Pharmacological Options for Acute Pancreatitis: An Overview

Raffaele Pezzilli1*
Department of Digestive Diseases and Internal Medicine, Sant’Orsola-Malpighi Hospital, Bologna, Italy
*Corresponding author: Raffaele Pezzilli, Department of Digestive Diseases and Internal Medicine, Sant’Orsola-Malpighi Hospital, Bologna, Italy Tel: +39-0516364148;
Fax: +39-0516364148; E-mail: raffaele.pezzilli@aosp.bo.it
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Abstract

Introduction

The pathophysiological processes leading to acute pancreatitis are so far largely unknown and therapy requires a precise knowledge of the pathophysiological mechanisms of the disease to be effective. In modern medicine an evidence-based approach is necessary to balance between the benefit of patients and the economic resources; thus we reviewed the literature data on the best pharmacological approaches on acute pancreatitis.

Methods: A literature of the last 10 years was searched by using PubMed database and a total of 7194 papers were found; only 78 papers were selected regarding control of pain, restoration of circulation, nutritional support during the acute phase of acute pancreatitis, early refeeding in patients recovering from an acute attack of acute pancreatitis.

Conclusions: The cornerstone of treatment is the control of pain and the restoration of circulation. Enteral nutrition is an essential therapeutic measure for the prevention of the catabolic state and bacterial translocation from the intestinal lumen to the pancreatic necrosis. Early refeeding is essential in patients recovering from an acute attack of acute pancreatitis and oral pancreatic extract supplementation should be given only when severe exocrine pancreatic insufficiency is demonstrated.

Introduction

Adequate therapy of for acute pancreatitis requires a precise knowledge of the pathophysiological mechanisms of the disease. It is well known that, until now, the mechanisms leading to an attack of acute pancreatitis are unclear; at present, we are able to control the pain and to cure the complications of the severe disease. We have reviewed the current knowledge of on the medical treatment of acute pancreatitis.

Methods

We searched the current literature data by using the PubMed database with the following strategy: (("Pancreatitis"[Mesh] OR "Pancreatitis, Acute Necrotizing"[Mesh]) OR "Pancreatitis, Alcoholic"[Mesh]) AND "therapy"[Subheading] AND (("1994/01/01"[PDAT]: "2014/03/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang]); a total of 7194 paper were found and, after exclusion of case reports, review articles, letters and papers not containing original data, 78 articles were selected regarding diagnosis of the disease, severity and etiological assessment of illness, pharmacological approach for control of pain, restoration of circulation, nutritional support during the acute phase of acute pancreatitis, and early refeeding in patients recovering from an acute attack of acute pancreatitis.

Clinical overview

Important points regarding the approach to this disease concern the assessment of the diagnosis, and the severity and etiology of the disease. Of course, the three steps are not consecutive but they must be evaluated simultaneously for essential therapeutic implications.

Assessment of diagnosis

The diagnosis of acute pancreatitis should be established as soon as possible within 48 hours of admission [1]; it is based on the typical abdominal pain associated with an elevation in amylase or lipase serum levels at least three times the upper normal limit. Serum concentrations of these enzymes may sometimes be normal on admission and their activity may increase in the days following hospital admission [2].

Differential diagnosis

The acute illnesses which are frequently involved in the differential diagnosis of pancreatitis are acute biliary diseases, such as cholecystitis, acute exacerbation of a duodenal ulcer, bowel perforation, intestinal obstruction, renal colic, aortic dissection and acute myocardial infarction. Acute myocardial infarction may pose some problems because it is well known that electrocardiographic alterations may be present at the early stages of acute pancreatitis [3], associated or not with abnormally high levels of cardiac enzymes [4] as well as echocardiographic alterations [5]. Thus, we should be aware of cardiac alterations when we see patients with acute pancreatitis for the first time, irrespective of the severity of the disease.
Assessment of severity

From 1993 to 2013, the commonly accepted criteria for stratifying the severity of acute pancreatitis were those released by the International Symposium of Atlanta in 1992 [6]. According to these criteria, severe acute pancreatitis was defined by the presence of persistent or progressive organ failure and/or local pancreatic complications including necrosis, abscesses or pseudocysts. Two new classification systems have recently been published to revise the Atlanta criteria [7,8]. These two new classification systems have complicated the severity assessment, one by introducing an additional class (moderate acute pancreatitis characterized by transient organ failure, local complications or exacerbation of co-morbidities) [7], and the other has introduced two additional classes (moderate, characterized by sterile necrosis and/or transient organ failure, and a critical form characterized by infected pancreatic necrosis and persistent organ failure) [8]. These systems require additional evaluation in clinical practice [9]; the majority of the studies published to date regarding the treatment of acute pancreatitis refer to the original Atlanta classification system [6]. However, all these criteria are applied after the patient has recovered or has died from acute pancreatitis in order to make the studies on acute pancreatitis comparable; criteria are needed to predict the course of the disease as soon as possible. In fact, the 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. 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. The preferred scoring system largely used in clinical practice is the Acute Physiology and Chronic Health Evaluation (APACHE) II score system; a score equal to or greater than 8 identifies those patients who may develop complications during the course of acute pancreatitis [10,11]. Another possibility for stratifying the severity of the disease is the presence of pathological findings at chest radiograph, associated or not with an increase in serum creatinine concentrations (>2 mg/dl) [12].

Laboratory tests may also be used for severity stratification; serum interleukin 6 >2.7 pg/ml within 48 hours from disease onset and a serum C-reactive protein (CRP) level >150 mg/L at 48 hours after pain onset [13] may be used to reach this aim. The good performance of IL-6 serum determination has been confirmed by a meta-analytic study [14]. Patients with severe disease and those with other severe comorbidities should be considered for admission to an intensive or intermediate medical care unit [15].

Assessment of etiology

The etiology of acute pancreatitis varies in different countries [16]; acute pancreatitis is mainly due to biliary causes in southern European countries [17] whereas, in northern European countries, the main associated etiological factor is alcohol [18].

On admission, bilirubin, transaminases and alkaline phosphatase levels should be determined for the initial evaluation of biliary acute pancreatitis; in addition, all acute pancreatitis patients without evidence of gallstones should be screened for serum triglyceride (at least 3 times the upper normal limit) and calcium levels (>10 mg/dL) in order to evaluate the possible presence of acute pancreatitis associated with hyperlipemia or hyperparathyroidism; Transabdominal ultrasonography should be carried out for rapid detection of stones in the gallbladder and/or common bile duct and, if the results of the transabdominal ultrasound examination are not convincing when there is suspicion of common bile duct stones, endoscopic ultrasonography (EUS) [1] or magnetic resonance cholangiopancreatography (MRCP) can be used as an accurate alternative approach at admission or thereafter. When an underlying pancreatic malignancy is suspected, contrast-enhanced computed tomography, magnetic resonance or endoscopic ultrasonography should be performed in those patients with unexplained acute pancreatitis.

Regarding recurrent pancreatitis, it has been shown that approximately one-fourth of patients having acute pancreatitis may have a recurrence of the disease [16], and alcohol is the most frequent factor related to recurrence (57%), followed by gallstones (25%), and idiopathic factors (10.4%). Thus, in patients with recurrent episodes of acute pancreatitis, evaluation with EUS and/or magnetic resonance should be considered; genetic testing is not recommended for routine use but should be considered in selected patients.

Pharmacotherapeutic Recommendations

Pain control

Analgesics, graded according to pain severity, must be provided for all patients in routine clinical practice [19]; in this setting, it has been found that analgesics are graded according to the severity of the pain; patients with mild acute pancreatitis received mainly NSAIDs and tramadol whereas patients with severe pancreatitis received a high percentage of opioids or an association of analgesics including NSAIDs, tramadol and opioids. It is quite surprising that, in a disease such as acute pancreatitis in which the pain represents the main symptom at onset, there is limited information regarding the best therapeutic approach to pain. A meta-analysis taking into consideration eight randomized controlled trials including 356 patients showed that compared with procaine, pentazocine lowered the severity of pain, thus decreasing the necessity for additional analgesics. In addition, a combination of fentanyl, atropine, droperidol and lidocaine rendered a lower pain score and patients treated with metamizole tended to have less pain than those treated with morphine [20]; it should be pointed out that the randomized controlled trials comparing different analgesics were of low quality. Another meta-analytic study evaluated the effectiveness and safety of opioids for treating acute pancreatitis pain [21]. This meta-analysis involved five RCTs with a total of 227 patients having acute pancreatitis pain. The opioids assessed were intravenous and intramuscular buprenorphine, intramuscular pethidine, intravenous pentazocine, transdermal fentanyl and subcutaneous morphine. Opioids may be an appropriate choice in the treatment of acute pancreatitis pain and, compared to other analgesic options, opioids decrease the need for supplementary analgesia. However, once again, mainly due to small numbers of patients enrolled, the findings of this review are limited by the lack of information as to a full appraisal of the risk of bias and the measurement of relevant outcomes. Additional studies on this topic are indicated in the near future.

Measures for supporting the circulation

All patients diagnosed with acute pancreatitis should be managed in the hospital and monitored for blood pressure, pulse and respiratory...
rates, body temperature, hourly urinary volume and blood oxygen saturation level using pulse oximetry.

More than 10% of patients with acute pancreatitis are admitted to the hospital with hypovolemia, defined as a systolic blood pressure of less than 100 mmHg [22]; in addition, hypovolemia correlates with increased hospital mortality [22]. In fact, at the time of admission, patients with severe acute pancreatitis are usually volume depleted due to poor oral intake, third space loss and increased vascular permeability as a result of a generalized inflammatory response [23]. The importance of early fluid administration to prevent circulatory complications has been demonstrated by an Italian multicenter study [19] showing that patients with severe acute pancreatitis need a significantly higher amount of fluids than those with mild acute pancreatitis. Gardner et al. [24] evaluated the impact of the initial intravenous fluid resuscitation rate within the first 24 h of presentation to the emergency room on outcomes in severe acute pancreatitis and divided 45 patients into two groups: 17 who received more than 33% of their cumulative 72-hour intravenous fluid volume within the first 24 h of presentation (early resuscitation group) and 28 who received less than 33% of their cumulative 72-hour intravenous fluid volume within the first 24 h of presentation (late resuscitation group). The amount of fluid was 4.895 L during the first 48 hours in the early resuscitation group and 1.714 L in the late resuscitation group ($P<0.001$) whereas the amount of fluid administered within the first 72 hours after admission was 12.190 L in the early resuscitation group and 7.664 L in the late resuscitation group ($P=0.074$). They found that patients in the late resuscitation group had a higher mortality rate than those in the early resuscitation group (18% vs. 0%) and demonstrated a trend toward greater rates of persistent organ failure.

These data were further confirmed by a retrospective study on a larger number of patients [25]. Early resuscitation was defined as those patients receiving more than one-third of the total 72-hour fluid volume within 24 hours of presentation, and late resuscitation as subjects with acute pancreatitis receiving less than one-third of the total 72-hour fluid volume within 24 hours of presentation. The fluids administered in the two groups were significantly different in the early resuscitation group as compared to the late resuscitation group. Early resuscitation was associated with decreased systemic inflammatory response syndrome (SIRS), reduced organ failure, a reduced rate of admission to the intensive care unit and a reduced length of hospital stay. Thus, early fluid administration should be considered a valuable therapeutic measure for the early management of acute pancreatitis. The fact that, in a subgroup analysis, the beneficial effects of early fluid resuscitation were most pronounced in patients admitted with interstitial rather than severe disease further supports the fact that the need for adequate fluid administration should be the first line therapeutic approach to acute pancreatitis. The amount of fluids needed by patients with acute pancreatitis comes from the study of de-Madaria et al. [26]. These authors prospectively included consecutive adult patients with acute pancreatitis; they found that the administration of more than 4.1 L of fluids administered during the initial 24 hours was significantly and independently associated with persistent organ failure, acute collection, respiratory insufficiency and renal insufficiency. The administration of less than 3.1 L during the initial 24 hours was not associated with organ failure, local complications or mortality and, finally, patients who received an amount of fluids between 3.1 and 4.1 L during the initial 24 hours had an excellent outcome. The optimal amount of fluid administered in this study is similar to that administered by Warndorf et al. [25], and is lower than that of Gardner et al. [24]. The type of fluid which should be administered comes from the study of Wu et al. [27]. The authors carried out a randomized controlled trial involving 40 patients with acute pancreatitis; the patients received goal-directed fluid resuscitation with lactated Ringer’s solution, goal-directed fluid resuscitation with normal saline, standard fluid resuscitation with lactated Ringer’s solution or standard fluid resuscitation with normal saline. Goal-directed resuscitation did not significantly reduce the incidence of SIRS as compared to standard resuscitation or levels of CRP after 24 hours. By contrast, there was a significant reduction in SIRS after 24 hours among the subjects resuscitated with lactated Ringer’s solution as compared to normal saline; the administration of lactated Ringer’s solution also reduced the levels of CRP as compared to normal saline.

Colloids should be no longer used for resuscitation; a review paper on this topic suggests that colloid administration is not supported by definitive scientific evidence in the long-term treatment of ascites, nephrotic syndrome, pancreatitis, abdominal surgery, acute distress respiratory syndrome, cerebral ischemia, and enteric diseases [28].

We should point out that, in the absence of important cardiac dysfunction, an adequate amount of fluids should be administered. Fluids should be administered with at least two peripheral lines and both urine output as renal function be monitored. In cases of simultaneous renal dysfunction or hemodynamic instability, a central venous line should be placed; in addition to electrocardiograms, appropriate continuous oxygen saturation and fluid balance should be monitored [23].

### Specific drugs: antiproteases, somatostatin and octreotide, leupafant

The use of these drugs, even if theoretically correct, has had discordant results in clinical trials.

Two studies, found a beneficial effect of gabexate mesilate because the drug was able to reduce the need for surgery and reduce mortality [29,30]. On the other hand, a multicenter study showed that there was no statistical difference in either mortality or complications associated with acute pancreatitis between the placebo and the gabexate mesilate groups [31]. A 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 [32]. In contrast, another meta-analytic study concluded that gabexate mesilate does not improve the outcome of patients with severe acute pancreatitis, and its routine use in patients with severe pancreatitis is not recommended [33].

Regarding somatostatin and its long-acting analogue octreotide, it has been shown in the only trial using a correct methodological approach that octreotide at a dosage of 0.1 and 0.2 mg t.i.d is not able to reduce mortality, the rate of newly-developed complications, the duration of pain, surgical interventions or the length of the hospital stay [34]. These data have also been confirmed by a meta-analysis [35] showing that octreotide does not reduce surgical interventions, sepsis, mortality or overall complication rates.

Platelet activating factor antagonists have ameliorated acute pancreatitis in humans by two phase II randomized trials involving a total of 133 patients with acute pancreatitis who showed significant improvement in organ failure scores [35,36]. However, a randomized,
double blind, placebo controlled, multicenter trial showed that lexipafant had no effect on new organ failure during treatment [37].

**Enteral nutrition**

Nutritional support seems to be the best medical interventional approach for reducing systemic inflammation, ameliorating the nutritional state and preventing infection of pancreatic necrosis. [38]. During the course of acute pancreatitis, the intestinal mucosa atrophies due to oral fasting, inducing bacterial translocation from the gastrointestinal tract to the areas of pancreatic necrosis [39] and increasing the possibility of infection of necrotic pancreatic tissue [33,40]. Nutritional support reduces the inflammation, balances the nutritional state and prevents the infection of pancreatic necrosis. In fact, as reported in a systematic review, enteral nutrition significantly reduced mortality, multiple organ failure, systemic infections and the need for operative interventions in patients with acute pancreatitis as compared to those who received total parenteral nutrition [38]. Therefore, enteral nutrition should be considered the standard of care for patients with acute pancreatitis requiring nutritional support. Only patients with severe acute pancreatitis benefit from enteral nutrition, and enteral nutrition is better than total parenteral nutrition in the prevention of pancreatic necrotic infection [41]. Parenteral nutrition should be added to enteral nutrition to obtain sufficient nutrient intake [15,42].

Regarding the route for administering enteral nutritional support, it has been demonstrated that early enteral feeding by means of a nasogastric route is no less effective than using a nasojejunal route in terms of the appearance of infectious complications, the appearance of pain in refeeding, intestinal permeability and endotoxiaemia [43]. The optimal energy and protein delivery for the best clinical outcome is still unknown, but it has been suggested that an intake greater than 65-70% of the daily caloric requirement in the first week may be associated with poorer outcomes, especially in patients who have supplemental parenteral nutrition to achieve the caloric target [44]. This topic requires adequate and well-designed studies in the near future. Regarding the formula to be used for enteral nutrition, we should remember that the European Society of Parenteral and Enteral Nutrition (ESPEN) and the Italian practical guidelines on acute pancreatitis (ESPEN) and the Italian practical guidelines on acute pancreatitis [63]. In fact, a probiotic prophylaxis does not reduce the risk of infectious complications and is associated with an increased risk in mortality; the main complication of probiotic treatment was bowel ischemia. The results of this study have also been confirmed by a meta-analytic study [64] showing that a probiotic prophylaxis is not able reduce the infection of pancreatic necrosis and mortality.

**Antifungals**

Fungal infections have increased and now account for 10-20% of the microorganisms involved in infected pancreatic necrosis. 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 [59]. In addition, a fungal prophylaxis in patients operated on for pancreatic necrosis is less convincing [60]. Patients with yeast on Gram’s stain following CT-guided FNA or direct culture during the necrosectomy should receive fluconazole for Candida albicans which is the most common fungal isolate in pancreatic infections. In the case of detection of Candida glabrata, a higher dose of fluconazole or caspofungin should be used [61]. Patients who have been treated prophylactically with fluconazole and subsequently develop infected necrosis with yeast should be treated with caspofungin [60].

**Probiotics**

Even if an early study showed that probiotics administered for 1 week by nasojejunal tube were effective in reducing pancreatic sepsis and the number of surgical interventions related to pancreatic damage [62], a subsequent multicenter study on predicted severe pancreatitis yielded disappointing results on the clinical usefulness of probiotics [63]. In fact, a probiotic prophylaxis does not reduce the risk of infectious complications and is associated with an increased risk in mortality; the main complication of probiotic treatment was bowel ischemia. The results of this study have also been confirmed by a meta-analytic study [64] showing that a probiotic prophylaxis is not able reduce the infection of pancreatic necrosis and mortality.

**Antioxidants**

Several substances, such as alpha tocopherol, ascorbic acid, betacarotene, caffeic acid phenethyl ester, carnitine, green tea, melatonin, N-acetyl-cysteine, resveratrol, quercetin and selenium, alone or in combination, were added to the fluid therapy in human studies to evaluate their usefulness in treating pancreatitis. The results are conflicting; while some authors reported no beneficial effects of an intravenous antioxidant formula comprising selenium, N-acetyl-cysteine and vitamin C [65,66], others [67,68] found that antioxidant supplementation associated with standard medical treatment may decrease the length of hospital stay and rates of complications in patients with acute pancreatitis. In conclusion, there are insufficient clinical data to support the use of antioxidants alone or in combination together with conventional therapy for the treatment of hospital admission is ineffective in preventing infected necrosis and clinical sepsis [55]. The last two studies on this topic [56,57] failed to demonstrate any utility in preventing the infection of necrosis, and a meta-analytic study [58] confirmed that an antibiotic prophylaxis had no protective effect on mortality for infection of necrosis but only for morbidity. Thus, this topic remains open and additional well-conducted studies are needed. In the meantime, the suggestion is to use antibiotic only in case of a firm diagnosis of infection of pancreatic necrosis and we should be aware that the antibiotics used for the treatment of extrapancreatic infections (such as cephalosporins, carbapenems, glycopeptides and antifungal antibiotics) are almost the same used for the treatment of proven infected pancreatic necrosis [19].

**Antibiotics**

More than 20 years have passed from the first clinical trial demonstrating the utility of antibiotic prophylaxis with imipenem in preventing pancreatic infection in patients with necrotizing pancreatitis [46]. After this study, several other multicenter [47-50], as well as single-center [51-54], studies were carried out, and all demonstrated the need for antibiotic prophylaxis in preventing the infection of pancreatic necrosis. Thus, for several years, numerous guidelines regarding acute pancreatitis have suggested 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 [1]. Subsequently, a study demonstrating that antibiotic prophylaxis established days after Pancreat Disord Ther
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acute pancreatitis, and double blind, randomized, placebo-controlled clinical trials with a larger sample size are necessary.

Treatment of fluid collections and pseudocysts

Acute fluid collections do not usually require specific therapy in the absence of infection while symptomatic pseudocysts should be managed by endoscopic, percutaneous or surgical approaches. However, some evidence exists regarding the treatment of symptomatic pancreatic pseudocysts in patients temporarily unfit for surgery and in patients with pancreatic fistulae by using long-acting somatostatin analogue at a dosage of 0.1-0.2 mg t.i.d. [69,70].

Refeeding in mild acute pancreatitis

It has been suggested that patients recovered from a mild acute pancreatitis can eat normal light food only when the pancreatic gland has returned to normal at imaging [71]. More recently, it has been 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, even if these measures do not result in a shorter length of hospitalization [72,73]. Another randomized study has shown that, in patients with mild acute pancreatitis, a soft diet as the initial meal is well tolerated and leads to a shorter total length of hospitalization [74]. Thus, our recommendation is to initiate refeeding when the 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 [75]. The possible intolerance to refeeding may be due to various factors, such as lithiasis of the common bile duct, fasting time, refeeding with a complete diet, length of symptoms before admission and dosage of metamizole [76].

Pancreatic enzyme supplementation

It is very important to evaluate the exocrine pancreatic function in patients who have recovered from an acute episode of pancreatitis in order 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 [77]. It has also been suggested that enzyme supplementation positively affects the course of acute pancreatitis if administered during the early refeeding phase after an attack of acute pancreatitis because enzyme supplementation has a positive impact on the course of the disease and overall health status, causing less weight loss, less flatulence and improvement of the quality of life [78]. However, these data should be confirmed in randomized studies involving a large number of patients.

Conclusions

Pharmacological treatment options in acute pancreatitis remain limited but current research yields promise for the future. At present, supportive care remains the cornerstone of treatment, especially for the severe form of the disease in order to prevent and treat pancreatic necrosis and its infection as well as multiple organ dysfunction syndromes. A multidisciplinary approach and multidrug strategy are able to improve the survival of severe pancreatitis patients and additional studies are needed to cover the grey areas in order to determine the appropriate treatment for acute pancreatitis.

References


