Acute Pancreatitis: Pathophysiology, Clinical Aspects, Diagnosis e Treatment

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ABSTRACT

Acute pancreatitis is an acute inflammation of the pancreas. The clinical classification of the disease recognizes the mild acute pancreatitis, characterized by the absence of local and/or systemic complications, and the severe disease, characterized by the presence of local complications such as necrosis, abscess or pseudocysts and/or distant organ failure. Gallstones constitute the predominant etiological factor. The severity assessment is essential for proper initial treatment of the disease. Primary objectives to achieve in the treatment of acute pancreatitis essentially are: pain control, electrolyte support and energy intake, removal of the causal agent, attenuation of the inflammation, and prevention and eventual treatment of local and systemic complications of necrotizing forms.
Keywords: *Acute pancreatitis; Disease management; Severity assessment; Therapy.*

Introduction

Acute pancreatitis is an acute inflammation of the pancreas with variable involvement of peripancreatic tissues and/or distant organs. 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, so the clinical manifestations range from mild abdominal pain to very serious presentations with high mortality rate [1]. Episodes of acute pancreatitis in patients who will subsequently develop anatomical, clinical and functional features compatible with chronic pancreatitis are classified as the former until the final diagnosis is established. The now widely accepted classification of the disease and its complications is a clinical classification prominently known as the Atlanta classification [2] and is shown below.

Mild acute pancreatitis is characterized by a favorable clinical course in the absence of local and/or systemic complications. The predominant pathological expression is interstitial edema more or less associated with peripancreatic steatonecrosis (Figure 1).

Severe acute pancreatitis is characterized by the presence of local complications such as necrosis, abscess or pseudocysts and / or organ failure. In most cases it is the clinical expression of the presence of pancreatic necrosis; in fact, patients with acute edematous-interstitial pancreatitis rarely present a clinically severe form of the disease. The organ failure was defined as shock (systolic blood pressure < 90 mmHg), pulmonary insufficiency (PaO_2 < 60 mmHg), renal failure (serum creatinine > 2 mg/dl after rehydration) or gastrointestinal bleeding (> 500 cc/24h).

Pancreatic necrosis is a focal or diffuse area of non-viable parenchyma, which typically is associated with peripancreatic steatonecrosis. Computed tomography with intravenous contrast bolus is currently the best diagnostic method (accuracy 80-90%). Pancreatic necrosis rarely involves the entire gland in its entire thickness; usually it remains confined to the periphery and spares the glandular core. Haemorrhagic foci are present in varying degrees. The necrosis may become infected (10-30% of cases) and the distinction between sterile and infected pancreatic necrosis is important because the therapeutic approach (mainly medical therapy in sterile pancreatic necrosis, surgical in the infected type) and prognosis (mortality rate about three times higher in infected pancreatic necrosis) differ considerably. The diagnostic gold-standard for suspected infection of pancreatic necrosis is represented by microbial cultures of material from percutaneous needle aspiration (Figure 2).

Acute fluid collection is a localized effusion in or near the pancreas, without granulation fibrous wall. It tends to appear early and regresses spontaneously in most cases. It is not considered a sign of disease severity unless it becomes infected.

Pseudocysts is a collection of pancreatic juice enclosed by a wall lacking epithelialization and appearing as a result of acute pancreatitis, chronic pancreatitis or pancreatic trauma. The maturation of a pseudocyst after acute pancreatitis requires at least 4 weeks after the onset of the disease. A post-acute pancreatitis pseudocyst is therefore an acute fluid collection persisting more than 4 weeks surrounded by a well-defined wall (Figure 3).

Walled-off pancreatic necrosis is an intra-abdominal collection of pus (usually near the pancreas), appearing after an attack of acute pancreatitis or after pancreatic trauma. Pus predominates and there is only small amount of necrotic tissue, distinguishing it from non-infected pancreatic necrosis. A pseudocyst presenting pus within its walls is also correctly defined as a walled-off pancreatic necrosis [3].

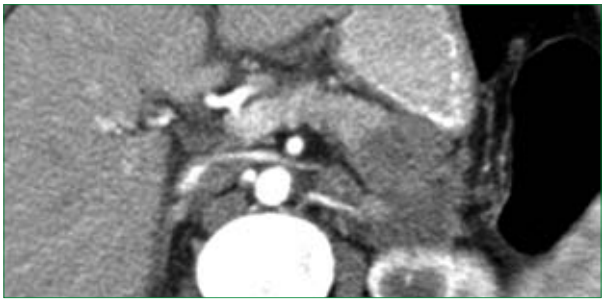

Fig. 1 - Multidetector computer tomography: edematous pancreatitis.

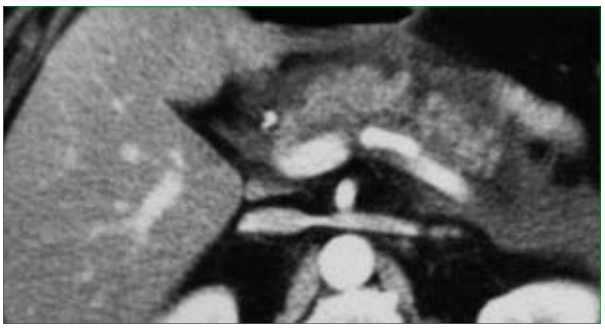

Fig. 2 - Multidetector computer tomography: Necrotizing pancreatitis.

Pathophysiology

There are many recognized causes of acute pancreatitis, but surely gallstones constitute the predominant etiological factor in our geographical area [4]. Less frequently, acute pancreatitis is related to chronic use or abuse of alcohol and even more rarely is secondary to abdominal surgery, diagnostic and/or interventional endoscopical procedures on the papilla of Vater, abdominal trauma, dyslipidemia or the use of drugs with pancreatic toxicity [5-7]. The mechanisms by which the various etiological factors trigger pancreatic inflammation have not yet been fully identified but it seems proved with sufficient certainty that, whatever the initial pathogenic noxious stimuli, the earliest pathogenetic events are triggered inside the acinar cells [8] . Under normal conditions these cells produce digestive enzymes and lysosomal enzymes, the former segregated in lysosomal vacuoles, the latter in the vacuoles of zymogen. In acute pancreatitis this strict compartmentalization can be overridden by alteration of a complex biological process, calcium-dependent, defined as "stimulus-secretion coupling". A colocalization of lysosomes and zymogen granules in a unique vacuole is thus determined: the lysosomal enzyme cathepsin B can activate trypsinogen at this point with consequent cascade activation of other proteases and phospholipases. It follows the rupture of vacuoles, cell damage, necrosis and release of cellular activated enzymes in the interstitium. Local processes of vasoconstriction-dilatation determine infiltration of inflammatory cells and increased necrosis. In the most severe forms of acute pancreatitis it is present a complex biochemical cellular and humoral response not substantially different from what happens in other serious diseases such as septic shock, the poly-trauma and extensive burns. The magnitude and the continuation of such events, assignable to the so-called SIRS (systemic inflammatory response syndrome), affect the extent and severity of local damage and progression to systemic complications [9]. Implicated mediators are various cytokines such as interleukin-1 (IL-1), IL-6, IL-8, TNF (tumor necrosis factor), PAF (platelet activating factor) [9,10]. All these mediators are markedly elevated in the first 24 hours of illness, whereas the anti-inflammatory cytokines to (IL-2, IL-10) are reduced. The result is the activation of neutrophils, monocytes, lymphocytes, platelets and endothelial cells. The increased expression of cell adhesion molecules and integrins on neutrophils results in increased adhesion to the endothelium, diapedesis and invasion of distant organs (first of all the lungs) where hyperactive neutrophils call forth other polymorphonuclear leukocytes and result in extensive tissue destruction [11]. The presence of trypsin, chymotrypsin and elastase in the pancreatic interstitium, in serum and peritoneal fluid is responsible for activation

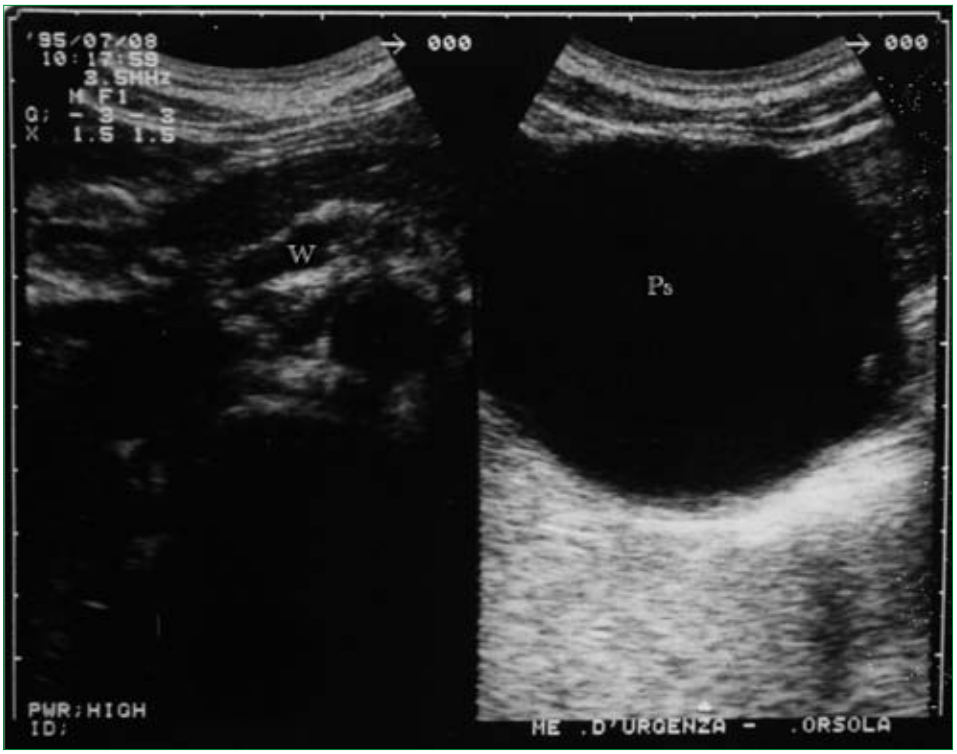

Fig. 3 - Ultrasonography: pancreatitis pseudocyst (Ps) The main pancreatic duct is dilated (W).

of the coagulation-fibrinolysis systems, endothelial cells, PMN leukocytes and monocytes-macrophages with synthesis and release of cytokines, superoxide ions and PAF [8]. The latter is a key mediator capable of stimulating the release of other pro-inflammatory cytokines, increase vascular permeability, induce a negative inotropic effect, leukocyte chemotaxis, tissue edema and cellular damage. It is possible to clearly appreciate the possibility of a serious involvement of distant organs up to the development of the "fearsome" multi-organ failure syndrome.

Evaluation and stratification of severity of acute pancreatitis

Severity assessment is essential for proper initial treatment in the management of acute pancreatitis and this constitutes a recommendation of grade A in the Italian guidelines on acute pancreatitis [12]. These guidelines also suggest that assessment of severity should be done by a scoring system such as Acute Physiology and Chronic Health Evaluation (APACHE) II [12]: an APACHE-II score greater than 8 is important for determining treatment policy and identifying the need for transfer to a referral unit. Serum C-reactive protein values grater than 150 mg/dL are useful for severity assessment, but they may not reflect severity within the first 48 h after onset. In addition contrast-enhanced CT scanning and contrast- enhanced MRI play an important role in severity assessment. The CT severity index, as proposed by Balthazar et al. [13], should be used. In fact, the gold-standard for the presence of pancreatic necrosis is the computed tomography (CT) with intravenous contrast medium, which should be done after 72 hours from pain onset and after rehydration of the patient; it may be possibly repeated according to the clinical situation. Management in, or referral to, high-volume units is necessary for patients with extensive necrotizing pancreatitis or other complications who may require care in the intensive therapy unit or interventional radiological, endoscopic or surgical procedures and this constitutes a recommendation of grade B [12].

Therapy

Background

One of the recurring features of acute pancreatitis is the frequent presence of a variably long period of time, sometimes days, between the onset of symptoms and hospitalization. This is a factor that affects the very effectiveness of therapeutic measures and ensures that treatment is more often aimed at controlling the progression of the disease rather than at interfering with initial pathogenetic phenomena. The delay in hospital makes it difficult to interpret results of therapeutic trials and impossible a homogeneous analysis of aggregate data from multiple studies, as the timing of treatment is often not specified, or the onset of symptoms is considered at the time of hospitalization. The time frame in which there is a reasonable chance of specifically antagonize the inflammatory mediators and activated pancreatic enzymes to mitigate or prevent the development of a partial or total impairment of distant organs is about 2-3 days after the onset of pain and this period is also called interventional window [14]. All this should lead to a "specific" treatment as early as possible and at the same time confirms that it is absolutely unnecessary and wasteful to use these same drugs in patients who come late to the observation, often in the second week of illness, at a stage where there are already signs of impairment of distant organs. In this clinical scenario, treatment should be more rationally targeted toward measures useful in supporting cardiovascular, respiratory and renal systems and preventing septic complications. It is possible to affirm that for every four patients with acute pancreatitis, three will respond favorably to conservative medical treatment, while the fourth will present complications with a one in three chance of suffering a fatal outcome [15]. From these simple evaluations are derived three important corollaries:

a) the majority of patients benefits from a conservative therapy, not surgery,
b) the early identification of those patients at increased risk of developing complications is crucial for prognosis and therapy;
c) surgical therapy is to be reserved for those patients who develop specific complications, primarily the infection of pancreatic necrosis and / or peripancreatic fluid collections.

Essentially, the severity of an acute attack leads to the development of a necrotizing form of the disease and pancreatic necrosis is not only responsible for the clinical severity, but also the onset of complications and, ultimately, mortality. At the present state of knowledge a severe form of acute pancreatitis can not adequately be dealt without the support of a CT scan available full-time and other multi-specialistic skills/human resources and equipment. The guidelines of the British Society of Gastroenterology [16] and the Italian of the Italian Association for the Study of the Pancreas [12] suggest that a specialized center for the treatment of severe acute pancreatitis should have the following characteristics:

1. allocation in a general hospital where the major medical and surgical specialties are present;
2. multidisciplinary team with specialists in Internal Medicine, Surgery, Endoscopy, Critical Care and Intensive Care and Pathology,
3. day and night availability of CT and ultrasound with staff expert in percutaneous treatments, the availability of magnetic resonance and angiography may be useful but not essential,
4. the presence of daytime endoscopists experienced in endoscopic retrograde cholangiopancreatography (ERCP) and related interventional procedures.

Objectives and methods of conservative treatment

Primary objectives to achieve in the treatment of acute pancreatitis essentially are:

1. pain control,
2. electrolyte support and energy intake,
3. removal of the causal agent, when possible,
4. attenuation of inflammatory and autolytic processes at the glandular level ("specific" therapy),
5. prevention and eventual treatment of local and systemic complications of necrotizing forms.

For mild forms of disease, in most cases the first three steps are sufficient for clinical resolution. In severe forms, the therapeutic engagement is more complex and patients may, with reasonable frequency, require periods of hospitalization in intensive care units. The therapeutic approach to severe acute pancreatitis is reported in Figure 4.

The control of pain must be swift and effective: for this purpose, meperidine is the drug of choice [15].

Supportive therapy is a measure of fundamental importance that counterbalances the seizure of the fluids and hypercatabolism particularly important in severe forms. The maintenance of cardiovascular parameters, renal and respiratory can in many cases prevent the onset of multisystem complications. The pancreatic hypoperfusion, secondary to inadequate maintenance of plasma volume is indeed able to trigger and increase the phenomena of pancreatic necrosis. Patients with mild forms, for which it is expected an oral refeeding within 4-6 days of hospitalization, do not need an aggressive nutritional approach [15]. In contrast, in severe forms total parenteral nutrition (TPN) must be used, which must take into account in its formulation of any metabolic imbalances (such as acidosis or alkalosis, hyperglycemia, hypocalcemia, and hypokalemia ipomagenesiemia) and cardiovascular complications [15]. Recently, enteral nutrition through naso-jejunal probe has been used with good results in patients with severe acute pancreatitis

instead of the NPT. The pathophysiological assumption is that the NPT does not provide all essential nutrients (eg glutamine) and does not fuction as intestinal barrier which can increase intestinal permeability to toxins and bacterial translocation.
The early removal of the causative agent makes it paramount to achieve a sufficiently precise etiologic diagnosis and early intervention. In clinical practice, this translates, at least in our population, in the identification of a mechanism for biliary obstruction, transient or persistent, complete or partial, in about 2/3 of cases. The removal of biliary obstruction using endoscopic techniques has now entered into the routine treatment of these patients.[12, 16]. The "specific" therapy of acute pancreatitis relies on antisecretory and antiprotease drugs.
The use of somatostatin and its synthetic analogue octreotide is much debated. The results of published studies, many uncontrolled and with small case series or not stratified by severity of illness, are controversial, although a metanalytical evaluation shows, in general, a therapeutic advantage. From the theoretical point of view, the negative effects of vasoconstriction of the splanchnic circulation and contraction of the sphincter of Oddi outstripped the hypothetical beneficial effects related to inhibition of exocrine pancreatic secretion.
Among antiprotease drugs the gabexate mesylate showed a positive effect in patients with severe acute pancreatitis, with significant reduction of systemic complications and the need for surgery but not mortality compared with placebo. The dosage used in early studies was 3 g/day by continuous intravenous infusion, but subsequently it was found that a dose of 1.5 g/day in the same manner for a period of treatment of 7-8 days is also a viable option [17]. The best results are obtained when the administration starts earlier than the onset of symptoms.
The use of systemic antibiotics for the prevention of pancreatic infections is one of the cornerstones of conservative treatment of severe forms of acute pancreatitis. Several studies have shown a significant reduction in the incidence of pancreatic and extrapancreatic infections but not mortality in patients treated with imipenem-cilastatin [18]. Quinolones, due to their pharmacokinetic characteristics and their range of action, should ensure an effective prophylactic action as well. However, in a recent randomized prospective trial, patients treated with pefloxacin showed an incidence of infected necrosis significantly higher than patients treated with imipenem (34% vs 10%) [19]. At present, therefore, it is recommended for all patients with acute necrotizing pancreatitis an early administration of imipenem-cilastatin at a dose of 1.5-2 g/day, lasting for at least two weeks.

Objectives and indications of surgical treatment

The infection of pancreatic necrosis in the course of acute pancreatitis is a very serious medical condition and its presence is associated with a marked increase in risk of death; it developes in percentages varying from 15 to 70% of all patients with acute necrotizing pancreatitis and accounts for more than 80% of deaths from acute pancreatitis. The risk of infection increases with the extent of necrosis and the days after initiation of acute pancreatitis, reaching a peak incidence (70%) after three weeks [20]. In most cases the infection is caused by Gram-negative bacteria of enteric origin, and about two thirds of infections are caused by a single microbiological agent. Therefore, E. coli is the most frequent causative agent (26%), followed by Pseudomonas, Klebsiella and Proteus species. Frequently Gram positive infections are also detected, such as Staph.aureus (15%), Streptococcus faecalis and Enterococcus or other anaerobic bacteria, and in some cases by fungi. In clinical terms acute pancreatitis with sterile necrosis can be difficult to distinguish from a form with infected necrosis, because both can give fever, leukocytosis and abdominal pain. But this distinction is very important, since the mortality in patients with infected necrosis that did not underwent early surgery is high. TC or ultrasound-guided percutaneous suction of the necrotic material and/or peripancreatic fluid collections, with a fresh microscopic examination and bacterial culture, is safe and accurate (sensitivity and specificity exceeding 95%) and must be used, even repetitively, usually from the second week of illness, in patients whose clinical condition worsens or does not tend to improve, despite the removal of any causative agent and the implementation of a vigorous supportive treatment. Debridement is the surgical treatment of choice of infected necrosis and the only therapeutic doubt concerns the type of intervention to perform (classic necrosectomy with drainage-washing or open packing technique). Recently other treatment options, such as percutaneous, endoscopic or minimally invasive surgery have been proposed [21-23]. These methods require highly experienced operators, are not risk-free and should be for the moment limited to patients unfit for surgery because of a high anesthetic risk.

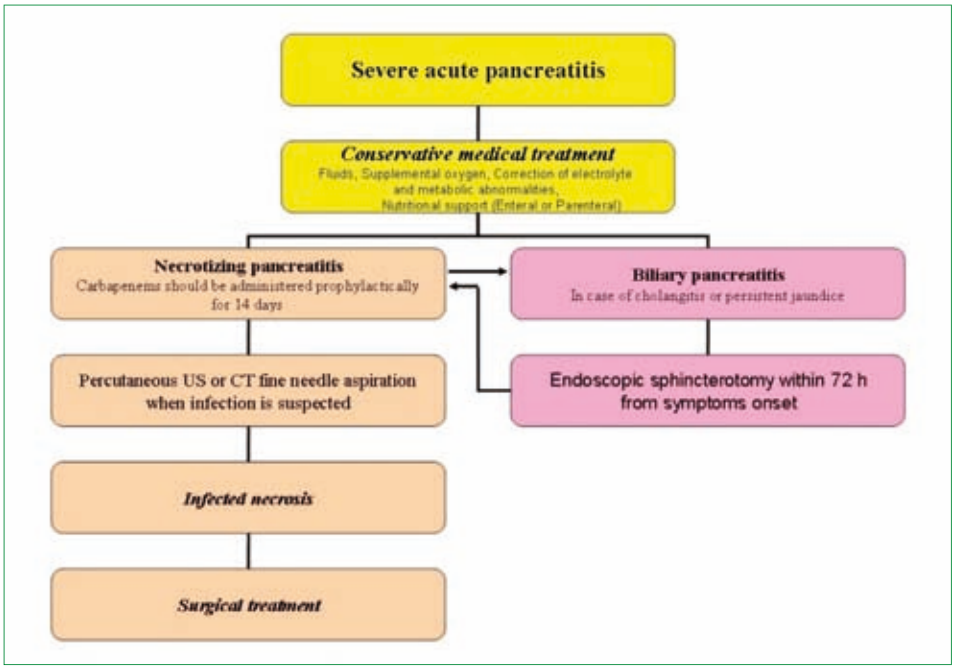

Fig. 4 - Therapeutic approach to severe acute p ancreatitis.

The treatment of patients with sterile pancreatic necrosis remains controversial. Surgical treatment offers no demonstrable survival benefits compared with supportive treatment; in addition, because the surgery may cause postoperative infection of necrotic tissue in 25-50% of cases with a very high secondary mortality, a surgical indication in any case sterile necrosis should be considered with prudence and care. Even when the necrotic process determines rupture of the main pancreatic duct and necrosis remains sterile, there are good prospects for a resolution of the disease with conservative therapy. The precise role of surgery in the treatment of sterile necrosis is therefore limited and should be reserved for selected cases, such as those patients in whom repeated attempts at oral re-feeding after 5-6 weeks of therapy are associated with abdominal pain, nausea, vomiting or recurring pancreatitis. At this stage of the disease, however, generally necrosis is more demarcated and the surgical act is easier. In other cases, supportive care associated with prophylactic antibiotic treatment should be the primary treatment [24-28]. It is therefore very important to perform in due time (possibly during the same hospitalization for mild forms, usually at a distance of three to four weeks for severe) a cholecystectomy in case of gallstones in order to prevent recurrence of acute episodes [12].

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