Pharmacotherapy for acute pancreatitis

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Our knowledge of acute pancreatitis is still far from complete and there is no unanimous agreement concerning the pathophysiological processes leading to typical alterations during the course of acute pancreatitis. We reviewed the paper published in the last decade on the pathophysiology and treatment of acute pancreatitis. It is difficult to translate the experimental therapeutic results into clinical practice. For example, lexipafant was efficacious in decreasing the severity and mortality of lethal pancreatitis in rats, but seems to have no effect on severe acute pancreatitis in humans. Thus, the main problem in acute pancreatitis, especially in the severe form of the disease, is the difficulty of designing clinical studies capable of giving reliable statistically significant answers regarding the benefits of the various proposed therapeutic agents previously tested in experimental settings. Thus, analgesia, supportive care, and treatment of the pulmonary and renal complications remain the cornerstones of the treatment of acute pancreatitis, especially in the severe form of the disease.

Keywords: acute necrotizing pancreatitis, antisecretory drugs, diagnostic techniques and procedures, lexipafant, pancreatitis, protease inhibitors; routine diagnostic tests, severity of illness index, trypsinogen

1. Introduction

More than a century ago, Chiari [1] suggested that the cause of pathophysiological changes in acute pancreatitis lay in the autodigestion of the pancreas itself, mediated by the pancreatic enzymes. Although this concept is generally accepted, our knowledge of acute pancreatitis is still far from complete and there is no consensus concerning the pathophysiological processes that lead to typical alterations during the course of acute pancreatitis, especially in its severe presentation. Thus it is difficult to decide on a therapeutic approach, as this should be guided by the pathophysiology of the disease: at present, we are only able to control the pain and to cure the complications of the disease. This article reviews the current knowledge of medical treatment of acute pancreatitis based on the scientific literature, and describes the most important aspects of the pathophysiology and the clinical aspects of the disease.

2. Pathogenesis

2.1 The role of trypsin and trypsin inhibitors

The protein trypsinogen is synthesized in the endoplasmic reticulum and then transported to the Golgi system, where it is sorted – together with other pancreatic enzymes – into core particles. Trypsinogen is activated by hydrolysis; the cleaved region, called trypsinogen activation peptide (TAP), is a small peptide composed of 7 – 10 amino acids (depending on the species and isoform), with a molecular weight of approximately 900 Daltons [2]. The removal of TAP from the proenzyme renders...
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the trypsinogen active (trypsin) by inducing conformational changes. Trypsin is the key enzyme for the rapid activation of all other pancreatic proenzymes, including its own proenzyme (2,3). Thus, immunoreactive TAP reflects the amount of pathological intrapancreatic trypsinogen (irrespective of whether the resulting trypsin is active or blocked by inhibitors) entering the peritoneal cavity and circulation, after which the peptide is rapidly filtered by the kidney and excreted into the urine due to its small size [3]. It seems logical to assume that the greater the quantity of trypsinogen activated, the greater the injury to the pancreas.

To better understand the activation of trypsin, we must remember that the co-localization theory postulates that trypsin activation occurs within cystolic vacuoles containing both digestive enzymes and lysosomal enzymes, such as cathepsin B. Some authors [4] have detected immunoreactivity against TAP in vacuoles positive for lysosomal markers (GRAMP-92) and cathepsin B. Cathepsin B is capable of removing the TAP region from the trypsinogen; thus, cathepsin B seems capable of transforming trypsinogen into trypsin in cellular compartments. Another possible mechanism in the activation of trypsinogen involves intracellular calcium. It has been demonstrated that premature trypsin activation occurs in the apical cells in response to supramaximal cholecystokinin stimulation, and that this activation is dependent on the spatial and temporal distribution of Ca2+ release within the same subcellular compartment [5]. In resting acinar cells, trypsinogen is stored within zymogen granules located in the apical part of the cells and, after stimulation with physiological doses of cholecystokinin, the granules are exocytosed in a calcium-dependent manner. However, using supramaximal doses of cholecystokinin, trypsin activation begins in the apical acinar cells, and a sustained rise in calcium triggers vacuole formation in response to supramaximal cerulein stimulation. Both trypsin activation and vacuole formation can be inhibited by the interruption of Ca2+ signals [6]. Finally, the role of interstitial protease activation is relevant in the progression to severe disease. Hartwig et al. [7] found large amounts of trypsinogen in the interstitium of secretagogue-induced pancreatitis. This drains via the portal and lymphatic circulation and activation of this extracellular trypsinogen induces hemorrhagic necrosis in a setting of mild edematous pancreatitis.

Most importantly, as a protective mechanism against active trypsin and other proteases, several inhibitors are secreted by the pancreas; one of these is the pancreatic secretory trypsin inhibitor (PSTI). Other inhibitors of active trypsin are the alfa-1-proteinase inhibitor, also known as alfa-1 antitrypsin, and the alfa-2 macroglobulin. In acute pancreatitis, both activated trypsin and trypsin inhibitors are unbalanced; thus, the increased amount of inactivated trypsin causes autodigestion of the gland.

2.2 The chemokine cascade

The destruction of the pancreatic parenchyma during acute pancreatitis quickly induces an inflammatory reaction at the site of injury. The initial cellular response involves the infiltration of polymorphonuclear leukocytes into the perivascular regions of the pancreas. Within a few hours, macrophages and lymphocytes accumulate and phagocyte-derived oxygen radicals participate in a primary injury to the pancreatic capillary endothelial cells. The increased microvascular permeability facilitates margination and extravascular migration of additional neutrophils and monocytes, amplifying the inflammatory process. Following an experimental insult, there is rapid expression of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, and other chemokines (e.g., IL-6 and IL-8) by pancreatic acinar cells and/or transmigrated leukocytes [8]. IL-1 and TNF-α are primary inducers of IL-6 and IL-8 production and are known to initiate and propagate many metabolic consequences of sepsis, including fever, hypotension, acidosis, and acute respiratory distress syndrome (Figure 1). Furthermore, in severe forms of acute pancreatitis, a low production of anti-inflammatory cytokines such as IL-10, which is capable of inhibiting the action of the proinflammatory cytokines, is seen [9].

2.3 Modification of the kallikrein–kinin system

Kinins released during the course of inflammatory injury are the major cause of vascular symptoms, such as pancreatic edema formation and its related consequences of hemococoncentration and hypovolemia. Kinins are also involved in the accumulation of potentially cytotoxic factors in the pancreatic tissue [10]. Whereas glandular prekallikrein is synthesized in the pancreas, both kininogens and plasma prekallikrein are most likely primarily produced in the liver. The kinin system also interacts with the prostaglandins – mostly through kininogens and kallikreins, and not through bradykinin. Whereas bradykinin is rapidly degraded by kinases, kallikrein is inactivated by complex formation with alfa-2 macroglobulin and C1 inhibitor, as well as some other inhibitors. Studies of the kinins system in acute pancreatitis have been carried out mainly in animal models, in which activation was most pronounced in the peritoneal cavity. Although there are few studies on human models, it has been found that plasma prekallikrein decreased in acute pancreatitis, and there was a negative correlation between plasma prekallikrein and kallikrein-like activity [11].

2.4 Activation of the complement system

Complement activation has been shown to occur in patients with acute pancreatitis. In fact, the serum complement system is able to damage viable unaltered cell membranes [12]. Although the diagnostic potential of complement activation products in plasma for predicting severe disease remains unclear, Gloor et al. [13] recently determined the daily levels of the complement anaphylatoxin C3a and the soluble terminal complement complex sC5b-9 in the plasma of patients with mild or severe acute pancreatitis during the first week after the onset of symptoms and in healthy control subjects. They found that, during the first 7 days, both C3a and sC5b-9
were significantly more elevated in the plasma of patients with severe acute pancreatitis as compared to patients with mild disease or controls. The analysis of both parameters in combination during the first week after the onset of symptoms revealed a high sensitivity (93%) and specificity (88%), as well as high negative and positive predictive values (93 and 87%, respectively) with an odds ratio of 91.0 for the development of pancreatic necrosis.

2.5 Alteration of the coagulation system
The importance of disseminated intravascular coagulation (DIC) during the course of acute pancreatitis is well known. The levels of the DIC parameters [plasma platelet count, plasma thrombin–antithrombin III (AT-III) complex (TAT), alpha-2 plasmin inhibitor-plasmin complex, plasma FDP-E and D-dimer, plasma AT-III, and plasma-soluble fibrin monomer complex] were evaluated at admission in 139 consecutive patients with acute pancreatitis [14]. The DIC was diagnosed based on the following criteria: presence of an underlying disorder frequently associated with the DIC, positive soluble fibrin monomer complex and elevated fibrin/fibrinogen degradation products-E levels (> 500 ng/mL), and the presence of clinical bleeding or organ failure. The levels of the DIC parameters were significantly associated with the severity and the prognosis of acute pancreatitis. Thus, aggravated coagulation parameters predict a fatal outcome in patients with acute pancreatitis.

2.6 The renin–angiotensin system and pancreatic inflammation
The characterization of the renin–angiotensin system (RAS) in the pancreas has been reported both in laboratory animals and in humans [15-17]. Demonstration of the angiotensin II receptors and the expression of key RAS component genes have confirmed the presence of such a system in the pancreas [18]. Furthermore, it has been shown that locally formed angiotensinogen and angiotensin receptor subtype-specific expression was increased in an animal model of acute pancreatitis [19]. Both angiotensinogen and angiotensin receptors may possibly play an important role in the induction of inflammation and microcirculatory regulation in the pancreas and they consequently contribute to pancreatic tissue injury in acute pancreatitis. Therefore, a logical question is whether a local RAS could control or determine the extent of inflammatory activation in the pancreas, such as in the regulation of vascular injuries. Unfortunately, the data on the effects of blocking local RAS activation in models of acute pancreatitis are lacking. Molecules in the families of reactive oxygen metabolites and reactive nitrogen species have been shown to be mediated by RAS in the circulatory system [20] and their roles in acute pancreatitis relative to the local RAS are still under investigation.

2.7 Alteration of pancreatic microcirculation
Some authors have reported that acinar cell injury is a constant, rapidly appearing consequence of severe pancreatic ischemia, even if of brief duration. Acinar cell injury is typically subclinical but can also manifest itself clinically as severe acute pancreatitis [21]. Furthermore, the exocrine pancreas has a higher susceptibility to cold ischemia/reperfusion than the endocrine pancreas, and these events are associated with significant alterations in nutritive perfusion and, thus, with limitations of the oxygen supply to the tissue. The loss of endothelial wall integrity determines an alteration of capillary perfusion leading to the adhesion and migration of polymorphonuclear leukocytes, which aggravate tissue damage [22]. Furthermore, tissue reperfusion in the presence of hypoxanthine and xanthine oxidase determines the free oxygen radical production, which results in further damage to the cellular membranes. In turn, the free oxygen radicals activate the polymorphonuclear leukocytes, which induce the release of proteolytic enzymes such as elastase, collagenase, and gelatinase from the granulocyte granules; these proteolytic enzymes attack the extracellular matrix and determine the damage of the microvascular and tissue structures. This was well demonstrated in an experimental study by Keck et al. [23], who found that both trypsin and elastase upregulate the expression of adhesion molecules on leukocytes and endothelial cells in the presence of serum. Increased leukocyte–endothelial interaction and reduced perfusion of the pancreas is induced in vivo by infusion of pancreatic proteases and this effect is partially abrogated by their inhibitors such as nafamostat mesilate and gabexate mesilate. Yet another damaging factor in this context is calcium; in fact, after reperfusion, the arrival of this ion determines the destruction of the cellular membranes through...
activation of the phospholipases and the production of free fatty acids [24].

To ameliorate the local and systemic blood flow, the administration of hypertonic saline solution in experimental models of acute pancreatitis attenuated hemodynamic alterations, decreased inflammatory cytokines, diminished systemic lesions and pancreatic acinar necrosis, prevented pancreatic infection, and reduced the mortality rate [25]. Finally, pentoxifylline, a methylxanthine derivative and a phosphodiesterase inhibition and related production of proinflammatory cytokines [29]; additionally, it has rheological properties, being able to increase blood cell deformability, to decrease platelet aggregation, to lower blood viscosity, and to reduce thrombus formation [26]. Thus, in experimental models of acute pancreatitis pentoxifylline determines a reduction of inflammatory cytokine levels, pancreatic histological damage, occurrence of bacterial translocation and pancreatic infection associated with a significant reduction in mortality rate [30].

2.8 Factors promoting the infection of pancreatic necrosis

In a prospective, clinical study dealing with acute necrotizing pancreatitis, Beger et al. [31] reported that, after excluding patients with a pancreatic abscess, intestinal microorganisms were cultured in 39.4% of 114 patients. The contamination rate was 23.8% in patients operated on within the first 7 days of the attack; this increased to 71.4% in the third week but decreased to 32.5% after the fourth week. Intra- and extra-pancreatic necrosis were more widespread and pancreatitis-associated ascites were more frequent in patients with proven contamination. Postoperative mortality was 37.8% in bacteriologically positive subjects, whereas it was 8.7% in bacteriologically negative patients. Morphologic and clinical alterations were more severe, and the mortality rate was significantly elevated in patients with a short history of disease and bacterial contamination of necrotic tissue. All five patients with pancreatic sepsis who were operated on within the first 7 days of the disease died, compared with 2/16 patients with sterile necrosis. Thus, bacterial contamination of pancreatic necrosis occurs early and frequently, causing a significant increase in morbidity and mortality, particularly when it develops in the initial stages of the attack. One explanation for the mechanism of the infection of necrosis is gut barrier dysfunction; increased intestinal permeability determines subsequent bacterial translocation through the gut wall [32]. However, other mechanisms might explain the possibility of increased infection in patients with severe pancreatitis. In fact, the number of total lymphocytes is significantly lower in patients with severe illness than in those with mild pancreatitis [33]. Furthermore, the peripheral lymphocyte proliferative response to mitogen stimulation in patients with acute pancreatitis decreased during the early phases of the disease, and lymphocyte proliferation was significantly lower in patients with severe disease than in those with mild disease [34]. These findings demonstrate that additional factors, other than bacterial translocation, might contribute to the infection of necrosis in patients with severe acute pancreatitis.

2.9 The mechanisms of pain generation

Pain is mainly due to the release of the tachykinin substance P and calcitonin-gene-related peptide. The pathological activation of sensory neurons and inflammatory sequelae are known as neurogenic inflammation and appear to be important in many organ systems, including the pancreas. Factors that stimulate primary sensory neurons include hydrogen ions, heat, leukotrienes, arachidonic acid metabolites, bradykinins, and proteases such as trypsin, all of which might participate in the generation of acute pancreatitis [35].

3. Clinical overview

Acute pancreatitis is a disease with an increasing annual incidence (Figure 2) [36]; in the United States, the disease consumes enormous healthcare resources [37]. From a pathological point of view, we recognize two forms of acute pancreatitis: edematous pancreatitis and necrotizing pancreatitis. From a clinical point of view, the majority (86%) of patients is usually admitted to the hospital for mild disease, whereas 14% suffer from severe acute pancreatitis; the mortality rate is about 3% when considering all patients with acute pancreatitis and about 19% when considering only those with severe acute pancreatitis [38]. Severe acute pancreatitis is a two-dimensional disease: outcome determinants are the development of multiorgan dysfunction, which appears in a subgroup of patients early after onset of pain; after 2 weeks severe clinical sepsis develops caused by infected necrosis [39].
The management of acute pancreatitis has evolved over several decades, but there is no unanimous consensus among the several medical approaches from various national and international scientific societies, which differ in their recommendations [40]. However, some important points on the approach to this disease regarding the assessment of the diagnosis, severity, and etiology of the disease are largely accepted.

### 3.1 Assessment of diagnosis

The diagnosis of acute pancreatitis should be established within 48 h of admission [36]. The diagnosis should be based on typical abdominal pain associated with an elevation in amylase, pancreatic isoamylase, or lipase serum levels at least twice the upper normal limit. It should be pointed out that the serum concentrations of these enzymes might be normal on admission in a small percentage of patients, and might increase in the days following hospital admission [41]. The diagnosis should be confirmed by imaging techniques such as ultrasonography and/or computed tomography (CT) and/or magnetic resonance (MR) [36].

### 3.2 Assessment of severity

An International Symposium was held in Atlanta, Georgia, in 1992 to discuss the diagnostic evaluation and management of acute pancreatitis and to agree on an acceptable series of clinical definitions for classifying the disease and its complications [42]. According to these criteria, severe acute pancreatitis is defined by the presence of persistent or progressive organ failure and/or local pancreatic complications, including necrosis, abscesses, or pseudocysts.

Early identification of patients at risk of developing a severe attack of acute pancreatitis is of paramount importance because prompt therapeutic intervention improves the outcome of the illness. Close monitoring of the clinical condition is needed in order to identify the possible occurrence of complications. The prediction of severe disease is achieved by careful clinical assessment; for this purpose, the use of a multiple factor scoring system and imaging studies is also suggested (Table 1). The preferred scoring system is the Acute Physiology and Chronic Health Evaluation (APACHE) II score system, which is preferred, utilizing a cutoff of >8, bearing in mind that this scoring system is valid at its extremes [43].

Another possibility for stratifying the severity of the disease is the presence of pathological findings at chest radiograph associated or not with an increase of serum creatinine concentrations (>2 mg/dL) [44].

Contrast-enhanced CT is recommended at the end of the first week after onset of the pain to identify the presence and extent of pancreatic necrosis (Figure 3). Patients suffering extended necrosis including more than 50% of pancreatic tissue have a high risk of death without support in an intensive care unit [45]. CT should be used selectively, based on clinical features in those patients not satisfying these criteria.

Laboratory tests can also be used for severity stratification; serum IL-6 > 2.7 pg/mL within 48 h from disease onset and a serum C-reactive protein level > 150 mg/L at 48 h after pain onset [46] can both be used.

Patients with severe disease and those with other severe comorbidities should be considered for admission to an intensive or intermediate medical care unit.

### 3.3 Assessment of etiology

In Mediterranean countries, the acute pancreatitis is mainly due to biliary causes (69.3%); other associated factors are reported in Table 2 [38]. In other countries, the main associated etiological factor is alcohol [47].

At admission, all acute pancreatitis patients should be screened for serum triglycerides (at least three times the upper normal limit) and calcium levels (>10 mg/dL) to evaluate the possible presence of acute pancreatitis associated with hyperlipemia or hyperparathyroidism; bilirubin, transaminases, and alkaline phosphatase levels should also be determined in all patients for an initial evaluation of biliary acute pancreatitis.

Transabdominal ultrasonography should be carried out at admission for the detection of stones in the gall bladder and/or common bile duct. If the results of the transabdominal ultrasound examination are not convincing when there is suspicion of common bile duct stones, endoscopic ultrasonography (EUS) [36] or magnetic resonance cholangiopancreatography (MRCP) can be used as an accurate alternative approach at admission or thereafter. When an underlying pancreatic malignancy is suspected, CT, MR, or EUS should be performed in those patients with unexplained acute pancreatitis.

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**Table 1. Score systems and laboratory indexes used to predict severe acute pancreatitis.**

<table>
<thead>
<tr>
<th>Score systems or single-laboratory indexes</th>
<th>Findings</th>
<th>Time of evaluation</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score</td>
<td>&gt; 8</td>
<td>On admission and daily</td>
<td>60</td>
<td>85</td>
</tr>
<tr>
<td>Chest X-ray ± serum creatinine</td>
<td>Chest alterations</td>
<td>On admission</td>
<td>60</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>Creatinine &gt; 2 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast-enhanced CT</td>
<td>Balthazar criteria</td>
<td>72 h after the onset of pain</td>
<td>85</td>
<td>100</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>&gt; 2.7 pg/mL</td>
<td>Within 48 h of pain onset</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>&gt; 150 mg/L</td>
<td>At 48 h of pain onset</td>
<td>85</td>
<td>90</td>
</tr>
</tbody>
</table>

APACHE: Acute Physiology and Chronic Health Evaluation; CT: Computed tomography.
In patients with recurrent episodes of acute pancreatitis, evaluation with EUS and/or MRCP using secretin stimulation (if available) should be considered; genetic testing is not recommended for routine use but should be considered in selected patients.

4. Pharmacotherapeutic recommendations

4.1 Pain control
Analgesics, graded according to pain severity, must be provided for all patients. An observational multicenter study on the treatment of acute pancreatitis in Italy [48] demonstrated that analgesics were graded according to the severity of the pain in routine clinical practice; patients with mild acute pancreatitis received mainly non-steroidal, anti-inflammatory drugs (NSAIDs) and tramadol, whereas patients with severe pancreatitis received a high percentage of opioids or an association of analgesics including NSAIDs, tramadol, and opioids. However, as reported in a previous review on this issue [40], there are no extensive studies regarding the pharmacological control of pain in acute pancreatitis and this is quite surprising due to the importance of this factor. There is also a lack of evidence about the different efficacies of various pharmacological substances in the different forms of acute pancreatitis; therefore, studies comparing different schedules of pain-relieving drugs in patients with acute pancreatitis and utilizing objective methods to evaluate pain decrease are needed.

4.2 Measures for supporting the circulation and for the treatment of lung and kidney alterations
All patients diagnosed with acute pancreatitis should be managed in the hospital and monitoring of blood pressure, pulse and respiratory rate, body temperature, hourly urinary volume, and blood oxygen saturation level (SpO2) by pulse oximetry is essential for the correct management of the disease.

4.2.1 Fluids and electrolyte supplementation
Fluids should be administered early irrespective of the severity of acute pancreatitis; electrolyte and metabolic abnormalities should be corrected. This takes place in routine clinical practice as demonstrated by an Italian multicenter study [48]; in this observational study, patients with severe acute pancreatitis received a significantly higher amount of fluids than those with mild acute pancreatitis.

4.2.2 Respiratory support
The incidence of pulmonary complications in acute pancreatitis ranges from 15 to 55%, and their severity vary from mild hypoxemia without clinical or radiologic abnormalities to acute lung injury syndrome or acute respiratory distress syndrome [49]. About 10% of patients may have alveolar edema on chest radiograph [50] and progressive hypoxemia develops in about one-third of patients within hours or within 2 – 3 days. Acute respiratory distress syndrome (ATDS) and
acute lung injury syndrome have no specific treatment, only supportive care: treating the underlying cause, when possible, and using mechanical ventilation [51]. A high-volume, high-pressure ventilation strategy might lead to lung lesions indistinguishable from ARDS. Subsequent randomized clinical trials showed improved survival using low tidal volumes and limiting plateau pressure to 30 cmH2O, although the optimal level of positive end expiratory pressure (PEEP) remains controversial [51]. Prone positioning should be reserved for severely ill patients. Inhaled nitric oxide, which is a pulmonary vasodilator with anti-inflammatory properties, is associated with limited improvement in oxygenation without improvement in survival [52].

4.2.3 Renal support
Continuous hemodiafiltration is a combination of continuous hemofiltration with hemo dialysis developed as a continuous renal replacement therapy for patients with severe condi tions. It is usually performed continuously for 24 h and for 3 – 14 days, and it can be used to control fluid balance in patients having excessive fluid resuscitation with inadequate diuresis. In some centers this procedure is performed even if there is sufficient urinary volume, because continuous hemodiafiltration can remove excess humoral mediators [53-55].

4.3 Specific drugs
4.3.1 Antiproteases
The use of these drugs, even if theoretically correct, has had discordant results in clinical trials. The largest double-blind study of aprotinin was carried out on 161 patients with acute pancreatitis, randomly allocated to receive either aprotinin (500,000 units bolus and then 200,000 units 6-hourly for 24 h from the onset of pain and for at least 7 days) or a placebo. There were 14 deaths, 7 in each group, and there was no difference in the complication rate.

Another multicenter, randomized, double-blind study included 223 patients with moderate or severe pancreatitis [57]. In this study, patients received a low-molecular-weight antiprotease called gabexate mesilate (4 g per day i.v. for 7 days) or a placebo. There was no difference between the groups with regard to mortality (15 vs 16%), complications or the need for surgery. A possible explanation of why these agents did not have the expected beneficial effect on outcome in these studies is the lag time between the onset of the pancreatitis and the drug administration.

Conversely, two studies, one coming from Italy [58] and the other one from Taiwan [59], found a beneficial effect of gabexate mesilate; in these two studies, the drug was able to reduce the need for surgery and the mortality. A recent meta-analysis has shown that treatment with protease inhibitors does not significantly reduce mortality in patients with mild acute pancreatitis, but antiproteases may reduce mortality in patients with moderate to severe acute pancreatitis [60]. As suggested by a multicenter Italian study comparing two different dosages of gabexate mesilate, antiproteases should be administered within 24 h from the onset of pain and for at least 7 days [61]. At present, we believe that further studies are necessary to definitively assess the usefulness of these drugs in treating severe acute pancreatitis.

4.3.2 Somatostatin and octreotide
Somatostatin and its long-acting analogue octreotide are potent inhibitors of pancreatic secretion [62,63]. They also stimulate activity of the reticuloendothelial system and play a regulatory role, mostly inhibitory, in the modulation of the immune response via autocrine and neuroendocrine pathways. Both are cytoprotective with respect to the pancreas [64]. Somatostatin has also been shown to block the release of the cytokine tumour necrosis factor and interferon-gamma by peripheral mononuclear cells. Furthermore, octreotide increases the phagocytic activity of monocytes [65]. These actions may be important in the modulation of the pathogenesis of ARDS and septic shock, both of which can complicate severe acute pancreatitis. However, both agents are powerful splanch nic vasoconstrictors and this should be kept in mind because the development of pancreatic necrosis has been linked to hypoperfusion of the gland and vasoconstrictors have been shown to worsen the histological severity of experimental pancreatitis [66]. Consequently, these agents seem to have beneficial and detri mental effects. The only trial using a correct methodological approach was that by Uhl et al. [67]. These authors used octreotide at a dosage of 0.1 and 0.2 mg t.i.d., and found no differences in the placebo group with respect to mortality, the rate of newly developed complications, the duration of pain, surgical interventions, or the length of the hospital stay. Furthermore, a meta-analysis by Heinrich et al. [68] has revealed that octreotide does not reduce surgical interventions, sepsis, mortality, or overall complication rates. Finally, none of the available guidelines recommends the use of these drugs in the early phases of acute pancreatitis [36].

4.3.3 Lexipafant
Platelet-activating factor (PAF), together with other proinflammatory cytokines such as IL-1-β, IL-6, IL-8, TNF-α and the anti-inflammatory cytokines IL-2 and IL-10, is involved in the pathogenesis of acute pancreatitis [69]; the PAF increases vascular permeability, induces leukocyte infiltration, edema and tissue injury, and has a negative inotropic effect [70]. PAF antagonists have ameliorated acute pancreatitis in experimental models of acute pancreatitis [71], and lexipafant is one of the most powerful PAF antagonists developed so far. Two Phase II randomized trials involving a total of 133 patients with acute pancreatitis showed significant improvement in organ failure scores [72,73]. However, a randomized, double-blind, placebo controlled, multicenter trial of lexipafant involving 290 patients with an APACHE II score > 6 was carried out [74] and showed that lexipafant had no effect on new organ failure during treatment. Some positive aspects of this...
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study should be pointed out; in the lexipafant group, there was a significant reduction of the incidence of pseudocysts, systemic sepsis and deaths in patients treated within the first 48 h from the onset of symptoms. Thus, for anticytokine therapy, the therapeutic window is crucial in testing its efficacy an, other and associated therapeutic approaches should also be used together with the immune-therapy for the appropriate treatment of acute pancreatitis. At present, no other studies on humans using lexipafant or other anticytokine drugs are in progress.

4.4 Antacids

An open question in the treatment of acute pancreatitis is the efficacy of inhibiting gastric acid secretion. There are very few studies on this issue and the results are not conclusive [40]. However, in an observational study [48], gastric acid secretion inhibition is largely used in patients with acute pancreatitis and the duration of treatment with drugs inhibiting gastric acid secretion was significantly higher in patients with severe acute pancreatitis than in patients with the mild form; this may be due to the fact that the hospital stay of patients with severe pancreatitis is significantly longer than that of those having mild disease. In conclusion, at present we need well-designed studies on this important topic in order to avoid the unnecessary use of costly drugs.

4.5 Specific nutritional measures.

Failure of the intestinal barrier, together with bacterial overgrowth due to motility changes and immunosuppression, constitute the pathways of continuous pancreatic contamination from bacterial translocation in patients with severe acute pancreatitis. The maintenance of gut barrier integrity is one of the goals in the treatment of severe acute pancreatitis and, for this reason, enteral nutrition has been proposed for restoring and preventing morphological changes in the gut associated with fasting. One of the first studies on this topic [75] demonstrated that total enteral nutrition was able to moderate the acute phase response evaluated by serum C-reactive protein determination, serum IgM antiendotoxin antibodies and total antioxidant capacity as well as to improve disease severity and clinical outcome despite unchanged pancreatic injury on computed tomography scan. Even if the effectiveness of nutritional support in patients with severe pancreatitis is quite difficult to demonstrate, some studies are available to illustrate the usefulness of this nutritional measure in reducing both the complications of severe pancreatitis [75-77] and those resulting from infections related to other nutritional measures such as total parenteral nutrition [76]. Other studies, also using different ‘immunoactive’ formulae, such as glutamine [78] and omega-3 fatty acids [79,80], have been published. The authors of these studies have claimed that the nutritional formulas proposed worked better than traditional nutritional support. Most importantly, the immediate institution of nutritional support in the form of total enteral nutrition is as safe as total parenteral nutrition in predicted severe acute pancreatitis [81]. Finally, substrate metabolism in severe acute pancreatitis is similar to that in response to severe sepsis or trauma. There is increased protein catabolism, characterized by an inability of exogenous glucose to inhibit gluconeogenesis, increased energy expenditure, increased insulin resistance and increased dependence on fatty acid oxidation to provide energy substrates. Energy needs may differ and change substantially according to the severity and stage of the disease, patient comorbidities and specific complications occurring during the clinical course of the disease. Thus, nutritional support should be provided only in severe patients [82] and enteral nutrition can not be applied in those patients having abdominal compartment syndrome [82]. Standard enteral feed should provide 12 g nitrogen and 7.11 non-protein mega joule (MJ) in 2000 mL per 24 h once established; of the non-protein energy, 36% should be lipid based. The enteral feed should be introduced at 30 mL/h and the rate should be increased, depending on tolerance, up to 100 mL/h. Total parenteral nutrition should be used in patients unable to tolerate enteral nutrition [83]. A standard parenteral formula should have a volume of 2500 mL, providing 9.4 g nitrogen and 7.52 non-protein MJ per 24 h; lipids should contribute 55% of the non-protein calories.

4.6 Antibiotics

Earlier studies on antibiotic treatment do not indicate favorable effects on the outcome of acute pancreatitis [84-86]. However, these studies were carried out before the CT era, without the possibility of exactly stratifying pancreatic necrosis as sterile necrosis, infected necrosis, and pancreatic abscess, and before the observation that bacterial contamination of pancreatic necrosis is the cause of a significant increase in morbidity and mortality. Furthermore, these studies were also not able to take into account the new advances in antibiotic pancreatic penetration, especially during the acute phase of the disease [87].

These achievements have enabled Pederzoli et al. to design the first clinical trial on antibiotic prophylaxis in acute pancreatitis with a less empiric approach based on a broad-spectrum antibiotic in which pancreatic penetration at therapeutic minimal inhibitory concentration was proven [88]. In this randomized, multicenter study, 74 patients with computed tomographic scans demonstrating necrotizing pancreatitis within 72 h of onset were assigned to two groups receiving no antibiotic treatment or 0.5 g of prophylactic imipenem administered intravenously every 8 h for 2 weeks. Pancreatic sepsis was always detected by means of cultures (percutaneous computed tomography or ultrasound-guided needle aspiration and intraoperative samples). The incidence of pancreatic sepsis was much lower in treated patients (12.2 vs 30.3%, p < 0.01); however, this study failed to demonstrate a significant reduction in mortality from sepsis even if the mortality in the placebo group (12.1%) was higher than that in the treated group (7.3%). After this study, several other multicenter [89-92] and single-center [93-96] studies were carried out. Except for those of Sainio et al. [93] and Luiten...
et al.[89], all these studies failed to demonstrate any significance in the mortality rate between the treated groups in comparison with the placebo groups. Whereas in the Luiten et al. study[89], late mortality was significantly reduced using selective decontamination of the gut, in the Sainio et al. study[93], the reduction in mortality was due not only to antibiotic treatment but also partly to adequate fluid resuscitation and effective intensive care combined with the correct timing and type of surgical intervention, as suggested by the same authors.

On the basis of these studies, several guidelines on acute pancreatitis suggest that carbapenems should be used prophylactically and should be continued for 14 days, and that the development of infected necrosis should be assessed using fine-needle aspiration and the sample should be cultured for germ isolation and characterization[36]. In routine clinical practice, antibiotics are used to cure both extrapancreatic infections that appear during the course of acute pancreatitis and infected pancreatic necrosis, and also as a prophylaxis in those patients who have pancreatic necrosis to prevent possible infection from the necrosis. Antibiotic prophylaxis, established days after hospital admission, are ineffective to prevent infected necrosis and clinical sepsis[97]. In the treatment of extrapancreatic infections, the antibiotics most frequently used were cephalosporins; carbapenems, glycopeptides, and antifungal antibiotics were the most used antibiotics in the treatment of proven infected pancreatic necrosis[48]. Moreover, there are very few topics in pancreatology that cause as much debate as that regarding the utility of antibiotic prophylaxis in severe acute pancreatitis. There are few human randomized studies and more meta-analyses than studies have been published.

The latest meta-analytic study comes from the United States[98]. In brief, the authors carried out a systematic search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials, using PubMed, Google Scholar, and Ovid as search engines without language restriction until the end of May 2008. They screened 367 articles, of which 55 were found to be relevant to pancreatitis and antibiotics. Of these 55 articles, only eight met the inclusion criteria: randomized controlled studies; severe acute pancreatitis diagnosed with contrast-enhanced computed tomography and any of the severity criteria such as APACHE II, the Imrie classification, increased C-reactive protein levels greater than 120 mg/L, necrosis evaluated by contrast-enhanced computed tomography, prophylactic antibiotics administered intravenously, defined length of antibiotic treatment, and morbidity and mortality measured objectively. Sensitivity analysis was applied to the results to determine heterogeneity among the studies. The authors pooled 502 patients from eight studies[88,93,95,99-102]. The majority of the patients (56%) had alcoholic pancreatitis, followed by biliary pancreatitis (24%), and pancreatitis due to other causes (20%). The age of these patients ranged from 43 to 59 years and the length of the hospital stay ranged from 18 to 95 days. There were 253 patients with severe acute pancreatitis who received prophylactic antibiotics and 249 patients were randomized to the placebo arm. Overall, there was no protective effect of the antibiotic treatment with respect to mortality. With respect to morbidity, the antibiotic prophylaxis did not protect against infected necrosis or surgical intervention. There was, however, an apparent benefit as regards non-pancreatic infections, with a relative risk reduction of 40%, absolute risk reduction of 15% and number needed to treat of 7. Some comments are necessary. First, there was heterogeneity in the studies considered and only five studies [93,95,99,101,102] were considered to be of high quality according to the Jadad et al. scale[103]. Thus, very few studies were available for a meta-analytic study. Second, regarding the antibiotics used as prophylaxis, only half of the studies used carbapenems; other studies used cefuroxime, ofloxacin, and ciprofloxacin, associated or not with metronidazole, or ciprofloxacin plus metronidazole. This is a crucial point, because the differences in the ability of the various antibiotics to penetrate into necrotic pancreatic tissue are well known. In fact, the choice of antibiotics in preventing infected necrosis during necrotizing pancreatitis should be based on their antimicrobial activity, penetration rate, persistence and therapeutic concentrations in the necrotic pancreatic area; these requisites are provided by pefloxacin and metronidazole and, to some extent, by imipenem and mezlocillin[87]. Finally, two studies considered in the meta-analysis[101,102] did not reach the number of patients required by the calculated sample size. One study was stopped after an adaptive interim analysis[101] and, as pointed out by the authors themselves, the sample size was not large enough to detect potential beneficial effects of low magnitude or potential benefits involving infrequent secondary end points such as mortality, pancreatic necrosis, shock and renal insufficiency. The second study[102] was stopped due to limited resources for continuing the trial. It is also important to note that an apparent benefit was found in the meta-analysis regarding the development of non-pancreatic infections.

A recent multicenter study from the Dutch Acute Pancreatitis Study Group[104] found that the mortality rate was higher in patients with pneumonia, bacteremia, infected necrosis, and pancreatic necrosis when patients with each specific infection were compared with all other patients in the study. It is now clear that half of relevant infections occur in the first few days of acute pancreatitis; thus prophylactic strategies should be initiated immediately after admission and randomized controlled trials of antibiotic prophylaxis, commencing treatment in the first 72 – 120 h after the onset of symptoms[101,102], should be programmed. In fact, results from a recent randomized trial, showing a significant reduction in ’extrapancreatic sepsis’ by starting antibiotic prophylaxis on admission to the hospital, support this hypothesis[97]. As pointed out by the authors of the meta-analyses published to date[98], other limitations of the studies considered in the meta-analysis – such as inclusion criteria, duration and dosing of antibiotics, assessment of disease severity, nutritional
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support, and resuscitative measures, the relatively small number of patients in each individual study, and different outcome measurements – were inherent in the primary study design. In addition, the inclusion of nonblinded studies limits the findings because these patients should have received surgical intervention when investigators realized that they were not receiving antibiotics.

In conclusion, we do not need more meta-analytic studies on this topic; on the contrary, additional and well-carried out studies are required to explore the benefits of antibiotic prophylaxis in severe acute pancreatitis. These also need to take into account the adverse effects, the effects of the varying duration of the therapy, and whether the outcome of the infection is related to the etiology.

4.7 Antifungals
Fungal infections have increased and now account for 10 – 20% of microorganisms involved in infected pancreatic necrosis. In a series of 207 consecutive patients admitted for severe acute pancreatitis, Vege et al. [105] found that 52% of them had an intra-abdominal infection; 30 patients with bacterial infections (15%) developed concomitant fungal infections; there were seven primary fungal infections and 23 postoperative infections. Compared with patients with intra-abdominal bacterial infection, patients with intra-abdominal fungal infection had longer hospital and ICU stays and higher rates of organ failure but similar mortality rates. Multivariate analysis revealed the presence of organ failure and the need for ICU care to be associated with intra-abdominal fungal infection; thus, patients with severe acute pancreatitis and intra-abdominal fungal infection suffered greater in-hospital morbidity than did patients with intra-abdominal bacterial infection alone, even if concomitant fungal infection did not increase the in-hospital mortality rate. These results suggest that the early documentation of infection and aggressive antimicrobial treatment of intra-abdominal fungal infection can improve mortality rates without standard prophylaxis. Antifungal prophylaxis may be advocated in selected patients, i.e., those having risk factors for fungal infection, such as patients with intravenous catheters for parenteral nutrition and those in whom antibiotics are used for a long period of time [106].

4.8 Probiotics
Probiotics have been proposed to reduce the infection of necrosis by intestinal bacteria. A study from Hungary [107] demonstrated that Lactobacillus plantarum 299 together with a substrate of oat fiber administered at a dose of 10⁹ organisms for 1 week by nasojejunal tube is effective in reducing pancreatic sepsis and the number of surgical interventions related to pancreatic damage. Conversely, a multicenter study on the clinical usefulness of probiotics in predicted severe pancreatitis gave disappointing results [108]. In fact, the results of the study showed that probiotic prophylaxis did not reduce the risk of infectious complications and was associated with an increased risk of mortality. The main complication of probiotic treatment was bowel ischemia in nine probiotic-treated patients (eight of whom had fatal outcomes); probiotic prophylaxis should therefore not be administered to this category of patients. The results of this study have also been confirmed by a meta-analytic study [109] and the authors of this meta-analysis concluded that probiotics could not reduce the infection of pancreatic necrosis and mortality.

4.9 Treatment of fluid collections and pseudocysts
Acute fluid collections usually do not require specific therapy in the absence of infection while symptomatic pseudocysts should be managed by endoscopic, percutaneous or surgical approaches. However, some evidence exists for their efficacy in the treatment of symptomatic pancreatic pseudocysts in patients temporarily unfit for surgery and in patients with pancreatic fistulae at a dosage of 0.1 – 0.2 mg t.i.d. [110,111].

5. Refeeding in mild acute pancreatitis

This topic is crucial for patients who have recovered from an acute episode of mild acute pancreatitis. It has been suggested that patients can eat normal, light food only when the pancreatic gland has returned to normal at imaging [112]. Others have suggested that initiating oral nutrition after mild acute pancreatitis with a low-fat, solid diet is safe and provides more calories than a clear liquid diet, but did not result in a shorter length of hospitalization [113,114]. Thus, the recommendation is to initiate refeeding when pain disappears using a low-fat, solid diet; in fact, in mild acute pancreatitis, immediate oral feeding is feasible and safe, and may accelerate recovery without adverse gastrointestinal events [115].

It is also necessary to establish the exocrine pancreatic function in patients who have experienced an acute episode of pancreatitis, so as to cure possible maldigestion. For example, in patients with alcoholic pancreatitis, there is the need for enzyme supplementation during refeeding if the elastase-1 fecal determination is clearly abnormal [116].

6. Prevention of recurrences

The withdrawal of alcohol must be recommended to patients with alcoholic pancreatitis and, if smokers, the abolition of smoking should be recommended. Patients with gallstone pancreatitis should undergo elective cholecystectomy and/or endoscopic sphincterotomy [36]. Patients with hyperlipemia should be adequately treated and carefully monitored. In the case of acute pancreatitis due to drugs, patients should be warned not to assume the drug responsible for the disease.

7. Quality of life in medically treated patients

Very few studies have investigated patient-reported outcomes (PROs) in subjects with acute pancreatitis, and these studies have all focused on surgical patients with severe pancreatitis.
There are also no studies in which the PRO was assessed in acute pancreatitis patients who were treated medically and, in addition, data were lacking at short term from the onset of the disease. Thus, we have recently used two questionnaires (SF-12 and EORTC QLQ-C30) for evaluating the 1-year quality of life in 40 medically treated patients with acute pancreatitis [117]; the questionnaires were administered during the acute phase of the disease as well as at 2 and 12 months after recovery. Two different patterns of the quality of life were recognized in these patients: physical impairment immediately present during the attack followed by mental impairment which appears progressively in the follow-up period. Thus, the expected quality of life and productivity of patients with acute pancreatitis justifies the utilization of quality-of-life questionnaires in future studies as a part of new medical treatment options for curing acute pancreatitis.

8. Conclusion

Supportive care is the cornerstone of the treatment for acute pancreatitis, especially for the severe form of the disease. In fact, in severe acute pancreatitis, the aims of pharmacological support are the prevention and the treatment of pancreatic necrosis, multiple organ dysfunction syndromes and the infection of pancreatic necrosis. No specific pharmacological intervention (gabexate, somatostatin and its long-acting analogues, lelipant) has proven to be beneficial in clinical practice because when the acute pancreatitis patients, and especially those with severe disease, are hospitalized, the pathophysiological processes cannot be stopped or reversed. Only a multidrug strategy can improve the survival of severe patients, but we need studies confirming this assumption. We also need to prevent further attacks of pancreatitis, especially in those patients who are at risk such as alcoholics, by suggesting alcohol abstinence and, in patients with gallstone pancreatitis, by suggesting an elective cholecystectomy, possibly during the same hospitalization for the attack of acute pancreatitis.

9. Expert opinion

One of the recurring characteristics of acute pancreatitis is the long waits involved in the hospital, from hours to days, from the appearance of pain and hospitalization. This greatly affects the efficacy of therapeutic measures and ensures that treatment is more often aimed at an attempt to control the progression of the disease rather than modify the pathogenetic phenomena. The delay in hospital admission makes it difficult to interpret the results of therapeutic trials and, in some ways, it is difficult to have a homogeneous analysis of data from multiple studies. The timing of the start of treatment is often not specified and, in many cases, is considered to start at the time of hospitalization. The interventional window in acute pancreatitis, i.e., the time during which there is the possibility of specifically antagonizing the inflammatory mediators and pancreatic enzyme activation, is 24 – 48 h after the onset of pain. Thus, ‘specific’ treatment should be carried out as early as possible and, after this time, the use of specific drugs is unnecessary. In this clinical scenario, medical treatment should be more rationally targeted to support cardiovascular, respiratory, and renal dysfunctions, and to prevent septic complications. Currently, the hypothesis that for every four patients with acute pancreatitis three will respond favorably to conservative medical treatment is plausible. The remaining fourth patient will present complications, having a one-third probability of a fatal outcome. The following three corollaries derive from these estimates: i) the majority of patients will benefit from a conservative therapy without surgery; ii) the early identification of those patients at increased risk of developing complications is crucial for both prognosis; and iii) therapy and surgery should be reserved only for those patients who develop specific complications, especially the infection of pancreatic necrosis. A summary of recommendations is reported at the end of this article. In view of future therapeutic protocols, a logical approach would be to limit organ damage by the selective suppression of the inflammatory mediators involved in the systemic inflammatory response syndrome and protect the patients against systemic complications. At present, there are several possibilities for modulating the inflammatory response such as manipulating the cytokine network, suppressing the inflammatory response, promoting active immunization, inducing tolerance, administering immunoglobulin, and evaluating gene therapy. In acute pancreatitis, only the first two points have been explored until now, experimentally as well as in clinical practice.

So, what do we ask of immune-modulation therapy? For the most part, we ask that the progression from edematous to necrotizing pancreatitis be avoided, both the systemic inflammatory response syndrome and organ dysfunction be prevented, and the infection of pancreatic necrosis be avoided. Thus, with regard to the progression from edematous to necrotizing pancreatitis, we need drugs capable of blocking NF-kB activation or blocking the effects of TNF-α. Regarding the prevention of the systemic inflammatory response syndrome and organ dysfunction, substances capable of blocking or inactivating the cytokine cascade should be tested. Finally, with regard to the possibility of preventing the infection of necrosis, cytokine therapy might play a role. However, as the period during which specific therapy can be administered is short, we need rapid diagnosis and assessment of the severity of acute pancreatitis. We must also bear in mind that, in the treatment of acute pancreatitis, modulation of the immune response is only a part of the multimodal treatment of acute pancreatitis involving several specialists such as internists, gastroenterologists, surgeons, endoscopists, and intensivists.

Summary

- Acute pancreatitis is a disease of increasing annual incidence.
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- The diagnosis of the disease should be established within 48 h of admission.
- Early identification of patients at risk of developing a severe attack of acute pancreatitis is of paramount importance because rapid therapeutic intervention improves outcome.
- Supportive care is the cornerstone of the treatment of acute pancreatitis, especially of the severe form of the disease.
- The role of antiproteases is still under investigation.
- The role of modulating inflammation in acute pancreatitis has been found to be useful in animal models but not in human acute pancreatitis.
- The inhibition of secretion, using somatostatin and its long-acting analogues, does not improve outcome in patients with established acute pancreatitis, and, therefore, their use is not recommended.
- The data supporting the efficacy of an antibiotic prophylaxis to prevent infection of necrosis are conflicting and well-designed studies are needed.
- Refeeding is a crucial topic in patients who have recovered from an acute episode of mild acute pancreatitis, and the evidence suggests that low fat solid diet should be initiated when pain disappears.

**Declaration of interest**

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

**Bibliography**

Papers of special note have been highlighted as either of interest (●) or of considerable interest (●●) to readers.

2. Frossard JL. Trypsin activation peptide (TAP) in acute pancreatitis: from pathophysiology to clinical usefulness. JOP 2001;2:69-77

This study investigated the early changes in intestinal permeability in patients with acute pancreatitis, and it correlates these changes with subsequent disease severity and endotoxemia.


Following 3 days of group meetings and open discussions, unanimous consensus on a series of definitions and a clinically based classification system for acute pancreatitis was achieved by a diverse group of 40 international authorities from six medical disciplines and 15 countries. This classification system is of value to practicing clinicians in the care of individual patients and to academicians seeking to compare scientific data.


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- The authors demonstrated for the first time that early intravenous gabexate mesilate infusion results in improved survival in acute pancreatitis patients with organ dysfunctions.


- The myth bites the dust: octreotide is not useful in the treatment of acute pancreatitis.


- The first large study on anticytokine therapy in acute pancreatitis.


- The first well-done study on enteral feeding in acute pancreatitis demonstrating that this therapeutic approach modulates the inflammatory and sepsis response in acute pancreatitis and is clinically beneficial.


118. In patients with predicted severe acute pancreatitis, probiotic prophylaxis did not reduce the risk of infectious complications and was associated with an increased risk of mortality. Probiotic prophylaxis should therefore not be administered in this category of patients.
128. In mild acute pancreatitis, immediate oral feeding was feasible and safe and may accelerate recovery without adverse gastrointestinal events.
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