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EDITORIAL

Update on pathogenesis and clinical management of acute pancreatitis

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Abstract

Acute pancreatitis (AP), defined as the acute nonbacterial inflammatory condition of the pancreas, is derived from the early activation of digestive enzymes found inside the acinar cells, with variable compromise of the gland itself, nearby tissues and other organs. So, it is an event that begins with pancreatic injury, elicits an acute inflammatory response, encompasses a variety of complications and generally resolves over time. Different conditions are known to induce this disorder, although the innermost mechanisms and how they act to develop the disease are still unknown. We summarize some well established aspects. A phase sequence has been proposed: etiology factors generate other conditions inside acinar cells that favor the AP development with some systemic events; genetic factors could be involved as susceptibility and modifying elements. AP is a disease with extremely different clinical expressions. Most patients suffer a mild and limited disease, but about one fifth of cases develop multi organ failure, accompanied by high mortality. This great variability in presentation, clinical course and complications has given rise to the confusion related to AP related terminology. However, consensus meetings have provided uniform definitions, including the severity of the illness. The clinical management is mainly based on the disease´s severity and must be directed to correct the underlying predisposing factors and control the inflammatory process itself. The first step is to determine if it is mild or severe. We review the principal aspects to be considered in this treatment, as reflected in several clinical practice guidelines. For the last 25 years, there has been a global increase in incidence of AP, along with many advances in diagnosis and treatment. However, progress in knowledge of its pathogenesis is scarce.

Key words: Pancreas; Pancreatitis; Pathogenesis; Treatment

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INTRODUCTION

Acute pancreatitis (AP), defined as the acute nonbacterial inflammatory condition of the pancreas, is derived from the early activation of digestive enzymes found inside the acinar cells, with variable compromise of the gland itself, nearby tissues and other organs. AP is a disease with extremely different clinical expressions.

Most patients suffer a mild and limited disease but about one fifth of cases develop multiple organ disfunction syndrome (MODS), accompanied by high mortality. This great variability in presentation, clinical course and complications has given rise to the confusion related to AP related terminology. However, consensus meetings (Atlanta and later working groups) have provided more uniform definitions[1-3].

For the last 25 years, there has been a global increase in incidence of AP, along with many advances in diagnosis and treatment. However, progress in knowledge of its pathogenesis is scarce.

PATHOGENESIS

Given the great variability in the clinical manifestations of AP, there are many aspects that have been systematically reviewed and then reflected in consensus meetings and clinical guidelines[4-7]. It is well known that several situations may develop AP, but the innermost mechanisms and how they act to develop the disease are still unknown. Most concepts are based in experimental animal studies and relate to the mechanisms that originate the intracellular activation from trypsinogen to trypsin and, thus, the pancreas "self-digestion" that elicits the local and systemic inflammatory responses. However, these mechanisms are not strictly applicable to humans[8]. Two examples: biliary lithiasis and alcohol abuse are responsible for 70% to 75% of cases of AP in humans but no experimental animal model has reproduced the disease by these mechanisms. On the other hand, cerulein (a cholecystokinin analogue) and a diet supplemented with ethionine, deficient in choline, are very often used to induce pancreatitis in animals but are not accepted causes of AP in humans.

Biochemical and structural changes observed in the early stages of AP in different animal models, as well as in humans, are very similar. Multiple etiological factors involved generate these changes basically through three mechanisms: toxic-metabolic, genetic and mechanical (Table 1). What we do not know is why some individuals will develop an edematous pancreatitis and other individuals a much more severe necrotic pancreatitis[9]. An exhaustive review of the available literature about AP pathogenesis exceeds this article but it may be of interest to summarize some aspects known at present that have implications in the clinical management of AP. If we establish a phase sequence, we should mention some initial steps (alcohol abuse, the passage of calculi through the papilla, *etc*.) that can generate other steps inside the acinar cells (co-localization, zymogens activation, tissular damage, pro-inflammatory factors production) that favor AP development; besides some systemic events, such as chronic inflammation and fibrosis, that will favor chronic pancreatitis development[10,11].

Our current knowledge of the pathogenesis of AP can be summarized by the following points: (1) It has recently been confirmed that AP starts in acinar cells, as shown by animal models in which the main pancreatic duct was ligated[12]; (2) The initial mechanisms by which a diversity of situations develop AP and why they occur is not well known. Only a small percentage of individuals exposed to these developing situations will present with clinical manifestations of the disease. Not every patient with biliary lithiasis or hypercalcemia will develop AP; only 10% of alcohol abusers will develop the disease; (3) The exocrine pancreas synthesizes and secretes digestive enzymes that are mainly activated when they reach the duodenum. A small proportion of trypsinogen is activated spontaneously inside the acinar cells, although there are different substances and protective mechanisms that "wash out" a possible excess of activated trypsin (inhibitor of pancreatic trypsinogen secretion pancreatic secretory trypsin inhibitor or serine protease inhibitor Kazal type 1 (SPINK1), mesotrypsin, enzyme Y, α1-antitrypsin, α2-macroglobulin or autolysis of prematurely activated trypsin)[13]; (4) Once defensive mechanisms have been passed over, the situation favored by the co-localization with lysosomal enzymes, including catepsin B, intra acinar activation of proteolytic enzymes in excessive amounts, favors the pancreas self-digestion;

Table 1 Causes of acute pancreatitis[6,9]

Etiology of acute pancreatitis	
Toxic-metabolic	Alcohol
	Hyperlipidemia, hypercalcemia
	Drugs and pills
	Organophosphorus and other toxic substances
	Venoms (scorpion, spiders)
Mechanical	Biliary: lithiasis, microlithiasis, sludge
	Congenital malformations
	Pancreas divisum
	Annular pancreas
	Anatomical variants:
	Duodenal duplication
	Duodenal diverticulum
	Choledochal cyst
	Ampullary dysfunction and stenosis
	Trauma
Genetic	Familial
	Sporadic
Miscellanea	Vascular
	Hypotension
	Vasculitis
	Embolisms
	Hypercoagulability
	Autoimmune associated to other autoimmune disorders
	Sjögren syndrome
	Primary sclerosing cholangitis
	Celiac disease
	Autoimmune hepatitis
	Infections:
	Virus: mumps, Coxsackie A, HIV, CMV
	Bacteria: Mycobacterium tuberculosis
	Parasites: Ascaris
	Other: Mycoplasma
	Idiopathic

HIV: Human immunodeficiency virus; CMV: Cytomegalo virus.

(5) On the other hand, trypsin will activate other pathways, such as complement, coagulation or fibrinolysis, extending the process outside the gland. The vascular endothelium and the interstitium are affected, which causes a microcirculatory damage that increases the vascular permeability, favoring the liberation of free radicals, pro-inflammatory cytokines (tumor necrosis factor (TNF)-α, interleukins (ILs) 1, 6 or 8), arachidonic acid metabolites (prostaglandins, platelet activator factor, leukotrines) or lipolytic and proteolytic enzymes, that can induce thrombosis and tissular hemorrhage and finally necrosis. Other substances that may be involved are substance P, kinases activated by stress (mitogen-activated protein kinase, extracellular signal-regulated kinase or JUNK), adhesion molecules (P-selectin or E-selectin) and cyclo-oxigenase-2 or heat shock proteins, the only ones that have a protective role[14,15]; (6) Although fortunately not common, occasionally an acute inflammatory process is associated with a systemic inflammatory response syndrome (SIRS) mediated by cytokines and pancreatic enzymes released in to general circulation that may affect distant organs, giving rise to respiratory distress, renal failure, myocardial depression and shock or metabolic alterations. Finally, a MODS may occur with vital risk of necrotic tissue infection, a situation where translocation of intestinal pathogens plays an important role[16,17]; (7) Our understanding of the implication of genetic factors in pathogenesis or the clinical course of AP is poor, but several clear examples of the importance of genetic variability have been reported. The prototype susceptibility genes include the cationic trypsinogen gene (*PRSS1*) and the cystic fibrosis transmembrane conductance regulator gene (*CFTR*), as well as polymorphisms in SPINK1. Premature activation of pancreatic zymogens within the pancreas has also been proposed as the pathogenic mechanism for the acute attacks of pancreatitis seen in patients with hereditary pancreatitis but originated by these mutations. Mutations in at least one allele of the CFTR have been demonstrated in more than 35% of patients with idiopathic chronic pancreatitis and recurrent AP; also, in similar proportions, in patients with AP related to pancreas divisum. How these mutations might produce AP is unclear. One possible explanation is the production of a more concentrated pancreatic juice, leading to ductal obstruction or altered acinar cells function[18,19]; and (8) Genetic modifying factors are another interesting point: in clinical practice, the most important may be those that modify the severity of inflammatory response or increase the risk of specific complications. Some examples are the polymorphisms described in some pro-inflammatory or anti-inflammatory cytokines (TNF-α, IL-8, Il-10)[20].

Thus, AP is a disease that progresses through different phases. The initial step is triggered by an initial event (exposure to different and recognized etiological factors). This generates diverse changes inside acinar cells that produce digestive enzyme inhibition, associated with the co-localization of zymogens of digestive enzymes and lysosomal hydrolases. This generates the activation of zymogens inside the damaged acinar cells. This zymogens activation originates the release of different inflammatory mediators. These mediators regulate the severity of the disease, including its involvement in the development of a systemic inflammatory response. Repeated attacks of AP can promote the development of intrapancreatic fibrogenesis and chronic inflammation, which ultimately will generate chronic pancreatitis.

AP pathogenesis knowledge may have important implications in prevention and treatment. If the early events that generate the inflammatory process are understood, and if pro- and anti-inflammatory factors that modulate the severity of the disease are known, treatment will be implemented so the process will not happen or, at least, the possible associated complications will be minimized.

CLINICAL MANAGEMENT

The clinical management of AP is mainly based on the disease's severity. Two types of pancreatitis were defined at the Atlanta symposium in 1992: one light form, usually auto limited; and the other severe, where local complications may appear, such as necrosis and distant organ failure (OF) (Table 2). Fortunately, these complications are uncommon, occurring in approximately 15% of the cases; mortality, mainly when infected necrosis is present, is very high. The situation's severity will be determined by clinical, analytical and radiological criteria. Because some complications do not appear immediately (necrosis or pseudocysts), a severity definition will be made adequately at the end of the process[1,6]. The first step in the clinical management of AP is to estimate if it will progress as light or severe. The treatment of AP must correct the underlying predisposing factors and control the inflammatory process itself.

Patient's evaluation and prediction of illness severity

So far, there has been no precise method for this purpose, although in daily practice, following several clinical guidelines, a number of criteria are being used[5-7].

Prognosis scales and multiparametric methods: The most commonly used scales are characterized by having a high negative predictive value (NPV), i.e., the process considered mild will evolve in a favorable manner. At the same time, the positive predictive value (PPV) is not that high; many patients considered to suffer a severe disease will also evolve in a favorable manner. The Glasgow and Ranson scales have been and still are being used; they are easy to use, although they require 48 h for a complete evaluation[21-23]. The Acute Physiology and Chronic Health Evaluation (APACHE) Ⅱ scale and its modification for obese patients, is currently the most commonly used scale; a score higher than 8 indicates severe illness. The problem is that 14 variables must be recorded, but it can be useful to assess severity of illness at patient's ad-

Table 2 Definitions for acute pancreatitis according to the Atlanta classification[1,6]

Criteria of illness severity in acute pancreatitis	
Local complications	Necrosis: focal or diffuse area of non viable pancreatic parenchyma, with necrosis of peripancreatic fat (> 30% of the gland or > 3 cm)
	Pseudocyst: pancreatic juice collection surrounded by a wall of granulation or fibrous tissue that is developed as a consequence of acute or chronic pancreatitis or pancreatic traumatism
	Abscess: pus collection well defined that has scarce or no amount of pancreatic necrosis
Systemic complications (organic failure)	Respiratory failure: PaO2 < 60 mmHg
	Shock: systolic BP < 90 mmHg
	Renal failure: creatinine > 2 mg/dL after rehydration
	Upper gastrointestinal bleeding: > 500 mL/24 h
Bad prognosis data	Ranson's scale ⩾ 3
	APACHE II scale ⩾ 8

APACHE: Acute physiology and chronic health evaluation.

mission. More recently, the bedside index for severity in AP system has been developed (Table 3) with a predictive value similar to APACHE Ⅱ, but much simpler to implement because it only reflects five variables[24,25].

Clinical evaluation of MODS: The presence and severity of MODS is not a predictive method by itself, but it is the best indicator of AP severity and mortality, mainly if it appears early, persists for more than 48 h or is multi organic. At the Atlanta symposium, it was defined as shock, pulmonary insufficiency, renal failure and gastrointestinal bleeding; it can be quantified through diverse systems, but in our area, Sequential Organ Failure Assessment is perhaps the most commonly used.

The development of SIRS, characterized by tachycardia, tachypnea, hypocapnia, hyper or hypothermia, leucocytosis or leucopenia, can be recognized with a simple physical exam and often proceed to MODS. The patients that developed SIRS on admission and which persisted during their hospital stay, often developed MODS, with a mortality of 25%. In fact, some studies have assessed the predictive value of the clinical evaluation on admission, pointing out that this is comparable to some of the above mentioned parametric methods applied 48 h later.

Lab tests: The C reactive protein (CRP) is broadly recognized as an indicator of severity. Its serum peak appears 48 h after the disease onset and currently its precision as a prognostic factor is high. Values higher than 150 mg/L have a sensitivity of 80%, specificity of 76%, PPV of 76% and NPV of 86%, as an indicator of severe AP, even when correlated with necrosis. Marked hemoconcentration appears when a large amount of liquid has been accumulated in a third space. A prospective study showed that a hematocrit of 44%, together with the inability to decrease this level in 24 h, were good predictors of MODS and indicators of pancreatic necrosis. In fact, hematocrit NPV at 24 h was very high in predicting pancreatic necrosis and MODS. However, other authors do not report such results. Finally, we should mention that if the blood urea nitrogen (BUN) is increased at admission (> 20 mg/dL) or elevated 24 h later, it indicates poor progress.

Table 3 The bedside index for severity in acute pancreatitis prognosis system[25]

Parameters	
Blood urea nitrogen	BUN > 25 mg/dL
Impaired mental status	Conscious status impairment
Systemic inflammatory response	SIRS criteria presence[1]
Age	> 60 yr
Pleural effusion	Pleural effusion at X ray

[1]Systemic inflammatory response syndrome: presence of ⩾ 2 criteria. Heart rate > 90 bpm; Temperature > 38 ºC or < 36 ºC; Respiratory rate > 20 bpm or PaCO2 < 32 mmHg; Leucocytes > 12.000 or < 4.000/mm3 or > 10% immature forms. BUN: blood urea nitrogen; SIRS: Systemic inflammatory response syndrome.

Imaging studies: It is well known that a pleural effusion, seen in a chest X-ray on admission, predicts poor progress. However, it is more important to focus on the abdominal computed tomography (CT) scan findings, mainly when intravenous contrast administration has been completed, which will show the existence of necrosis, a severe criteria in the Atlanta classification.

A gradation system, used according to CT findings, was developed by Balthazar and has been broadly extended[26]. This, together with a score depending on necrosis extension, allows the calculation of a radiological severity index (CT Severity Index)[27]. Patients with a score higher than 5 had higher mortality, longer hospital stays and required more necrosectomies (Tables 4 and 5).

Not all patients with the diagnosis of AP require an abdominal CT scan. This should be reserved for those with severe AP or that show an evident deterioration during their stay. If a CT is to be obtained, it will preferably be done between the fourth and tenth day after the disease onset. Classically, it used to be said that a very early CT was not very helpful, but for some authors its utility has been demonstrated in the first 36 h to 48 h.

Treatment

The main causes of mortality in AP are MODS and infection of necrotic tissue. Prevention or diagnosis and early correction will be the first goal in the manage-

Table 4 Balthazar score system[26]

Grade	Computer tomography findings
A	Normal pancreas
B	Pancreatic focal or diffuse bigger size, including irregular contour or nonhomogeneous attenuation
C	Grade B + pancreatic inflammation
D	Grade C + fluid collection
E	Grade D + 2 or more fluid collections with or without the presence of gas in the pancreas or next to it

Table 5 Computer tomography index of illness severity for acute pancreatitis[27]

Balthazar's CT grade	Score	Necrosis at CT (%)	Score
A	0	None	0
B	1	< 30	2
C	2	30-50	4
D	3	> 50	6
E	4	-	-

CT index is obtained by the sum of the score obtained applying the Balthazar scale plus the score corresponding to the percentage of necrosis (maximum score = 10). CT: Computer tomography.

ment of these patients. Thus, support measures are very important, including an aggressive hydro-electrolytic replacement, analgesic control and nutritional support, as well as avoiding the recurrence of the process.

Support measures: In any AP patient, even in those that appear to present with light clinical AP, vital signs must be monitored and lab tests must be obtained periodically (oxygen saturation, respiratory and cardiac frequency, blood pressure, diuresis, red blood cell count, white blood cell count, BUN, blood glucose and electrolytes). In this way, SIRS or MODS may be detected, hydro-electrolytic derangements corrected and metabolic complications avoided.

Blood gases monitoring: Hypoxia is common in AP. In fact, O_2 saturation in arterial blood is one of the criteria included in multiparametric systems to assess severity of illness. Its origin is multifactorial and some studies have shown that its effect is similar to that of hypovolemia in the intestinal tissue; thus, it is essential to keep it above 95%.

Hydro-electrolytic replacement: This is a crucial aspect in the patient's outcome to which much attention is being paid. Vomiting, diaphoresis, fever, fluid sequester in a third space and the vessel's increased permeability, give rise to hypovolemia that must be replaced early and adequately. Hypovolemia compromises pancreatic circulation, favoring the development of necrosis. Similarly, hypovolemia compromises the bowel, allowing for bacterial translocation and endotoxin production which, in turn, facilitates the infection of necrotic tissues[28].

The amount and composition of fluids used for replacement is not standardized, but resuscitation must be aggressive from the beginning and the patient's response carefully monitored; urine output, hematocrit and BUN are used as an indirect measurement of hypovolemia, mainly in the first 12-24 h if they were elevated at the beginning (hematocrit > 44% and BUN > 20 mg/dL)[29,30]. In patients with a risk of fluid overload, it is necessary to monitor the central venous pressure or even to insert a pulmonary artery catheter (Swan-Ganz) to monitor the cardiac preload.

Over the last years, different studies evaluating fluid therapy effect on AP prognosis have been published. We mention a recent review paper[31] that includes most of these studies, including randomized controlled trials demonstrating the importance of hydro-electrolytic resuscitation in the initial 72 h, but with greater risk of infection complications in the case of too rapid hemodilutions. In this way, we must take into account the results obtained by de-Madaria *et al*[32] in a prospective controlled study: an aggressive fluid therapy during the initial 24 h of admission in patients without signs of fluid depletion may be detrimental.

Some recent studies have shown that, for fluid replacement in AP, Ringer's lactate is superior to normal saline, as assessed by CRP measurements and the development of SIRS. However, in AP secondary to hypercalcemia, Ringer's solution would be contraindicated because of the high calcium content[33,34]. So, fluid therapy remains the main goal of early management in AP, but it is necessary to review actual data for development of guided protocols.

Analgesia: Usually, abdominal pain is the main symptom in AP and its control is an essential goal of treatment. There is no evidence confirming the superiority of any analgesic. The treatment must be gradual and several drugs may be used, such as pirazolones (metamizol) or opioids (meperidine, morphine, tramadol), which are usually administered intravenously. Pump analgesia, instead of bolus, is a good option when the pain is intense.

It is controversial whether morphine is used or not; only elevated doses produce hypertony of Oddi's sphincter. There are no studies showing that morphine worsens the clinical course of AP. On the other hand, repeated doses of meperidine may generate the accumulation of normeperidine (a meperidine metabolite) than can produce neuromuscular irritation[35]. The use of phentanile has also been proposed. Phentanile, administered either subcutaneously or i.v., gives good

results in terms of pain control and security profile.

In patients with severe pain or difficult analgesic control with standard measures, the epidural administration of opioids or local anesthetics has been used with good results in terms of gas exchange and bowel motility. Similarly, clinical trials using bupivacaine have shown the improvement of pancreatic microcirculation, together with a lower development of necrosis and systemic complications[36].

Nutritional support: Patients with light AP generally respond to fluid replacement in a few days without any repercussions on nutritional status. Oral feeding is recommended when vomiting or ileus is not present. Occasionally, oral feeding may elicit pain and should be stopped. However, when pain remits, usually between 24-48 h after the onset, oral feeding should be resumed. Classically, a fluid diet is followed by a low fat diet (below 30% of total calories), progressing to adequate. Some authors have recently suggested providing a solid and low fat diet earlier in the course of the disease less gradually, since the standard way does not offer advantages and may increase the length of stay in hospital[37,38].

However, in severe AP, characterized by a hypercatabolic state that affects nutritional status, it seems reasonable to provide nutritional support together with other measures of treatment. Moreover, in severe AP, pain, vomiting and ileus take longer to disappear. At the same time, the external compression of the digestive tract by collections or inflammation may prevent the reintroduction of an oral diet.

There are a large number of scientific papers trying to establish when, how and what kind of nutritional support should be provided to AP patients and occasionally results are contradictory. Some recommendations, based on meta-analysis and controlled studies, are given in clinical guides. Evidence comparing enteral nutrition (EN) through a naso-jejunal tube with total parenteral nutrition (TPN) has been pursued. It has been shown that EN, compared to TPN, is associated with a lower incidence of metabolic complications and infection, since the integrity of the intestinal barrier is kept. On the other hand, EN is cheaper and requires a shorter hospital stay. Besides, EN avoids some mechanical and septic complications related to central venous catheters that may reduce mortality[39-43].

If required, nutritional support should be provided early in the course of AP, as soon as in the first 48 h. Once the severity of the disease has been assessed, it is preferable to use semi elemental formulas with high protein and low lipid content, increasing the amount according to tolerance. EN tolerance is variable and depends on the infusion's rate, nutrient's concentration, place of delivery (stomach, jejunum) and the phase of inflammatory response of AP. If the placement of a postduodenal tube is not possible, a nasogastric tube may be used. Some studies have shown no difference between both ways of administration. There are few studies assessing the influence of different formulas in the course of AP, but it is thought that supplements might be helpful, such as immunostimulants (arginine, glutamine, omega-3 fatty acids, vitamins C and E, beta-carotenes), micronutrients (zinc, selenium, cromium) or even pro-biotic components.

Currently, the presence of intra abdominal fluid collections or persistently elevated pancreatic enzymes is not a contraindication for EN. However, it is true that in some patients, pain reappears and pancreatitis worsens, increasing the size of collections, when oral feeding is resumed or EN is set up. In these cases, TPN should be used.

Admission to an intensive care unit: AP mortality is generally a consequence of MODS. In the first two weeks, this risk is mainly related to a systemic inflammatory response. Then, mortality is usually associated with pancreatic necrosis and infection. Intensive care unit admission must be considered under the following circumstances: (1) Persistent MODS for more than 48 h and early onset (during the first week) because it is associated with 50% mortality; (2) Clinical manifestations predicting MODS development, according to clinical status, multiparametric systems (more than 3 Glasgow or Ranson analytical criteria at 48 h or APACHE Ⅱ higher than 8), biochemical data (riboflavin carrier protein > 150 mg/dL at 48 h), radiological data (persistent pleural effusion for more than 48 h after admission) or associated obesity; and (3) Development of local complications.

Clinical management of local complications of AP

Similar to the presentation of MODS, hemodynamic instability or severe metabolic derangements, local complication developments requires the coordinated efforts of a multidisciplinary team, including gastroenterologists and other medical specialists, radiologists, intensive care specialists and surgeons.

Pancreatic necrosis: The presence of pancreatic necrosis is an inscrutable marker of illness severity. Often, necrosis is followed by early or late OF development, due to the inflammation itself or its associated infection. Necrosis infection is the most severe local complication that can appear and is associated with 40% mortality. According to these facts, prophylactic antibiotics have been assessed to reduce mortality.

Antibiotic prophylaxis: Antibiotic prophylaxis is one of most controversial matters of the clinical management of AP and nowadays it is not possible to make clear recommendations. A number of studies have been published with contradictory results that can be explained by the inclusion of heterogeneous patients, different antibiotic regimes, questionable designs of study, and different study objectives. At present, the American Association of Gastroenterology recommends antibiotic prophylaxis in extended necrosis, according to abdominal CT (involving more than 30% of gland). It is

recommended that prophylaxis should not extend longer than 14 d because then it would favor fungus infection. Recent studies, some of them meta-analysis of previous studies, as well as other well designed studies do not approve routine use of prophylactic antibiotics because there are no significant differences related to surgery or mortality. We must pay special attention to identify some subgroups of patients that might obtain a benefit with this antibiotic prophylaxis[6,44-51].

Sterile necrosis: It was classically advised to remove necrotic tissue to prevent the development of MODS. At present, there is broad consensus to try to manage the situation conservatively, at least for the first 3 or 4 wk; delayed necrosectomy is associated with lower morbidity and mortality. In this timeframe, a spontaneous resolution of necrosis may occur or necrosis may organize, giving the opportunity of minimally invasive therapy. A percutaneous or endoscopic treatment may be attempted, but the material density may prevent complete drainage. Open or laparoscopic surgery can removed necrotic tissue and effective drainage and washing can be established[52,53].

Infected necrosis: Around one third of necrotic AP are infected, a complication that may appear during the second week of evolution. This situation should be suspected if a systemic inflammatory response persists for more than two weeks after admission, clinical course worsens or air bubbles appear at CT. After excluding other infection origins, infected necrosis has to be confirmed by puncture guided ultrasonography or CT, followed by Gram smear and culture. If the initial puncture is not diagnostic, it can be repeated after a few days. While waiting for the culture's result, the intravenous antibiotic should be started. Carbapenem (imipenem or meropenem 1 g/8 h) or ciprofloxacin plus metronidazole will be maintained until obtaining the antibiogram result. If Gram positive bacteria are isolated, vancomycin (1 g/12 h) will be administered[54].

The standard treatment for infected pancreatic necrosis is open or laparoscopic surgical drainage. However, on occasions, percutaneous drainage may work well. As recommended by the International Association of Pancreatology Clinical Guideline, drainage should be effectively established when the patient is septic. A step by step treatment is proposed by which percutaneous or endoscopic drainage should be established first and then necrosectomy with drainage through a minimally invasive retroperitoneal access. When this method was compared with open surgery, it offered several advantages, including the chance to avoid surgery in some patients, less complications and lower cost[55-59].

The alternatives to open surgery should be considered, mainly in frail and critical patients that would not tolerate a more aggressive surgery. Some alternatives such as endoscopic necrosectomy or invasive percutaneous drainage should be evaluated through controlled trials. In clinical practice, it is important to consider the importance of a multidisciplinary management, considering the clinical situation as well as the comorbidity of the patient and the center experience.

Other local complications of AP: There are other situations that, although less common, should be considered.

Hemorrhagic complications: Hemorrhagic complications of AP are fortunately rare; however, they may present in a diversity of forms. Sometimes, upper or lower gastrointestinal bleeding occurs due to gastroduodenitis secondary to adjacent inflammation, bleeding peptic ulcer, pseudocyst rupture into the digestive tract or drainage of a pseudo aneurysm through the Wirsung. In severe cases of AP, bleeding may occur due to intra- or retroperitoneal erosion of the vessels of the celiac trunk, mainly the splenic artery. Diagnosis may be established by angiography or angio-CT. Angiography, besides identifying the bleeding point, sometimes allows embolization that may stop bleeding. If this method fails, the definitive treatment has to be surgery[60].

Pancreatic duct breaking: Generally this is produced in the context of pancreatic necrosis due to erosion of the duct. In cases of necrosis, complete or partial pancreatic duct breaking occurs in about 60% of cases. The pancreatic juice often accumulates inside the abdomen, in the neighborhood of the pancreas, originating a pseudocyst. However, pancreatic juice can also flow to other locations, causing pancreatic ascites, pleural effusion, distant pseudocyst or cutaneous fistula. To assess this situation, wirsungraphy by using CT, nuclear magnetic resonance (spectroscopy) or endoscopic retrograde cholangiopancreatography (ERCP) can be performed. This latter method may be associated with the placement of a stent, which will favor definitive resolution. Nutritional support and potent antisecretors such as octreotide should be associated. Collections can be removed by percutaneous or endoscopic drainage. Successful fistula sealing has been described by using cyanoacrylate or fibrine. If other treatments fail, which is common, surgery is indicated. If the duct is opened at the pancreatic tail, a distal pancreatic resection may be curative. Otherwise, internal drainage, through a pancreatic-digestive anastomosis, may be necessary[61,62].

Abdominal and retroperitoneal collections: They are only treated if they are symptomatic or complicated (infection, rupture, pseudoaneurysm). The treatment will depend on whether or not the collection communicates with the duct of Wirsung, the collection has a firm wall, the duration of process and the presence of necrosis or detritus inside the collection. For collections less than four weeks, the treatment with percutaneous or endoscopic drainage is preferable. However, the presence of semisolid detritus may require a surgical treatment as the best option.

Splenic venous thrombosis: This occurs in about 20% of AP. Thrombosis is usually resolved when pancreatitis heals but if the thrombus migrates or extends to the portal or superior mesenteric veins, intestinal perfusion can be compromised or liver failure may appear. When thrombosis is diagnosed, platelet antiaggregant treatment may be instituted. However, the theoretical risk of bleeding in necrotic AP should be considered.

Treatment of pancreatic pseudocysts: Fluid collections that appear during AP disappear spontaneously in 40% to 50% of cases. In about 10% to 15% of cases, these collections persist and become encapsulated, generating pancreatic pseudocysts (PP). A "true" PP (i.e. without an epithelial lining; the counterpart would be a pancreatic cyst) takes at least 4 to 6 wk from the beginning of symptoms to be encapsulated by a wall formed by inflammatory fibrosis of the adjacent tissues. Few studies have documented the natural evolution of PP. Classically, it was considered that PP more than 6 cm in diameter or those that persisted for more than 6 wk should be operated on. Currently, it has been shown that about half of all PP can be solved spontaneously; thus, the attitude has shifted towards a more conservative approach.

Asymptomatic PP may be followed-up for periods of six month or longer, if they do not grow, become symptomatic or present complications such as hemorrhage, infection or mechanical compromise of adjacent organs. In these situations, percutaneous, endoscopic or surgical drainage should be considered. Its election depends on multiple factors: patient's general status, size, number and location of PP, communication or not with the main pancreatic duct, solid necrosis inside or not and possible complications. At the same time, a differential diagnosis between PP and another kind of cystic lesion is essential[63,64]. No controlled study has compared these three options of treatment, but intramural or transpapillar endoscopic drainage seems to be the preferred technique. The availability of sono endoscopes facilitates drainage of PP, even in cases of associated segmentary portal hypertension. Percutaneous drainage should be chosen in complicated PP or in patients with high surgical risk. In turn, percutaneous drainage of PP may be complicated by a pancreatic fistula (up to 20% of cases) or infection. A percutaneous drainage should be avoided in cases of hemorrhage or pancreatic ascites. At present, surgical treatment (mainly by internal drainage) is reserved for patients that percutaneous or endoscopic treatment failed in, those with complications from chronic pancreatitis, those with multiple or giant PPs, or when malignancy cannot be ruled out[65-67].

Some considerations about treatment of biliary AP: ERCP and timing for cholecystectomy

Gallstones are the most common cause of AP in most countries. This is important since cholecystectomy prevents recurrences. What is the right thing to do once the patient has improved after the acute episode? Or when is the best moment for surgery? Since the development of laparoscopic surgery and ERCP, some situations have been reviewed, analyzed in meta-analyses and the conclusions reflected in clinical guidelines.

After a first episode of AP, recurrence ranges between 25% and 60%. One fourth of these recurrences appears in the first six weeks and the percentage increases with time[68]. If pancreatitis has been light and the patient has satisfactorily recovered, ideally, cholecystectomy should be performed before the patient's hospital discharge. Alternatively, patients should have definitive surgical treatment in the next 2-4 wk. If pancreatitis has been severe, with associated collections, surgery should be delayed until the collections have been resolved or are not clinically relevant[55,69,70].

Another important aspect to be considered in the management of these patients is the possibility of residual choledocholithiasis and, thus, the need to explore the main biliary tree. In light AP, it was questioned whether to perform a preoperative ERPC plus endoscopic sphincterotomy and calculi extraction (if adequate) or, alternatively, to treat a possible residual lithiasis at surgery if this was discovered through the intraoperative cholangiography. After evaluating some experiences with mild to moderate AP patients, it can be established that it is preferable to choose cholecystectomy with intraoperative cholangiography plus calculi extraction (if these are present), limiting the practice of ERCP if calculi extraction has not been completed at surgery[71-73]. On the other hand, if AP is severe or courses with associated cholangitis or jaundice, ERCP plus sphincterotomy is advisable early during the patient's admission. Then the question arises as to whether or not to operate later. There is not enough data to make a categorical recommendation. However, if the patient does not have a high surgical, i.e. ASA Ⅰ-Ⅲ [according to the American Society of Anesthesiologists (ASA) physical status classification system] it seems reasonable to operate since a new episode of AP might imply a greater risk than surgery. Contrarily, in high risk patients (ASA Ⅳ-Ⅴ), it may be preferable to "wait and see." Occasionally, in selected patients, ERCP plus sphincterotomy may be considered, along with a posterior treatment with ursodeoxicholic acid to treat gallstones[74-76].

CONCLUSION

Each of these sections could probably lead to a review with more comprehensive comments. We recall the usefulness of the recommendations reflected in several clinical guidelines, although it is necessary to review some topics, such as fluid therapy or pancreatic necrosis management. Knowledge of the environment in which we operate and the limitations, and this approach to current recommendations should be converging lines in the

management of patients with AP in daily clinical practice.

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