

Antibiotic prophylaxis in patients with severe acute pancreatitis

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BACKGROUND: The prophylactic use of antibiotics in patients with severe acute pancreatitis remains contentious. This study was undertaken to review the current studies on antibiotic prophylaxis in patients with severe acute pancreatitis.

DATA RESOURCES: All papers found by a Medline search were relevant to human trials of antibiotic prophylaxis in patients with severe acute pancreatitis.

RESULTS: In the 1970s, three small randomized studies of prophylactic ampicillin in the treatment of acute pancreatitis showed no effect on mortality or morbidity, but the inclusion of patients at low risk for infection and the use of an ineffective antibiotic were insufficient to detect any differences. From 1993 to 2001, eight prospective clinical trials of antibiotic prophylaxis were conducted in patients with severe acute pancreatitis (SAP). Seven of the 8 trials showed significant effect of the prophylaxis in prevention of pancreatic infections, and one showed significant improvement of clinical course documented by the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. Only two trials did demonstrate the significance of the prophylaxis in lowering the mortality rate. Despite variations in drug agents, study size and patient selection, duration of treatment, and methodology (None of the studies was double-blinded), a meta-analysis showed the positive effect of antibiotics in reducing the mortality. We suggested that antibiotic prophylaxis with proven efficacy in necrotic pancreatic tissues should be given to all patients with acute necrotizing pancreatitis. In recent years, however, the first double-blind, placebo-controlled multicenter study from Germany detected no benefit of antibiotic prophylaxis with respect to the risk of developing infected pancreatic necrosis.

CONCLUSION: Prophylactic antibiotics for severe acute pancreatitis is still a matter of discussion and further studies are required to provide adequate data to answer many ques-

tions and to define the role of antibiotic prophylaxis in patients with severe acute pancreatitis.

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KEY WORDS: severe acute pancreatitis;
antibiotics;
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Introduction

Acute pancreatitis (AP) is a mild and self-limiting disease in most patients. Clinically the overall mortality rate for AP is approximately 10%, but its severe form, severe acute pancreatitis (SAP), increases to 20%–30%.^[1] The natural course of SAP progresses in two phases. The first 14 days after onset of the disease are characterized by overactive systemic inflammatory response syndrome (SIRS), which may result in multiple organ dysfunction syndrome (MODS). Infection of pancreatic necrosis usually develops in the second and third week after onset of the disease and is the most life-threatening complication of the disease and predisposes to sepsis, multiorgan failure, and death.^[2-4] Therefore, prevention, diagnosis, and optimal treatment of infection in AP have become a principal therapeutic target in improving the outcome of this disease.^[5] The prophylactic use of antibiotics has been one of the approaches to reducing severe complications of the disease. In recent years, a number of clinical studies have been conducted to assess the role of prophylactic antibiotics in patients with SAP. Their results, however, have been contentious. In this article, we review the current state of research for the use of prophylactic antibiotics in patients with SAP.

Pathogens of pancreatic infection

The precise pathogenesis of pancreatic infection has not been fully elucidated. There are several ways in which pathogens might reach the pancreas: the hematogenous pathway via the circulation, transmural migration through the colon via the colonic translocation of bacteria to the lymphatics, via the biliary duct system, or ascending from the duodenum via the main pancreatic

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duct, via the urinary tract. Because predominant pathogens in pancreatic infection are of gastrointestinal origin, the gastrointestinal tract lumen seems to be the major source of organisms infecting necrotic pancreatic tissue. Disruption of the intestinal flora, damage to the enteric mucosa, and impaired host defenses promote bacteria and toxins translocate from the gut, with consequent infection of the necrotic pancreas.^[6] Studies in human severe acute pancreatitis support the hypothesis of bacterial translocation from the gut. In 1986, Beger et al^[7] reported bacterial contamination of pancreatic necrosis. In 144 patients with acute necrotizing pancreatitis, necrotic material taken at necrosectomy was tested bacteriologically. As a result, bacterial contamination rates were 23.8% at the first week, 36% at the second, and 71.4% at the third week, and in addition the mortality rate in patients with positive bacteria was significantly higher (37.8%) than in those with negative bacteria (8.7%). Microorganisms were found within infected necrotic pancreas at the time of necrosectomy in this study, which was conducted prior to the introduction of routine antibiotic prophylaxis (Table). The profile of organisms suggests an origin in the gastrointestinal tract. A randomized, controlled multicenter trial of selective decontamination of the digestive tract in patients with SAP showed a reduction of late mortality because a significant reduction of the incidence of gram-negative pancreatic infection supported that pancreatic infection most likely originates from the gut.^[8]

Choice of antibiotics

The choice of antibiotics is critical, because they must penetrate the pancreas and must have the right spectrum of activity against the microorganisms commonly found

Table. Bacteria isolated from operative specimens taken at necrosectomy prior to the introduction of routine antibiotic prophylaxis.^[7]

Bacteria isolated	No. of patients
Gram-negative	
Escherichia coli	24
Enterobacter aerogenes	16
Pseudomonas aeruginosa	5
Proteus spp.	5
Klebsiella pneumonia	3
Citrobacter freundii	1
Gram-positive	
Streptococcus faecalis	6
Staphylococcus aureus	4
Streptococcus viridans	1
Staphylococcus epidermidis	1
Others	
Candida species	3
Mycobacterium tuberculosis	1

in patients with infected necrosis. The ideal drug to use should be characterized by: (1) specific activity against the bacteria known to be responsible for pancreatic infections; (2) ability to penetrate the pancreatic tissue, pancreatic exocrine secretions, and peripancreatic fluid/exudates at therapeutic mean inhibitory concentrations (MIC); (3) ability to penetrate the pancreas during AP; and (4) Clearcut clinical capacity to reduce the development of infected necrosis.^[9]

Animal and human studies found that clindamycin, piperacillin, mezlocillin, fluoroquinolones, metronidazole, and imipenem showed adequate tissue penetration and bactericidal properties to be useful in infected pancreatic necrosis in contrast to the use of aminopenicillins, first-generation cephalosporins, aminoglycosides, and tetracyclines.^[10-12] Meropenem, a new carbapenem antibiotic, is as effective as imipenem in preventing septic complications of patients with SAP.^[13]

Human trials of antibiotic prophylaxis of acute pancreatitis

Unlike the use of antibiotics in the treatment of proven infection, the rationale for the use of prophylactic antibiotics in patients with SAP is to prevent infection from affecting areas of pancreatic necrosis and consequently to reduce the need for surgery as well as mortality.

In the 1970s, the results of three small randomised controlled studies showed that prophylactic ampicillin in patients with AP had no effect on the mortality or morbidity,^[14-16] but the studies included patients with mild disease who are at low risk for infection. The antibiotic, ampicillin, used in these early studies, had also subsequently been shown to have poor penetration into the pancreatic tissue.^[11] So these studies showed insufficient power to detect any differences.

In 1993, Pederzoli and colleagues^[17] reported a multicentre randomized controlled study in which 74 patients with AP due to various causes and confirmed necrosis on CT from six centers in Italy were randomly assigned to two groups; control group; no antibiotic treatment and treatment group; 0.5 g of prophylactic imipenem administered intravenously every 8 hours for 2 weeks. Pancreatic sepsis was always detected by means of cultures (percutaneous CT or ultrasound-guided needle aspiration and intraoperative samples). The incidence of pancreatic sepsis was much less in treated patients (12.2% versus 30.3%, $P < 0.01$), but no difference was observed in surgical intervention, multiorgan dysfunction, or death between the two groups.

Sainio et al^[18] conducted a randomised controlled study of 60 consecutive patients with alcohol-induced necrotising pancreatitis to find out whether early antibiotic treatment can improve outcome. Thirty of the 60 patients were given cefuroxime intravenously (4.5 g/day)

from admission. In the other 30 patients, no antibiotic was prescribed until clinically or microbiologically verified the existence of infection or after a secondary rise in C-reactive protein. A significant reduction in septic complications and death was seen in the antibiotic group. There was no difference in the number of patients requiring surgery, being 7 (23%) in the antibiotic group and 14 (47%) in the control group. However, two patients in the control group died very early in the course of their attack, and 76% of the patients in the control group received an antibiotic at some point during their admission, factors that could have skewed results.^[19]

In a French study, 23 consecutive patients with alcohol-induced SAP were randomized to ceftazidime, amikacin and metronidazole, or to no antibiotic. The overall mortality was not different in three patients (25%) in the control group versus one patient (9%) in the antibiotic group, but the incidence of sepsis was reduced in the antibiotic treated group (0% versus 58%, $P < 0.05$).^[20]

In a prospective randomized, controlled study, 13 patients with acute necrotizing pancreatitis (ANP) and sterile necroses (quantified by contrast-enhanced computed tomography) were given intravenously 200 mg ofloxacin twice daily and 500 mg metronidazole twice daily. The results were compared to those in a control group of patients with ANP ($n = 13$) who had not initially received antibiotics. If there was evidence of infection by CT-guided fine needle aspiration (FNA), antibiotics were then also given to the patients of the control group. Prophylactic use of antibiotics significantly improve the clinical course documented by the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores on days 1, 5 and 10, but was found to be no better than supportive therapy in either delaying or preventing occurrence of infection in the necrotic pancreas. The mortality rates in both groups did not reach a statistically significant difference. The authors concluded that antibiotic prophylaxis neither prevented nor delayed bacterial infection of the necrotic pancreas. But it significantly improved the clinical course if started before the onset of infection of the pancreatic necroses.^[21] Bassi and colleagues^[12] compared imipenem with pefloxacin for the prevention of local pancreatic infection in patients with SAP. Pefloxacin was found to be inferior to imipenem in preventing local pancreatic and extrapancreatic infections. A single-center randomized study did show early imipenem-cilastatin therapy appears to significantly reduce the need for surgery in the patient with ANP.^[22]

The concept of prevention of pancreatic infection has been addressed by a different route of antibiotic administration. Considering that gastrointestinal tract lumen seems to be the major source of organisms infecting necrotic pancreatic tissue, Luiten et al^[8] reported a re-

duction in mortality rate (35% versus 22%) in patients with severe pancreatitis treated with selective intestinal decontamination (norfloxacin, colistin, amphotericin) administered enterally. This effect was related to a reduction in late deaths (more than 2 weeks) and was secondary to a decrease in Gram-negative pancreatic infections ($P < 0.05$). Takeda et al^[23] evaluated the usefulness of continuous regional arterial infusion (CRAI) of protease inhibitors and antibiotics in 156 patients with ANP collected in a cooperative survey carried out in 1997 in Japan. This study found that CRAI of both protease inhibitors and antibiotics was effective in reducing mortality and preventing the development of pancreatic infection in ANP when initiated within 48 hours after the onset of ANP.

A meta-analysis analyzing six previously published trials of prophylactic antibiotics in patients with AP^[8,12,18-21] has shown a positive benefit for antibiotics in reducing the mortality. Thus, the authors suggested that prophylaxis with an antibiotic with proven efficacy in necrotic pancreatic tissue should be given to all patients with ANP.^[24] This has led to recommend prophylactic use of antibiotics in recent guidelines on the treatment of SAP.^[25] Unfortunately, the sample size in most of these studies was small. One study without a control group receiving no antibiotic prophylaxis^[12] and two included patients with SAP but without necrosis.^[8,20] None of the studies was double-blinded. Moreover, there are too many unanswered questions: when to start prophylactic treatment and how long about the duration? what is the optimal route of antibiotic administration? Intravenous or arterial infusion combine with selective intestinal decontamination or alone? and how to deal with adverse effects related to the long-term use of antibiotics such as fungal infection and bacterial resistance?

Isenmann et al^[26] first carried out a double-blind, placebo-controlled multicenter study on the use of antibiotic prophylaxis of AP. In this study, a total of 200 patients were calculated with a power of 90% to demonstrate that antibiotic prophylaxis reduces the proportion of patients with infected pancreatic necrosis from 40% placebo (PLA) to 20% ciprofloxacin/metronidazole (CIP/MET). One hundred fourteen patients with acute pancreatitis in combination with a serum C-reactive protein exceeding 150 mg/L and/or necrosis on contrast-enhanced CT scan were enrolled and received either intravenous CIP (2×400 mg/day) + MET (2×500 mg/day) or PLA. Study medication was discontinued and switched to open antibiotic treatment when infectious complications, multiple organ failure sepsis, or SIRS occurred. After half of the planned sample size was recruited, an adaptive interim analysis was performed, and the recruitment was stopped. Fifty-eight patients received CIP/MET and 56 patients PLA. Twenty-eight percent in the CIP/MET group required open antibiotic

treatment vs. 46% with PLA. Twelve percent of the CIP/MET group developed infected pancreatic necrosis compared with 9% of the PLA group ($P = 0.585$). The mortality was 5% in the CIP/MET and 7% in the PLA group. In 76 patients with pancreatic necrosis on contrast-enhanced CT scan, no differences in the rate of infected pancreatic necrosis, systemic complications, or mortality were observed. The authors concluded that no benefit of antibiotic prophylaxis with respect to the risk of developing infected pancreatic necrosis. The authors also revised criteria to initiate antibiotic treatment in patients with a predicted SAP; newly developed sepsis or SIRS, newly developed failure of 2 or more organ systems, proven pancreatic or extrapancreatic infection, and an increase in serum C-reactive protein in combination with evidence of pancreatic or extrapancreatic infection. However, a large number of subjects of the control group (26/56, 46%) were treated with antibiotic therapy during the course of the study period and 16 out of 58 (28%) treated subjects received antibiotics different from those of the study protocol, the large crossover rate could have introduced a bias in the study. The other limitation of the study as the authors pointed out, the sample size was not large enough to detect confidently potential beneficial effects of low magnitude or potential benefits involving infrequent secondary endpoints of the study such as shock, mortality, surgical treatment, intensive care unit stay, and duration of hospitalization. Thus, larger study would be needed to test conclusively whether prophylactic antibiotics prevent infrequent secondary endpoints like these.

In conclusion, the use of prophylactic antibiotics in patients with SAP still is a matter of discussion and further studies are required to provide more adequate data to answer many questions and establish the role of antibiotic prophylaxis of SAP.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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