Current Status in the Management of Acute Pancreatitis

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Abstract

Acute Pancreatitis is a clinical entity with a high morbidity and mortality in the most severe forms. The prediction of the severity in admission is difficult, and we recommend a protocolled clinical and analytical control. In the first days, patients need support measures with adequate fluid management, control of the intra-abdominal pressure, and enteral nutrition. A new challenge is the benefit of "long peritoneal lavage" conservative treatment of the 80s and now recovered and updated by researchers. The management of the infected necrosis is crucial, attempting to delay surgery when is possible. The conservative management results very interesting, but it are not clear its usefulness in patients with multiple organ failure and infected necrosis.

Introduction

Acute pancreatitis (AP) is a clinical entity with an increasing incidence [1]. This benign entity has a low global mortality, but could be high in its more severe forms. Mortality of 54% was described in series of patients with AP admitted in Intensive Care Units [2].

According to the clinical course, the mortality of AP presents two peaks: early mortality, in the first 14 days, mainly due to Systemic Inflammatory Response Syndrome; and late mortality, after two weeks of evolution, mainly originated by infected necrosis. Different authors discussed about if the distribution is similar between these groups, or if the late mortality predominates [2-4]. This article approaches different key-points in the management of patients with AP.

Classification of AP

The Classification of Atlanta has been used since 1992. Nevertheless, this classification system has different limitations, since includes very different criteria in the definition of a severe case. In last years, we learnt that there are two real determinants of mortality: the development and permanence of organ failure (with a persistence superior of 48 the mortality is higher), and the development of local complications, mainly infected necrosis [5,6].

In this base, two new classification systems have been described: The Revision of Atlanta Classification [7], and the Determinant-Based Classification [8]. Both classification systems are designed to be applied in the end of the clinical process, with the objective to order the case-mix, so they can´t be used in the initial phases of the disease. Nevertheless, they are useful to compare results between different centers, or to avoid inclusion biases in different studies of diagnostic or therapeutic options. Both classification systems are very similar, but with a basic difference: The Revision of Atlanta Classification mainly stresses the importance of persistent organ failure, while Determinant-Based Classification emphasizes the importance of not only persistent organ failure, but also associated infection of pancreatic and peripancreatic necrosis. These classification systems has been validated in different series [9,10], and their comparison didn´t observe significant differences [11,12], but with the drawback of the low inclusion of most severe forms in the series.

The Determinant-Based Classification only includes the (peri) pancreatic necrosis and its infection like a local determinant, but there are evidences about the transcendence of other local complications, mainly the intra-abdominal hemorrhage and intestinal bowel perforation [4]. Further, the Determinant-Based Classification includes in the same category patients with persistent organ failure and without infected necrosis, and patients with transient organ failure and with

infected necrosis. There is evidence about the different clinical course of both groups of patients, and probably should be separated.

Our research group included data of 374 patients admitted in 46 units of Intensive Care Medicine (EPAMI study group), constituting the greater series that we know. In a recent paper [13], we described a modified Determinant-Based Classification, with four different groups of patients: group 1, patients with transient organ failure and without local complications; group 2, patients with transient organ failure and with local complications; group 3, patients with persistent organ failure and without local complications; and group 4, patients with persistent organ failure and with local complications. These four groups had a very different clinical course: patients in group 1 has low mortality and morbidity; patients in group 2 had low mortality but high morbidity; patients in group 3 high mortality but low morbidity; and patients in group 4 high mortality and morbidity. This new classification system presented better statistical results in comparison to the Revision of the Atlanta Classification and the Determinant-Based Classification, and although needs validation in other series, we consider that describes better the different groups of patients with AP, with different clinical course.

It is not clear what is the best classification system for AP, and surely could be different according to the institution or our position in the assistance level. Doctors from hospitals of the first or second levels need a simple classification system, which allows to know if a patient should be transferred or no; while doctors from tertiary hospitals or specialized in the most severe forms, need more complex but exhaustive classification systems.

Need of an Initial Classification

Concept of potentially severe acute pancreatitis

As we described in the last point, the classification systems for acute

pancreatitis are useful in the end of the process, with the objective to order the case-mix. Nevertheless, they are not useful in the first days of the clinical course of an individual patient, because depends of the development or not of organ failure or local complications.

Due to this situation, our group developed the concept of "potentially severe acute pancreatitis", defined as a case of AP which begins to develop organ failure or local complications, or presents clinical, analytical or radiological signs which may indicate a complicated clinical course [14,15]. Although there is not a precise description, it allows the identification of a patient with a high probability of a complicated clinical course, and should be transferred to a specialized center, to be treated with a multidisciplinary team. There are not determined which clinical, radiological or analytical markers allow us the best selection of these patients, but we think that the concept is essential in pathology with a very different clinical course.

Unfortunately, in these moments there are not markers which can predict with reliability the clinical course of a patient. We advocate an exhaustive and protocolled clinical and analytical control of each patient in the first 48 hours, since the early detection and treatment of the most complicated forms is essential in the prognosis.

Initial Management of Acute Pancreatitis

As we described previously, we believe essential the protocolled management of patients with AP, with a multidisciplinary team formed by specialists in Emergency medicine, Gastroenterology, Surgery, Radiology, Laboratory and Intensive Care Medicine.

Volume replacement

AP could produce a great loss of volume due to a third space, and an adequate volume replacement is essential. An early replacement is fundamental [16], but within limits, so an excessive administration could be harmful [17,18]. For those patients with persistent organ failure, we recommend the volume monitoring with dynamic parameters.

Use of early enteral nutrition

Actually, the classic concept of "pancreatic rest", using parenteral nutrition, limited to reverse the catabolic situation, has changed. The use of early enteral nutrition is basic to decrease the incidence of infected necrosis and mortality [19,20], so all patients with AP should receive enteral nutrition in the first 48 hours, after stabilization of the hemodynamic situation.

Near of 80% of the patients with AP could tolerate enteral nutrition using a nasogastric tube [21], so it should be the first option, going to a nasojejunal tube in case of intolerance. If it is not possible to achieve a total enteral nutrition, a combined enteral and parenteral nutrition could be considered.

Early antibiotic treatment

Early antibiotic therapy was used during years with the aim to avoid bacterial translocation and infection of the (peri) pancreatic necrosis. Nevertheless, higher quality trials evidenced that empiric antibiotic treatment is not effective to decrease the incidence of infected necrosis and mortality, and there is no indication for use [22-24].

The monitoring of intraabdominal pressure is essential; due to increasing values can indicate the infection of (peri) pancreatic necrosis. The analysis of necrotic pancreatic tissue samples obtained by fine needle aspiration supposes the basic technic to confirm the infection and guide the antibiotic treatment, but its use is decreasing due to the step-up approach for the treatment of infected necrosis [25].

Control of the intra-abdominal pressure and abdominal compartment syndrome

AP is an essential cause of the increase of intraabdominal pressure and the development of Abdominal Compartment Syndrome [26,27].

syndrome, defined as a maintained intraabdominal pressure ≥ 20 mm Hg and associated to new organ failures, should be treated initially with medical measures: aspiration of the intestinal content using gastric and/or rectal tubes; administration of prokinetic drugs (metoclopramide, eritromicine, neostigmine); adequate sedation and muscle relaxants; and decrease of the third space using diuretics and continuous renal replacement therapy. If the medical treatment is not enough, the next step is the surgical decompression, without necrotic debridement, unless proven infected necrosis.

Peritoneal lavage or abdominal drainage using paracentesis: An old new option? Which patients could be benefited?

One of the usual complications of AP is the development of local acute fluid collections. These collections appear in the first days of the disease, and include proinflammatory factors and infectious mediators. In 80s, peritoneal lavage was proposed in the treatment of AP [28,29], based in the theory that the elimination of these collections could decrease the inflammation and the severity of the disease.

Ranson and Maraví showed a decrease of mortality since 80-90% to 22-36% using early and prolonged peritoneal lavages. These data were relevant in that moment, and were explained by the delay of the early surgical attitude, habitual in 70's and 80's. Nevertheless, this therapeutic tool has been used in the early phase of patients with AP. Their preliminary results show that the early removal of peritoneal liquid could decrease the severity of AP and the need of surgical intervention [30]. These data suggest that a step-up approach for the early treatment of peritoneal liquid could be beneficial. Also, another potentially beneficial factor could be the decrease of intraabdominal pressure [31].

In conclusion, the removal of liquid or peritoneal ascites, using peritoneal lavage or drainage by abdominal paracentesis, in the early phase of the disease, could be beneficial in a subgroup of patients with potentially severe acute pancreatitis, and decrease the need of invasive procedures. New well designed studies are needed to document prospectively the security and the clinical results of lavage or peritoneal drainage by paracentesis, and to determine which patients could benefit of this intervention.

Management of the Infected (Peri) Pancreatic Necrosis

Like we described previously, the development of infected (peri) pancreatic necrosis is one of the main factor in the clinical curse of AP, with a mortality of 35-45%. For many years, the surgical debridement was the main option for treatment, but the development of less invasive techniques has changed this concept. Next, we will describe the key-points for the management of infected pancreatic necrosis.

Diagnosis of infected (peri) pancreatic necrosis

The diagnosis of infection of the (peri) pancreatic necrosis was a key point in the management of AP, also the demonstration of its existence entailed an immediate surgical attitude. In this basis, protocols were developed suggesting a tight and periodic radiological control of pancreatic necrosis, using fine needle aspiration guided by imaging techniques if the patient developed fever or another sign of clinical deterioration.

But as we explained previously, new studies suggesting a

conservative management of infected necrosis are developed, and it is not crucial the microbiological diagnosis of infection. In some centers the use of periodic fine needle aspiration has been abandoned [32], and if there is a clinical suspicion of infected necrosis (persistence or new development of organ failure in the evolution of AP), the beginning of support measures, empiric antibiotics and minimally invasive drainage is advocated.

A biochemical marker could help us in the early diagnosis of infected necrosis. The endorsed by different studies is the procalcitonin (PCT). High values of PCT are correlated with the presence of infection, with a sensitivity and specificity of 90% and 100% respectively, and high negative predictive value. The cut-off established in literature is of 1.8 mg/ml [33].

Treatment of the infected (peri) pancreatic necrosis

Classically, the immediate open surgery was the initial option for the treatment, with the aim to remove the maximum of bacterium charge. Due to it is almost impossible to remove all the infected necrosis, the open necrosectomy was completed with different techniques of reintervention and/or continuous lavage systems. These techniques were associated with a high incidence of complications [32,34].

Since several years is known that if the surgery is late, after 3 weeks of evolution, the prognosis is better in comparison to early surgery [34]. This difference is explained by the reduction in the inflammatory response in the initial stages of the disease, and also by the better delimitation of the (peri) pancreatic necrosis in the late stages. This form of AP with several weeks of progression, without data of organ failure, but with a long hospital length of stay due to an incomplete recovery, is called "ongoing pancreatitis" by Castillo and has a better prognosis that the acute forms of the disease [35].

Deferred approach in the treatment of the infected necrosis

In 2005 originated the first experience against the axiom "infected necrosis, immediate surgery", and the deferred treatment of the infected necrosis was proposed. So, in a situation of suspected infected necrosis, empirical antibiotic therapy and support measures should be started, avoiding surgery unless the development of refractory multiple organ failure or local complications. There are different studies, more based in retrospective series in a lot of years, with beneficial results: decrease of need of surgery or need of late surgery, decreasing the morbidity and mortality of the early surgery approach [32,36].

This deferred approach could be done only with antibiotic treatment and support measures, or could be accompanied by techniques for the drainage or necrotic material. These drainage techniques have the objective to decrease the bacterial charge, using non-surgical techniques or minimally invasive techniques, avoiding the inflammatory response of the open surgery. This approach is called "step-up", and is based in the use of progressive measures, since less to more invasive techniques, according to the response of the patient. We will describe these techniques, explaining their indications, results and complications.

Radiological drainage techniques

The deferred approach is accompanied by the colocation of thick drainage tubes using radiological technique. The article of Dutch study group of AP is the reference in all the studies about the step-up [37], but should be noted that there is a descriptive prospective work, no a randomized clinical trial. A protocolled treatment was started in 639 with pancreatic necrosis in 4.5 years. Of them, 62% received conservative treatment, and 38% invasive treatment, that could be surgical, endoscopic or radiological.

There were not significant differences in mortality between patients treated with percutaneous drainage or surgical necrosectomy as first option, in opposition to the differences obtained in another historical series. But there were other interesting results: 35% of patients treated with percutaneous drainage didn´t need another intervention, and patients treated primarily with percutaneous drainage developed less post-surgical multiple organ failure then those treated with necrosectomy (17 vs 31%). Also, the prognosis was better in the group of patients with delayed necrosectomy, in comparison to patients with early necrosectomy.

Endoscopical drainage techniques

The endoscopic drainage, using trans-gastric or trans-duodenal way, is possible when the necrosis is located in the pancreatic head [38]. This kind of drainage is usually partial, and most of patients need several procedures (2.7 of media), being successful in the 80% of cases. Near of 25% of patients has complications, mainly bleeding and hemorrhage.

A randomized and blind study with 22 patients compared endoscopic drainage with video-assisted surgical necrosectomy [39] (PENGUIN study). Patients with endoscopic drainage had a lower elevation of 6-IL levels, and there was no multi-organ failure after endoscopic drainage, in comparison to 50% of patients who developed after necrosectomy. There was a decrease of mortality with endoscopic drainage (10% vs. 40%), although the difference was not statistical significant.

Minimally invasive surgical techniques

The open surgical access is associated with a higher incidence of postsurgical multi organ failure, and higher incidence of local complications as fistula or hemorrhage. The minimally invasive access, using the retro-peritoneoscopy, does not loss the abdominal compartments, produces a smaller trauma, and allows the extraction of necrotic tissue [40]. The main limitation is that is not useful when the necrosis is located in the cephalic area.

Limitations of the studies with deferred approach in infected (peri) pancreatic necrosis

Although the deferred approach is suggestive and interesting, the studies had main limitations. Firstly, many of these articles were based in retrospective, historical series, and could be differences in their management. Secondly, there could be biases in the severity of the patients. If the infected necrosis is associated with organ failure has worsen prognosis, and in several studies there was not a correct stratification of these patients. Another studies included only patients without organ failure, avoiding patients with the worst prognosis. And in other studies, patients in the open surgical option had a higher incidence of organ failure than patients in the deferral necrosectomy option, and results could be conditioned. Thirdly, there could be differences in the time of surgery. Patients with early pancreatic infection had higher mortality than patients with late pancreatic infection, and in several articles patients in the invasive treatment option had a higher incidence of early infection than patients in the deferred or minimally invasive treatment option. Finally, the incidence of severe forms of AP is low, and the results could be conditioned by the experience of the treatment group, affecting to the external validity.

Conclusions

AP is a clinical entity with a high morbidity and mortality in the most severe forms. The prediction of the severity in admission

Revision of the Atlanta Classification:
•   Mild acute pancreatitis
o   No organ failure
o   No local or systemic complications
•   Moderately severe acute pancreatitis
o   Organ failure that resolves within 48 h (transient organ failure) and/or
o   Local or systemic complications without persistent organ failure
•   Severe acute pancreatitis
o   Persistent organ failure (>48 h)
– Single organ failure
– Multiple organ failure

Table 1: Description of the Revision of the Atlanta Classification and Determinant-Based Classification [7].

is difficult, and we recommend a protocolled clinical and analytical control. In the first days, patients need support measures with adequate fluid management, control of the intra-abdominal pressure, and enteral nutrition. The management of the infected necrosis is crucial, attempting to delay surgery when is possible. The conservative management results very interesting, but it is not clear its usefulness in patients with multiple organ failure and infected necrosis (Table 1).

Determinant-Based Classification [8]

• Mild acute pancreatitis is characterized by the absence of both (peri) pancreatic necrosis and organ failure.

• Moderate acute pancreatitis is characterized by the presence of sterile (peri) pancreatic necrosis and/or transient organ failure.

• Severe acute pancreatitis is characterized by the presence of either infected (peri) pancreatic necrosis or persistent organ failure.

• Critical acute pancreatitis is characterized by the presence of infected (peri) pancreatic necrosis and persistent organ failure.

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