What is New in Acute Pancreatitis?

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Acute pancreatitis is associated with a wide range of clinical presentation varying from mild to severe clinical course with an overall mortality of about 10-15%. In recent years there has been a lot of research in understanding the multifactorial etiopathogenesis of acute pancreatitis. The areas of interest include the understanding of the genetic basis of disease, attempts at early predictions of severity and modifying the course with novel therapies. Although nothing much has changed regarding medical management, the role of nutrition and prophylactic antibiotics is getting defined. Minimally invasive interventional techniques for infected pancreatic necrosis are being progressively used in recent years.

Genetic basis of acute pancreatitis

Recent breakthroughs in understanding of genetic basis, of acute pancreatitis have helped in clarifying the pathophysiology and clinical course of patients with acute pancreatitis. Role of acute pancreatitis as the precursor of chronic pancreatitis has also been explored. Genetic research has strengthened the old hypothesis of unregulated, intracellular, premature activation of trypsin as a common pathway for pancreatitis. The focus of research is on three genes: PRSS 1, SPINK 1, and CFTR [1].

Cationic Trypsinogen gene (PRSS 1)

More than 20 mutations have been reported in this gene since the time of its recognition in 1996. Two of these mutations have been associated most commonly with the disease. The trypsin molecule translated from genes with these mutations is probably associated with gain of function with decreased degradation leading to pancreatitis. PRSS 1 mutations appear to be restricted almost exclusively to families with hereditary pancreatitis. Incidence of causative PRSS 1 mutations is approximately 80% in patients with symptomatic hereditary pancreatitis [2].

Phenotypic behavior of patients with hereditary pancreatitis [2]:

- 60-80% patients develop acute episode with 50 % of these developing chronic pancreatitis and a further 40% of these developing ductal adenocarcinoma, risk of which increases significantly after the age of 40.
- Early age of onset – median of 12 years in EUROPAC study.
- Higher lifetime risk of endocrine and exocrine insufficiency.

Recent consensus conference has laid out the guidelines for the genetic testing of patients with suspected hereditary pancreatitis. Indications include the following [4]:

1. Recurrent (two or more separate documented episodes of typical pain with hyper-amylasaemia) attacks of acute pancreatitis for which there is no explanation
2. Unexplained chronic pancreatitis.
3. Family history of pancreatitis in first degree or second degree relative.
4. Unexplained episode of documented pancreatitis in a child requiring hospitalization and where there is significant concern that hereditary pancreatitis should be excluded.
5. Part of an approved research protocol.

PSTI/SPINK 1 and CFTR

PSTI (pancreatic secretory trypsin inhibitor) or SPINK 1 (serine protease inhibitor, kazal type 1) gene mutations are associated with defective inhibition of prematurely activated trypsin. CFTR (cystic fibrosis gene) mutations lead to defective channel of anion transport resulting in decreased flow of pancreatic juice, allowing for premature activation of trypsinogen in the

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Table 1**Details of two most common reported PRSS1 mutations**

Authors	Mutation: amino acid change, position in genomic DNA, nucleotide change	Frequency	Proposed mechanisms
Whitcomb et al, 1996 [1]	R 122H (G > A transition, at nucleotide position 133283, CGC > CAC)	Most common	<ul style="list-style-type: none"> • Elimination of autolysis site • Increased autoactivation • Decreased degradation
Gorry et al, 1997 [3]	N29I (A>T transversion, at nucleotide position 131945, AAC > ATC)	Second most common	<ul style="list-style-type: none"> • Increased autoactivation • Decreased degradation?

duct leading to pancreatitis.

Despite above proposed mechanisms, the evidence linking these gene mutations to pancreatitis is still very unclear. Unlike PRSS 1 mutations, most individuals (> 99%) with these mutations do not develop acute or chronic pancreatitis. Because of the lack of a proper understanding of mechanisms linking these gene mutations to pancreatitis, and technical difficulties, the genetic testing of these two genes is still considered premature [1].

Early events and pathogenesis of acute pancreatitis

Role of premature, intracellular zymogen activation in acute pancreatitis has been an active area of interest. To understand the pathogenesis, we must know the protective mechanisms against premature zymogen activation [1]. Inadvert activation of proteases is kept in check by various mechanisms: synthesis as an inactive form called zymogen, compartmentalization of various zymogens in subcellular segments and tight control of intracellular calcium. Once activated, protective mechanisms like R122 (site on trypsin molecule) dependent trypsin autolysis and specific trypsin inhibitors (SPINK 1) play an active role. After secretion in the pancreatic duct, which is a calcium rich environment, the activation is kept in check by protease inhibitors and CFTR dependent rapid flushing of zymogens from the pancreatic duct.

Role of calcium

Various experimental models of acute pancreatitis have suggested that, increase in intracellular calcium concentration is a common denominator. This fact is strengthened by clinical observations of acute pancreatitis occurring as a complication of hypercalcemia caused by endocrine abnormalities or after cardiac bypass. Recent review by Sutton et al has emphasized the central role of calcium in pathogenesis of acute pancreatitis [5]. Increase in calcium stabilizes the activated trypsin molecule by limiting the exposure of autocatalytic site (R 122) to another trypsin molecule.

Role of Cathepsin B and Trypsin

Cathepsin B is a lysosomal hydrolase, which

prematurely activates trypsin. Cathepsin hypothesis has been recently strengthened by experimental pancreatitis in Cathepsin B gene knocked-out mice. There was significant reduction (80%) reduction in premature activation of trypsin molecule [6].

The evidence to support the role of trypsin in the premature activation of digestive protease is still confusing. Recent experimental study has suggested that, trypsin activity is neither required, nor involved in trypsinogen activation, that trypsinogen doesn't autoactivate in living pancreatic acinar cell, and that its most prominent role is in autodegradation [7].

In short, increase in intracellular calcium concentration resulting from various insults causing pancreatitis leads to fertile environment and largely unknown events for premature protease activation by Cathepsin B in physiologically co-localized classes of enzymes. Overall, the exact nature of early events is unknown and remains an active area of research. This may have important therapeutic implications.

Predictors of severity

Many recent studies have reported various clinical and biochemical parameters and their utility in assessing the severity of pancreatitis.

Multi-factorial scoring systems

Although APACHE II and Ranson's scoring systems remain the most practical and reasonably accurate predictors of severity, there has been realization that the dynamic nature of early organ dysfunction and so the need for dynamic scoring system instead of a scoring at a single point of time is required. Worsening [8] or persistent [9] organ failure during first week has been strongly correlated with severity of disease and mortality. According to a recent report, the 48-hour APACHE II score has improved predictive value compared with the admission scores and deteriorating APACHE II score at 48 hours after admission may identify patients at risk for an adverse outcome [10]. Measuring the initial severity of pancreatitis combined with the physiological response to intensive care treatment is a practical and clinically relevant approach for predicting mortality in patients with severe acute pancreatitis [11].

Routine laboratory data

A recent multicentric trial has reported significant correlation of serum creatinine > 2 mg/dl and blood sugar > 250 mg/dl measured at admission with mortality. Similarly abnormalities in chest radiographs combined with raised serum creatinine > 2mg/dl have been correlated with higher risk [12].

Markers of inflammation and cytokines

Recent trial has shown that, C- reactive protein levels > 150 by 48 hours is shown to have positive predictive value for prediction of severity ranging between 37% - 77%, which is similar to APACHE II [12]. Serum CRP an acute phase reactant, peaks about third day after initiation of pain. PMN elastase levels greater than 300 mg/L has been shown to be about 81- 98% accurate in prediction of severity at 24 hours [13]. Procalcitonin has been shown to have accuracy of about 85% in prediction of severity. A recent study has evaluated rapid serum detection of procalcitonin with dipstick method for values > 0.5 ng/ml [14]. Further studies are required to validate this method of detection. Amongst cytokines, the most widely and clinically useful cytokines seems to be IL- 6. It is shown to be most accurate predictor of severity with 90% accuracy within first 24 hours when compared to CRP and APACHE II [15]. All other cytokines (IL-1, IL-1ra, IL-1/IL-1ra ratio, and s TNFR), have been studied and may prove to be of clinical benefit. Detection of these cytokines is tedious and further studies are required to prove the clinical utility of these cytokines [16].

Pancreas specific markers

Amongst the number of markers (pancreas-associated protein, carboxypeptidase B activation peptide, amylase, lipase), urinary and serum trypsinogen activation peptide (TAP) levels, are most extensively studied and promising in predicting the severity of acute pancreatitis [16]. TAP is released on activation of trypsinogen to trypsin. Johnson et al reported that, if urinary TAP levels is > 25 nmol/l of any one estimate, out of three estimates at 12 h intervals, the likelihood of persisting organ failure or a local complication is increased by factor of 2.3 [17]. Sensitivity of combined CRP and urinary TAP was shown to be higher although a previous report showed no superiority of combined assay [18]. Plasma TAP levels with a cutoff of 2.8 nmol/l also has been shown to be of same accuracy as of urinary TAP [19].

In summary, urinary TAP levels and IL-6 levels within first 24 hours and CRP levels at 48 hours with worsening organ function, reasonably predicts the severity of pancreatitis.

Medical management of acute pancreatitis

Role of intravenous antibiotics

Majority of randomized trials and meta-analysis for use of antibiotic prophylaxis for necrotizing pancreatitis has shown significant reduction in infectious complications. Only a single adequately powered study [20] of cefuroxime has shown significant decrease in mortality with another small inadequately powered study [21] of ofloxacin/metronidazole combination showing no mortality in patients receiving antibiotic prophylaxis. Despite this inconsistent benefit of prophylactic antibiotics, most centers throughout the world are using such regimens. Two recent trials have added to the controversy of antibiotic prophylaxis.

Nordback et al conducted a randomized control trial using early versus late treatment with imipenem/cilastatin combination in acute necrotizing pancreatitis (CRP > 150 mg/L, necrosis on CT). Early imipenem/cilastatin combination was associated with significant reduction in need for surgery, overall number of major organ complications and, a trend towards reduction of mortality [22].

Isenmann et al recently conducted first well-designed double blind study comparing Ciprofloxacin (400 mg twice daily) + Metronidazole (500 mg twice daily) in acute necrotizing pancreatitis. Interim analysis of 114 patients didn't show any benefit of prophylaxis with regards to decrease in the rate of infected pancreatic necrosis or systemic complications. But 28% of patients in study group received open antibiotic treatment (newly developed sepsis/SIRS/MSOF or suspicion of extrapancreatic/pancreatic infection) as compared to 46% in placebo group [23].

The changing trend in spectrum of pancreatic isolates and concerns about emerging antibiotic resistance has complicated the issue of prophylactic antibiotic use. Gram positive organisms and fungi have been isolated from pancreatic and peripancreatic tissues with associated higher morbidity and mortality [24]. There have been no prospective studies till date to prove the effectiveness of prophylactic antifungal treatment [25].

Based on above studies and issues, recent guidelines have recommended against the routine use of intravenous antibiotics and antifungal agents in acute necrotizing pancreatitis [25].

Role of Nutritional support

Hypercatabolic patients with severe acute pancreatitis require some form of nutritional support. Until recently the enteral nutrition was feared to be associated with exaggeration of symptoms due to pancreatic stimulation. Recent studies have shown that the stimulation of

pancreatic secretions decreases with more distal feeding. The effects on pancreatic secretions are mitigated when feeding occurs significantly beyond the ligament of Treitz although accurate placement of such tube at this level is difficult. There is only one randomized controlled trial published in abstract form, which has shown no difference in nasogastric versus nasojejunal feeding [26].

A recent trial has shown safety and efficacy of total enteral nutrition in patients with predicted severe pancreatitis [27]. Another trial demonstrated an attenuated systemic inflammatory response in enterally fed patients with reduction levels of CRP, IL-6 and TNF- α [28]. The recent meta-analysis has analyzed 6 good quality trials concluding that the enteral nutrition is associated with significant reduction in infective complications, requirement for surgical intervention and shorter length of hospital stay with a trend towards reduction in mortality [29]. Although no meta-analysis can be without bias, the corpus of experimental and clinical evidence support the use of total enteral nutrition in patients with severe acute pancreatitis.

Role of glutamine enriched diets and immunonutrition has also been emphasized recently. In a recent randomized trial patients receiving 0.3g/kg L-alanine-L-glutamine enriched parenteral nutrition showed significant increase in cholinesterase, albumin and lymphocyte count, as well as decrease in CRP compared to standard TPN at day 14 resulting in trend to decrease hospital stay [30]. In a latest and the only RCT of enteral nutrition comparing glutamine-enriched diet with standard enteral nutrition has shown significant elevations in serum IgG, retinol binding protein and significantly more rapid recovery [31].

Prevention of ERCP induced pancreatitis

Prevention of ERCP induced pancreatitis is an active area of interest because of inability to decrease the incidence despite technical improvements. Recent studies on pharmacological prevention of pancreatitis have evaluated various agents. Gabexate, somatostatin and probably IL-10 are presently the only agents to show some benefit in prevention of pancreatitis.

A recent randomized controlled trial of intravenous bolus somatostatin in dose of 250mg immediately after diagnostic ERCP in selective patients (those undergoing therapeutic ERCP) has shown significant reduction in incidence of pancreatitis [32]. This modality seems to be a cost-effective measure as compared to continuous infusion of somatostatin, which has also been shown, be of proven value.

Role of novel therapies

Platelet activating factor inhibitor Lexipafant has been

shown to ameliorate SIRS in animal studies. A recent double blind, randomized controlled study of Lexipafant at doses of 100 mg/24h IV for 7 days, commenced within 72 hours of onset of symptoms in 270 patients with APACHE II > 6, was not able to show any clinical benefit [33]. Likewise the role of protease inhibitors like Gabexate Mesylate has also been questioned by a recent multicentric trial although experimental evidence has shown benefit [34].

Role of intervention/surgery

Timing of surgery for infected necrosis

There is no consensus about the timing of surgery in patients with infected pancreatic necrosis. Delayed surgery theoretically provides better chance of necrosis being demarcated. Only one small prospective randomized controlled trial has shown reduction in mortality by 50% with delayed (> 12d) surgery [25]. This study probably had a randomization bias with sicker patients entering in early surgery group. Recent retrospective analysis has shown trend towards higher mortality and higher number of major complications with early (less than 2weeks) necrosectomy [35]. Consensus guidelines have recommended for delay in necrosectomy by at least 2-3 weeks if the patient's condition and clinical picture allows for the same [25].

Timing of cholecystectomy

Till recently, cholecystectomy during same hospitalization for gall stone-associated pancreatitis after symptomatic improvement was considered standard treatment. The same may remain true for mild pancreatitis. A recent retrospective analysis for patients with moderate-severe gall stone-associated pancreatitis has stressed upon appropriate timing of cholecystectomy. The cholecystectomy should be delayed in patients with moderate to severe gall stone-associated pancreatitis until the fluid collections or pseudocysts either resolve or persist beyond 6 weeks, at which time pseudocyst drainage can safely be combined with cholecystectomy [36]. Such a recommendation is based on the hypothesis that, recurrence of pancreatitis after moderate to severe pancreatitis is almost unknown and we can safely wait. Delayed treatment was associated with lesser need for percutaneous drainage, less chances of infecting fluid collections, lesser complications of cholecystectomy, and shorter mean stay in the hospital.

Minimally invasive approaches pancreatic necrosis

Laparoscopic surgery

In 1996 Gagner reported 8 patients managed with laparoscopic technique utilizing one of three approaches:

transgastric, retroperitoneoscopic, and retrogastric/retrocolic. Recently Gambiez et al in 1998 have reported their experience of endoscopic retroperitoneal approach in 20 patients via a 6-cm lumbotomy centered on 12th rib with mean number of 5 lumboscopic procedures required [37].

Percutaneous sinus tract necrosectomy

With high mortality associated with open necrosectomy, investigators have tried percutaneous procedures for necrosectomy. Freeny et al reported overall sepsis control of 74% of patients, converting an emergency into an elective procedure. 47% had complete control of sepsis with no surgery required. This required a mean of four catheter insertions and 8 hourly lavage for a mean of 85 days. Echenique et al also reported encouraging results in 20 patients who underwent percutaneous catheter debridement. Recently Carter et al described the technique and results of percutaneous necrosectomy and sinus tract endoscopy for infected pancreatic necrosis. Initial procedure involved guided placement of 8°F pigtail in the cavity followed by dilatation of tract to 32°F and necrosectomy with nephroscope in operation theatre under general anesthesia. Residual sepsis was managed with repeated necrosectomy [38].

Laparoscopically assisted percutaneous drainage

Horvath et al recently described laparoscopic-assisted percutaneous drainage of infected pancreatic necrosis in 6 patients' with favorable outcome [39].

All above techniques although feasible, are new and further studies are required to substantiate the evidence for such procedures.

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