Antibiotics in severe acute pancreatitis

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Abstract: Acute pancreatitis (AP) is a local inflammatory response with systemic effects and an adverse evolution in 20% of cases. Its mortality rate is 5-10% in sterile and 15-40% in infected pancreatic necrosis. The evidence to enable a recommendation about antibiotic prophylaxis against infection of pancreatic necrosis is conflicting and difficult to interpret. Up to date, there is no evidence that supports the routine use of antibiotic prophylaxis in patients with severe AP. Treatment on demand seems to be the better option, avoiding excessive treatment and selection of bacterial. In infected acute pancreatitis, antibiotics of choice are imipenem, meronem or tigecycline in patients allergic to beta-lactams. Also fluconazole must be given in determinate clinical situations.

Keywords: Acute pancreatitis • Antibiotic prophylaxis • Antibiotic treatment

Acute pancreatitis (AP) is a local inflammatory response with systemic effects and an adverse evolution in 20% of cases. Its mortality rate is 5-10% in sterile and 15-40% in infected pancreatic necrosis \([1,2]\). Incidence of AP seems to be rising in western countries. Gallstones or alcoholism causes about 75% of AP. The relative rate of these etiologies depends on the patient age and the area of enrollment. A thorough evaluation allows identification of the cause in another 10% of cases, leaving about 15-20% as idiopathic.

This name of AP is given to two different diseases, mild and severe AP. Most patients with the mild form recover after a few days without any specific treatment, including antibiotics. This edematous form of AP needs only to correct its etiological factor to avoid recurrence. By the opposite, severe AP presents a poor prognosis, with local and/or systemic complications, high morbidity and mortality \([3]\).

A significant correlation exists between the development of pancreatic necrosis, the frequency of bacterial contamination of necrosis and the evolution of systemic complications. Pancreatic infection basically occurs in patients with pancreatic or peripancreatic necrosis and/or fluid collections. Pancreatic necrosis become infected in a percentage ranging from 20 to 70% and, as a rule, a time dependent increase of the infection rate with the duration of the disease is registered \([4-7]\) (Figure 1). The late course of necrotizing pancreatitis is determined by bacterial infection of pancreatic and peripancreatic necrosis. Mortality is related to necrosis extent and associated to multiple organ failure and other infectious complications. Bacterial translocation is considered the most important trigger of septicemia in these patients \([8]\).

Prevention and treatment of infection seems to be a profitable method to decrease hospital stay and mortality in necrotizing AP. Several controlled clinical trials proved a significant reduction in pancreatic infections or a significant reduction of hospital mortality with the use of prophylactic antibiotics. However, the results of these clinical trials are controversial and not convincing. The high number of papers related to this issue, most of them with different antibiotics regimens and some of them with important methodological defects, generates controversial results. More recent articles and meta-analysis on this subject tend to recommend the...
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avoidance of antibiotic prophylaxis in this setting. The largest randomized placebo-controlled, double blind trial has been able to demonstrate that antibiotic prophylaxis with ciprofloxacin and metronidazole has no beneficial effects with regard to the reduction of pancreatic infection and the decrease of hospital mortality. This trial does not support antibiotic prophylaxis in all patients with necrotizing pancreatitis, but in specific subgroups of patients with pancreatic necrosis and a complicated course [2].

1. Mortality

Mild form of AP accounts for 80% of the cases; 95% of deceased patients for AP comes from the remaining 20%. Mortality rate has two peaks, early mortality (within the first six days of hospitalization) and late mortality (after the sixth day). The former is usually caused by a systemic inflammatory response syndrome (SIRS) through shock and multiple organ failure, effect of the circulating pancreatic enzymes and activated inflammatory mediators (cytokines, interleukins, prostaglandins, etc.). SIRS can evolve independently of the original injury and its management consists in the treatment of the damages caused by systemic inflammation. Late mortality is generally caused by local complications (necrosis infections or peripancreatic collections infections) or distant complications (pneumonia, sepsis). For some authors, late mortality has decreased because of better antibiotic treatment and nutritional support and learned surgical decisions [9], while others guess that mortality rate has not changed but moved from early to late peak [10,11].

Infection is widely accepted as the main reason for death in AP, mainly infected pancreatic necrosis, although older patients and those with comorbidities present high mortality attributed to others causes. The rate of infection correlates with the extent of necrosis and, therefore, with the severity of the disease [12]. This infection has an enormous impact in mortality, multiplying it by 4 to 15 times [13]. In general, infections are involved in 80% of deaths caused by AP [14]. Mortality in patients without necrosis is nearly 0%, with sterile necrosis is between 0 and 11% [15], and with infected necrosis reaches 40% [16].

2. Antibiotic prophylaxis

Antibiotic prophylaxis in the setting of pancreatic necrosis refers to the use of antibiotics to avoid infection in severe AP. This issue has remained controversial for the last four decades. The most important questions raised are about antibiotic indications, antibiotic selection and length of treatment. Inappropriately selected or distributed over time antibiotics may carry complications such as anaphylaxis and selection of resistant bacteria. The later affects not only the patient, but also the hospital bacterial flora and the population around the hospital. The same subjects may be applied to the treatment of fungal infections.

Available studies are not conclusive although some have shown benefit from antibiotic prophylaxis. These last studies used different antibiotic drugs, different selection criteria, and different length of treatment. Also, definitions of severe disease varied between trials although in each the aim was to deliver antimicrobial prophylaxis to patients with severe AP and evidence of pancreatic necrosis. Duration of prophylaxis was relatively long (up to 14 days). All of these studies were small and several did not have sufficient power to assess the effect of antibiotics on mortality rate. Combination of the numbers observed in these studies suggests that there may be a significant reduction in complications and deaths in patients with predicted severe AP treated with prophylactic antibiotics (Table 1), but this ignores the major inconsistencies within and between these trials [17-21]. The difficulties of interpretation were examined in detail in a Cochrane review [22]. There were variations in the findings between studies, which also had different end points. This heterogeneity makes meta-analysis less reliable and indicates the need for further double blind randomised controlled trials.