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Review Article

Acute Pancreatitis: Review Article

Jesús Velázquez Gutiérrez[1]* and Morella Vargas Useche[2]

[1]Digestive Tract Surgeon, Specialist in Clinical Nutrition, Spain

[2]Nutritionist Doctor, Magister in Clinical Nutrition, Spain

***Corresponding Author:** Jesús Velázquez Gutiérrez, Digestive Tract Surgeon, Specialist in Clinical Nutrition, Spain.

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Abstract

Acute pancreatitis (AP) is defined as an acute inflammatory process of the pancreas which can compromise other organs and tissues. The diagnosis requires at least 2 of the following characteristics: moderate to severe abdominal pain, accompanied by nausea and vomiting; biochemical evidence of pancreatitis and/or imaging evidence through dynamic computed tomography (DCT) and/or magnetic resonance imaging (MRI) of the pancreas. It is the most common acute gastrointestinal disease that requires hospital admission, with a favorable evolution in most cases (80%). However, necrotizing pancreatitis can develop in up to 20% of patients and is associated with significant rates of early organ failure (38%). Metabolic disorders and fasting compromise the nutritional status which could aggravate the course of the disease, therefore the route of administration of nutritional therapy has been shown to have an impact on the evolution of patients. There is now a better definition of which AP patients need aggressive nutritional therapy.

Keywords: Acute Pancreatitis; Early Enteral Nutrition; Review Article

Introduction

Acute pancreatitis (AP) is defined as an acute inflammatory process of the pancreas with variable involvement of other tissues. Two different phases of AP have recently been identified: (I) early phase of the disease (first week), characterized by a systemic inflammatory response syndrome (SIRS) and/or organ failure; and (II) a late phase (> 1 week), characterized by local complications. It is essential to recognize the primary importance of organ failure in determining the severity of the disease and the role that nutritional therapy plays in the evolution, likewise, to recognize the appropriate time to perform a surgical intervention.

Methods

For this review, the most recent international evidenced-based guidelines on acute pancreatitis, American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis, European Society of Parenteral and Enteral Nutrition (ESPEN) guideline on clinical nutrition in acute and chronic pancreatitis, World Society of Emergency Surgery (WSES) guidelines for the management of severe acute pancreatitis were used as the starting point. PubMed was searched for studies on acute pancreatitis.

Definition: AP is an inflammatory condition of the pancreas most commonly caused by bile stones or excessive use of alcohol that can cause local injury, systemic inflammatory response syndrome and organ failure.

Etiology: In Western countries, gallstones and/or biliary sludge are the most prevalent (approximately 40% - 50%) cause of acute

pancreatitis. With approximately 20% of cases, alcohol is the second most frequent cause of AP in most countries. Less frequent causes of AP include medication, endoscopic retrograde cholangiopancreatography, hypercalcemia, hypertriglyceridemia, surgery and trauma [1].

Pathophysiology: The mechanism of gallstone-mediated AP is likely obstructive. Once the obstruction occurs, there is backup of bile into the pancreas, as well as stagnation of bile in the biliary tract. Acinar cells of the pancreas take up bile acids via bile acid transporters. Once within the cell, bile acids increase intra-acinar calcium concentrations and activate proinflammatory mediators signaling pathways causing pancreatic parenchymal damage. Pancreatic duct obstruction also impedes exocytosis of zymogen granules from acinar cells. Accumulation of trypsin within pancreatic vacuoles leads to digestive enzymes autodigesting the pancreas. Acinar injury due to autodigestion stimulates inflammation of the pancreatic parenchyma, leading to AP. Early phases of AP cause mitochondrial damage and adenosine triphosphate depletion in pancreatic ductal cells driving the cell death, ultimately leading to pancreatic necrosis [2].

The AP generates a state of hypermetabolic stress which leads to deterioration of the general state and compromise of the nutritional state. As in sepsis, patients with AP present a typical metabolic pattern of systemic inflammation; elevated protein catabolism and skeletal muscle proteolysis increase serum aromatic amino acid concentrations, with decreased levels of branched-chain amino acids, accelerated ureagenesis, and decreased glutamine concentration in serum and skeletal muscle, Net nitrogen loss can be up to 20 to 40 g/d and negative nitrogen balance is associated with higher mortality [3].

Similarly, there is an alteration in carbohydrate metabolism which is caused by an increase in the secretion of cortisol and catecholamines, an increase in the glucagon/insulin ratio, a disorder in the function of β cells and insulin resistance, in consequently, glucose intolerance has been evidenced in 40 - 90% of patients. Evidence of carbohydrate intolerance has been demonstrated in an increase in mortality of over 15% [4].

Disorders in fat metabolism occur only in 12 to 15% of patients, it can result in hypertriglyceridemia with increased mortality above 33% [4,5].

In relation to micronutrients, hypocalcemia occurs in 25% of patients, increases in calcitonin and hypoalbuminemia. Chronic ethanol abuse predisposes patients to hypomagnesemia, decreased zinc concentrations, and thiamine and folate deficiency.

The intra-acinar activation of trypsinogen that results in acinar injury, upregulates pro-inflammatory mediators, cytokine release, systemic inflammation, and microcirculatory injury, this ultimately leads to hypoperfusion of the intestinal mucosa, resulting in a loss of the integrity of the intestinal barrier and translocation of the intestinal flora [3].

With the knowledge that inflammation plays a central role in the initiation and progression of AP, the benefits of nutritional therapy to modulate the response to oxidative stress and counteract catabolic effects during the initial phase of AP are overriding.

Classification: In the latest revision of the Atlanta classification the AP is classified into three categories:

1. Mild AP: Clinical evolution characterized by the absence of organ failure and the absence of local and/or systemic complications, with a very low mortality. It is a self-limited process during the course of hospitalization and can be managed with IV fluids, pain relievers, and a rapid return to the oral route [6].
2. Moderately severe AP: It is characterized by local complications in the absence of persistent organ failure [6]. Organ failure is transient with a duration < 48 hours [2].
3. Severe AP: This occurs in 15 - 20% of patients [7] and is defined by the presence of persistent organ failure (cardiovascular, respiratory or renal) and high mortality [6]. Patients who have organ failure and infected necrosis are at the highest risk of death and should be admitted to an intensive care unit whenever possible [8].

In a systematic review and meta-analysis with a total of 6,970 patients, the mortality rate in patients with infected necrosis and organ failure was 35.2%, while concomitant sterile necrosis and organ failure was associated with a mortality rate of 19.8%. In patients who had infected necrosis without organ failure, mortality was 1.4% [9].

There are tools that allow predicting the severity of AP, categorized as clinical scoring systems, aiming at stratifying severity and identifying patients at risk of developing significant negative outcomes, including persistent organ failure, infected pancreatic necrosis, and death. They also allow patients to be classified at the appropriate level of care to reduce morbidity and mortality. The most commonly used are the Ranson criteria, APACHE II, bedside AP index (BISAP), Glasgow-Imrie scale, DCT severity index, and the Japanese severity scale.

BISAP, a recently developed prognostic scoring system, is a simple method for predicting severe AP compared to traditional scoring systems; evaluates blood urea nitrogen level, deterioration of mental status according to the Glasgow scale, presence of Systemic Inflammatory Response Syndrome, age > 60 years and pleural effusion on radiography; with a score of ≥ 3 points, the risk of mortality is 5 - 20%. It is useful because it stratifies patients within the first 24 hours of admission [10,11].

Other clinical factors used to assess severity include comorbidities, oliguria, rebound abdominal pain, altered mental status, and abdominal and flank bruising [12].

Diagnosis: The diagnosis of AP requires at least 2 of the following characteristics: abdominal pain accompanied by nausea and vomiting; biochemical evidence of pancreatitis and/or imaging evidence (DCT) and/or MIR of the pancreas, however, these two studies should be reserved for patients who do not improve clinically in the first 48 - 72 hours after hospital admission or to assess complications [13,14]. From the biochemical point of view, in addition to the elevated levels of amylase and lipase, (> 3 times the upper limit of normal) it is considered that a level of C-reactive protein (CRP) ≥ 150 mg/dl on the third day after the start of the pancreatitis can be used as a prognostic factor for severe acute cases [6]. Hematocrit > 44% represents an independent risk factor for pancreatic necrosis [15] and urea values > 20 mg/dl represents a predictor of mortality. Procalcitonin is the most sensitive laboratory test for the detection of pancreatic infection, serum values ≥ 3.8 ng/ml at 96 hours after the onset of pancreatitis is an indicator of infected necrosis with a sensitivity and specificity of 93% [8].

The evolution of the disease is favorable in most cases (80%). However, necrotizing pancreatitis can develop in 20% of patients and is associated with significant rates of early organ failure (38%), need for intervention (38%), and death (15%). Therefore, early diagnosis is important, or better yet, predicting a severe AP episode and identifying patients at high risk of developing complications [16].

Medical management: General guidelines recommend early fluid resuscitation, starting with 250 - 500 mL/hr [2] with the goal of maintaining urine output at ≈0.5 mL/kg/hr if there is no acute kidney injury [12]. Supplemental oxygen, especially in elderly patients, also improves results. Analgesia is another important aspect of treating early AP; control glycemia, a blood sugar level > 180 mg/dL on admission in a non-diabetic patient is associated with increased mortality [11].

Nutritional therapy: The principles of nutritional therapy in the AP patient have undergone important changes in recent years. Failure to maintain the integrity of the intestinal mucosa is correlated with a greater severity of the disease and an increase in the frequency of complications.

The main benefit of enteral nutrition (EN) is its immunological effect, which includes the maintenance of normal intestinal motility and the production of IgA, the prevention of bacterial overgrowth and the decrease of bacterial translocation and intestinal permeability [3]. Nutrition therapy reduces the general severity of the disease, measured by CRP and hyperglycemia, and causes a more rapid resolution of the systemic inflammation process and a reduction in hospital stay [17].

Traditionally, patients with AP were kept without oral treatment or nothing by mouth until resolution of pain or normalization of pancreatic enzymes to allow "pancreatic rest", this dogma lacks justification as current evidence demonstrates the benefits from the opposite approach, that is, early feeding. Maintaining EN has been shown to help protect the intestinal mucosal barrier and reduce bacterial translocation, thereby reducing the risk of infected peri-pancreatic necrosis [14].

In recent years, several studies have shown that septic complications can be reduced when the patient receives early EN. A meta-analysis by Petrov., *et al*. included 11 randomized controlled trials, the authors demonstrated that the optimal benefits of EN occurred when it was started within 48 hours after the start of AP, as well as the rates of multiple organ failure, infectious complications and

mortality were significantly reduced [18,19]. Bakker., *et al*. demonstrated that, in the EN group of 8 randomized clinical trials, mortality, organ failure, and infectious necrosis were significantly reduced in patients who received EN within 24 hours compared to patients who received EN at 24 hours after admission (19% vs 45%, $p < 0.05$) [20,21].

Jiang K [22] through a meta-analysis assesses the effectiveness and safety of early EN via nasogastric tube in a patient with severe AP. Three prospective controlled studies that included 131 patients were evaluated, the meta-analysis showed that there were no significant differences in terms of the percentage of mortality in patients fed nasogastric via versus conventionally, there were no differences in relation to length of hospital stay, infectious complications or multiple organ deficiency syndrome.

Three randomized clinical trial that compared nasojejunal with nasogastric feeding in patients with severe AP [23-25] showed no differences in tolerance, complication rates, and mortality. Four meta-analysis [26-29] conclude that nasogastric tube feeding is feasible, safe and well tolerated and, compared to nasojejunal tube feeding, does not increase the rate of complications, mortality, recurrence of refeeding pain, or prolongs hospital stay in patients with severe AP. Despite these results, around 15% of patients will experience digestive intolerance, mainly due to delayed gastric emptying [26,27], in this situation, nasojejunal tube feeding is required. The American College of Gastroenterology [13] and the European Society for Clinical Nutrition and Metabolism ESPEN recommend that, if EN is required in patients with AP, it should be administered by nasogastric tube, nasojejunal tube should be used in case of intolerance [16].

The actual time to start gastric feeding may vary according to the individual characteristics of each patient, but as a guide, it should start between 24 and 48 hours after hospital admission [30]. This recommendation is supported by the results of a recent randomized controlled trial and a previous meta-analysis [31,32]. In another randomized controlled trial of early and late feeding in patients with AP admitted to an ICU, the onset of tube feeding between 24 and 48 hours after hospital admission led to a significantly lower risk of organ failure (5 of 30 patients in the initial group vs 13 of 30 patients in the late group) and pancreatic infectious complications (3 of 30 patients in the initial group vs 10 of the 30 patients in the late group) [31].

EN in patients with severe AP: In patients who present intolerance to EN, measures should be taken to improve tolerance, these measures include minimizing the period of ileus by initiating EN as soon as possible within the first 48 hours of admission to the ICU, by shifting the NE infusion level more distally in the gastrointestinal tract, changing from a standard polymeric formula to one containing small peptides and medium chain triglycerides, and switching from bolus to continuous infusion [33].

Complications of severe AP that may contraindicate the use of EN include intestinal obstruction, abdominal compartment syndrome, prolonged paralytic ileus, and mesenteric ischemia [34] and occur in approximately 20% of patients.

When it is impossible to access the gastrointestinal tract or when there is intolerance to EN, it may be necessary to provide nutrients through the parenteral route. The most important thing at this stage is to achieve IV fluid restoration, correct fluid and electrolyte imbalances, and provide analgesia. After this period, if it is expected that patients do not start the oral route for a period of 5 to 7 days, total parenteral nutrition (TPN) should be started, which must be progressively increased by controlling glucose levels below 150 - 200 mg/dl. The probabilities of glucose intolerance are in the range of 60 - 80% and the resulting hyperglycemia can exacerbate the incidence of nosocomial infection and catheter-related sepsis.

Parenteral glutamine supplements in patients receiving PN have reported a prognostic benefit with a shorter hospital stay, a reduction in infectious complications, less need for surgery, better glycemic control, and faster resolution of inflammatory biochemical markers [3].

When to go oral diet: The severity of the disease determines the progression to the oral diet. In mild AP, oral intake is generally rapidly restored, oral feeding can be started immediately if there is no nausea and/or vomiting, and abdominal pain has resolved regardless of pancreatic enzyme levels [13,16]. Immediate oral feeding with a soft diet appears to have better tolerance compared to clear liquid diets [16]. Patients with moderate AP are less prone to complications and are likely to initiate the oral route within five days after admission. Patients with severe AP have a longer gastric and duodenal atony, a higher risk of complications and a greater probability of requiring at least one operation and consequently

less probability of progressing to the oral route within the next five days.

Surgical management: The signs or suspicion of infected necrosis in a symptomatic patient require intervention, indicating a stepped treatment that begins with percutaneous or endoscopic drainage [35-38]. Another indication for performing percutaneous or endoscopic drainage is clinical deterioration with signs or suspicion of infected necrotizing pancreatitis [8]. Most patients with sterile necrotizing pancreatitis can be treated without interventions [39].

Surgical management: Surgery is indicated when the patient presents complications such as abdominal compartment syndrome, continuous acute bleeding, intestinal ischemia, or acute necrotizing cholecystitis in the course of AP [8].

Delaying surgical interventions for more than 4 weeks after disease onset results in lower mortality [6,8]. With late surgery, demarcation of necrosis occurs, resulting in fewer injuries to vital tissues. Therefore, in late surgery, there is less bleeding and necrosectomy is more effective. In a recent meta-analysis, late surgery was compared with early surgery, the timing of surgical interventions was compared at three different cut-off points (72h, 12 days, and 30 days). At all cut-off points, late surgery resulted in a clear survival benefit [39]. If emergency surgery is needed earlier for other indications, drainage or necrosectomy is not routinely recommended [35,38].

Minimally invasive surgical strategies, such as transgastric endoscopic necrosectomy or video-assisted retroperitoneal debridement (VARD), result in less new-onset postoperative organ failure, but require more interventions [8].

When percutaneous drainage does not result in resolution of the infection, management options include open surgery, minimally invasive surgery, endoscopic surgery, and a combination of these. In general, it is assumed that open surgery elicits a more severe inflammatory response. The mortality rate after open necrosectomy varies between 8.8% and 22% in contemporary series [41-43]. Recent meta-analysis suggest similar short-term mortality in open and minimally invasive necrosectomy. However, open necrosectomy could be associated with an increase in adverse events and postoperative organ failure compared to minimally invasive necrosectomy, although the quality of the evidence is low [44,45]. The recently published World Society for Emergency Surgery for the Treatment of Severe Pancreatitis, open necrosectomy remains a valid treatment option for complicated pancreatic necrosis after a staggered regimen of treatment [8].

Conclusion

Pancreatitis involves a wide spectrum of illness severity, from mild to severe pancreatitis with infected necrosis. Systemic inflammation is involved in all types of AP, but dysregulation of this inflammation promotes worsening disease severity. The vicious cycle of inflammation that characterizes severe acute pancreatitis generates a number of defects in physiologic processes that exacerbate the level of oxidative stress and lead to the adverse outcomes seen clinically. The decades-long practice of "putting the pancreas to rest" was based on the premise that once inflammation set up in the gland, providing supportive care while allowing the inflammation to subside was the only management option. New approaches to fluid resuscitation, antibiotic use, nutritional support, and treatment of necrosis have changed management. In mild disease, it is safe to provide an oral diet on demand, not limited to clear liquids. In the case of complications, nutritional therapy is essential; Gastric feeding with a standard polymeric formula is recommended. If there is intolerance, post-pyloric feeding can be tried. PN is indicated when there is intolerance to NE.

Interventions for necrotizing pancreatitis should preferably be performed within four weeks of disease onset by stepwise management beginning with percutaneous drainage, minimally invasive surgical drainage, or open necrosectomy.

Conflict of Interests

The authors declare no conflict of interest.

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