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Severe Acute Pancreatitis and its Management

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Abstract

Severe acute pancreatitis (SAP) is a severe form of acute pancreatitis, which requires often intensive care therapy. The common aetiology varies with geographic locations. In Middle East, biliary pancreatitis is the commonest type. Initial phase of the disease is due to profound release of the proinflammatory marker, then the organ dysfunction takes over. It mainly divided into three types depending upon the pathological changes that are oedematous, necrotic and haemorrhagic. The common clinical presentation is typical abdominal pain radiating to the back and relieved by typical positioning i.e. sitting or leaning forwards. Raised pancreatic amylase and lipase with imaging will help to diagnose the SAP. The outcome of SAP is dictated by various criteria and scores. The commonly used scoring systems are Ranson's and Glasgow scores, whereas the local complication is diagnosed and predicted by the Balthazar's score. The management of SAP is mainly analgesia, prevention of complications and supportive care. Initially, laparotomy was recommended routinely for SAP complicated by necrosis of the pancreas and continuous lavage, but nowadays, minimal invasive image guided drainage is the recommended modality. The most common complications of concern are the abdominal compartment syndrome, Acute respiratory distress syndrome (ARDS), and infection of the pancreatitis necrosis. SAP has a high mortality rate (up to 40%), but initial aggressive supportive management will improve the outcome.

Keywords: analgesia, Balthazar score, Glasgow score, image guided drainage, Ransom Score, severe acute pancreatitis

1. Introduction

Acute pancreatitis is an inflammatory condition of the pancreas with a wide spectrum of pathological and clinical manifestations. It ranges from mild and self-limiting condition to severe pancreatitis with multiorgan failure with high mortality [1, 2].

It was one of the most frequent gastrointestinal causes of hospital admissions in the United States with a total of 275,000 admissions in 2009. In the United Kingdom, hospitals serving a population of 300,000–400,000 people admit about 100 cases each year. Patients with severe acute pancreatitis need ICU admission and multidisciplinary team approach for treatment. It increases the health care cost enormously, and those survive will live with pancreatic endocrine and exocrine dysfunction.

This chapter will focus mainly on severe acute pancreatitis.

2. Definition

Acute pancreatitis is an acute inflammatory process of the pancreas. It is an acute condition presenting with abdominal pain and is usually associated with raised pancreatic enzyme levels in the blood or urine as a result of pancreatic inflammation. It is a disorder of the exocrine pancreas and is associated with acinar cell injury with local and systemic inflammatory responses [3].

3. Classification

There is a wide range of classifications for acute pancreatitis. The Revised Atlanta Classification in 2012 classified acute pancreatitis according to the severity of the disease, morphology and temporal relation [1, 3].

3.1. Classification according to the severity of pancreatitis

Acute pancreatitis is classified into three forms based on the severity [3].

1. Mild acute pancreatitis, which is characterized by the absence of organ failure and local or systemic complications.
2. Moderately severe acute pancreatitis, which is characterized by transient organ failure (resolves within 48 hours and without persistent organ failure >48 hours) and/or local or systemic complications.
3. Severe acute pancreatitis, which is characterized by persistent organ failure that may involve one or multiple organs.

3.2. Classification according to the phases of pancreatitis

Temporally, two phases of acute pancreatitis are as follows:

(i) Early-first week

Only clinical parameters are important for treatment planning and are determined by the systemic inflammatory response syndrome (SIRS), which can lead to organ failure.

(ii) Late-after the first week

Morphologic criteria based on CT findings combined with clinical parameters determine the care of the patient [4].

3.3. Classification according to the morphology of pancreatitis:

Morphologically, there are three types of acute pancreatitis as follows:

- (i)** Acute oedematous (interstitial) pancreatitis
- (ii)** Acute necrotizing pancreatitis
- (iii)** Haemorrhagic

Usually, the necrosis involves both the pancreas and the peripancreatic tissues, less commonly the peripancreatic tissues alone and rarely the pancreatic parenchyma alone [1].

The commonest cause in the western world is gallstones (50%) and alcohol (25%). Rare causes (<5%) include drugs (for example, valproate, steroids, and azathioprine), endoscopic retrograde cholangiopancreatography, hypertriglyceridaemia or lipoprotein lipase deficiency, hypercalcaemia, pancreas divisum and some viral infections (mumps and coxsackie B4). About 10% of patients have idiopathic pancreatitis, where no cause is found [5]. The aetiological factors are enumerated in **Table 1**.

Aetiology of Acute Pancreatitis

Toxic Alcohol	Methyl alcohol Smoking Organophosphates Scorpion bite, certain spiders, Gila monster lizard
Mechanical obstruction/duct damage	Biliary pancreatitis—Cholelithiasis, Biliary sludge Malignancy—pancreatic, ampullary, cholangiocarcinoma Parasitic infections—ascariasis Periampullary diverticulum Penetrating duodenal ulcer, Duodenal obstruction
Trauma	Abdominal trauma—duct disruption
Metabolic	Hyperparathyroidism Hypertriglyceridemia Hypercalcaemia Diabetic ketoacidosis End-stage renal failure Pregnancy Post-renal transplant
Vascular	Necrotising vasculitis—SLE, Thrombotic thrombocytopenia Atheroma Shock
Immune-related—Auto-immune pancreatitis	Vasculitis—SLE, polyarteritis nodosa

Drugs	Corticosteroids, furosemide, tetracyclines, thiazides, oestrogen, valproic acid, Metronidazole, pentamidine, nitrofurantoin, erythromycin, methyldopa, ranitidine 5-ASA/salicylates, azathioprine/6-MP, didanosine, pentamidine, L-asparaginase
Infections	
Viral:	Mumps, varicella-zoster, coxsackie, HSV, HIV
Bacterial:	Mycoplasma, Leptospira, Legionella
Parasitic:	Toxoplasma, cryptosporidium
Fungal:	Aspergillus
Miscellaneous/Idiopathic	Post-ERCP pancreatitis Pancreas divisum in some patients Ischaemia, hereditary pancreatitis is a rare familial condition

Table 1. Aetiology of acute pancreatitis.

4. Pathophysiology

The exact pathogenesis of acute pancreatitis is unknown, and there is an ongoing research at the molecular level. There are many pathophysiological hypothesis put forward to explain the processes. These hypotheses are based on the aetiology and risk factors. The final result of the pathophysiological process is activation of proteolytic enzymes (intra-acinar activation of trypsinogen) leading to breakdown of the junctional barrier between acinar cells and leakage of pancreatic fluid and enzymes into the interstitial space causing autophagy and autodigestion of acinar cells [2, 3]. **Diagram 1** depicts the hypothetical aetiopathogenic process of acute pancreatitis.

Three different phases can be seen during the pathogenesis of acute pancreatitis. The first phase is the acinar cell damage and death. The second phase is local inflammation of the pancreas. The third and final phase is the SIRS. The first two phases take place in the pancreas itself, while in the third phase causes the distant organ damage and extrapancreatic symptoms.

Pancreatic ductal obstruction and hypersecretion have been mentioned as factors that contribute to the initiation of the inflammatory process. Different pathophysiological mechanisms have been proposed for ethanol-induced pancreatitis. Explanations like ethanol-induced direct toxicity to the acinar cell, sphincter of Oddi dysfunction, hypertriglyceridaemia, free oxygen radical formation, and protein deposition within the pancreatic duct, which favours retrograde flow of enzymatic. These processes lead to activation of inflammation and membrane destruction. Newer hypotheses include ischaemia/reperfusion injury and enzymatic co-localisation. Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis: 1–3% develops pancreatitis, probably due duct disruption and enzyme extravasation. Patients at the risk of developing post-ERCP pancreatitis have sphincter of Oddi dysfunction or a history of recurrent pancreatitis, those who undergo sphincterotomy or balloon dilatation of the sphincter.

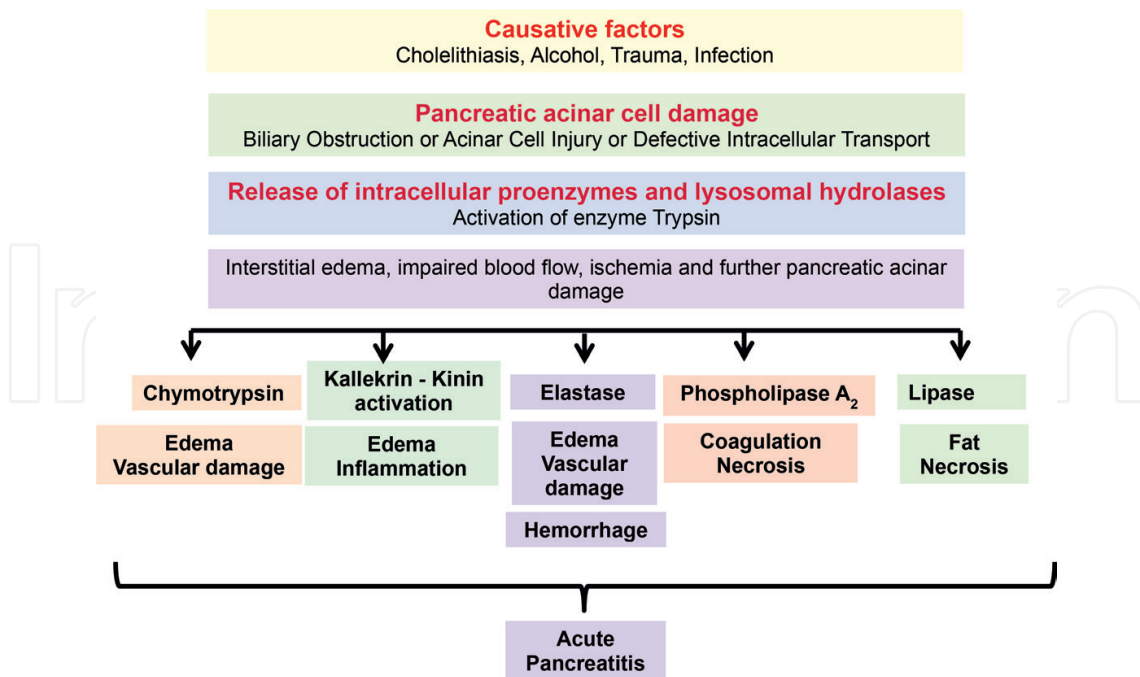


Diagram 1. Aetiopathogenesis of acute pancreatitis.

Systemic inflammatory response syndrome (SIRS) due to acute pancreatitis is because of the acinar cell death which releases activated pancreatic enzymes. This sets up a local inflammatory response which then activates systemic inflammatory response by release of cytokines, tumour necrosis factor, activation of immunocytes and the complement system activation [2–5].

5. Diagnosis of severe acute pancreatitis

5.1. Clinical presentation

Symptoms of acute pancreatitis are sudden onset of severe, persistent epigastric pain with or without radiation to the back. Radiation to the back is seen in about 50% of patients. It may be relieved by sitting or leaning forwards. Some patients complain of right upper quadrant pain. Pain is usually associated with nausea and vomiting.

5.2. Physical examination

Signs vary according to the severity of the disease. It ranges from mild epigastric tenderness to a diffusely tender abdomen.

Tachypnoea, tachycardia, and hypotension may be present. Fever due to inflammatory response. Acute swinging pyrexia suggests cholangitis. Icterus may be seen in biliary pancreatitis. Cullen sign, i.e. ecchymotic discoloration in the periumbilical area and Grey Turner sign, i.e. ecchymotic discoloration along the flanks due to bleeding into the fascial planes, but these signs are not specific for acute pancreatitis. Abdominal distension due to ileus, guarding in the

upper abdomen, free fluid may elicit shifting dullness. Pleural effusion is present in 10–20% of patients. Acute confusion due to metabolic derangement and hypoxaemia. Tetany is seen in some patient because hypocalcaemia [6, 7]

Perforated peptic ulcer, acute myocardial infarction, and cholecystitis should be rule out in differential diagnoses for acute pancreatitis.

5.3. Laboratory investigation

Serum amylase and lipase are both elevated in acute pancreatitis. The rise can be within 4–12 hours. The rise of >3 times the normal upper limit is the threshold for the diagnosis of acute pancreatitis [6, 7].

5.3.1. Serum amylase

It is an enzyme that hydrolyses the starch. The principal sources of amylase are the pancreas, salivary glands and fallopian tubes. Amylase has a shorter half life of 10 hours and returns to normal within 3–5 days. Hyperamylasaemia is seen in many other conditions. It may be increased in a number of other conditions like intestinal ischaemia and perforation, parotitis and acute renal failure, it is a less specific marker in acute pancreatitis. Its levels begin to rise 6–12 hours after the onset of acute pancreatitis, and they return to normal in 3–5 days. It has a high sensitivity (>90%) but a low specificity (as low as 70%) for the diagnosis of acute pancreatitis. Normal serum amylase level will not exclude acute pancreatitis if the patients present late to hospital [1, 6, 7].

5.3.2. Serum lipase

It a pancreatic enzyme that hydrolyses triglycerides. Its level increases within 4–8 hours of the onset and peaks at 24 hours and then returns to normal after 8–14 days. The rise in levels should be >3 times the upper limit of normal. It has excellent sensitivity in acute alcoholic pancreatitis. It is more specific than serum amylase for the diagnosis of acute pancreatitis. It has a sensitivity and specificity of 80–100% for acute pancreatitis. The principal sources of lipase are pancreas. The other sources are the tongue, liver, and intestine. These enzymes are useful in diagnosis of acute pancreatitis, but daily levels of these enzymes add no advantage in management. The levels are not useful in assessment of the severity of pancreatitis or decreasing levels are not marker of improvement. Simultaneous estimation of amylase and lipase levels does not improve accuracy [1, 6, 7].

5.3.3. Other lab data

In other laboratory investigations which help in etiological diagnosis are liver function test and serum triglycerides. Elevated liver enzymes, especially levels alanine transaminase Alanine Aminotransferase (ALT), level >150 U/L, it has a positive predictive value of 85% for gallstones. It will aid in diagnosis of acute biliary pancreatitis. Liver Function Test (LFT) should be done in all patients acute pancreatitis, patients within 24 hours of admission. C reactive Protein (CRP) levels will help in assessment of the severity of the disease process [5–7].

5.3.4. *Imaging*

The most commonly used imaging modalities in acute pancreatitis are transabdominal ultrasound, endoscopic ultrasound, dynamic contrast enhanced CT scan and Magnetic Resonance Cholangiopancreatography (MRCP). Imaging studies are not indicated for diagnosing acute pancreatitis as it does not predict disease severity at the time of presentation to emergency department. Imaging studies are indicated when there is diagnostic dilemma due to non-conclusive biochemical tests or because of the severity clinical condition or unexplained MODS, which warrants to rule out other intra-abdominal pathologies like gastrointestinal tract perforation and peritonitis.

It also helps in rule out other conditions during the differential diagnosis of acute pancreatitis. The role of CT scan and magnetic resonance imaging (MRI) lies in the detection of complications of acute pancreatitis, such as pancreatic necrosis, peripancreatic fluid collections or pseudocysts; the presence of these complications can also be used to predict the severity of the disease [6].

5.3.5. *Ultrasonography*

5.3.5.1. *Transabdominal ultrasound*

Transabdominal ultrasound is less sensitive and less useful to visualize the inflamed or necrotic pancreas. The distended abdomen because of the gas-filled bowel obscures the pancreatic view. It cannot assess the extent of necrosis.

It helps in detection of gall stones, which are found in about 50% patients with acute pancreatitis or dilatation of biliary tract secondary to obstruction.

Only indication of US scanning abdomen on presentation to emergency department is to rule out cholelithiasis as a cause for pancreatitis. Transabdominal ultrasound in later stages can help diagnosis of infection and therapeutic intervention-like guiding aspiration [6, 7].

5.3.5.2. *Endoscopic ultrasonography*

It is a combination of ultrasonography and endoscopic simultaneously. It is comparatively less invasive than endoscopic retrograde cholangiopancreatography (ERCP). It has a high sensitivity when compared to transabdominal ultrasound, especially in detecting the common bile duct microlithiasis and biliary sludge. It has a diagnostic yield of up to 88%. It helps in identifying patients who might benefit from endoscopic retrograde cholangiopancreatography and its therapeutic interventions. The added advantage of endoscopic ultrasonography is that it can be performed beside in unstable ICU patients, pregnant women where CT is contraindicated, and patients with metallic implants where MRCP is contraindicated [6, 7].

5.3.5.3. *CT scan*

Contrast-enhanced computed tomography is the gold standard to detect necrosis and to grade the severity of acute pancreatitis. This imaging modality also helps detecting local complication. CT scan findings range from localized oedema, pancreatic tissue inflammation (**Figure 1**), necrosis to extensive peripancreatic fluid collections (**Figure 2**).

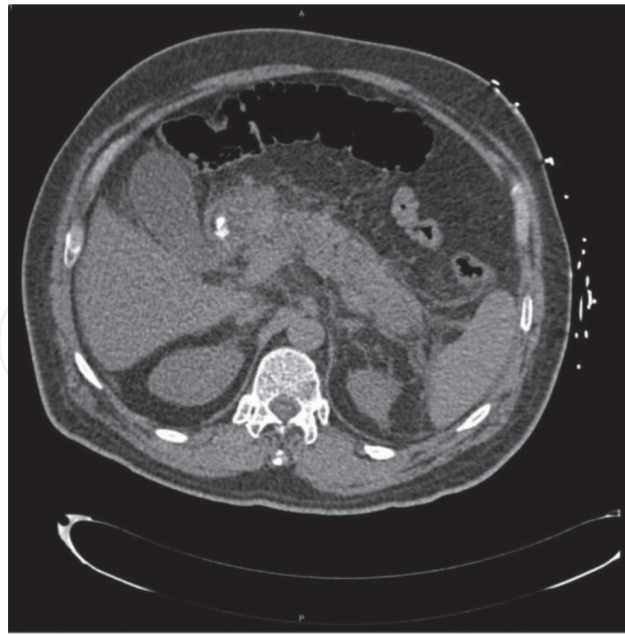


Figure 1. Oedematous pancreatitis.

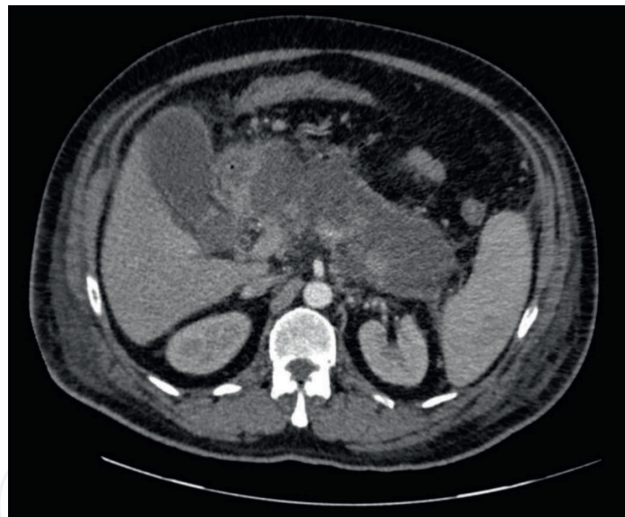


Figure 2. Pancreatic necrosis.

CT findings of acute pancreatitis are diffuse or segmental enlargement of the pancreas due to interstitial oedema and irregular contour. Contrast non-enhancement represents pancreatic necrosis which is heterogeneous in appearance, peripancreatic fluid collection. Whole pancreatic necrosis is rare, multifocal areas are common. Necrosis is seen after 96 hours from the start of symptoms. CT scan performed before 72 hours will underestimate the degree of necrosis. The necrosis pancreas is variable involving the periphery with preservation of the

core or involving the head, body, or tail separately or in combination. The outcome depends on the part of the pancreas involved. Necrosis of the entire pancreas has a relatively better outcome when compared to the head of pancreas involvement. Necrosis of the head of pancreas causes obstruction of the pancreatic duct there by an increase in pancreatic duct pressure causing to damage to acinar cells and leakage of destructive enzymes. Necrosis only in the distal portion of the pancreas has a favourable outcome and fewer complications [8]. **Figure 2** shows the CT image of pancreatic necrosis.

5.3.5.4. Efficacious use of computed tomography scanning in suspected acute pancreatitis

- (i) Patients in whom the clinical diagnosis is in doubt
- (ii) Patients with hyperamylasaemia and severe clinical pancreatitis **Figure 3** abdominal distension, tenderness, high fever ($>39^{\circ}\text{C}$), and leucocytosis
- (iii) Patients with Ranson's score >3 or the acute physiology and chronic health evaluation (APACHE) II >8
- (iv) Patients showing lack of improvement after 72 hours of initial therapy,
- (v) Acute deterioration following the initial clinical improvement [8].

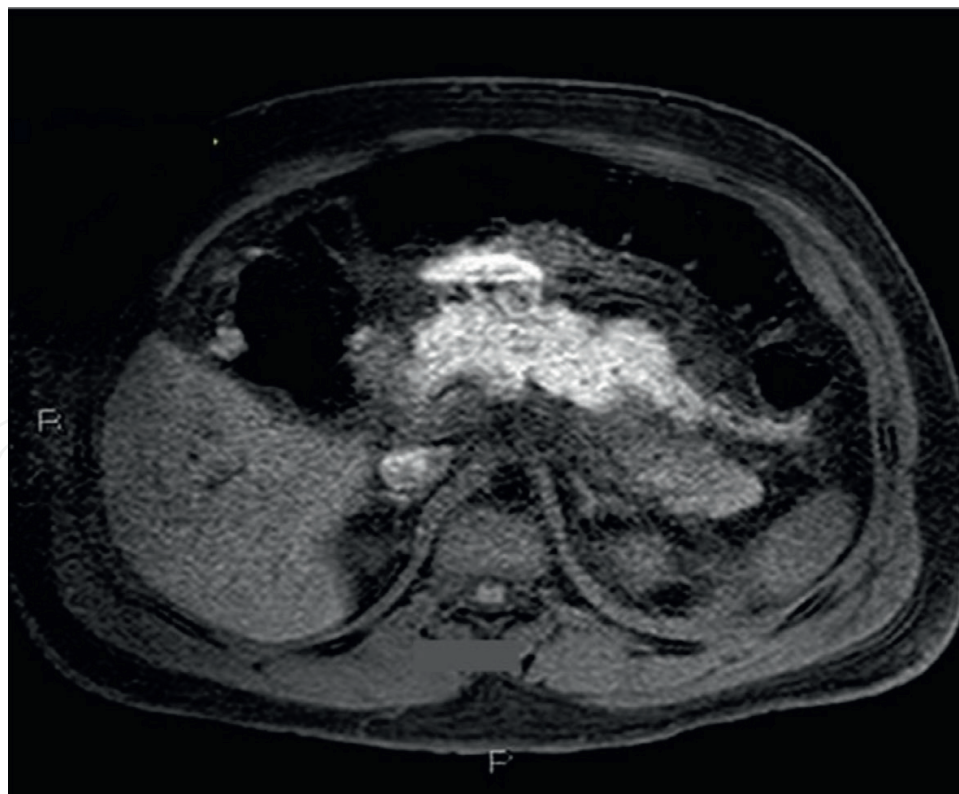


Figure 3. Haemorrhagic pancreatitis.

5.3.5.5. CT severity index

The modified CT severity index is a modification of the original CT severity index developed by Balthazar and colleagues in 1994. **Table 2** enumerates the details of the evaluation of Balthazar's computed tomography scoring system for acute pancreatitis.

The two factors that are useful in grading the severity of pancreatitis by CT are the extent pancreatic necrosis and the degree of peripancreatic inflammation. CT finding of necrosis and peripancreatic fluid collection strongly correlates with the complications (morbidity) and mortality [6, 7, 9, 10].

5.3.5.6. Grades of peripancreatic inflammation

- (a) Normal pancreas
- (b) Focal or diffuse pancreatic enlargement
- (c) Pancreatic gland abnormalities associated with peripancreatic inflammation
- (d) Single fluid collection
- (e) Two or more fluid collections and/or gas present in or adjacent to the pancreas [10].

Inflammatory process	Grade	score
Normal	A	0
Focal or diffuse enlargement	B	1
Contour irregularity		
Inhomogeneous attenuation		
Grade B plus peripancreatic haziness/ Mottled densities	C	2
Grade B, C plus one ill-defined peripancreatic fluid collection	D	3
Grade B, C plus two ill-defined peripancreatic fluid collection or gas	E	4
Necrosis		
None	0	0
<30%	0	2
50%		4
>50%		6

Notes: Total score: Total points are given out of 10 to determine the grade of pancreatitis and aid treatment:

0–2: mild

4–6: moderate

8–10: severe.

Table 2. Evaluation of Balthazar's computed tomography scoring system for acute pancreatitis.

Repeat scanning is only indicated if there is any deterioration in clinical condition to rule out/diagnose pancreatic necrosis, abscess or pseudocyst, haemorrhage, or bowel ischaemia or perforation.

5.3.5.7. *Magnetic resonance imaging (MRI)*

Magnetic resonance imaging (MRI) and MRCP are non-invasive imaging modalities. It has several advantages over CT, like no risk from radiation, can detect pancreatic duct continuity and parenchymal changes. It helps diagnose acute pancreatitis and identifying the aetiology of acute pancreatitis. MRI can accurately differentiate between necrotic and non-necrotic tissue.

5.3.5.8. *Magnetic resonance cholangiopancreatography*

It is especially useful to visualising the pancreatic duct and detecting lithiasis. MRCP is performed when ERCP has failed. The advantage of MRCP over CT scan is that iodinated contrast agents can be avoided and thereby avoid the risk for acute kidney injury.

Disadvantages of MRI and MRCP is transportation of critically ill patients to the MRI suite are limited access to patient during the acquisition of images and longer time to complete the study.

6. Assessment of severity

6.1. Why to assess the severity of the acute pancreatitis

1. To classify the disease process.
2. To predict the level of care needed, ICU or HDU for monitoring and supportive care.
3. To predict the outcome depending the severity of the acute pancreatitis, especially the mortality.
4. Select patients for specialised interventions as therapy to improve the outcome.
5. If patients are managed by the nonspecialist clinicians, then the scoring system will help them identify patients who need consultation and transfer to specialist centre.
6. For comparisons of severity within and between patient series.
7. In research for rational selection of patients for inclusion in trials.
8. It helps in intra-, inter-departmental and patient and patient family communication—using the same language.

Severity assessment should be carried out within 48 hours of diagnosis of acute pancreatitis. Patients with a body mass index over 30 are at higher risk of developing complications.

6.2. How to assess the severity of the acute pancreatitis

There are various scoring systems in vogue, using the clinical data, laboratory markers and radiological findings to assess and grade the severity of the acute pancreatitis. The scoring systems are of two types: one that correlates clinical features and lab indices and the other being the use of non-specific physiological scoring, namely, APACHE II and III. The commonly used scoring systems are the Ranson's criteria, Glasgow (Imrie) scoring systems, the APACHE II and III scoring systems (mainly used in ICU), the Simplified acute physiology score, bedside index of severity in acute pancreatitis (BISAP) scoring system, and the CT severity index. None of the scoring systems have a high sensitivity, specificity, positive predictive value or negative likelihood ratio. The scoring systems used at present are often inadequate in patients with severe Acute necrotizing pancreatitis (ANP), which is characterised by rapidly progressive multiple-system organ dysfunction [3, 4, 10].

6.3. Ranson's criteria

The Ranson's criteria were introduced in clinical practice in the early 1970s. It is the most widely used scoring system. Note that, 11 criteria are taken into account. **Table 3** enumerates the Ranson's criteria for assessment severity of acute pancreatitis. They were designed after analysis of 100 patients with alcohol-induced pancreatitis. It makes use of a combination of

Ranson's Criteria

Severity assessment

On admission

- Age > 55 years
- WBC > 16,000/ μ L
- Glucose > 11 (200 mg/dL)
- Lactate dehydrogenase (LDH) > 400 IU/dL
- AST > 250 IU/dL

After 48 hours

- Haematocrit fall > 10%
- Increase in urea > 1.8 mmol/L (>5 md/dL)
- Calcium < 2 mmol/L
- PaO₂ < 8 kPa (60 mmHg)
- Base deficit > 4 mmol/L
- Fluid deficit > 6 L

Risk factors mortality rate

- 0–2 < 1%
 - 3–4 \approx 15%
 - 5–6 \approx 40%
 - >6 \approx 100%
-

Table 3. Ranson's criteria for assessment severity of acute pancreatitis.

clinical and biochemical parameters obtained at admission and during the first 48 hours after admission. It reflects the extent of metabolic derangement and estimates the risk for mortality.

Drawbacks of the scoring system are that the study was only for alcoholic pancreatitis, do not take into consideration the ongoing treatment and predicts high mortality which is not the case in today's practice.

The Ranson's criteria have a sensitivity 74%, specificity 77%, positive predictive value 49% and negative predictive value 91% [3, 4, 10].

6.4. Modified Glasgow criteria (Imrie score)

A decade after the Ranson's criteria were introduced, a re-evaluation of those criteria was done and found that the eight of the criteria were most predictive of the severity and outcome. **Table 4** enumerates the modified Glasgow criteria (Imrie score) for assessment severity of acute pancreatitis.

Those eight criteria were renamed as Glasgow criteria or Imrie score. It's use is limited in Emergency department (ED) as some of the variables are only evaluated at 48 hours. The criteria excluded from the Ranson's criteria are Lactate dehydrogenase (LDH), base deficit, and fluid deficit, and these were found to be least contributory in assessment of severity and outcome [9, 10].

The Glasgow (Imrie) criteria are valid for both alcohol induced and biliary pancreatitis. A scores 3 or more after 48 hours of presentation indicates severe acute pancreatitis.

6.5. Other markers of severity

6.5.1. C-reactive protein

It is an acute phase reactant. It should be done after 48 hours of presentation. It can be used both for the assessment of severity and monitoring the progress of the disease. Levels more than 100 mg/L late in the first week after presentation indicate that patient is developing pancreatic

Modified Glasgow criteria

On admission

- Age > 55 years
- WBC > 15,000/ μ L
- Glucose > 10 ((no history of diabetes)
- PaO₂ < 8 kPa (60 mmHg)

After 48 hours

- Calcium < 2 mmol/L
 - Serum albumin < 32 g/L
 - Lactate dehydrogenase (LDH) > 600 IU/dL
 - AST/ALT > 600 IU/dL
-

Table 4. Modified Glasgow criteria (IMRIE SCORE) for assessment severity of acute pancreatitis.

necrosis. Procalcitonin will help identifying the pancreatic infection. IL-6, trypsinogen activation peptide, polymorphonuclear elastase, and carboxypeptidase B activation peptide can also be used for assessing the severity and monitoring the progress of the disease, but these are either used as a research tool or not yet routinely available.

Persistent high haematocrit is also an indicator of pancreatic necrosis and organ failure. If initial resuscitation is inadequate, then haemoconcentration is not a useful marker [3, 4, 10].

6.6. The acute physiology and chronic health evaluation (APACHE) II scoring system

The acute physiology and chronic health evaluation (APACHE) II is (Knaus et al.) used to quantify the severity of the illness in ICU patients. It contains 12 continuous variables, the age and the pre-morbid conditions (which reflect a diminished physiological reserve). Patients with an APACHE II score >8 have severe acute pancreatitis and are likely to develop organ failure. It can be used in monitoring the patient's response to therapy throughout the patient's hospital stay unlike Ranson's and Glasgow, which is assessed in the first 48 hours. Hence, it can assess both the severity and progress/deterioration. Disadvantages being that it is complex to perform and has been evaluated prospectively only in first 24–48 hours after the onset of pancreatitis. In criteria used, factors with most predictive value for mortality include advanced age, presence of renal or respiratory insufficiency and presence of shock. It has a sensitivity of 65%, specificity of 76%, positive predictive value of 43% and negative predictive value of 89%. APACHE III is also been used in predicting the severity of pancreatitis [10].

6.7. Bedside index of severity in acute pancreatitis (BISAP) score

BISAP score is a bedside scoring system with fewer variables than Ranson's criteria. The data used in scoring are the basic data recorded during the time of admission or taken from the first 24 hours of the patient's evaluation. **Table 5** enumerates the criteria of bedside index of severity in acute pancreatitis (BISAP) score for assessment severity of acute pancreatitis. It is a prognostic scoring system that predicts the mortality, whereas Ranson's score predicts

Bedside index of severity in acute pancreatitis (BISAP) score		
	Scores	
	1	0
BUN >25 mg/dL (8.9 mmol/L)	>25 mg%	<25 mg%
Abnormal mental status with a Glasgow coma score <15	Present	Absent
Evidence of SIRS (systemic inflammatory response syndrome)	2/4	Absent
Patient age	>60 years old	<60 years old
Imaging study reveals pleural effusion	Present	Absent

Table 5. Bedside index of severity in acute pancreatitis (BISAP) score for assessment severity of acute pancreatitis.

persistent organ failure. BISAP scores have the advantages over Ranson's and Glasgow scores of being calculated within 24 hours of admission, use fewer variables. BISAP score is higher in patients having SIRS, in older patients and in patients with altered mental status. It has the disadvantage that it cannot easily distinguish transient from persistent organ failure [3, 4, 10].

Patients with a score of zero predict a mortality of less than 1 whereas patients with a score of 5 predict a mortality rate of 22%. The way forward may be to use a combination of the Ranson's score, the radiological scoring systems and a descriptive organ failure score such as the sepsis-related organ failure assessment.

7. Management

Management of acute pancreatitis should be aggressive and begins early in the emergency department once the diagnosis is made. Initial resuscitation can affect the outcomes of acute pancreatitis significantly.

The treatment can be divided into three major parts as follows:

1. ICU admission and management
2. Treatment of the local complications
3. Treatment of the aetiology [2, 3, 8]

7.1. ICU/HDU admission

ICU/HDU admission is needed in patients with severe acute pancreatitis for close monitoring, organ support, and follow up. It is difficult to decide which patient is a candidate for ICU/HDU admission at the time of presentation. There is a lack of early and adequate predictors of impending organ dysfunction. But the patients present with signs of organ dysfunction like hypotension, respiratory insufficiency, coagulopathy (including Disseminated intravascular coagulation (DIC), and acute kidney injury are definite candidates for ICU/HDU admission. Other than organ dysfunction patients with severe metabolic derangements like hyperglycaemia, severe hypocalcaemia and patients with comorbidities like heart failure, chronic kidney disease where the acute on chronic organ dysfunction may develop are the candidates for ICU admission [10]

7.2. Monitoring

Monitoring a patient with acute severe pancreatitis can be divided into the following:

1. Monitoring of vital signs: Heart rate, blood pressure, respiratory rate, oxygen saturation, urinary output and level of consciousness
2. Biochemical evaluation of organ function: Blood gases, lactic acid, renal function test, coagulation profile, haematocrit, blood glucose and serum electrolyte levels, especially calcium,

magnesium, and liver function test. These test may alert impending organ dysfunction, improvement or worsening of the organ function

3. Development of local complications like pancreatic necrosis and infection, which are associated with increased morbidity and mortality.
 - a. Pancreatic necrosis is detected by contrast enhanced CT scan
 - b. Pancreatic infection needs repeated contrast enhanced CT scan with CT/US guided fine needle aspiration
4. Intra-abdominal pressure (IAP): Intra-abdominal hypertension (IAH) is related to the development of complications, especially necrosis and infection, bowel oedema. High IAP is one indication for intervention like aspiration or surgery [6, 7, 10].

7.3. Organ support

7.3.1. Cardiovascular dysfunction: hypotension and early fluid resuscitation

Hypotension is one of the most common presentations with acute pancreatitis. It is a sign of impending organ dysfunction. The hypotension is due to the third space loss secondary to the inflammatory response, this contributes to hypoperfusion and end organ perfusion dysfunction. Aggressive fluid resuscitation and rapid restoration of intravascular volume are the main stay of the treatment. It requires several liters of fluids. Both crystalloids and colloids can be used as resuscitation fluids. There is no evidence that colloids have any added benefit over crystalloids. Among the crystalloid, use of 0.9% sodium chloride is to be avoided. As it causes hyperchloraemic metabolic acidosis, which is associated with renal impairment, infections and activation of trypsinogen in a pH-dependent manner. Lactated Ringer's solution is a crystalloid, it is a balanced salt solution, It is fluid of choice it has been found to be less incidence of SIRS compared to normal saline. Both under resuscitation as well as over resuscitation can lead to adverse outcomes, hence very close monitoring is recommended. Over resuscitation can lead interstitial oedema, bowel oedema, Acute respiratory distress syndrome (ARDS) which can lead to organ dysfunction. Monitoring of fluids status should be done by physical examination (clinical condition, vital signs and urine output), volume responsiveness and dynamic parameters by sonography or invasive or semi invasive haemodynamic parameters. Metabolic indicators like serial measurements of blood urea nitrogen and haematocrit [11, 12].

7.3.2. Pulmonary dysfunction

Pleuropulmonary abnormalities are commonly associated with pancreatitis, respiratory dysfunction is rarely seen at the time of presentation to Emergency department (ED) but usually develops after fluid resuscitation. It manifests as acute lung injury or acute respiratory distress syndrome. It is one of the major components of multiple organ system dysfunction syndromes. Other manifestations are bilateral infiltrates, pleural effusion, pulmonary hypertension, and decreased thoracic compliance [11, 12].

7.3.2.1. *Pulmonary management*

Patients with acute severe pancreatitis should be monitored closely for early detection of failure. Respiratory support usually initiated by supplemental oxygen and mechanical ventilation is often required depending on the severity of respiratory dysfunction. Nasogastric decompression will decrease the distension and improve the compliance and prevent aspiration. Non-invasive ventilation is poorly tolerated in most of the patients because of abdominal distension and reduced functional residual capacity, careful selection of patient is warranted. Non-invasive ventilation is good choice to start with as it may avoid endotracheal intubation. Acute lung injury and Acute respiratory distress syndrome (ARDS) secondary to acute severe pancreatitis is similar to any other condition using lung protective strategies. Pleural effusion may need ultrasound-guided drainage. Good analgesia will help in chest physiotherapy, early physiotherapy will prevent atelectasis and related complications [11, 12].

7.3.3. *Pain relief*

Pain is one of the symptoms of acute severe pancreatitis. It causes discomfort and heightened sympathetic activity, impairment of oxygenation due to restriction of abdominal wall movement. Effective analgesia can be provided by the use of opioids and parenteral route, i.e. intravenous route is the preferred route. Analgesia may improve pulmonary dysfunction. In the past, morphine was supposed to exacerbate acute pancreatitis by promoting contraction of the sphincter of Oddi and increase pressure in the sphincter of Oddi dysfunction, but there is no good supportive evidence. Another modality of pain management is use of drugs like local anaesthetics through in epidural route [13, 14].

7.3.4. *Nutrition support in acute pancreatitis*

Acute pancreatitis is a catabolic and hypermetabolic pathophysiological condition. This disease process increases protein demand and the calorie requirements. This altered metabolic state is further deranged by poor oral intake due to pain, ileus or partial obstruction of the duodenum from pancreatic oedema. There are increased protein losses locally in the retroperitoneum due to inflammation and through pancreatic fistulae. These features may be compounded by the pre-existing malnutrition, e.g. in alcohol abuse [11, 12, 13].

If malnutrition and a prolonged negative nitrogen balance are not taken care, it may result in poor pancreatic healing, increased risk of infection, impaired immunity, gut dysfunction leading to translocation of bacteria. Nutritional care and therapy along with other therapeutic measures will result in faster recovery and better outcome.

Feeding during severe acute pancreatitis may be challenging. The questions to address during the initiation of the nutritional support are when? How? and what?

Earlier concept of feeding in acute pancreatitis: the pathogenesis of pancreatitis is assumed to be perpetuation of premature enzymatic activation. 'Resting the pancreas' the approach to avoid stimuli to exocrine secretion from the pancreas was thought to be most physiological method to treat the pancreatitis. Hence, parenteral nutritional was the preferred option

to avoid stimulation of the inflamed pancreatic gland. The other hypothesis is that systemic inflammatory response syndrome is caused by the absorption of the pancreatic endotoxins and ultimately leads to multiorgan failure. If the gut mucosal barrier is maintained, then it reduces the absorption of endotoxin. The present concept of nutritional support in acute pancreatitis: the preferred route of nutritional support is 'enteral route', it should be initiated as early as possible within 24–48 hours of presentation. Parenteral route is second choice, especially if the presentation is severe and it is unlikely to start oral intake within the next 5–7 days. The advantages of the enteral feeding are improved gut blood flow, maintenance of mucosal integrity and barrier function there by reduction in microbial translocation and pancreatic infection, and better glycaemic control, avoidance of central venous access-related complications are benefits of enteral nutrition. These benefits are translated in lower incidence of infections, multiorgan failure and outcome, i.e. mortality and length of stay when compared to parenteral nutrition [11–13].

7.3.5. Route of enteral nutrition

If nutritional support is supplemented by the enteral route, then it is usually delivered by tube feeding. There is a controversy about nasogastric versus nasojejunal feeding. But there is not much evidence to support any one over the other. Though traditionally nasojejunal feedings (to be delivered distal to the ligament of Treitz) have been preferred with the concept of less stimulation of the exocrine pancreas, cholecystokinin (CCK) cells that are present in the distal third part of the duodenum get stimulated when food passing through duodenum. It releases CCK that stimulates the pancreas and increased volume of pancreatic enzymes and bicarbonate secretion. This may worsen the course of the disease. Nasogastric tube feedings have now been shown to be as safe as the jejunal feeding. Nasogastric insertion can be at bedside. Fluoroscopy endoscopic (endoscopically placed guide wire) and specialist help is not needed. With the Nasogastric (NG) feeding, the standard precautions of aspiration like elevation of head end of bed should be followed.

The indication for nasojejunal feeds is when patients cannot tolerate gastric feeding due to ileus and slow bowel transit time. Nasojejunal (NJ) tube placement needs fluoroscopy, endoscopic, and specialist help. NJ tube may get displaced back into the stomach. Prokinetics and right-lateral positioning pass the tube through the into-duodenum. The correct positioning of the tube should be ascertained regularly by radiography [2, 7, 13].

7.3.6. Enteral nutritional supplements

No specific enteral nutrition supplement or immunonutrition formulation had any advantage. Low fat formulas with medium-chain triglycerides should be used enteral because it helps in better assimilation by direct absorption into the portal vein as there is lipase deficiency.

7.3.7. Complications of nutritional therapy

The common complications are metabolic and splanchnic. They are as follows:

Hyperglycaemia: Beta-cell death, peripheral insulin resistance irrespective of the route of feeding, needs monitoring of serum glucose and use IV insulin.

Hypertriglyceridemia is usually due to overfeeding. Monitor serum triglyceride level and titrate fat content.

Feed intolerance: Monitor abdominal pressure, bowel distension, residual volume and diarrhoea. Displacement of NJ tube [2, 9].

8. Pathogenesis of pancreatic infection and antibiotic prophylaxis

Infection is common in pancreatic necrosis, it occurs in approximately 40–70% of patients. Infection causes an increase in morbidity and mortality. There are various theories proposed for the mechanisms of infection in severe acute pancreatitis, namely bacterial translocation from the colon, via the biliary tree, especially in biliary pancreatitis, bacterial migration through the pancreatic duct from the lumen of the duodenum and haematogenous spread from bacteraemia due to other causes like infected central venous lines [5, 9, 10].

8.1. Role of antibiotic prophylaxis in severe acute pancreatitis

Prophylactic antibiotics in severe acute pancreatitis have been a topic of debate in the last 4–5 decades. Pancreatic necrosis more than 30% increases the chances of infection. The right choice of antibiotics is very important, those which have high penetration into pancreatic tissue. Carbapenems are both broad spectrum and excellent pancreatic penetration properties. Other antibiotics, which penetrate well in the pancreatic tissue, are cephalosporin, ureidopenicillins, fluoroquinolones, metronidazole and imipenem. Aminoglycosides have a poor penetration ability. Patients with mild pancreatitis do not benefit from antibiotics. In a meta-analysis by Sharma et al. [16], use of prophylactic antibiotics has shown mortality benefit in patients with Acute necrotizing pancreatitis (ANP) confirmed by contrast-enhanced CT (21–12.3%). Ref. [15, 16] prophylactic antibiotics use has not shown to decrease the need for interventional and surgical management but no effect on mortality.

8.2. Prophylactic antifungal therapy

Fungal infection in severe acute pancreatitis is associated with high morbidity and mortality. It has been noted that the incidence depends on the severity of the disease, extent of necrosis and use of broad spectrum antibiotic administration. Prophylactic use of fluconazole has shown to be effective in decreasing the morbidity but not the mortality [10].

9. Treatment of local complications

9.1. Pancreatic necrosis and abscess

The presence of non-viable tissue in the pancreatic parenchyma, which is detected by the non-enhancement on the contrast-enhanced CT, is called as pancreatic necrosis. It can be focal or diffuse with associated peripancreatic involvement. It can be sterile necrosis or get infected

in approximately 70% of the cases. The diagnosis of infection of the necrotic pancreas is difficult. Infected necrosis is diagnosed in the patients who show no signs of improvement, signs of sepsis (leukocytosis and fever are confounded by the SIRS), worsening of clinical condition, especially after improvement. The lab data to confirm the infection of the necrotic pancreatic tissue are not reliable. Biomarker like CRP is usually high in severe acute pancreatitis, but procalcitonin can be used as a marker, but still it is not specific because in patients who are critically ill, there are other infection like Central Line-associated Bloodstream Infection (CLABSI), Ventilator-Associated Event (VAE) (Ventilator-Associated pneumonia (VAP)), Catheter-associated Urinary Tract Infections (CAUTI), etc. wherein procalcitonin is raised.

The best method to confirm the diagnosis of infected pancreatic necrosis is CT/US guided fine needle aspiration, Gram's staining, and culture. Multiple samples from all pockets should be taken or sampling needs to be repeated. Pancreatic abscess is a collection of pus in close proximity to pancreatic necrosis, which develops as a local infection of the necrotic pancreatic tissue after severe acute pancreatitis.

9.2. Management of sterile pancreatic necrosis

Sterile pancreatic necrosis is usually managed conservatively (non-operatively). Earlier in the 1990s, all necrotic pancreatitis use to undergo necrosectomy. Surgical intervention in sterile pancreatic necrosis may increase the risk of infection and thereby an increase in the mortality. Patients with sterile pancreatic necrosis need close observation for evidence of infection. In selected patients with extensive necrosis may need surgical intervention if they do not improve for more than 6–8 weeks [3, 8, 11, 12].

9.3. Management of infected pancreatic necrosis pancreatic necrosis and abscess

Infected necrotic pancreatitis requires debridement and there is a consensus on surgical intervention in such cases. There is still a controversy about the best approach for debridement of the infected necrotic pancreatic tissue.

The aim of the intervention is removal of the infected necrotic substance. To achieve this goal, there are several techniques suggested. It ranges from drainage, debridement, lavage laparoscopy to laparotomy and packing.

9.4. Percutaneous drainage

- Anterior
- Retroperitoneal

This can be done when there are infected fluid collections or pus. It will be difficult to drain if it is just infected necrotic tissue or fluid/pus is too viscous. It has to be done CT/US guided and needs expertise. Complications are rare in expert hands. Usual complications with percutaneous drainage are bleeding, viscous perforation, fistula formation and super infection [3, 11, 12].

9.5. Surgical debridement/necrosectomy

- Minimally invasive
- Open surgical

These procedures can be performed transperitoneal or retroperitoneal which is decided on the location of necrosis and collections. Some patients need multiple sitting and planned relaparotomies. The open surgical approach carries higher risk of morbidity and mortality when compared to laparoscopic technique. There is higher risk of bleeding, perforation multiple organ failure, enterocutaneous fistula, incisional hernia, and new-onset diabetes mellitus [13, 14]

9.6. Management of the etiological factor

There is very few or nothing to do for the etiological management other than biliary pancreatitis. The treatments depend on the severity of the pancreatitis. In severe pancreatitis, there is no role of surgery. Surgery increases the morbidity and mortality. ERCP (endoscopic retrograde cholangiopancreatography) with sphincterotomy is indicated in patients with acute cholangitis. This will help in decreasing the pressure in pancreatic duct and lessens the severity of the disease. ERCP with sphincterotomy decreases the morbidity but not the mortality [13, 14].

10. Prevention of acute pancreatitis

Change in dietary habits and consumption of balance diet will prevent the gall stone formation, earlier cholecystectomy will prevent the recurrence of pancreatitis. Regular exercise, avoiding the high caloric intake, regular use of low fat diet will control the serum triglyceride levels and early introductions of statins will help in preventing the hyperlipidaemia associated pancreatitis. Moderation in alcohol intake will reduce the incidence of alcoholic pancreatitis [13, 14].

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