

A glance at acute pancreatitis (AP)

Abstract

Pancreatitis is the necroinflammation of the pancreatic tissue based pathologically on autodigestion, and deranged microvasculature that finally result in necrosis and later be complicated by bacterial infection. Pancreatitis takes place mainly due to calculi gall bladder, alcohol consumption, hypercholesterolaemia, immunologic, and blunt trauma, however it may be idiopathic. Pancreatitis varies in clinical severity i.e mild –severe, and presentation i.e acute -chronic. Many scoring systems have been proposed in assessing the severity of pancreatitis. Diagnosis must be considered in clinically suspected cases, and confirmed biochemically and radiologically. Treatment is directed to treating the cause, supportive measures e.g fluids, and managing complications.

Volume 7 Issue 2 - 2017

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Introduction

Acute pancreatitis (AP) is one of the commonest reasons for hospitalized cases due to gastrointestinal disease.¹ It is a severe disease affecting millions of people worldwide. Although supportive and critical care are advancing, no targeted pharmacologic treatment is used specifically to treat AP.²

A global epidemiologic study applied in 188 countries documented the rising incidence of pancreatitis; 4-8% before 1998, 14.9% 1998-2013, and overall 16%.³ A British study showed significant increase of AP from 27.6 per 100 000 in 1999 to 36.4 in 2010 (average annual increase=2.7% per year), particularly among young women aged <35 years, during the Christmas and New Year weeks in alcoholic aetiology, and socially deprived (1.9 times higher).⁴

An American study proved that AP affects both genders comparably, and generally increases with age. It also found its higher incidence among black races more than the others. Regarding the aetiology, gallstones are the most common cause AP, and conversely, early cholecystectomy eliminates the risk of recurrence.⁵ Smoking is an independent risk factor for AP [5,6], including the recurrence, incidence in young age, and regardless the aetiology.⁶

Common aetiologies of AP are summarized as follows, provided that gallstones and alcoholism constitute 75% of causes:

- i. Obstructive (Gallstones, Biliary sludge and microlithiasis, Tumors, helminthes), and functional (Sphincter of Oddi Dysfunction)
- ii. Alcohol, toxins, drugs
- iii. Metabolic disorders (Hypertriglyceridemia, Hypercalcemia)
- iv. Iatrogenic e.g Post ERCP
- v. Trauma
- vi. Infections
- vii. Vascular-Ischemia
- viii. Hereditary
- ix. Congenital anomalies (Pancreas Divisum, annular pancreas, choledocele, duodenal diverticula)⁷ Idiopathic (10-20%)⁸
- x. Miscellaneous (autoimmune pancreatitis,⁹ Crohn's disease,¹⁰ Celiac disease)¹¹

Pathology

It can be divided into four different pathogenologic categories: i) Ductular where intraductal pressure and permeability increase with premature enzyme activation, ii) Acinar in which autoactivation of pancreatic enzymes take place after misdirected basolateral secretion into the interstitium of the pancreas and/or by localization of lysosomes and proenzyme-rich zymogen granules inside the acinar cell, iii) Mixed ductular-acinar which is a combination of increased intraductal pressure, duct permeability and a potential direct toxic effect, and iv) Altered pancreatic microcirculation which plays a key role in the progression of edematous to necrotizing pancreatitis. Haemoconcentration and hypercoagulability, impaired perfusion by vasospasms of capillary flow by direct endothelial injury and edema, and of venous outflow by thrombosis, leukocyte endothelial direct toxic injury by activated enzymes, kinins and other mediators¹² altogether play in the pathogenesis of AP.

Activated enzymes and oxygen free radicals injure the acinar cell and cause a release of cytokines and vasoactive mediators, attract inflammatory cells and activate the vascular endothelium and the adhesion molecules. The disturbance of the pancreatic microcirculation induces a progression from edematous to necrotizing pancreatitis.¹³

Systemic inflammatory response syndrome (SIRS), secondary to cytokine release from the initial pancreatic parenchymal injury, is the main cause of early complications within the first 14 days.¹⁴ Moreover, intestinal dysfunction is thought to be related to the SIRS via intestinal ischaemia-reperfusion injury, and stimulation of local fluid collection in the retroperitoneal space and abdominal cavity.¹⁵ Synergistic element mediated by the intestinal hormones i.e motilin, vasoactive intestinal peptide, and cholecystokinin are incorporated as well.¹⁶

Clinical picture

Abdominal pain is the cardinal symptom that occurs in about 95% of cases. It is a deep dull aching pain which takes place typically in the upper abdomen radiating backwards in a band/ belt-like pattern, but it may be more localized to the right upper quadrant, epigastric area, or, less commonly in the left upper quadrant. Also, it characteristically occurs acutely, without a prodrome, and progresses soon afterwards, and may last for days. Eating or drinking particularly alcohol exacerbates the pain. In severe pain, patient attains the faetal position (knee-to-chest) to reduce its intensity. On examination, signs depend

on the severity of pain. Mild cases present with mild abdominal tenderness, while severe ones present guarding as well, but rebound tenderness is unusual. Ileus, signify the spread of the inflammation to the adjacent transverse colon. Tachycardia and mild hypotension may result from hypovolemia from sequestration of fluid in the pancreatic bed. About 60% of patients develop low-grade pyrexia from peripancreatic inflammation without evident infection.¹⁷

The evaluation of AP severity has been firstly defined by Atlanta Classification which was a clinically based classification system as mild and severe forms in an International Symposium on AP,¹⁸ that

Table 1 Severity of AP:²³

Severity of AP	Atlanta criteria (1993)	Atlanta revision (2013)
Mild	Absence of organ failure Absence of local complications	
Moderate (in revised Atlanta 2013)		1. Local complications AND/OR 2. Transient organ failure (<48h)
Severe	1. Local complications AND/OR 2. Organ failure GI bleeding (>500cc/24hr) Shock = SBP ≤90mm Hg PaO ₂ ≤60% Creatinine >2mg/dl	Persistent organ failure >48h

GI, Gastrointestinal; PaO₂, arterial oxygen saturation

Several scoring systems have been proposed in evaluating the severity of AP resulting in mortality; a) Ranson et al.²⁴ based on 11 objective variables assessed on admission and at 48hrs later, that was modified by AbuEshy et al.²⁵ who proved 4 of them i.e serum glucose value of ≥160 mg/dl, blood urea nitrogen (BUN) rise of ≥35 mg/dl, Blood pressure ≤55 mm Hg, and serum calcium value of <8 mg/dl (the most significant one) related to complications. b) Acute Physiology and Chronic Health Evaluation (APACHE)-α scores were applied since 1970s.²⁶ c) A new prognostic scoring system, the Bedside Index for Severity in AP (BISAP), has recently been proposed as an accurate and simple method for early identification of patients at risk of in-hospital mortality²⁷ based on 5 parameters i.e BUN >25 mg/dl, altered conscious level, SIRS, age >60 years, and pleural effusion.

However, those scoring systems showed rather similar predictive accuracy for severity of AP.²⁸ The majority (80%) of acute pancreatitis cases are of mild picture, and without complications,²⁹ and generally resolve themselves spontaneously within few days, without the need for specific treatment.³⁰

Early complications i.e within 2 weeks of the attack are biliary obstruction, haemorrhage, extensive sterile necrosis, infection of the necrosis, peritonitis, multi-organ failure, deterioration, Wirsung rupture.³¹ Variables found to be related to systemic complications were the APACHE II score as well as Sequential Organ Failure Assessment (SOFA) and Marshall scores³² greater than 3. The variables related to mortality were SOFA score > 3, leukocytic count > 19,000mm⁻³, CRP > 19.5 mg/dL and length of hospital stay were related to necrotizing pancreatitis.³³

Prognosis

The overall mortality rate of acute pancreatitis ranges from 4.8%³⁴ - 9.2%.¹⁴ Its range was reported 10-24%;³⁵ 7.7%³³ -13.5% of severe cases, and early deaths i.e ≤14 days occur in the half of patients (55%) due to multi-organ system failure (MOF), while later deaths occur due to complications secondary to the infection of pancreatic

was revised 20 years later regarding severity grades as mild, moderate and severe, and definition including duration of complications.¹⁹

According to the timing of complications, AP has 2 distinct phases; early (≤1 week) characterized by the SIRS and/or organ failure; and late (> 1 week), characterized by local complications.²⁰ Bacterial infection of pancreatic necrotic tissue is a frequent (30-70%) complication and is the leading cause of deaths in severe cases.²¹ Pancreatic necrosis is defined as nonviable pancreatic tissue, whether focal or diffuse, > 3 cm in size or > 30% of the pancreas.²² Severity of AP is summarized in Table 1.²³

necrosis which may be secondarily result in multi-organ system failure.³⁴ Duration and timing of organ failure is the limiting factor in determining outcome such that resolution within 48 hours suggests a good prognosis while its persistence is a marker for subsequent death or local complications.³⁶

Diagnosis

AP is diagnosed by at least the first 2 of 3 features (4): a) abdominal pain (typically epigastric pain radiating to the back), b) serum amylase and lipase levels ≥3 times normal, and (c) characteristic findings on computed tomography (CT), magnetic resonance imaging (MRI).¹⁹ *Amylase* is considered the elementary test used in diagnosing AP as it rises rapidly within the first 12 hours after the onset of symptoms and returns to normal within 3-5 days.³⁷ However, it may be normal in 19-32% of cases. Conversely, it may be elevated in other intraabdominal and salivary inflammatory conditions, and also in renal impairment or macroamylasaemia.³⁹

On the other hand serum *lipase* activity remains increased for up to 8 -4 days, thus is higher in sensitivity, and it may reach > 4 times that its upper normal limit. Moreover, less influenced by pancreatic insufficiency.⁴⁰ *The actim Pancreatitis strip test* recorded 93% sensitivity, 92% specificity, and 99% negative predictive value of. It is superior to serum lipase (sensitivity 79% and specificity 88%).⁴¹

Novel serum markers procalcitonin and Interleukin 6 (IL-6) allow earlier prediction (12 -24 hours after admission). Serum alanine aminotransferase (ALT) >150 IU/l and jaundice suggest a gallstone aetiology requiring ERCP. For obscure aetiologies, serum calcium and triglycerides should be measured. Genetic polymorphisms may have an important role in "idiopathic" acute recurrent pancreatitis.⁴²

Imaging is done when the blood tests are not elevated and the diagnosis is questionable.⁴³ It is recommended to confirm the clinical diagnosis, diagnose its cause, exclude alternative causes of abdominal pain, and grade the extent and severity.⁴⁴

US is the basic imaging modality in most centers to confirm the diagnosis of AP and ruling out of other causes of acute abdomen,⁴⁵ yet, sometimes of limited value.⁴⁴ US shows focally or diffusely enlarged hypoechoic pancreatic gland. Ill defined anechoic areas signify peripancreatic free fluid collections, and internal echoes/ septations suggest hemorrhage or a superimposed infection.⁴⁶

CT is considered superior as it enables staging the severity of AP, while MRI characterizes pancreatic and peripancreatic fluid collections and assessing an abnormal or disconnected pancreatic duct, particularly in iodine allergic patients.⁴⁵ Balthazar CT severity index (CTSI)⁴⁷ is considered a reliable imaging scoring system as it stratified pancreatitis severity and correlated pancreatic necrosis with parenchymal affection including fluid collection.

Treatment

Strategy of treatment plan is summarized in Table 2.² The most effective intervention for acute pancreatitis is early aggressive fluid resuscitation as it provides adequate pancreatic perfusion microcirculation, and maintains its intravascular volume.²² Antibiotics should be discontinued whenever blood and other cultures are negative and no source of infection is identified.²³

Enteral nutrition is beneficial as it reduces infectious complications, MOF, and mortality. Regarding the route of enteral feeding, nasogastric tube is equally as effective as nasojejunal feeding, while regarding the timing of enteral nutritional support, relatively early administration within 48 -72 h of hospital admission is recommended.⁴⁸ Only, in mild AP with resolved abdominal pain, and with neither nausea nor vomiting, oral low-fat solid diet can be started immediately.²³

However, minimally invasive approaches to pancreatic necrosectomy including laproscopic surgery, percutaneous, radiologic catheter drainage or debridement, video-assisted or small incision-based left retroperitoneal debridement, are increasingly becoming the standard of care.⁴⁹ Percutaneous drainage without necrosectomy may be the most frequently used minimally invasive method for managing fluid collections complicating necrotizing AP. Sometimes these modalities can be combined at the same time or sequentially.⁵⁰ Angiography is used to diagnose some complications like pseudoaneurysm due to the lytic effect on vascular wall by the activated pancreatic enzymes or selective embolization to control bleeding.⁵¹

Finally, an integrated multidisciplinary approach is required in patients with severe pancreatitis e.g gastroenterologists, radiologists, intensivists, and surgeons. Identification of the cause and its proper treatment is very crucial.⁵²

Table 2 Strategy of treatment plan .²

Intervention recommendation	
Fluid resuscitation	Early aggressive fluid resuscitation with 250 to 500 mL/hour in the first 24 hours of admission Use of isotonic crystalloid fluids – Lactated Ringer's
Antibiotics	Not recommended unless there is a documented infection No prophylaxis for necrotizing acute pancreatitis
Feeding	Attempt enteric feeding within the first 72 hours of admission if tolerated (may be supplemented with oral low-fat diet)
Pharmacologic strategies	No current targeted pharmacologic therapies recommended Rectal indomethacin 100 mg for post-procedure prophylaxis in those at high risk for post ERCP pancreatitis

Conclusion

AP is a serious medical condition that is potentially lethal. Its diagnosis has to be considered whenever any of the aetiologies exist with its classical presentation.

Recommendation

Proper assessment and evaluation of AP with prompt intervention to avoid complications and mortality.

Acknowledgments

None.

Conflicts of interest

The authors declare there are no conflicts of interest related to the article.

Funding

None.

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