NARRATIVE REVIEW

Acute pancreatitis: A narrative review

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Abstract

Acute pancreatitis is a common cause of acute abdominal pain and can range from mild oedema to severe necrosis of the pancreas. It has a significant impact on morbidity, mortality and financial burden. The global prevalence of pancreatitis is substantial, with the highest rates observed in central and eastern Europe. Diagnosing acute pancreatitis involves considering clinical symptoms, elevated serum amylase and/or lipase levels, and characteristic imaging findings. The causes of acute pancreatitis include obstructive disorders, such as gallstones and biliary sludge, alcohol consumption, smoking, drug-induced pancreatitis, metabolic disorders, trauma, medical procedures, infections, vascular diseases and autoimmune pancreatitis. Appropriate management of acute pancreatitis involves determining the severity of the condition, providing supportive care, addressing the underlying cause, and preventing complications. Advances in classifying the severity of acute pancreatitis and implementing goal-directed therapy have contributed to a decrease in mortality rates. Understanding its prevalence, aetiology and management principles is crucial for clinicians to appropriately diagnose and manage patients with acute pancreatitis.

Keywords: Acute pancreatitis, Aetiology, Outcomes.

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Introduction

Acute pancreatitis (AP) is a commonly differential of abdominal pain seen in the emergency department (ED). This condition exhibits a wide spectrum of symptoms varying from mild oedema to severe gland necrosis. It is not limited by age and can occur in individuals regardless of age, leading to significant morbidity and mortality if not managed appropriately, and pose a high financial burden on patients, particularly in low- and middle-income countries (LMICs).[1]

According to World Health Organisation (WHO) data on acute pancreatitis, the global point prevalence of pancreatitis in 2017 was 76.2 per 100,000 population. The highest prevalence was seen in central and eastern Europe (222.1 and 213.8 per 100,000, respectively). In the Asian region, South Asia had the highest increase in incidence rate (23.4%).[2]

AP is a major cause of hospitalisation, leading to an increased economic burden on an already financially strained population. Scarce literature is available in Pakistan regarding its prevalence, aetiology and outcomes. A study comprising data from India, Latin America, North America, and Europe Showed that the Indian population had a younger age at AP onset (mean: 39 years), a higher prevalence of severe AP (23% vs 9%), and a higher rate of admission in the intensive care unit (ICU) (37.9%).[3]

Over the past few years, the mortality of AP has decreased significantly mainly as a result of development of principles of its goal-directed therapy. The current narrative article was planned to highlight the common causes of AP, its severity assessment, and management principles to help clinicians appropriately manage such patients.

Diagnostic criteria

According to multiple international bodies, AP can be diagnosed based on the presence of 2 of the 3 criteria: sudden onset of severe abdominal pain radiating to the back; elevation of serum amylase and/or lipase levels at least three times above normal and typical findings of AP on ultrasound, or magnetic resonance imaging (MRI).[4]

Disease course

About 85% of Ap patients will have acute interstitial oedematous pancreatitis where the pancreas is enlarged secondary to inflammation. Most of these patients will have a smooth recovery within 3-5 days and will not develop any complications or organ failure. On the other hand, 15% of patients have necrotising pancreatitis characterised by necrosis of the pancreatic parenchyma, the peripancreatic tissue, or both. Severe AP has a high reported mortality rate of 30%.[5,6] High annual relapse rate has been observed in AP secondary to biliary aetiology (5.3%) whereas smoking and alcohol intake have been found to be the major risk

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factors for the progression of acute to chronic pancreatitis.[7]

Aetiology

In Pakistan, gallstones remain the commonest cause of AP. There is also a high incidence of idiopathic AP, mainly as a result of lack of diagnostic facilities.[8]

Obstructive disorders

Mechanical ampullary impediment can be induced mainly by gallstones, but also occur for aide variety of other diseases. Obstruction causes increased pressure in the pancreatic duct, resulting in injury of the gland with release of pancreatic enzymes, causing auto-digestion and triggering AP.

1) **Gallstones:** Gallstones are the leading cause of obstructive AP, counting for approximately 35-45% of its total cases. Only 3-7% of those with gallstones go on to develop pancreatitis. This risk goes up with age, obesity as well as in females and in patients with small gallstones.[8,9]

2) **Biliary sludge:** It is a viscous fluid suspension in gallbladder bile that may contain small stones measuring <5mm in size (microlithiasis). Its development is linked to bile-stasis, causing conditions (both mechanical and functional), such as distal bile duct blockage, fasting for prolonged periods, parenteral feeding, or use of ceftriaxone. After all other potential reasons have been ruled out, biliary sludge should be taken into consideration as the likely underlying cause in patients diagnosed with idiopathic pancreatitis.[10]

3) **Anatomical and functional abnormalities:** These abnormalities, which include pancreas divisum and sphincter of Oddi dysfunction (SOD), can cause idiopathic acute recurring pancreatitis with prevalence of 15-72%.[11]

Toxins

1) **Alcohol:** Alcohol consumption is the second most common reason for AP globally. It usually occurs in patients who consume 4-5 drinks per day for 5 or more years. Less than 5% of people who consume alcohol will develop this condition. Its annual incidence is reported to be 13-45 per 100,000 people. Alcohol causes direct acinar cell damage by promoting the synthesis of enzymes, activates proteases, alters cellular lipid metabolism, induces oxidative stress, activates stellate cells, and makes the gland more prone to damage by genetic and environmental factors by increasing its sensitivity. Additionally, it can make the pancreatic juice more lithogenic which can result in the development of protein plugs and stones.[12,13]

2) **Smoking:** Tobacco and alcohol raise the risk of pancreatitis. Furthermore, both habits often coexist and are intensified in a dose-dependent way. A prospective cohort study shows a hazard ratio (HR) of 1.45 of AP patients with a history of smoking compared to non-smokers.[14]

3) **Drugs:** Drug-induced AP is a relatively uncommon occurrence seen in <2% of cases. There have been reports linking over 100 different medications to the development of AP by several mechanisms. These mechanisms include immunologic reactions, accumulation of toxic metabolites, ischaemia of the gland, intravascular thrombosis, and increased viscosity of pancreatic juice.

The drug-induced pancreatitis has been categorised into 4 classes (I-IV) according to the number of reported cases, latency period and reactions observed during re-challenge: Class Ia includes alcohol, hypertriglyceridaemia,, gallstones and other drugs. It includes alpha (α) methyldopa and cytosine; Class Ib includes all-trans retinoic acid, losartan and amiodarone; Class II includes acetaminophen, oestrogen and tamoxifen; Class III includes captopril, metformin and naproxen; and Class IV includes ampicillin and cisplatin.[15]

Metabolic disorders

1) **Hypertriglyceridaemia:** Incidence of AP secondary to hyperlipidaemia ranges 1-4%. It occurs when the triglyceride (TG) levels are >11.3mM. This is particularly common in patients with a history of familiar hyperlipidaemia and/or an associated secondary factor as uncontrolled diabetes, alcohol consumption, hypothyroidism, or pregnancy. Suggested mechanisms for this condition include increased amylase release, acinar cell damage secondary to free fatty acids, and pancreatic ischaemia due to sluggish capillary blood. A dose-dependent relation has been observed between lipid levels and incidence of local complications and organ failure in AP.[16]

2) **Hypercalcaemia:** Hypercalcaemia is a very uncommon cause of AP and usually seen in patients with hyperparathyroidism. Endogenous Hypercalcaemia as seen in disseminated cancers, parenteral nutrition or in vitamin D toxicity can also lead to AP. This is because calcium gets deposited in pancreatic duct, leading to blockage as well as activation of trypsinogen. Its incidence has been reported to range 1.5-8%.[17]

3) **Hereditary/genetic pancreatitis:** It is an autosomal dominant disorder with high penetrance rates up to 80%. Trypsinogen gene PRSS1 (Protease Serine 1), cystic fibrosis transmembrane conductance regulator (CFTR) gene, serine protease inhibitor kazal type 1 (SPINK1) gene and chymotrypsin C (CTRC) are found to be the associated genes for this condition. PRSS1 is responsible for the conversion of trypsinogen to trypsin prematurely, leading to auto-digestion of pancreas.[18]

Trauma and medical procedures

1) **Blunt or penetrating trauma:** Both blunt and penetrating trauma can cause AP. Nevertheless, <10% of abdominal injuries will present with this condition. Acute ductal rupture and pancreatic ascites may develop in such circumstances. The relatively low frequency of AP after trauma is accounted by the retroperitoneal location of the gland. As the injury heals, it may cause constriction of the main pancreatic duct, which would then result in obstructive pancreatitis downstream from the stricture.[19]

2) **Post-endoscopic retrograde cholangiopancreatography:** Pancreatitis may arise from instrumentation of the gland, such as during endoscopic retrograde cholangiopancreatography (ERCP). The incidence has been reported to be 6.9%.[20] Risk factors include SOD, young age, female gender, repeated attempts of papilla cannulation and inadequate emptying of the pancreatic duct after contrast injection.[19]

3) **Postoperative pancreatitis:** This complication has been documented in approximately 5% of patients after heart surgery and can arise after abdominal or thoracic surgery as well. Risk factors that significantly increase the likelihood of postoperative pancreatitis include renal failure, hypotension and infections.[21]

Infectious diseases

There are several infectious organisms connected to AP development. These organisms include mumps, coxsackie B virus, cytomegalovirus, hepatitis B and salmonella typhi. Parasites, such as clonorchis sinensis and ascaris, can cause pancreatitis by causing invasion and blockage of the pancreatic duct.[22,23]

Autoimmune pancreatitis

This condition has unique clinical and histological characteristics and can manifest itself in a variety of ways among affected individuals. It has subtypes. Type 1, also known as lymphoplasmacytic sclerosing pancreatitis, is a multi-organ disease associated with immunoglobulin G4 (IgG4), while type 2, or idiopathic duct centric pancreatitis, primarily affects the pancreas and produces granulocyte-epithelial lesions.

Immunologic abnormalities, such as hyper-gamma-globulinaemia, elevated serum IgG4 levels and autoantibodies against lactoferrin and carbonic anhydrase are important in type 1 autoimmune pancreatitis (AIP). These serological markers are essential for diagnosing type 1 AIP. Approximately 41% patients with systemic IGG4-RD also present with this condition.[24]

Miscellaneous conditions

Coeliac disease

There is an increased risk of developing pancreatitis in patients with coeliac disease. Studies have shown that patients with coeliac disease have a three-fold increased risk of any form of pancreatitis.[25,26]

Several underlying mechanisms have been explored to explain this association. The earliest proposed mechanism was malnutrition, as it can impact bile composition and can potentially induce microlithiasis formation. Malnutrition also leads to elevated levels of pro-inflammatory cytokines that can cause pancreatic acinar cell damage, ductal disruption, and other structural changes, such as acinar atrophy. Additionally, immunopathogenic mechanisms are also considered to be involved in the development of AP. T helper cell class 1 (TH1) has been implicated in coeliac disease as it causes polymorphisms in tumour necrosis factor-alpha (TNF-α), leading to upregulation of inflammatory cytokines.[26]

Idiopathic pancreatitis

This condition is defined as pancreatitis where the aetiology remains unknown despite initial laboratory and imaging studies. In some instances, further work-up may reveal the aetiology, but it remains unknown in majority of the cases. A comprehensive study is recommended, since biliary sludge/microlithiasis may be detected in up to 75% of individuals with recurrent AP initially labelled as idiopathic. Genetic testing may have a potential role in this condition. However, it has yet to be determined.[27]

Complications

Complications of AP can be divided into local, ductal, vascular and systemic complications.

Local complications

AP can lead to multiple local complications, including peripancreatic fluid collection, pseudocyst formation, acute necrotic collection, and walled-off necrosis. Acute peripancreatic fluid collections and acute necrotic collections usually manifest within 4 weeks after the onset of pancreatitis. On the other hand, pseudocyst and walled-

off necrosis usually occur after 4 weeks of AP onset. It should be noted that both acute necrotic fluid collections and walled-off necrosis have the potential to become infected.

Ductal complications

Pancreatic necrosis can lead to ductal disruption in 40% of cases, leading to persistent leakage of pancreatic fluid. This may further lead to peripancreatic ascites and pancreaticopleural fistula formation. Ductal strictures may also form secondary to inflammation in AP.[28,29]

Vascular complications

Splenic vein is the commonest vessel involved in acute pancreatitis. AP can lead to porto-spleno-mesenteric venous thrombosis (PSMVT). Furthermore, leakage of digestive pancreatic enzymes can lead to erosion of the vascular wall, leading to pseudoaneurysm formation or spontaneous haemorrhage.[28]

Systemic complications

As per the revised Atlanta classification,[29] systemic complications of AP are characterised by the exacerbation of an underlying comorbidity, such as coronary artery disease (CAD) or chronic lung disease (CLD). In contrast, organ failure in AP is an entity distinct from systemic complications. Pancreatic inflammation leads to a cytokine cascade that manifests clinically as a systemic inflammatory response syndrome (SIRS). Patients with persistent SIRS are at a heightened risk for failure of one or more organs that may involve one or more systems, such as respiratory system and renal system. Furthermore, this organ failure can be characterised as transient (resolving within 48 hours) or persistent (lasting >48 hours).[4]

Severity

The severity of AP is classified according to the Atlanta classification as follows:

Mild

It is distinguished by the lack of organ failure and local or systemic complications.

Moderately severe

It is characterised by local or systemic complications without any chronic organ failure (>48 hours) as well as short-term organ failure (<48 hours).

Severe

This condition is characterised by prolonged organ failure lasting >48 hours that may affect one or multiple organs.[29]

Multiple scoring systems have been devised to assess the severity of AP. The modified Glasgow score has been shown to have high sensitivity, whereas the Ranson score has shown to have a high diagnostic accuracy in predicting the severity.[30] The commonly used scoring systems are described below:

Ranson score

It is done on admission and 48 hours after admission, giving 1 point for each of the following findings on admission: White cell count (WBC) >16000/µl, age >55 years, blood glucose >200mg/dl, AST (Aspartate Aminotransferase)>250IU/L and LDH (Lactate Dehydrogenase)>500IU/L.

Furthermore, 1 point is given for each of the following findings present at 48 hours of admission: >10% decrease in haematocrit, >5mg/dl increase in blood urea nitrogen (BUN), <8mg/dl serum calcium, arterial pO_2 (Partial pressure of oxygen) <60mmhg, base deficit >mEq/L and fluid requirement >6L. A Ranson score of <3 has 0-3% risk of mortality, score of 3-5 and ≥6 have 11-15% and 40% risk of mortality, respectively.[30]

Modified Glasgow score

Under the scoring system, 1 point is given for each of the following findings: age >55 years, PaO2 (Partial pressure of oxygen in alveoli) <60mmhg, WBC >15,000/µl, serum calcium <8mg/dl, LDH >600IU/L, AST >200IU/L, glucose >180mg/dl, urea >45m/dl, and serum albumin <3.2gm/L. Patients with a score of ≥3 are likely to develop severe pancreatitis.[30]

Modified computed tomography Severity Index

The system uses contrast-enhanced computed tomography (CT) scan to assess pancreatic necrosis. Normal pancreas on CT scan is scored 0, pancreatic abnormalities with or without peripancreatic inflammation is scored 2 and represents <30% pancreatic necrosis, while pancreatic or peripancreatic fluid collection or fat necrosis on CT is scored 4 and represents >30% pancreatic necrosis.[30]

Acute Physiology and Chronic Health Score

The Acute Physiology and Chronic Health Score (APACHE) score uses 13 variables, including age, underlying conditions and mentality at admission to assess which patients will require ICU admission.[31]

Management of pancreatitis

There are 4 major principles of managing acute pancreatitis; fluid resuscitation; nutritional support; antibiotics; and management of complications.

Fluid Resucitation

Fluid and electrolyte optimisation is the cornerstone in the

management of AP. It can be done using crystalloid, colloid, or a combination of both. Ringer's lactate is the preferred crystalloid if no contraindications are present. Fluid administration should be titrated according to the patient's vital signs, urine output, haematocrit, urea and creatinine levels. The major intervention for pain management in AP is also aggressive hydration as loss of fluids in this condition leads to reduced bowel perfusion which is responsible for pain due to ischaemia, leading to lactic acidosis.

Nutrition in AP

Pancreatitis leads to a hypercatabolic state, and, hence, adequate nutritional support is essential for early recovery. Previous studies suggested that AP patients be kept nil per oral (NPO) till their condition improved.[32] However, recent literature has provided sufficient evidence for that immediate enteral feed after admission in patients with mild AP, can significantly reduce the length of hospital stay and intolerance of feeding.[33]

The preferred diet is soft, low-fat. Oral feeding leads to shorter hospital stay and has shown no significant pain relapse after the initiation of refeeding in mild AP. Nevertheless, it is necessary to proceed with caution in patients whose pain relapses following early after resuming oral feed. However, a meta-analysis has shown that patients with severe AP who received enteral feeding as opposed to parenteral nutrition had a lower risk of infection and organ failure.[34]

Antibiotic Therapy

Prophylactic antibiotic use is not recommended for AP as limited evidence is available regarding its efficacy. In cases where other infections coexist with AP, such as cholangitis, bacteraemia and pneumonia, appropriate antibiotics should be administered. Infection should be considered in patients with CT-proven pancreatic necrosis if there is no improvement or clinical deterioration after 7-10 days of hospitalisation. In such cases, two approaches are recommended. They can either undergo a fine needle aspiration (FNA) of the pancreatic fluid for gram staining and culture for starting appropriate antibiotics, or broad-spectrum empiric antibiotic therapy can be given. In cases where pancreatic necrosis is sterile, antibiotic use is not advised.[35]

Management of complications

Conservative management is recommended in patients with asymptomatic pancreatic pseudocysts or pancreatic necrosis whereas delayed surgical intervention should be done in cases of infected pancreatic necrosis if the patient is stable. A delay of 4 weeks is suggested to allow for the necrosis to become walled-off. Symptomatic necrosis should, however, be managed by minimally invasive necrosectomy.[35]

Role of ERCP

ERCP is recommended within 24 hours of admission in patients with cholangitis. In patients with strong suspicion of choledocholithiasis without cholangitis, magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound is recommended over ERCP for diagnostic purposes.[35]

Role of Surgery

Cholecystectomy should be done in patients with mild biliary AP before discharge, whereas in case of necrotising AP, cholecystectomy should be deferred till the inflammation resolves.[35]

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ZS: Writing and reviewing.
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