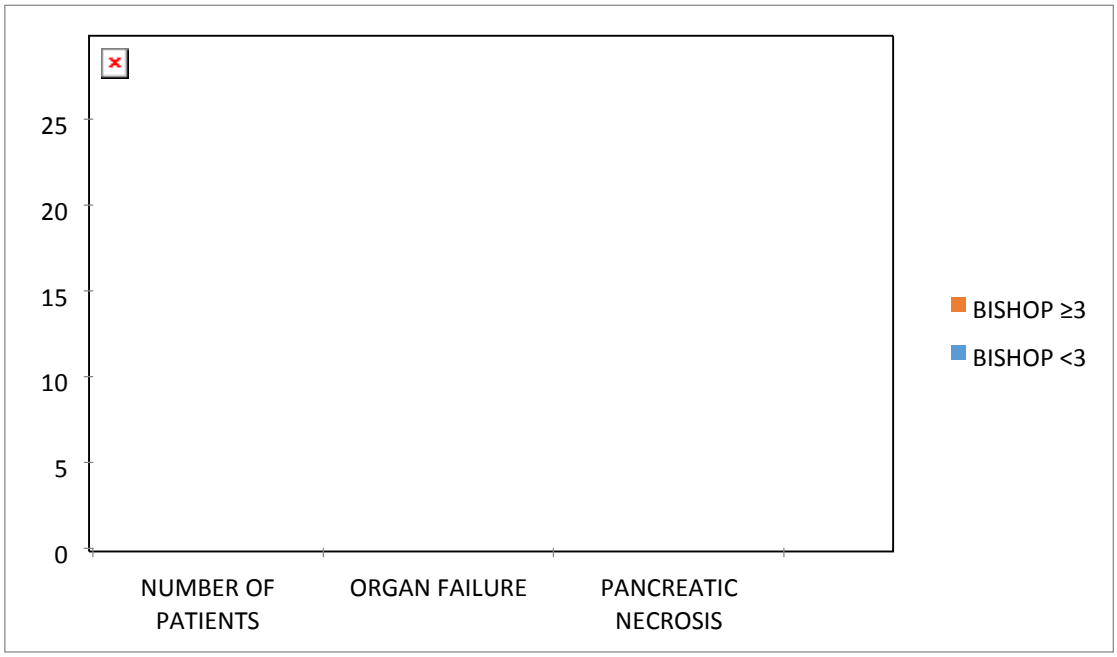
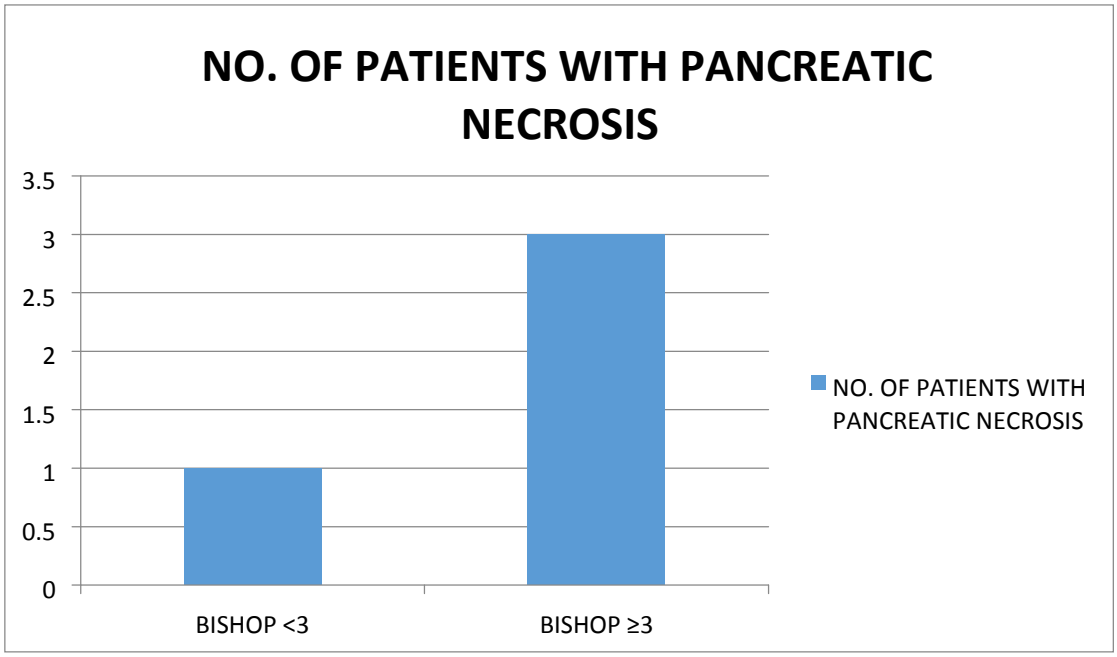


TABLE :7 NECROSIS

		NECROSIS		TOTAL
		YES	NO	
BISHOP SCORE	<3	1	18	19
	≥3	3	3	6
TOTAL	25	4	21	25

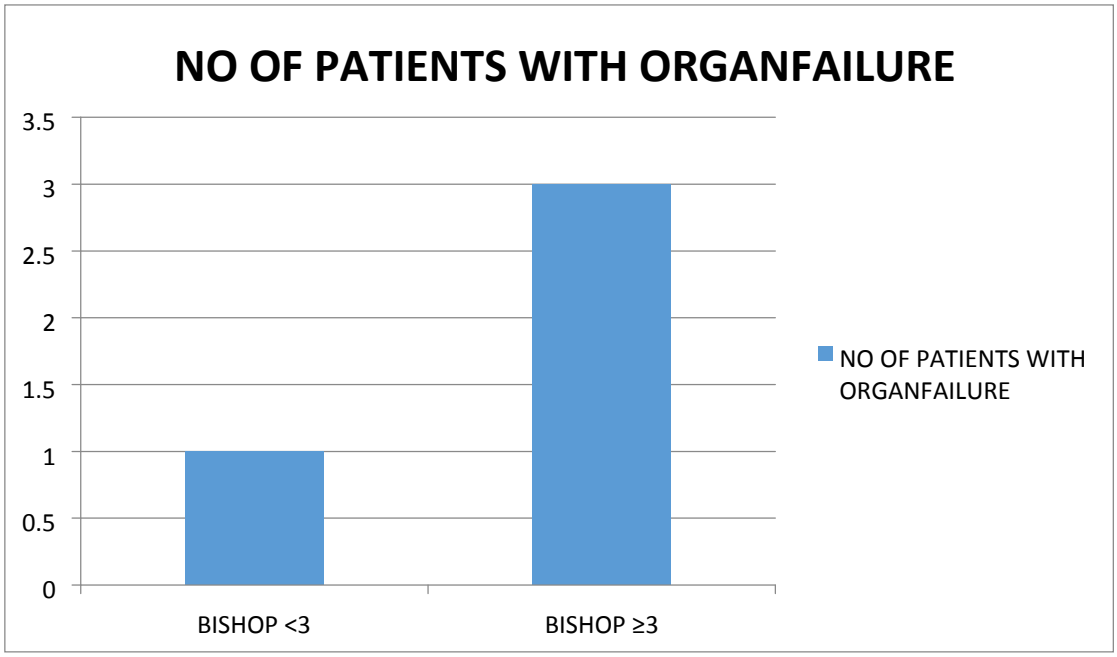


Parameter	Estimate
Sensitivity	50%
Specificity	94%
Positive prediction value	75%
Negative prediction value	85%
Diagnostic accuracy	94%

Out of 25 patients, 19 patients presented with mild acute pancreatitis and 6 patients presented with severe acute pancreatitis. Out of the 6 patients who presented with severe attack, 2 patients expired.
In mild group the BISAP score ranges from 0 to 2
In severe attack group the BISAP score ranges from 3 to 5.
The severity of acute pancreatitis was assessed by correlating the scoring systems with outcome in terms of organ failure, pancreatic necrosis and mortality, based on revised Atlanta classification system of acute severe pancreatitis.
Out of 19 patients presented with BISAP score<3, organ failure, pancreatic necrosis were presented in1&1patients respectively. There was no mortality in this group.
Of the 6 patients presented with score >3, 3 patient developed organ failure and 3 patient developed pancreatic necrosis. There were 2 mortalities in this group.

TABLE : 8 CORRELATION WITH ORGAN FAILURE

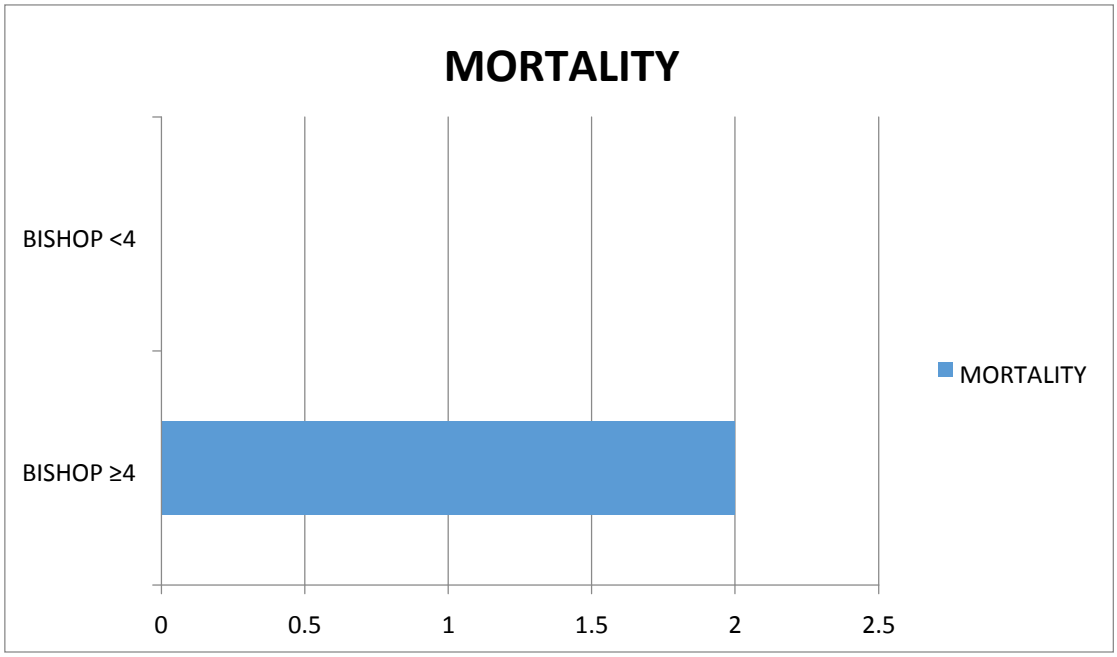
		ORGANFAILURE		TOTAL
		YES	NO	
BISHOP SCORE	<3	1	18	19
	≥3	3	3	6
TOTAL	25	4	21	25



Parameter	Estimate
Sensitivity	50%
Specificity	94%
Positive prediction value	75%
Negative prediction value	85%
Diagnostic accuracy	94%

TABLE : 9 - CORRELATION WITH MORTALITY

		M0RTALITY		TOTAL
		YES	NO	
BISHOP SCORE	≥4	2	-	2
	<4	-	23	23
TOTAL		2	23	25



Parameter	Estimate
Sensitivity	100
Specificity	100
Positive prediction value	100
Negative prediction value	100
Diagnostic accuracy	100

DISCUSSION

Acute pancreatitis is a relatively common disease with varied clinical presentations. Severe acute pancreatitis has a high morbidity and mortality rate. Early hospitalization and management according to disease severity maybe beneficial to identify those who require aggressive interventions to prevent the severe attack.

In this study, a relatively simple and bedside scoring system,

BISAP is studied to assess the severity in patients with acute pancreatitis.

An attempt also made to compare this study with previous similar studies done by others.

Acute pancreatitis was found to be 9 fold more common in males than females in this study. However this result did not exactly match with previous study results, Vikesh K. Singhet et al[44] (6:1), Papachristou et al[1] (5.1:1). This could be explained by alcohol ingestion being the commonest etiology in this study.

In this study, the mean age was 40.06 years which matches with the study of Sarath et al (40.8 yrs), and is comparable to the study done by Vikesh K. Singh et al[44] (49.6yrs), Papachristou et al (51.7yrs).

The mean age of non-survivors in this study was found to be 60.5 years as compared to survivors being 40.34 years. Taking 61 yrs of age as cut-off value, increasing age was found to be correlated well with **INTRODUCTIO N**increasing incidence of mortality. Thus age is considered as a significant contributory factor in predicting the outcome of severe acute pancreatitis. The most common etiological factor in this study was alcohol (48%) & matches with Bidarkundi et al[45](46.67%), but didn't correlate with results of Vikesh K. Singh et al[44] (21.4%), Papachristou et al (14%) in which gallstone disease found to be the most common cause, 27% & 36% respectively.

The mean length of hospital stay was 9.2 days in this study. In this study, increasing BISAP score was correlated well with the duration of hospital stay.

The most common presentation was predominantly abdominal pain (100%), followed by vomiting (80%), fever (40%) & other manifestations.

In this study, 19 patients were diagnosed to have mild acute pancreatitis and 6 patients found to have severe acute pancreatitis. All the 6 were correctly predicted by BISAP Score. The severity was assessed by correlating the scores with three factors: organ failure, necrosis and mortality.

Set cut off of BISAP score ≥3 was used to assess disease severity, based on previous studies done in this regard. 1) Papachristouet al[1] where AUC (0.81, 0.78) significant correlation with prediction of the occurrence of organ failure ($p < 0.01$), 2) Vikesh K. Singh et al[44] and B U Wu etal[46]

In this study, 3/6 with BISAP > 3 developed pancreatic necrosis. Sensitivity and specificity of predicting organ failure, in this study with a BISAP score of ≥ 3 was found to be 50% and 94% respectively, with a positive and negative predictive value of 75% and 85% respectively.
Diagnostic accuracy of this study was found to be 94%.
Sensitivity and specificity of predicting necrosis failure, in this study with a BISAP score of ≥ 3 was found to be 50% and 94% respectively, with a positive and negative predictive value of 75% and 85% respectively. Diagnostic accuracy of this study was found to be 94%.
BISAP ≥ 3 has significant correlation with prediction of pancreatic necrosis ($p<0.01$); (by Vikesh K. Singh et al) In this study, there was mortality in 2 patients. Both predicted by a score of >4. Cause of death in both patient was found to be MODS. The analysis for prediction of mortality showed a sensitivity of 100.00% and specificity of 100% respectively. Positive and negative predictive values in the study were found to be 100% and 100% respectively. Diagnostic accuracy of this study was found to be 100%, for a BISAP score of >4.
This matches well with BUWuetal[46], Papachristouetal, where specificity 87.6% PPV 15.4%, NPV 98.1%for BISAP and respectively.
BISAP ≥ 4 was found to be significantly associated ($p<0.04$) with high mortality
It was found to have high sensitivity ,specificity, PPV and NPV for mortality.
This again matches well with previous study by Vikesh K. Singh et al[44] and Papachristou et al[1]
In this study, 12% developed acute renal failure, 24% developed MODS, 16% developed septicemia .These complications were more likely
INTRODUCTION seen in patients with BISAP ≥ 3, hence concluded that these are the patients in high risk group, who requires intensive monitoring and probably early intervention if necessary.
BISAP score was found to have more sensitivity, specificity, positive and negative value, and diagnostic accuracy in predicting the severity of acute pancreatitis. Hence, BISAP score found to predict more number of patients, likelihood of progressing to severe disease. Larven et al stated in their study that, a prognostic scoring as say should preferably have high positive and negative predictive values or high negative predictive value to assess the severity of acute pancreatitis. Hence, BISAP is considered a simple and good bedside scoring system in predicting severity in acute pancreatitis.

LIMITATIONS OF THIS STUDY

- Small number of patients in this study.
- The etiology in this study were found to be different from world wide accepted one, hence might not be correct to compare with other studies.
- The GCS score used to assess the mental status of the patient gotadmitted were subject to inter observer variation.
- Recently, it has been suggested that severe acute pancreatitis may have variable disease progression; therefore the lack of predictability might be associated with this disease variability.
- Variation in timing of presentation of patients to the hospital after onset of symptoms may interfere with assessment of the scoring systems.

SUMMARY AND CONCLUSION

- From this study, Alcohol (54 %) was found to be the most common etiological factor for acute pancreatitis.
- Males were most commonly affected than female with a ratio of 5:1.
- The most common age groups of patients affected were in 4th decade of life.
- The overall mortality in patients with severe acute pancreatitis was 8%.
- The BISAP score predicted disease severity and mortality significantly in this study

From this study, we conclude that the BISAP score can be a simple, bedside and accurate clinical scoring system for the evaluation of disease severity in acute pancreatitis. Hence early identification and initiation of treatment can significantly alter the outcome.

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