

Antibiotic prophylaxis in acute pancreatitis: Yes

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Received: 05-09-10

Accepted: 15-09-10

Abstract

Acute pancreatitis continues to be an entity with a varied course and different degrees of morbidity. There continues to be an important controversy regarding management of this entity in which many areas of uncertainty still need to be resolved. In this section we present a discussion about the role of antibiotics in the prevention of pancreatic infections. These infections are the primary cause of death among patients with acute pancreatitis. Interestingly, evidence exists both for and against the use of antibiotic prophylaxis. In fact successive guides published within a relative short period of time have opted for one or the other option. In these two articles we review the literature and extrapolate its implications for practice in our environment.

Key words

Acute pancreatitis, antibiotics, prophylaxis.

Acute pancreatitis (AP) has a 10% to 15% mortality rate and a severity that varies from slight (apache < 9) to severe (apache > 9). It can present as edematous pancreatitis or necrotizing pancreatitis. The two factors that are directly related to its morbidity and mortality are organ failure and infection. Organ failure may occur as early as the first week and can cause either early or delayed mortality. Infection is a complication whose appearance is delayed until the second or third week. It usually compromises the necrotic tissue of the pancreas (1) most commonly beginning with bacterial translocation of the gastrointestinal tract (*Escherichia coli*, *Klebsiella* spp, *enterobacter* spp, *proteus* spp, *pseudomonas* spp). However it can come from the biliary route or by generally hematogenous dissemination usually associated with the use of monitoring catheters (*staphylococcus aureus*, fungi).

OUTCOMES OF ANTIBIOTIC PROPHYLAXIS

In a recent meta-analysis (2) to identify the determinants of mortality in AP, 14 studies of a total of 1,478 patients

with AP were analyzed. A total of 600 developed organ failure, of which 179 died (mortality 30%). 314 developed infected acute necrotizing pancreatitis, of which 102 died (mortality 32%). In the stratified analysis patients with organ failure and infected acute necrotizing pancreatitis had a mortality rate of 42% (RR = 1.94; 95% CI: 1.32 to 2.85; P 0.007).

Adequate resuscitation upon admission, followed by identification of patients at greatest risk, is important for diminishing the number of organ failures which occur and for optimizing patient monitoring and management in intensive care units. Risk indicators include:

- Body mass index greater than 30 kg/m².
- APACHE II greater than or equal to 9 in the first 24 hours
- C-reactive protein (CRP) greater than 150 mg/l 48 hours later.

Early identification, prevention and control of the infection become the next important objectives for patients with AP. A diagnosis of AP is suspected when abdominal symptoms

get worse and fever appears or when there is an increase of leucocytosis. Nevertheless, patients with sterile necrosis can present the same characteristics, and radiological diagnosis is impossible unless gas is observed in the center of the necrosis. Consequently, diagnosis of an infection of the necrosis must be performed by fine needle aspiration, sonography or CAT scan when there is clinical suspicion (12).

CAT scan identification of the necrosis and its extension is based on the Balthazar classification system for determining the presence and extension of necrosis. Since necrosis does not become evident in the earliest stage of AP, the CAT scan should be performed at least 48 hours after initiating treatment, not before. Performance of a CAT scan 4 to 10 days after AP is diagnosed allows diagnosis of necrosis in nearly 100% of all patients (3-14).

CLINICAL STUDIES WITH PROPHYLACTIC ANTIBIOTICS

In last the 3 decades great interest has developed in clarification of whether or not antibiotic prophylaxis diminishes or prevents infection of pancreatic necrosis in any significant way. If it can, the result would be diminution of the necessity for surgery and a reduction in the mortality rate, thus lending support to its use in the presence of severe AP with necrosis of over 30%.

Selective decontamination of the gastrointestinal tract has varied results. The only randomized controlled study was performed by Luiten (4). It combined decontamination with intravenous administration of cefotaxime, an antibiotic. Although diminution of the infection in the pancreatic necrosis was achieved, it is not possible to determine if this was the result of oral decontamination or the intravenous prophylactic antibiotic. An additional factor is the finding that decontamination of the gastrointestinal tract increases the risk of Gram positive resistant infections, thus we do not advise this method as an option for managing infected pancreatic necrosis.

In 1993 Pederzoli and colleagues (5) conducted a multicentric randomized study which compared imipenem 0.5 g administered every 8 hours for 14 days with administration of placebos. They found that use of the antibiotic to treat pancreatic necrosis reduced infection of abscesses and pseudocysts and reduced complications from sepsis (12.2% versus 30.3%, $P > 0.01$). However, they were not able to reduce multiple organ failure, surgery required, or mortality. A study by Sainio and colleagues (6) compared patients with necrotizing pancreatitis of alcoholic etiology who were given daily doses of 4.5 gr of cefuroxime with

patients who did not receive antibiotics. They observed a significant reduction of complications related to sepsis and of mortality.

A Norwegian study with imipenem (7) included 73 patients with severe pancreatitis (CRP over 120 mg/l in the first 24 hours or PCR 200 mg/dl in the next 48 hours). That study compared prophylaxis with imipenem and administration of placebos. It found that there the group treated with imipenem had a significantly lower rate of complications (33% versus 59% $p < 0.05$) and less pancreatic and extra pancreatic infections (14% versus 43%) than did the group receiving placebos. However, there were no significant differences in mortality, multi-organ failure or requirements for surgical intervention.

This and other studies gave satisfactory results prophylactic use of antibiotics for acute necrotizing pancreatitis. Consequently meta-analyses performed before 2004 indicated the benefits of this use.

In 2004 one of two early double blind studies was published (8). It compared prophylaxis with ciprofloxacin and metronidazole to administration of placebos. The study concluded that the antibiotic therapy did not show any benefits for preventing infection of pancreatic necroses. However, since its design allowed adding another antibiotic to the treatment when there was clinical suspicion of pancreatic or extra pancreatic infection (28% of the patients in the antibiotic group, and 46% of the patients in the placebo group), the double blind design was terminated. Additionally, although they evaluated severity at the beginning of the study, 38 patients without necrosis were included. The second multi-centric study (9) was performed in Europe and the United States. The study, which included 100 patients, compared administration of placebos to treatment with meropenem. Use of the antibiotic did not reduce mortality, pancreatic infections or the need for surgery. An objection to this test was that there was difference between the rate of infections among patients with biliary pancreatitis (12%) and the rate of infections among patients with alcoholic etiology (9%) which resulted in a greater number of patients with biliary pancreatitis in the meropenem group.

Two recent meta-analyses have reached different conclusions. The one performed in 2007 by Zilvinas Dambrauskas (10) concluded that the use of antibiotic prophylaxis reduces the risks of acute pancreatitis with infected necrosis, sepsis and the need for surgery. A second meta-analysis performed in 2008 (11) concludes that the use of prophylactic antibiotics for acute necrotizing pancreatitis neither decreases infections of pancreatic necroses nor mortality among these patients.

OPINION

There is no doubt that extensive randomized tests of higher quality are needed to clarify the crucial question: does a reduction of the infected necrosis reduce mortality? To demonstrate a significant reduction of 10% in the rate of infections among patients with pancreatic necrosis between 240 and 400 patients would have to be included in the study. In order to really demonstrate that a reduction of infected necroses diminishes the mortality rate from 20% to 10%, at least 3000 patients would have to be included in the study (12).

Our first conclusion should be that the use of antibiotic prophylaxis for the handling of acute pancreatitis has shown benefit only for those cases of severe pancreatitis in which there is necrosis of 30% or more of the pancreatic tissue. Necrosis is defined according to the Atlanta classification: localized or diffuse zones of nonviable pancreatic tissue that are generally associated with peripancreatic fat cell necrosis. In a CAT scan they appear as zones of in which the density is lower than in normal tissue but greater than the density of fluid. Their density does not increase when contrast is added, nor in the presence of pancreatic or extra pancreatic fluid collections.

In an environment such as ours there are limitations on diagnosing infected acute necrotizing pancreatitis by means of percutaneous puncture and on following up non-infected necrosis with CAT scans and percutaneous puncture every 5 to 7 days. Taking these difficulties into account, together with the increased mortality associated with organ failure in the presence of infection, I consider that we should *not discard the use of antibiotic prophylaxis from our therapeutic arsenal*. When we decide to use this option, we should choose an antibiotic that has suitable pancreatic tissue penetration, reaching an adequate minimum inhibiting concentration in a maximum time of 7 days.

According to their penetration of the pancreas, antibiotics can be divided into 3 groups (13):

- Group A: low penetration. The pancreatic concentration does not reach the Minimum Inhibitory Concentration (MIC) level of the bacteria present. In this group we find aminoglycosides, ampicillin and 1st generation cephalosporins.
- Group B: moderate penetration. The concentration in the pancreas reaches the MIC of some bacteria. In this group we find the 3rd generation cephalosporins and broad spectrum penicillins.
- Group C: high penetration. These reach concentrations above the MIC of sensitive bacteria. In this group we find quinolones, carbapenems and metronidazole.

As a final comment, I would like to add that, given the complexity of acute necrotizing pancreatitis, and considering that organ failure and infected necroses are the two factors that contribute most to increased mortality, patients with serious acute pancreatitis must be taken care of in a multi disciplinary way at a center that has an Intensive Care Unit (ICU) and the capacity for interventionist radiology and endoscopy. The latter should including ERCP (Endoscopic Retrograde Cholangio-Pancreatography) (14).

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