Review Article

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Acute Pancreatitis

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Abstract

Acute pancreatitis (AP) is a systemic immunoinflammatory response to auto-digestion of the pancreas and peri-pancreatic organs. Is a frequent gastrointestinal disease with an important morbi-mortality, reaching 30% in severe cases. Different studies and reviews by international groups develop multiple classification systems to assess the severity and address the correct management along time, identifying the better molecular markers, clinical outcome determinants and reaching conservative management as the angular piece in AP. In this review we present a compilation of the latest studies and international consensus about AP physiology, etiology, risk factors, diagnosis, severity assessment, imaging and treatment.

Introduction

Acute pancreatitis (AP) is a systemic immunoinflammatory response to auto-digestion of the pancreas and peri-pancreatic organs. AP is a common and life threatening disease. Annual incidence worldwide is 4.9–73 cases per 100000 people; affect male's predominantly young adults 2.5:1. The mortality rate for pancreatitis is between 1.5% and 4.2% in large epidemiological studies, but varies according to the severity of pancreatitis, increasing to 30% in those with infected pancreatic necrosis [1,2].

Pathophysiology

There are plenty of theories about the patophysiology of AP, most of them conclude that distal ductal obstruction, irrespective of the mechanism, leads to upstream blockage of pancreatic secretion, which in turn impedes exocytosis of zymogen granules (containing digestive enzymes) from acinar cells. Consequently, the zymogen granules coalesce with intracellular lysosomes to form condensing or autophagic vacuoles containing an admixture of digestive and lysosomal enzymes [3].

The activation of this normally intra pancreatic inactive enzimes produce a proinflammatory signals cascade along the gland, with posterior release in the circulatory system and the consequently systemic inflammatory response síndrome (SIRS). The Interleukine-1(IL-1), Interleukine-2(IL-2), Interleuckine-6 (IL-6) and Interleukine-8 (IL-8) release favour monocytes and macrophages quimiotaxis and signal amplification with Tumor Necrosis Factor-α (TNF - α) release by this last, and final permeability increase in different systems like vascular and gastrointestinal [4]. Once the initial damage is stablished the progress and outcomes would depend on the medical management during the first 24 hours [5]. In case of limit the pancreatitis origin and the correct initial management with aggressive fluid therapy, the pancreatic injury and the cytokine release can be limited, with the consequent decrease in SIRS and better outcome. If it is not accomplished acinar cells would develope ischemia and necrosis secondary to hipoperfusion [6]. Persistent citokynes release by necrotic tissue would increase vascular permeability favouring pulmonar effusion and respiratory distress, hypovolemia, hypotension, acute renal failure, intestinal edema and intra-abdominal hypertension [7,8].

Interstitial edema, absent peristalsis and increased gut permeability have been associated with bacterial translocation and sepsis. Intra-abdominal hypertension (IAH) and abdominal compartimental síndrome (ACS) can be developed in 35% of cases with severe pancreatitis secondary to intestinal edema, ascites and retroperitoneal liquid collections sometimes precipitated by an aggressive fluid therapy. Actually IAH and ACS are considered a severity parameter [8-11].

There is consistent evidence that alcohol increases the propensity for precipitation of pancreatic secretions and the formation of protein plugs within pancreatic ducts owing to changes of lithostathine and glycoprotein 2, two non-digestive enzyme components of pancreatic juice with self-aggregation properties; and to increased viscosity of pancreatic secretions because of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction. The protein plugs enlarge and form calculi, causing ulceration of adjacent ductal epithelium, scarring, further obstruction and eventually, acinar atrophy and fibrosis. Experimental studies have shown that alcohol increases digestive and lysosomal enzyme content within acinar cells and destabilises the organelles that contain these enzymes, thereby increasing the potential for contact between digestive and lysosomal enzymes, and facilitating premature intracellular activation of digestive enzymes. These effects of alcohol on acinar cells are probably a result of the metabolism of alcohol within the cells, leading to the

generation of toxic metabolites (acetaldehyde, fatty acid ethyl esters, and reactive oxygen species) and changes in the intracellular redox state [12].

Genetic factors related to digestive enzymes, trypsin inhibitors, cytokines, CFTR, alcohol- metabolizing enzymes, oxidant stress-related proteins, and detoxifying enzymes have not shown an association with alcoholic pancreatitis. Investigators of a genome-wide association study reported an association between overexpression of claudin 2 (a tight-junction protein) and increased risk of alcoholic pancreatitis, with the protein overexpressed on the basolateral membranes of acinar cells in these patients. However, the functional significance of this finding remains unclear and need more research [12].

Etiology

There are plenty of AP causes (Table 1). Alcohol and gallstones are responsible of 80% of cases. Incidence of idiopathic pancreatitis is increasing, maybe related with risk factors as obesity and metabolic síndrome, and the 57% of this have been demonstrated with microlitiasis as cause [13,14]. People with gallstone disease will develope pancreatitis in 5%, and 25% of this a severe one [15]. Without definitive treatment in this case recurrence is as high as 40% [16]. Choledocholithiasis is uncommon (20%–30%) following a mild attack of ABP [17]. Gallstones <5 mm in diameter are more likely to cause pancreatitis than larger stones. The presentation of acute pancreatitis in only 2-3% of alcoholic people suggest a genetic factor implicated [18]. In this etiology consumption of >100 g of alcohol in 24 hours and low intake of fat are significant risk factors [15].

Frequent	Less Frequent
Gallstones	Autoimmune
Alcoholism	Genetic
Hypertrigliceridemia	Abdominal trauma
Post–endoscopic retrograde cholangiopancreatography	Postoperative Ischemia Infections
Idiopatic (Microlitiasis 57%)	Hypercalcemia and hyperparathyroidism
Drug induced: Azathioprine, 6-Mercappurine, Trimethroprim-sulfamethoxazole, Pentamidine, 2,3 Dideoxyinosine, Asparginase, Methyl-dopa	Posterior penetrating ulcer
	Scorpion venom
	Pancreas divisum

Table 1: AP causes.

Risk factors

Multiple risk factors are associated with the developement and severity of AP. Diabetes mellitus 2 have been documented to increase the risk of AP in a 1.86-2.89 times. A double-blind, placebo-controlled, randomized clinical trial in patients with type 2 diabetes mellitus reported a cumulative incidence of AP of 0.47% in the placebo group over the 5 years of the clinical trial, a rate higher than the general population estimates. Some patients with type 2 diabetes have comorbidities requiring the use of medications that have been associated with pancreatitis and possibly the increased incidence of AP in this population results from the same spectrum of aetiologies that may result in the development of type 2 diabetes or from comorbidities, and is reflective of the selected trial population. In a large United States of America database study by Girman et. al., the

annual incidence rate of AP in the cohort without diabetes was found to be 22.0/100000 patient-years [13]. In contrast, the annual incidence rate of AP among the cohort with type 2 diabetes was found to be 65.9/100 000 patient-years, which was comparable in men and women [13,14,16-19].

There is a significative association between body mass index and developement of biliary AP. Although there is a high prevalence of metabolic síndrome it have been demonstrated that waist circunference, body mass index, age or sex were not related with pancreatitis severity [20]. In the other hand obesity is a chronic low-grade inflammatory state characterized by high circulating levels of proinflammatory cytokines. Alternatively, obesity may intensify the immune response, which is able to exacerbate pancreatic injury and is related with a poor prognosis [12,20,21].

Current and former smokings are associated with increased risk for AP. Several expeimental studies on rat models have investigated the effect of smokin showing increased inflammatory activity, focal inflammation, decreased number of acinar structures and up-regulation of genes expresing digestive enzymes [22-24].

Multiple genetic factors are being studied to elucidate the patophysiology of AP because some patients with a seemingly mild pancreatic injury (eg. during endoscopic retrograde cholangio-pancreatography [ERCP] without pancreatic duct injection) develop severe AP, whereas other subjects with extensive injury have a relatively mild course. For example the angiotensin-converting enzyme I (rather than D) allele was significantly associated with alcohol-related AP (P = 0.03). The renin rs5707 G (rather than A) allele was associated with AP (P = 0.002), infected necrosis (P = 0.025) and mortality (P = 0.046) [25]. In preliminary studies, the authors found that the MCP-1–2518 A/G single nucleotide polymorphism predicted that the physiological response to pancreatitis would be severe and was associated with death [26].

Diagnosis and etiology assessment

The diagnosis of acute pancreatitis is based on the fulfillment of 2 of the following criteria [27]:

Clinical upper abdominal pain

Serum amylase or lipase >3x upper limit of normal

Computed Tomography (CT), Magnetic Resonance Imaging (MRI), or ultrasonography criteria.

Once the diagnosis is established the etiology must be elucidated (Table 1), for the correct management and better outcomes. The principal etiology is gallstones in 40% of cases. Abdominal ultrasonography (USG) is the primary imaging study for abdominal pain associated with jaundice and for excluding gallstones as the cause of acute pancreatitis. Pancreas visualized inadequately in 30% of cases, with about 50% sensitive for the detection of choledocholithiasis. Gallstones <5 mm in diameter are more likely to cause pancreatitis than larger stones. ALT>150 UI/L had a postitive predictive value of 95% in diagnosing acute gallstone pancreatitis [28-31].

Alcohol origin is seen in 30% of pancreatistis. Clinical history can elucidate the origin, like drinking more than eight alcoholic drinks/day (>100 g/d) for more tan 5 years. It is present in males predominantly, most of them are young adults 2.5:1[32].

Proposed mechanisms of alcohol damage include sphincter of Oddi spasm, precipitation of insoluble protein plugs that obstruct the pancreatic secretion by cholecystokinin [33].

Hipertriglyceridemia account for 2% of cases, and >1000 mg/Dl is diagnostic.

5% of Endoscopic retrograde cholangiopancreatography (ERCP) develop AP by 2 main mechanisms: traumatic intubation of the ampulla or hydrostatic pressure during contrast injection, in most of cases with a mild AP [18].

Drug induced pancreatitis is present in 2% of cases with angiotensin-converting enzyme inhibitors, corticosteroids, diuretic and azathioprine as the principal precipitating drugs. In 0.2% of cases blunt trauma and 1% of penetrating injuries AP can develop. Postoperative, ischemia, autoinmune, hyperparathyroidism, coxsackie, cytomegalovirus or herpes are less frequent causes [15].

In idiopathic acute pancreatitis 74% had biliary sludge detected by USG or had colesterol monohydrate or calcium bilirubinate crystals detected by biliary microscopy. In cases of idiopathic pancreatitis an endoscopic USG or CPMR must be done to discard microlitiasis, present in 57% of cases [1]. Endoscopic ultrasound has 90% sensitivity and 95% specificity for detecting choledocholithiasis and is somewhat more sensitive that MRCP in detecting choledocholithiasis [33].

Severity assessment

Atlanta classification defines three degrees of severity: mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis but Determinant - based classification (DBC) adds critical acute pancreatitis (Table 2) [34] and is the current classification to be employed.

DBC	Mild AP	Moderate AP	Severe AP	Critical AP
Pancreatic necrosis	No	Sterile	Infected	Infected
-	Both present	One or two present	Either one criterion	Both present
Organ failure	No	Transient	Persistent	Persistent

Table 2: Classification Sistem for severity of Acute Pancretitis.

System	0	1	2	3	4
Renal Creatinine(mg/dl)	<1.4	1.4-1.8	1.9-3.6	3.6-4.9	>4.9
Respiratory PaFi	>400	400-301	300-201	200-101	≤100
Cardiovascular (systolic blood pressure, mmHg)*	>90	<90 Fluid responsive	<90 Not Fluid responsive	<90 pH<7.3	<90 pH<7.2
*Without inotropic support					
Organ failure is defined as a score ≥2 for one of the three scoring systems.					
Multiple organ failure is defined as ≥2 systems affected.					

Table 3: Modified Marshall Score.

This classification includes transient organ failure, persistent organ failure, and local or systemic complications. Transient organ failure is organ failure that is present for <48 h and persistent organ failure >48 h, according to the modified Marshall score (Table 3). Local complications include peripancreatic fluid collections, pancreatic pseudocyst, pancreatic necrotic collections and walled-off necrosis (Table 4), while systemic complications can be related to exacerbations of underlying co-morbidities related to the acute pancreatitis. Mild acute pancreatitis is characterised by the absence of organ failure and the absence of local or systemic complications.

Local complication	*CECT	Developement time
Acute peripancreatic fluid collection	-Heterogeneous collection with fluid density adjacent to páncreas. -No recognizable wall encapsulation the collection. -Occurs only in instestitial edematous AP.	First 4 weeks after onset of interstitial edematous AP
Pancreatic pseudocyst	-Round or oval well circumscribed, homogeneous fluid collection. -No nonliquid component -Well-defined wall	>4 weeks after onset of interstitial edematous AP
Acute necrotic collection	-Heterogeneous nonliquid density of varying degrees -No definable encapsulating Wall -Intrapancreatic and/or extrapancreatic	Occurs in setting of acute necrotizing pancreatitis
Walled-off necrosis	-Heterogeneous liquid and nonliquid density varying degrees of loculations. -Welldefined encapsulating Wall -Intrapancreatic and/or extrapancreatic	>4 weeks after onset of nerotizing pancreatitis.
*CECT Constrast Enchanced Computed Tomography		

Table 4: AP local complications.

Moderately severe acute pancreatitis is characterised by the presence of transient organ failure, local or systemic complications in the absence of persistent organ failure [35]. One would expect the presence of a local complication by persistence of abdominal pain, secondary increases in serum amylase/lipase activity, organ failure, fever/chills, and so forth. Such symptoms usually prompt a cross-sectional imaging procedure to search for these complications [36].

Severe acute pancreatitis is characterised by persistent organ failure. When SIRS is present and persistent, there is an increased risk that the pancreatitis will be complicated by persistent organ failure. Persistent organ failure may be single or multiple organ failure. Patients with persistent organ failure usually have one or more local complications. Patients who develop persistent organ failure within the first few days of the disease are at increased risk of death, with a mortality reported to be as great as 36–50%. The development of infected necrosis among patients with persistent organ failure is associated with an extremely high mortality, classified as critical acute pancreatitis [37].

Attempts to define objective criteria for assessing disease severity and prognosis were pioneered by John Ranson and Clement Imrie in the 1970s including basic laboratory data and clinical variables obtained within 48 h after hospital admission. These scoring system have found widespread application and underwent numerous modifications [38]. The Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system for critical illness may also be useful in predicting severity of pancreatitis, mortality, and need for ICU admission. This was superior to both Ranson and Glasgow scores at 48 h. Although the APACHE II scoring system has gained some recognition for its performance and flexibility, the complexity of the system hinders its everyday use [16].

Abdominal hypertension (AH) and Abdominal Compartimental síndrome (ACS) has emerged as one important parameter of severity by the relation with further complications and persistent organ failure. In a study by Ke Lu et al. the Intra-abdominal pressure (IAP), APACHE II, C-reactive Protein and D-dimer was compared for the prediction of severity at 24 hours of admission [8]. IAP and APACHE II was the more accurate to predict severe pancreatitis with a 50% higher mortality for each 1 mmHg of IAP>12 mmHg [8,11].

Independent markers like C reactive protein has an excellent positive predictive value for severe pancreatitis at 48 h [39-41].

In a meta-analysis of 399 patients presenting with AP, a haematocrit of >44% was predictive of the development of severe AP (along with a raised BMI and pleural effusion) [42].

Rise in blood urea nitrogen (BUN) of >5 mg/dl within 48 hours of admission was associated with the development of infected pancreatic necrosis (IPN) in 15.4% of patients, while a rise of >10 mg/dl was associated with primary IPN in 55.5% [43].

Other novel markers of severe AP include serum procalcitonin, amyloid A and cytokines such as IL-6, IL-8, IL-15, IL-12 and plasma angiopoietin-2. In a multi-centre study of 104 patients with predicted severe AP, a procalcitonin value of >3.5 ng/ml on two consecutive days was a more reliable marker of infected necrosis with MODS than a CRP of >430 mg/litre [44,45].

Only overweight has been related to AP severity, local complications and mortality. However, waist circumference (WC), body mass index (BMI), sex, or age does not correlate with disease severity [20]. Age greater than 70 has been correlated with 19% increased risk of death but is not corroborated by other studies [10].

Higher morbi-mortality and interventions are needed in the AP patients with acute kidney injury, and hypertriglyceridemia is an independent risk factor for acute kidney injuri (AKI). Obesity and hypertriglyceridemia increase the oxidative stress, endotelial disfunction, inflammation and AKI [20,46].

Imaging

During intial evaluation an USG to discard gallstones as AP origin must be performed.

The gold standard for pancreas evaluation is a contrast-enhanced computed tomography (CECT). An early (<72 h) CECT may underestimate the eventual extent of pancreatic and peripancreatic necrosis [34]. CECT is indicated only in patients with severe pancreatitis 72-96 h after onset of AP, in patients with an uncertain diagnosis or when the clinical course is worse with correct treatment looking for local complications. It allows us to identify pancreatic lessions and define if is an edematous or necrotic pancreatitis. The local complications to be identified include infected necorsis (gas presence), walled of necrosis, pseudocyst and peripancreatic fluid collections. One week CECT for follow up is recommended to perform, with thin collimation and slice thickness (i.e. 5 mm or less), 100-150 ml of non-ionic intra-venous contrast material at a rate of 3 mL/s, during the pancreatic and/or portal venous phase (i.e. 50-70 seconds delay). During follow up only a portal venous phase (monophasic) is generally sufficient. For MR, the recommendation is to perform axial FS-T2 and FS-T1 scanning before and after intravenous gadolinium contrast administration [27].

Treatment

Fluid therapy

Fluid therapy must be 5-10 ml/k/h after AP onset, with lactated ringer solution because it reduces the incidence of SIRS by 80% compared with saline resuscitation [9,27,47].

Nutritional support

Oral feeding in predicted mild pancreatitis can be restarted once abdominal pain is decreasing. Nutritional support is indicated 48 hours after severe AP onset. Enteral nutritional support will always be preferred. In case of not tolerating oral feeding a nasogastric or nasojejunal tube most be installed and polymeric or elemental formulations can be used. Enteral feeding preserve physical gut barrier function, reduce microbial translocation, improve gut blood flow, preserve gut mucosal surface immunity, and maintain gut-associated lymphoid tissue mass and function [48,49]. This factors contribute to better outcomes and limited SIRS, less infectious complications and inclusive pain release in 25% of cases [27,47]. Parenteral nutrition can be administered in acute pancreatitis as second-line therapy if nasojejunal tube feeding is not tolerated and nutritional support is required. Immunonutrients like glutamine and ω-3 fat acids added to parenteral formulas can improve prognoses in patients with acute pancreatitis. Parenteral immunonutrition significantly reduced the risk of infectious complications (RR ¼ 0.59; 95% CI, 0.39-0.88; p= 0.05) and mortality (RR ¼ 0.26; 95% CI, 0.11-0.59; p= 0.001). Length of hospital stay was also shorter in patients who received immunonutrition (MD ¼ 2.93 days; 95% CI, 4.70 to 1.15; p=0.001) [50].

Abdominal hypertention

Intra-abdominal hypertension (IAH) is a life- threatening sustained elevation of the intraabdominal pressure that is associated with new onset organ failure or acute worsening of existing organ failure. It is defined as >12 mmHg intra-abdominal pressure. The incidence of IAH in this population is very high varying from 60 to 85% [39,51]. Abdominal compartment syndrome (ACS) is defined as a sustained intra-abdominal pressure >20 mmHg that is associated with new onset organ failure [27].

Zhao et al. and Wu Bu et al. found that using a resuscitation protocol with only normal saline, patients had higher intra-abdominal pressure (IAP) and ACS more often, compared to patients treated with a combination of colloids and crystalloids [52,53].

The noninvasive alternative for management include: sedation, neuromuscular blockade, nasogastric decompression, and correction of a positive cumulative fluid balance [52].

Babu et al. found that percutaneous catheter drainage (PCD) resulted in sepsis reversal in almost two-thirds of the patients, and avoided open necrosectomy despite the presence of infection in the majority of the patients undergoing PCD, in about half of them [54]. If this therapeutic is not effective median laparotomy is indicated [51-55].

Biliary pancreatitis management

During admission for mild biliary pancreatitis cholecystectomy appears safe and is recommended. Interval cholecystectomy (4 weeks) after mild biliary pancreatitis is associated with a substantial risk of readmission for recurrent biliary events, especially recurrent biliary pancreatitis in 60% of cases [56].

In patients with peripancreatic collections cholecystectomy should be delayed until the collections either resolve or if they persist beyond 6 weeks. If patient have undergone sphincterotomy and are fit for surgery, cholecystectomy is advised [27].

ERCP is probably indicated in biliary pancreatitis with common bile duct obstruction. Early ERCP (<24h after onset) is only indicated only in the course of billiar AP and colangitis. ERCP should be performed within 72 hours from admission when an impacted biliary stone has been demonstrated [27,57].

Local complications treatment

The optimal interventional strategy for patients with suspected or confirmed infected necrotizing pancreatitis is initial image-guided percutaneous (retroperitoneal) catheter drainage or endoscopic transluminal drainage, followed, if necessary, by endoscopic or surgical necrosectomy. This must be delated after 4 weeks with medical treatment when possible, when the necrosis has become walled-off [27].

Endoscopic transgastric necrosectomy compares favourably with surgery [58]. Clinical trials are needed to validate the various options for intervention. Van Santvoort and colleagues compared step-up management of infected necrosis (placement of percutaneous catheters in addition to treatment with antibiotics, if necessary followed by minimally invasive necrosectomy) with open necrosectomy. This step-up approach reduced new-onset multiorgan failure by 29% [59]. Laparoscopic retroperitoneal necrosectomy is an option to avoid posible contamination of abdominal cavity and has demonstrated good outcomes.

Pseudocyst spontaneous resolution occurs in a third of patients with a pseudocyst <4 cm [60]. Symptomatic pseudocysts can be successfully decompressed by endoscopic cystogastrostomy with endoscopic ultrasound guidance [61].

Ductal disruption can result in unilateral pleural effusion, pancreatic ascites, or enlarging fluid collection, and placement of a briding stent via ERCP usually promotes duct healing if the disruption is focal [18].

Surgical management

Surgical intervention is only indicated in the course of infected necrosis, clinical deterioration after the failure of conservative management, persistent symptoms such as gastric, intestinal or biliary obstruction, pain due to the mass effect or ACS. Initial management of ACS must be medical, and if it fails, a percutaneous guided drainage must be installed. Only if these two steps fail a decompressive laparotomy must be done.

Surgical necrosectomy, if indicated, should be done at a late stage, at least 2 weeks after the onset of pancreatitis, and only after minimally invasive methods have fail for the high morbi-mortality associated with the procedure and poor outcomes [62].

Conclusions

Systemic involvement is the main determinant of outcome in AP, having in mind that the pathogenesis of this disease is a dynamic process that, with the notable amount of data and recent high quality research of many groups, can be better understood, diagnosed and treated. Evolution in knowledge is supporting the systematic and conservative management as the angular piece to obtain better results, setting specific indications for each intervention in the evolution of the disease. All this progress leave minimal invasive procedures and molecular biology as potential targets for new advances in the field.

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