Antibiotic prophylaxis in acute pancreatitis: No

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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.

KEY CONCEPTS

Acute pancreatitis (AP) is a local inflammatory process with systemic effects. Approximately 20% of AP cases evolve into severe cases. Mortality rates vary between 10% for sterile necrosis and 25% for infected necrosis (1). Mortality rates are related to the extent of pancreatic necrosis and are primarily associated with multiple organ failure and complications of infections. It is well accepted that bacterial translocation is the main mechanism initiating sepsis (2). Several decades ago this understanding led to the development from treatment of to preventative treatment for infections in necrotizing pancreatitis as a useful strategy to reduce mortality and length of hospital stay. Many articles and papers related to antibiotic prophylaxis strategies for acute pancreatitis have been published. Some of them have had methodological flaws affecting the validity of their results. An enormous controversy has arisen over whether or not to administer prophylaxis. The results of recent studies and meta-analyses are inclined toward *not managing AP with antibiotics.*

WEAK EVIDENCE FOR PROPHYLAXIS

Currently no consensus exists about the use of antibiotics in treatment of severe acute pancreatitis. One of the main reasons for this is the methodological quality of the studies that were basis for guidelines that previously recommended their use. Until 2003 studies showed reductions in incidences of infections in pancreatic necrosis, and in sepsis and mortality (3,4,5,6,7,8). However, not all of these studies showed consistent results, and some had major methodological flaws.

Although these initial papers studied intervention they had no control groups or did not use groups of patients receiving placebos as control groups (necessary in the absence of prior evidence of the effectiveness of the intervention), or they were not double blind studies.

The proper way to evaluate the effect of therapeutic intervention is through randomized double-blind clinical trials. This type of trial decreases the possibility of bias and asymmetric co-interventions that could affect results. Only three of the studies of antibiotic prophylaxis for pancreatitis are of this type (9,10,11).

In a systematic review of the methodological quality of studies published since 1990 on prophylactic antibiotics for pancreatitis, De Vries et al. (12) found that only 6 studies covering a total of 397 patients achieved a score of at least 5 out of 17 on the methodological quality assessment scale. These 6 were subsequently included for meta-analysis. From those patients, 203 received prophylaxis and 194 were included in the control group. No significant reduction in the infection of pancreatic necrosis was observed. Absolute risk reduction (ARR) was 0.055 (95% CI -0,084 to 0.194) and the mortality rate was RAR 0058 (95% CI -0,194 to 0.154). The Spearman correlation coefficient showed an inverse relationship between the methodological quality of each study and the magnitude of the relative risk reduction for mortality (correlation coefficient -0.948, p = 0.004).

PROPHYLAXIS EFFICACY

The two studies, with adequate study design and negative results that initially led to rethinking the usefulness of prophylaxis were performed by Isenmann et al. (9) and Dellinger et al. (10) Later, a study by Xue (11) confirmed these findings.

In 2004 the German school (Isenmann et al.) published a double-blind study of ciprofloxacin plus metronidazole in which no benefits were found from treatment with antibiotics for preventing infection of pancreatic necrosis. 114 patients were studied, of which 76 had necrosis. There were no differences in mortality or infection rates.

In 2003 (Dellinger et al.) began a multicenter, double blind, placebo-controlled randomized study at 32 hospitals in Europe and North America in order to analyze the efficacy of meropenem for severe acute pancreatitis with pancreatic necrosis. It involved 100 patients with severe pancreatitis and confirmed necrosis. Within the first 5 days after onset of symptoms and continuing for 7 to 21 days, 50 patients received 1 g of meropenem intravenously every 8 hours, while the other 50 received placebos. The primary objective was to observe whether or not pancreatic or peripancreatic infections developed within 42 days after randomization. Secondary issues observed included overall mortality, need for surgical intervention and development of nosocomial infections. Pancreatic infection developed in 18% of the patients in the meropenem group and 12% in the placebo group (p = 0.401). The overall mortality rate was 20% in the meropenem group and 18% in the placebo group (p = 0.799). Surgical intervention was required in 26% of the meropenem and 20% of the placebo group (p = 0.476). In no situation was there a significant difference in favor or against one or the other branch. The meropenem group had a greater number of patients with biliary pancreatitis, among whom there was a higher rate of infections (15%) than there was among patients with alcoholic pancreatitis (9%). However; the overall distribution was not significantly different between groups (p> 0.1). There were also no differences in the time of onset or in the use of intravenous feeding.

In 2009, Ping Xue et al. (11) published a randomized clinical trial with 276 patients with severe acute pancreatitis. 56 of these patients had pancreatic necrosis greater than 30% in CAT scans. They were divided into two groups. 500mg Imipenem was administered intravenously 3 times/day, starting within 72 hours of onset of symptoms and continuing for 7 to 14 days to one group. The other group received no prophylaxis. The primary outcomes studied were the incidence of infectious complications, secondary cancer mortality, incidences of necrosectomies due to infected necroses and incidences of organ failure. There were no significant differences in the incidences of infected pancreatic necroses (37% *vs.* 27.6%), mortality (10.3% *vs.* 14.8%) or the need for necrosectomies (29.6% *vs.* 34.6%) (*P*> 0.05). The incidence of extrapancreatic infections and organ failure presented no significant differences. There was however, a significantly higher rate of fungal infections in the study group than in the control group (36.1% *vs.* 14.2%, *P* <0.05).

These three most recently published meta-analyses regarding the usefulness of antibiotic prophylaxis for severe acute pancreatitis with pancreatic necrosis include the studies of Issenman, Dellinger and Xue. They show how diluted the apparent beneficial effect of prophylaxis shown in previous studies and meta-analysis is. Moreover they show that prophylactic antibiotics do not prevent infection in patients with pancreatic necrosis and do not alter mortality in patients with severe pancreatitis (13,14,15).

DO DELAYS IN INITIATION OF PROPHYLAXIS NEGATES ITS USEFULNESS?

An experimental study of rats (16) showed that early use (2 hours after injury) of imipenem decreased infection of pancreatic necroses more than when treatment was delayed treatment or when infections were not treated. Based on these findings some authors (18) pose the potential usefulness of prophylactic antibiotics in the early course of severe acute pancreatitis (SAP) before the onset of necrosis. During this time pancreatic ischemia is a strong predic-

tor of the subsequent development of necrosis (19). These authors take into account the knowledge that any antibiotic penetration into areas of necrosis or perfusion is limited, (17) possibly limiting the usefulness of prophylaxis if it is not started early. Until now, identification of which patients with SAP will develop pancreatic necrosis is not possible by clinical methods or with any predictive models available. Perfusion CT (PCT) should be considered as an alternative for identifying patients with pancreatic ischemia (20) who could benefit from the use of antibiotics, even with necrosis is not present. In a separate study of 30 patients PCT showed sensitivity of 100% and specificity of 95.3% for detecting pancreatic ischemia. Additional studies are needed to validate PCT as a useful test for detecting pancreatic ischemia, and for evaluating antibiotic therapy in such patients prior to reassessing the currently held position against the use of prophylaxis. In clinical practice, the early realization of the PCT would be limited by the risk of nephrotoxicity associated with intravenous administration of the contrast agent. This is especially important in early stages of management of severe acute pancreatitis when the patient is volume depleted.

POTENTIAL RISKS ASSOCIATED WITH THE USE OF ANTIBIOTIC PROPHYLAXIS

Early and extensive use of antibiotics in critically ill patients exposes them to changes in flora, development of resistant flora (9) and subsequent emergence of infections (21). The use of prophylactic broad-spectrum antibiotics can lead to fungal infections (11, 22), overgrowth of pathogens that can lead to pseudomembranous colitis such as *Clostridium difficile* (23) and increased costs (24).

CONCLUSIONS

Antibiotic prophylaxis, understood as administration of antibiotics in the absence of infection, usually for short periods of time (sometimes a single dose) for patients at high risk of infection, is clearly different from empirical antibiotic therapy in which the antibiotic is started before a suspected serious infection is confirmed microbiologically and which is continues for longer periods of time. C*urrent evidence does not support the use of prophylactic antibiotics in patients with acute necrotizing pancreatitis,* but it does permit the recommendation that physicians should search for signs of early infection in the necrotizing area (present in 20% of patients with pancreatic necrosis). Samples for laboratory confirmation should be obtained in these cases and initial empirical antimicrobial therapy should be started. It should be adjusted later depending on cultures. In places where it is technically difficult to obtain samples for culturing from the site of the necrosis, once other causes are ruled out and infection is still suspected, it is recommended that empirical antibiotic therapy be started using drugs that reach minimum inhibitory concentrations in the pancreas. The first choice is carbapenem.

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