REVIEW ARTICLE

Acute Pancreatitis : An Update

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Acute pancreatitis is not an uncommon disease, with high morbidity and mortality. It is an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or other organ systems (1). A definite diagnosis is often elusive. Elevation of serum levels of pancreatic enzymes > 3-5 times of normal values (>10 SD) and USG or CT abdomen offer a high degree of diagnostic specificity and sensitivity (>80-90%). Recent concepts in etiopathogenesis, diagnosis and management are being reviewed in this article.

Pathology & pathogenesis

The pathologic spectrum of acute pancreatitis includes acute oedematous pancreatitis, necrotizing pancreatitis, haemorrhagic pancreatitis, pseudocyst pancreas, pancreatic abscess and pancreatic ascites. The pathogenesis of acute pancreatitis is not clear but considerable recent advances have been made in the elucidation of its pathogenesis. Autoactivation of trypsinogen, role of clotting cascade, cytokines, immunocytes and PGI_2 have enabled us to understand the mechanism of autodigestion. This theory of autodigestion of pancreas explains many of the pathogenic and clinical manifestations of acute pancreatitis (2) (Fig 1).

Various other pathogenetic hypotheses leading to autodigestion are – common channel hypothesis, reflux of duodenal contents, altered pancreatic duct permeability (due to ethanol, drugs, histamine, calcium), premature activation of zymogens and embolic occlusion of small pancreatic vessels (3-5).

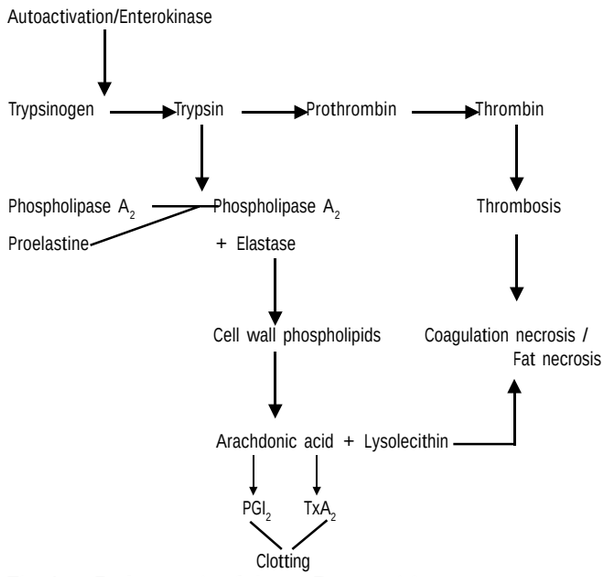

Fig. 1:- Pathogenesis of Acute Pancreatitis. (Autodigestion Theory).

Clinical features

Abdominal pain is the major symptom. Pain may vary from mild and tolerable discomfort to severe, constant & incapacitating distress in the epigastrium and periumbilical region radiating to the back. Low grade fever, tachycardia, hypotension, jaundice and pulmonary findings may occur in 10-20 percent. Bluish discoloration (Cullen's sign) and green, brown discoloration of the flanks (Turner's sign) may be seen (6).

Laboratory diagnosis

Estimation of pancreatic enzymes *viz.*, serum amylase and lipase >3-5 times the normal and urinary amylase have sensitivity and specificity of >90-92% (7). Non-

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specific markers of acute pancreatitis like C-reactive protein (CRP), tumour necrosis factor (TNF), β_2 microglobulin, complement levels, interleukin-6 (IL-6), procalcitonin and urinary tryspinogen activation peptide (UrTAP) are useful indicators (8). Measurement of isoamylase-P increases the diagnostic specificity. Another new rapid test for diagnosing acute pancreatitis is urinary trypsinogen-2 strip test (9).

Radiology

Radiological investigations include plain x-ray abdomen which may show sentinel loop, colon cut-off sign, mass shadow (pseudocyst) and duodenal distention. Ultrasound abdomen can show diffusely enlarged hypoechoic areas, peripancreatic fluid collection and pseudocyst. CT abdomen (unenhanced and contrast enhanced) further adds to diagnostic value. ERCP is another important investigation for diagnosing pancreatitis (10).

Aetiology

Causes of acute pancreatitis are variable. They are gallstones, and other causes of mechanical ampullary obstruction, hypertriglyceridemia, drugs, ERCP. Alcohol is known to be a major cause of pancreatitis, toxic effects of alcohol are at the cellular and microvascular levels. A high concentration of ethanol reduces gastrointestinal and pancreatic blood flow. Gastrointestinal haemorrhage and pancreatitis are initiated by microvascular disturbances of gastrointestinal mucosa and pancreas. Vasoactive agents, such as endothelins, nitricoxide and oxidative stress does have a pathogenetic role in ethanol induced pancreatitis. Ten percent of chronic alcoholics develop acute pancreatitis (11, 12).

Drugs

The drugs which are incriminated to cause acute pancreatitis include antimicrobials (metronidazole, stibogluconate, sulfonamides and tetracyclines); diuretics (frusemide, thiazides); sulphasalazine; 5ASA; Immunosuppressive drugs (L-asparaginase, azathioprine); anti-inflammatory (salicyaltes); calcium and drugs used in AIDS treatment (didanosine, pentamidine).

Infections

Various viruses like Mumps, Coxsackie, HBV, CMV, Varicella, Herpes simplex; bacteria like Mycoplasma, Leptospira, Salmonella and Legionella; fungi (Aspergillosis); and parasitic infections (Toxoplasmosis, Cryptosporidium, Ascariasis) have been invariably associated with pancreatitis (14).

In over 30% cases of acute pancreatitis in younger age <35 years there is no obvious cause. Recent discovery of genes for cationic trypsinogen (PRSSI), pancreatic secretory trypsin inhibitor (PSTI or SPINKI) and cystic fibrosis transmembrane conductance regulator (CFTR) and sphincter of oddi dysfunction in hereditary (idiopathic recurrent pancreatitis) further adds to our understanding of this entity (15-16).

Management of acute pancreatitis

Advances in our knowledge of pathogenesis of the disease and together with newer techniques of timely diagnosis and management of severe cases in intensive care unit helped in decreasing the morbidity and mortality of acute pancreatitis.

Mild acute pancreatitis is clinically a self limiting disease that accounts for the majority (70-80%) of acute pancreatitis cases, patient generally need only a short hospitalization of 3-7 days with medical supportive therapy, and do not suffer organ failure or local complications (17).

Severe acute pancreatitis (20-30%) is frequently a progressive disease and can progress to multiple organ failure, which is difficult to treat outside an intensive care unit (ICU) and contributes to a very high mortality (70-90%). Very often, a multi-disciplinary approach is required in the management of such patients (17).

Assessment of severity

It is done by various scoring systems as described below :-

a) Ranson's criteria (17)
b) Glasgow scoring (18)
c) APACHE-II (19)
d) Balthazar's scoring system based on CT scan findings (20).

Assessment of severity's scoring systems

Ranson's criteria :

At admission	:	Age >55 years Leucocytosis > 16000/mm^3 Hyperglycaemia >200 mg/dL S. LDH>400 IU/L AST >250 IU/L
Initial 48 hours	:	Fall in HCT >10% Fluid deficit >4000 ml Hypocalcemia <8 mg/dL Hypoxemia PaO_2 <60 mmHg

↑ In BUN to >5 mg/dL after IV fluid
Hypoalbuminemia <3.2 g/dL

Score >6 indicates severe acute pancreatitis

Glasgow system to predict severity of acute pancreatitis :

Poor prognostic factors in patients with acute pancreatitis.

White blood cell count	> 15,000 / L
Serum glucose concentration	> 180 g/dL (10 mmol /L) with no history of diabetes
Blood urea nitrogen	> 45 mg/dL (16 mmol/L) with no response to fluids
PO_2	< 60 mmHg
Serum calcium concentration	< 8 mg/dL (2 mmol/L)
Serum albumin concentration	< 3.2 g /dL (32 g/L)
Lactate dehydrogenase	> 600 U/L
Aspartate aminotransferase (AST)	> 200 U/L

The presence of three or more of these criteria within the first 48 hours is indicative of severe pancreatitis.

APACHE-II

1. Physiologic points :
   - Temperature
   - MAP (Mean Arterial Pressure)
   - Heart rate
   - Respiratory rate
   - Oxygenation (PaO_2)
   - Arterial pH
   - Serum sodium
   - Serum potassium
   - Hematocrit
   - White cell count
   - Glasgow coma score
2. Age points
3. Chronic health points :
   - Liver
   - Cardiovascular
   - Respiratory
   - Renal
   - Immunocompromised

1+2+3 = Total Score

Score >8 indicate severe pancreatitis

Obesity (BMI>29): Obesity is a prognostic factor favouring the development of systemic and local complications in pancreatitis (21).

Balthazar's scoring system for severity of acute pancreatitis :

CT grade of acute pancreatitis	**Score**
A = Normal	0
B = Pancreatic enlargement	1
C = Peripancreatic inflammation	2
D = Peripancreatic fluid collection (one)	3
E = Two or more peripancreatic fluid collections	4
Necrosis grade	
A = No necrosis	0
B = Necrosis of 1/3 of pancreas	2
C = Necrosis of 1/2 of pancreas	4
D = Necrosis of more than 1/2 of pancreas	6

Appropriate measurements and bedside care in severe acute pancreatitis

Vital signs : atleast hourly
CVP : atleast hourly
PAP : if indicated
ABG : every 12 hours
Intake / output charting every 8 hours
Catheterisation
NG tube with suction (maintain intragastric pH at 7, antacids every 2 hours)
Humidified oxygen at 2 lt. per min
Pain management
Record weight daily
ECG, daily
Blood tests (haemogram & biochemistry) once or twice daily
Liver function tests every 2 to 4 days

Nasogastric aspiration

Nasogastric tube is indicated only if there is persistent nausea or vomiting, or ileus. For mild cases, oral feeding may be started when symptoms subside or usually within 3-7 days. For severe acute pancreatitis, oral feeding may be considered after 3 weeks if not contraindicated (22).

Fluid therapy

Fluid input is modulated according to haemodynamic stability and fluid balance. Electrolyte imbalance should be corrected to reduce the complications.

Analgesic medication

NSAIDS, mepridine or fentanyl are used for pain control. Morphine is contraindicated as it increases the contractility and tone of sphincter of oddi & also increases serum amylase (23).

Total parentral nutrition / artificial nutrition

Where it is feasible and when enteral nutrition is contraindicated, use of amino acid infusion about 1-1.5 g/kg/day and the use of intravenous lipids, unless contraindicated by elevated triglyceride levels, in several cases especially in sepsis cases has helped to decrease morbidity and mortality.

Recent studies on intensive care patients with trauma and sepsis showed that enteral feeding was associated with a reduction in the acute phase response and the severity of septic complications compared to total parentral nutrition (24, 25).

Antibiotics

Cefuroxime (1.5 g tds), ciprofloxacin (200 mg bd), imipenam (500 mg tds) in combination with drugs effective against anaerobes like metronidazole (500 mg tds) for 2 weeks are used via intravenous route for control of infection. Recently prophylactic use of anti-fungal drugs has been recommended (26, 27).

Somatostatin/octreotide

These are useful and effective in acute pancreatitis and in preventing complications following ERCP (28). Somatostatin and its 8 amino acid analogue, octreotide, share similar cytoprotective effects on the pancreas. They inhibit basal and stimulated pancreatic secretion, stimulate reticuloendothelial system activity and modulate the cytokine cascade. However, they have different onset of action and exert different effects on sphincters of oddi motility. Somatostatin relaxes the sphincter of oddi whereas octreotide increases its contractility (29).

Inhibition of MAPKs (Mitogen-activated proteinkinases)

In a recent study, it was concluded that simultaneous inhibition of TNF-α products (by pentoxifylline) and xanthineoxidase activity (by oxypurinol) greatly reduced local and systemic inflammatory response in acute pancreatitis and decreased mortality rate. These act by inhibiting MAPKs (30).

Surgical treatment

Early surgery is indicated only for infected pancreatic necrosis and pancreatic abscess. Emergency surgery is indicated when there is haemoperitoneum or intestinal ischaemia (31, 32).

Endoscopic treatment for gallstone pancreatitis

Based on various studies, it is recommended that an emergent ERCP should be performed in patients with acute pancreatitis and suspected or proven gallstone aetiology when criteria for severity are met and / or there is co-existent cholangitis, jaundice, dilated CBD or when there is clinical deterioration in patients with initial mild prognostic signs (33, 34).

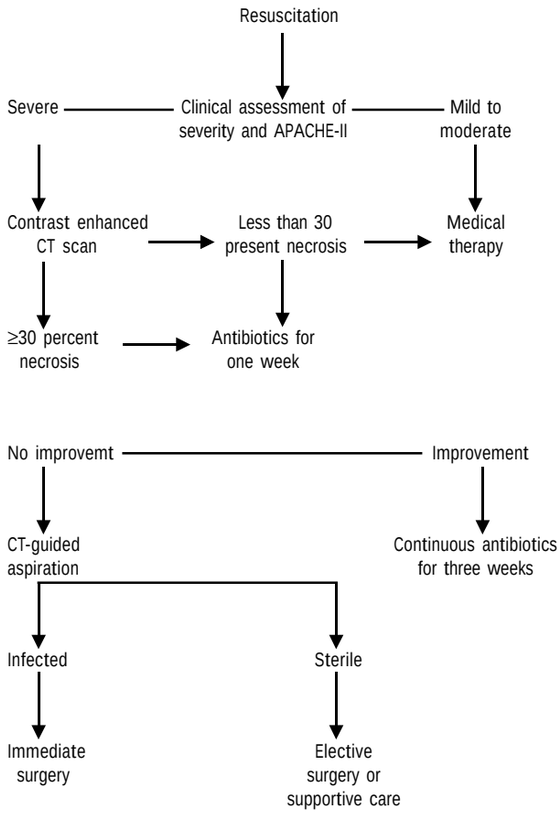

Fig. 2:- Management alogrithm for severe acute pancreatitis.

"In acute pancreatitis'', the goal is an early detection and early treatment of systemic complications because this is probably the most important policy to reduce mortality.

References

1. Sarles H. Definitions and classifications of acute pancreatitis. *Pancreas* 1991; 6: 470.
2. Steer ML. Pathogenesis of acute pancreatitis. *Digestion* 1997; 58 (1): 46.
3. Jones BA, Salsberg BB, Mehta MH, Bohnen JM. Common pancreaticobiliary channels and their relation to gallstone size in gallstone pancreatitis. *Ann Surg* 1987; 205: 123.
4. Gorelick FS, Modlin I, Leach SD *et al*. Intracellular proteolysis of pancreatic zymogens. *Yale J Biol Med* 1993; 65: 407.

5. Gress TM, Arnold R, Adler G. Structural alterations of pancreatic microvasculature in cerulein induced pancreatitis in rat. *Res Exp Med* 1990; 190: 401.
6. Green Berger NJ, Toskes PP. Acute and chronic pancreatitis. In: Kasper DL, Braunwald E, Fauci AS *et al* (eds). Harrison's Principles of Internal Medicine 16th edition. Vol 2. The McGraw Hill Companies, USA 2005; pp-1897.
7. Ghozdz GP, Steinberg WM, Werner M *et al.* Comparative evaluation of the diagnosis of acute pancreatitis based on serum and urine enzyme assays. *Clin Chem Acta* 1990; 187-243.
8. Pezilli R, Billi P, Miniero R *et al.* Serum interleukin-6, interleukin-8 and b_2 microglobulin in early assessment of severity of acute pancreatitis: Comparison with serum C-reactive protein. *Dig Dis Sci* 1995; 40: 2341-48.
9. Kylanpaa Back M, Kemppainen E, Puolakkainen P *et al.* Reliaible screening for acute pancreatitis with rapid urine trypsinogen-2 test strip. *Br J Surg* 2000; 87: 49.
10. Balthazar EJ, Freeny PC, Van Sonnerberg E. Imaging and intervention in acute pancreatitis. *Radiol* 1994; 193: 297.
11. Banks, Indaram A. Causes of acute and recurrent pancreatitis, clinical considerations and clues to diagnosis. *Gastroenterol Clin North Am* 1999; 28: 571-89.
12. Grewe M, Tsiotos GG, Sarr MG *et al.* Fungal infection in acute necrotizing pancreatitis. *J Am Coll Surg* 1999; 188: 408-14.
13. Mallory A, Kern F Jr. Drug induced pancreatitis: A critical review. *Gastro Enterol* 1980; 78: 813.
14. Gorelick FS. Acute pancreatitis. In: Yamada T, Alpers DH, Owyang C *et al* (eds). Textbook of gastroenterology. 2nd edition. Vol. 2. JB Lippincott Company Philadelphia 1995; pp-2072.
15. Cohn JA, Friedman KJ, Noone PG *et al*. Relation between mutations of cystic fibrosis gene and idiopathic pancreatitis. *N Engl J Med* 1998; 339: 653.
16. Sherman S, Hawes RH, Troiano FP, Lehman GA. Pancreatitis following bile duct sphincter manometry utility of aspirating catheter. *Gastro Intest Endos* 1992; 38: 347.
17. Banks P. Acute pancreatitis. Medical and surgical management. *Am J Gastroenterol* 1999; 89: 578-85.
18. Imerce CN, Bejamin IS, Mckay AJ *et al.* A single center double blind trial of trasylol therapy in primary acute pancreatitis. *Br J Surg* 1978; 65: 337-41.
19. Knous WA, Draper EA, Wagner DP *et al.* APACHE-II. A severity of disease classification system. *Crit Care Med* 1985; 13: 818-29.
20. Balthazar EJ, Robinson DL, Ranson JH *et al*. Acute pancreatitis: Value of CT in establishing prognosis. *Radiol* 1990; 174: 331-36.
21. Martiney J, Paya Sanchez J, Palazon JM *et al*. Is obesity a risk factor in Acute Pancreatitis? *Pancreatol* 2004; 4: 42-48.
22. Eatock FE, Brombacker GD, Steven A *et al.* Nasogastric feeding in severe acute pancreatitis may be practical and safe. *Int J Pancreatol* 2000*;* 28: 23-29.
23. Mathieson DR, Gross JB, Power MH. Elevated values for serum amylase and lipase following administration of opiates, a preliminary report. *Mayo Clin Proc* 1951; 26: 81.
24. Moore EE, Moore FA. Immediate entral nutrition following multisystem trauma: A decade perspective. *J AM Coll Nut* 1991; 10: 633-48.
25. Austrums S. Post-operative enteral nutrition improves outcome in severe acute pancreatitis. *Nutrition* 2003; 19: 487-91.
26. Garg PK, Khanna S, Bohidar NA *et al.* Incidence, spectrum and antibiotic sensitivity pattern of bacterial infection among patients with acute pancreatitis. *J Gastroenterol Hepatol* 2001; 16: 1055-59.
27. Pederzoli P, Bassi C, Vesentini S *et al.* A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute pancreatitis with imipenam. *Surg Gynaecol Obst* 1998; 176: 480-83.
28. Uhl W, Buchler MW, Malfertheiner P *et al.* A randomized double blind, multicenter trial of octreotide in moderate to severe pancreatitis. *Gut* 1999; 45: 97-104.
29. Pezzilli R, Gullo L, Distefano M *et al*. Treatment of pancreatic ascites with somatostatin. *Pancreas* 1993; 8: 120-22.
30. Perada J, Sabter L, Carrinello N. Effects of simultaneous inhibition of TNF-alfa production and xanthine oxidase in experimental acute pancreatitis: role of nitrogen activated protein kinases. *Ann Surg* 2004; 240: 108-16.
31. Rattner DW, Legermate DA, Lee MJ *et al*. Early surgical debridement of symptomatic pancreatic nacrosis is beneficial irrespective of infection. *Am J Surg* 1992; 163: 105.
32. Mier J, Leon EL, Castillo A *et al.* Early versus late necrosectomy in severe necrotising pancreatitis. *Am J Surg* 1997; 173: 71.
33. Fan ST, Lai EC, Mok FP *et al.* Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. *N Engl J Med* 1993; 328: 228-32.
34. Neoptolemos JP, Carr Locke DL, London NJ *et al*. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. *Lancet* 1988; 2: 979-83.