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Review

Review on diagnosis of acute pancreatitis

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Abstract

Acute pancreatitis is an acute inflammation of the pancreas with variable involvement of surrounding tissues and/or distant organs. Acute pancreatitis is mild and resolves itself without serious complications in 80% of patients; however it has complications and mortality in about 20% of patients despite the aggressive intervention. This paper covers the various etiologies attributing to acute pancreatitis, pathophysiology of acute pancreatitis and the diagnostic markers used for acute pancreatitis. The diagnostic markers include: Amylase, Lipase, Trypsinogen, Interleukin-6, C reactive protein, Procalcitonin, Polymorphonuclear Elastase (PMN Elastase), Trypsin Activation Peptide (TAP), Trysinogen-2, Hepcidin, Copeptin, Soluble E-Selectin (sES) and Soluble Thrombomodulin (sTM), and Serum Intercellular Adhesion Molecule-1 (ICAM-1**).**

Key words: Acute pancreatitis, Amylase, C-reactive protein, Diagnostic markers, Interleukin-6, Lipase, Trypsinogen

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Acute pancreatitis is an acute inflammation of the pancreas with variable involvement of peripancreatic tissues and/or distant organs[1]. The inflammatory process may be limited to the pancreatic gland with edema or necrosis, or it may involve the surrounding tissues and/or distant organs, hence the clinical manifestations range from mild abdominal pain to very serious presentations[2]. Acute pancreatitis is mild and resolves itself without serious complications in 80% of patients, but it has complications and mortality in about 20% of patients despite the aggressive intervention[3]. Eland et al.[4] report that the incidence of alcoholic pancreatitis is higher in male, and the risk of developing gallstone pancreatitis is greater in female. Relevant studies to date done on the subject have been considered for this review article. The studies considered for this article are available in various books on the subject and research articles printed or hosted over the internet by reputable online journals.

Pathophysiology of acute pancreatitis

Acute Pancreatitis is the consequence of abnormal pancreatic enzyme activation inside acinar cells. Intra-acinar pancreatic enzyme activation induces auto-digestion of normal pancreatic parenchyma. In response to this initial injury, acinar cells release pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukins (IL)-1 and -6, and anti-inflammatory mediators such as IL-10 and IL-1 receptor antagonist[5]. These mediators do not initi-

ate pancreatic injury but propagate the response locally and systemically. As a result, TNF-α, IL-1, and IL-7, neutrophils, and macrophages are recruited into the pancreatic parenchyma and cause the release of more TNF- α, IL-1, IL-6, reactive oxygen metabolites, prostaglandins, platelet-activating factor, and leukotriene[5]. The local inflammatory response further aggravates the pancreatitis because it increases the permeability and damages the microcirculation of the pancreas. In severe cases, the inflammatory response causes local hemorrhage and pancreatic necrosis. In addition, some of the inflammatory mediators released by neutrophils aggravate the pancreatic injury because they cause pancreatic enzyme activation[6] (Fig 1).

Causes of acute pancreatitis

Etiologies that result to acute pancreatitis are listed in table 1.

Gallstones

Acute pancreatitis can be caused by the passage of gallstones through the cystic duct and into the distal common bile duct where they can obstruct the biliary and pancreatic ducts. Pancreatic ductal obstruction is felt to be the inciting event in gallstone pancreatitis[8].

Table 1: Causes of acute pancreatitis

Gallstones
Alcoholism
Endoscopic Retrograde Cholangiopancreatography (ERCP)
Hypercalcemia
Genetic causes
Hypertriglyceridemia
Drug-induced
Infections

Alcoholism

Alcoholism is responsible for about one-third of cases of acute pancreatitis[9]. The pathophysiology may be multifactorial. . Proposed mechanisms include sphincter of Oddi spasm, precipitation of insoluble protein plugs, gall stone or tumour that obstruct the pancreatic ductules, activation of pancreatic proteases, and overstimulation of pancreatic secretion by cholecystokinin[7]. Alcoholic pancreatitis generally requires drinking more than eight alcoholic drinks per day for more than 5 years[7]. Acute alcoholic pancreatitis most likely results in the development of chronic pancreatitis.

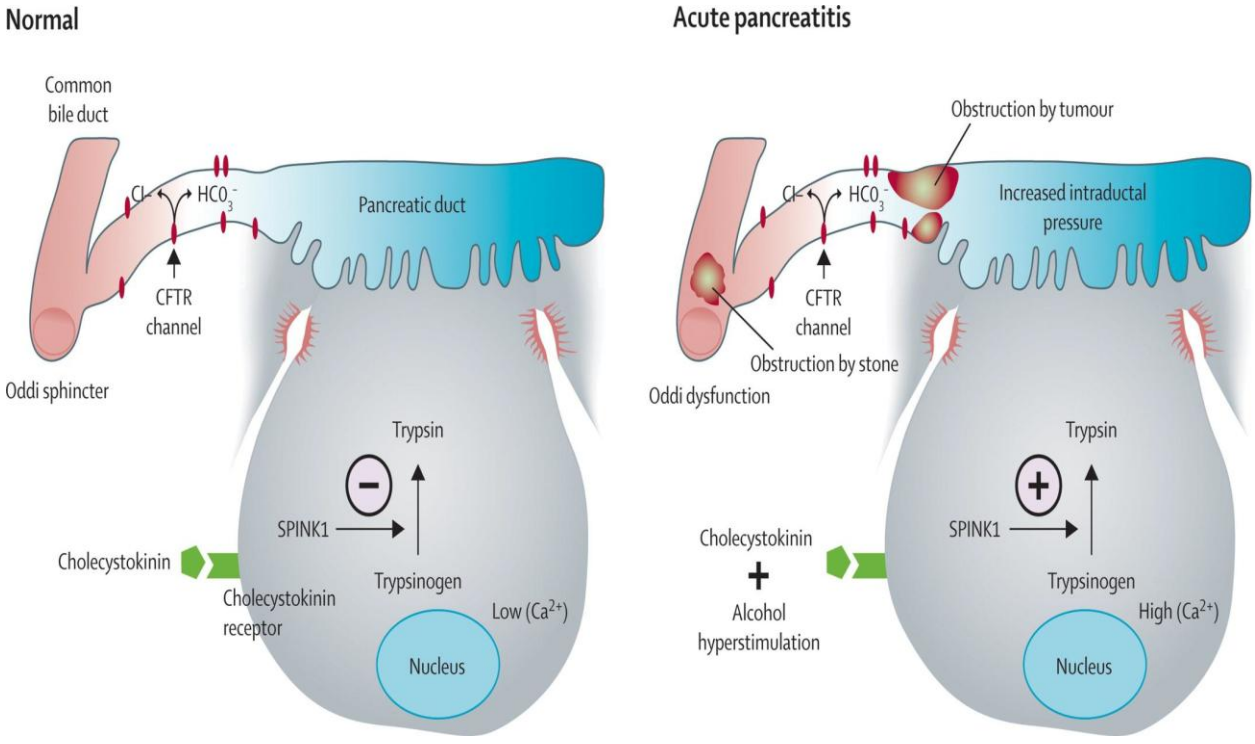

Fig 1. Acute pancreatitis caused by alcohol hyperstimulation. Alcoholism is responsible for about one-third of cases of acute pancreatitis. Proposed mechanisms include sphincter of Oddi spasm, precipitation of insoluble protein plugs, gall stone or tumour that obstruct the pancreatic ductules, activation of pancreatic proteases, and overstimulation of pancreatic secretion by cholecystokinin[7]. (Reproduced with permission)

Endoscopic retrograde cholangiopancreatography

Iatrogenic pancreatitis most commonly occurs following endoscopic retrograde cholangiopancreatography (ERCP)[10]. About 2% of cases of pancreatitis are caused by ERCP. Pancreatitis is the most common complication of ERCP. Pancreatitis is diagnosed reliably after ERCP by abdominal pain that is consistent with pancreatitis, and is associated with an at least a threefold increase in the serum lipase or amylase.

Hypercalcemia

Hypercalcemia is also a recognized etiology of acute pancreatitis[11]. Hypercalcemia can be associated with a malignancy, vitamin D toxicity and infusions of preoperative high-dose calcium during cardiopulmonary bypass[12].

Genetic causes of pancreatitis

Mutations of several genes can cause pancreatitis. Hereditary pancreatitis is associated with mutations in the trypsinogen gene PRSS1 that promotes premature conversion of trypsinogen to active trypsin that causes pancreatic autodigestion[13]. Mutations in SPINK1, a gene that encodes for a pancreatic trypsin inhibitor, are associated with acute and chronic pancreatitis resulting from an impaired ability to counteract the effects of activated trypsin within pancreatic acinar cells. Such mutations are a common cause of chronic pancreatitis in childhood.

Hypertriglyceridemia

Hypertriglyceridemia is reported to cause 1-4% of acute pancreatitis episodes. The mechanism for hypertriglyceridemic pancreatitis involves hydrolysis of triglycerides by pancreatic lipase and release of free fatty acids that induce free radical damage to the pancreas[14].

Drug-induced pancreatitis

Drug-induced pancreatitis may account for about 7% of all cases of acute pancreatitis[15]. Commonly implicated drugs are listed in table 2, according to their proposed mechanisms. Pancreatic injury in Drug-induced pancreatitis tends to be mild and self-limited.

Infections

The most common parasitic infections linked to the development of acute pancreatitis are Toxoplasma, Cryptosporidium and Ascaris[16,17]. Viruses known to cause acute pancreatitis include Mumps, Coxsackie virus, Hepatitis B, Cytomegalovirus and Varicella-zoster virus[18,19]. Only a few bacteria are well established as causes of acute pancreatitis: Mycoplasma, Legionella, Leptospira and Salmonella[11]. Aspergillus is the only fungus that has been reported to cause acute pancreatitis[19,20].

Table 2: Drug-induced pancreatitis

Mechanism	Drug
Drug-induced hypersensitivity reaction	Metronidazole
	Tetracycline
Toxic metabolite	Valproic acid
Drug-induced hypertriglyceridemia	Tamoxifen
Overdose reaction	Erythromycin

Diagnostic markers used for acute pancreatitis

The pancreatic enzymes derived from pancreatic acinar cells (amylase, lipase, and trypsinogen) are the cornerstone in the laboratory diagnosis of acute pancreatitis[21]. Serum lipase is a more sensitive and specific biochemical marker of AP than the more frequently used amylase. Moreover, serum amylase level offers no additional advantage if simultaneously measured with serum lipase[22].

Amylase

Amylase is a glycoside hydrolase primarily produced in the pancreas and salivary glands. In acute pancreatitis, the blood level of amylase rapidly increases within six hours of onset of disease, remains elevated for 3–5 days, and finally is excreted by the kidney. After reaching a peak level, subsequent return of serum amylase to its normal level does not correlate with resolution of clinical symptoms[23]. Furthermore, the increase of the elevated serum amylase does not show significant statistical correlation with disease severity[24]. Elevated serum amylase can also be found in many other intrabdominal inflammatory conditions and salivary disorders and in patients having decreased renal clearance. Macroamylasemia is a condition in which amylase remains bound to immunoglobulins or polysaccharides to form large molecular weight complexes leading to raised levels of serum amylase[21]. Hypertriglyceridemia competitively interferes with amylase assay, so a false low level of serum amylase can be found in patients having hypertriglyceridemia[21].

Lipase

The serum concentration of lipase increases within 3–6 hours of onset of disease and peaks within 24 hours[25]. The increased serum level stays for around 1-2 weeks before it comes down to the normal level[25]. In contrast to amylase, lipase is reabsorbed in renal tubules and stays for long at

higher concentration; Hypertriglyceridemia does not influence the serum lipase assay as happens in the case of serum amylase. Elevated serum level of lipase can also be seen in much intra-abdominal pathology including acute cholecystitis, appendicitits, inflammatory bowel disease, intestinal ischemia, obstruction, perforation, and renal insufficiency[23,25]. As with amylase, most studies suggest a poor correlation between lipase activity and disease severity[24].

Trypsinogen

Trypsinogen is the zymogen of the pancreatic enzyme trypsin which is cleaved by duodenal enterokinase to produce the active enzyme trypsin and trypsinogen activated peptide (TAP)[23]. Normally trypsinogen (trypsinogen-1 and trypsinogen-2) is secreted into the pancreatic fluid by the acinar cells, of which a small amount enters into the circulation and is excreted in urine. In pancreatitis large amounts of this enzyme enter the systemic circulation due to increased vascular permeability and there is a consequent increased clearance in urine. This forms the basis of the use of trypsinogen in the diagnosis and severity assessment of acute pancreatitis[25]. Both serum and urine concentrations rise within few hours of onset of disease and decline to normal level within 1 week[25].

Interleukin-6

Interleukin-6 (IL-6) is produced by a wide range of cells like monocytes, macrophage, endothelium, and fibroblast in response to potent proinflammatory stimulus like TNF-alpha and IL-1β[23]. A large number of studies have already confirmed the role of IL-6 in early and accurate prediction of severity in acute pancreatitis[26]. Value of IL-6 is significantly elevated in severe acute pancreatitis (SAP) on the first day and tends to peak at 72 hrs after the clinical onset of disease[23]. Among various proinflammatory and anti-inflammatory cytokines, IL-6 has the best sensitivity and specificity for early assessment of SAP[27]. The major drawback of IL-6 assay is that its serum concentration decreases very rapidly.

C reactive protein

C reactive protein is an acute phase reactant synthesized by the hepatocytes and is usually elevated in inflammatory conditions. Cytokines like IL-6 are potent inducers of CRP synthesis in liver. It takes nearly 72 hours for the serum level of CRP to peak after the onset of symptoms[28]. It is the most frequently used single biomarker for assessment of severity in AP today. A concentration of more than 150 mg/dL is often accepted as a predictor of severity in acute pancreatitis[23]. The demerit of CRP as marker is its delayed peak (48–72 hours) and its nonspecific nature as inflammatory marker.

Procalcitonin

It is a 116 amino acid propeptide of the hormone calcitonin which is released by hepatocytes and G-cells of the thyroid gland[28]. It is an acute phase reactant that has been extensively investigated as early marker in systemic bacterial infection, sepsis, and multiorgan failure[29]. Severe acute pancreatitis is associated with sepsis, infected pancreatic necrosis, and multi-organ failure. An increased procalcitonin level has been found to be an early predictor of severity, pancreatic necrosis, and organ failure in patients with acute pancreatitis.

Polymorphonuclear elastase (PMN elastase)

PMN elastase is the protease released by activated neutrophil as a first line defense following tissue injury[21]. Granulocyte infiltration and activation occur in the early phase of acute pancreatitis[30]. So PMN elastase has been proved as an early marker of severe acute pancreatitis within 48 hours of onset of symptoms. Quantification of plasma PMN elastase levels has been seen as a very accurate method for the early prognostic evaluation of acute pancreatitis[30].

Trypsin activation peptide (TAP)

This is a small peptide released during the process of activation of trypsin from trypsinogen. In humans, it is excreted in large amount in urine and peritoneal fluid[23]. TAP activity increases early in the course of the disease and attains maximal value within 24-48 hours. Urinary TAP may be used as a potential severity marker for acute pancreatitis[31].

Trysinogen-2

In acute pancreatitis the level of trysinogen-2 rises considerably more than that of trysinogen-1. High level of trypsinogen-2 can be found in both serum and urine. High serum level correlates better with complications and severity following ERCP induced pancreatitis[32]. High urinary trpsinogen-2 is used as a screening test for diagnosis of AP. A rapid dipstick method has been devised for rapid diagnosis of acute pancreatitis[33]. This test is particularly useful in rapid diagnosis of ERCP induced pancreatitis. Overall trysinogen-2 appears to be more useful as a diagnostic marker than as a predictor of severity[34].

Hepcidin

Abnormally high level of hepcidin can be found in acute inflammation. As it is primarily induced by IL-

6, high level of hepcidin can be found in patients with acute pancreatitis[23].

Copeptin

Copeptin is a long amino acid peptide derived from a preprohormone consisting of neurophysin II, vasopressin and copeptin[23]. Its level rises during stress in critically ill patients. Isman et al.[35] studied its role in acute pancreatitis as a predictive marker of severity. They found a significantly high concentration of copeptin at the time of admission in patients with SAP. They also found that copeptin can be used as a novel prognostic marker for prediction of local complication, organ failure, and mortality in acute pancreatitis.

Soluble E-Selectin (sES) and Soluble Thrombomodulin (sTM)

Soluble ES is an endothelial activation marker, whereas soluble TM is an endothelial injury marker. During acute pancreatitis activated neutrophils release elastase which damages the endothelium. These two markers have their significance in assessment of severe acute pancreatitis[23,36]. High levels of soluble ES can be found in all stages of the disease; therefore it can be used to monitor the disease severity. Soluble TM can be used as a predictive marker of mortality in acute pancreatitis[23,36].

Serum Intercellular Adhesion Molecule-1 (ICAM-1)

ICAM-1 levels increases significantly in acute pancreatitis. It can be used as a reliable early marker within the first 24 hours of SAP.

Conclusion

For diagnosis of acute pancreatitis, serum amylase is commonly used for early diagnosis of acute pancreatitis while lipase is used to confirm acute pancreatitis in a patient with elevated amylase level. For early prediction of severity, procalcitonin, interleukin-6 and C - reactive protein can be used.

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