Review

Pro/con clinical debate: Antibiotics are important in the management of patients with pancreatitis with evidence of pancreatic necrosis

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Published online: 17 March 2003 *Critical Care* 2003, **7**:351-353 (DOI 10.1186/cc2165)
This article is online at http://ccforum.com/content/7/5/351

Abstract

Pancreatitis is not an infrequent diagnosis in patients admitted to the intensive care unit. Prolonged stays, intense resource utilization and high morbidity/mortality are commonplace in such patients. Management for the most part is supportive, with the surgical team keeping close watch to intervene as the need arises. Over the past few decades there has been considerable debate regarding the usefulness of systemic antibiotics to prevent infectious complications in patients with evidence of pancreatic necrosis. In the present article of *Critical Care*, two expert groups debate the two sides of this contentious antibiotic issue.

Keywords antibiotic prophylaxis, critical care, multiorgan failure, pancreatic necrosis, pancreatitis

The scenario

A 29-year-old male develops severe pancreatitis, presumably as a result of heavy alcohol intake. He is admitted to the hospital ward for management but becomes hypoxic over the first 24 hours, requiring intubation and mechanical ventilation. The patient is admitted to the intensive care unit and, in the course of investigation, he has an abdominal computed tomography scan that shows an inflamed pancreas with some necrotic areas. Although there are no obvious signs of infection, you wonder whether antibiotics are useful in the patient's management.

Pro: Yes, antibiotics are important in the management of patients with pancreatitis with evidence of pancreatic necrosis

Graham Ramsay and Paul Breedveld

Antibiotic prophylaxis in necrotizing pancreatitis is attractive as 80% of all deaths from severe pancreatitis are due to infected necrosis, and the time scale for the occurrence of infection makes prophylaxis feasible.

Early trials of antibiotic prophylaxis in pancreatitis were negative, probably due to inappropriate antibiotic choice and also due to failure to focus on necrotizing pancreatitis. With more appropriate antibiotics, however, there are now a number of published randomized clinical trials on prophylactic antibiotic use in the management of acute necrotizing pancreatitis [1–4]. These include only randomized clinical trials that make specific mention of acute pancreatitis, of incidence of pancreatic infection, of related sepsis and mortality, and that the antibiotics used had a minimal inhibitory concentration in the pancreas [5]. All four randomized clinical trials complied with at least one of the criteria in the guidelines for assessment of the quality of

reports of randomized clinical trials of Jadad and colleagues [6].

Pederzoli and colleagues included 74 patients, used imipenem and found a significant ($P<0.01$) reduction of septic complications, such as infected pancreatic necrosis, peripancreatic abscesses or infected pseudocysts [1]. There was no significant reduction in multiorgan failure, in the need to operate or in mortality. Sainio and colleagues included 60 patients, used cefuroxime and found a significant reduction in the number of surgical interventions ($P=0.012$) and in mortality ($P=0.028$) [2]. There was no significant reduction in the incidence of infected pancreatic necrosis or pancreatic abscesses. Delcenserie and colleagues included 23 patients, used a combination of ceftazidime, amikacin and metronidazole, and found a significant reduction of septic complications ($P<0.03$) [3]. No significant reduction of mortality was found. Schwarz and colleagues included 26 patients, used a combination of ofloxacin and metronidazole, and found a better survival (0 versus 2 deaths; mortality rate, 0% versus 15%), but no difference in the rate of infection of pancreatic necrosis [4].

Pooling of the data from these 183 patients by Bosscha and colleagues in a meta-analysis resulted in a group of 95 patients treated with prophylactic antibiotics and 88 patients without [5]. These pooled data showed a significant risk reduction with prophylactic antibiotic for pancreas-related infection (–14%; $P=0.04$), for sepsis (–25%; $P=0.0002$), and for death (–13%; $P=0.007$).

In another meta-analysis, Golub and colleagues [7] also concluded that antibiotic prophylaxis reduced pancreatic sepsis and mortality. They included a study by Luiten and colleagues [8], which used selective decontamination of the digestive tract. Selective decontamination is attractive as it may allow the use of prophylaxis without the risk of inducing superinfections through the use of long-term broad-spectrum antibiotics.

These data support our opinion that patients who develop necrosis due to acute pancreatitis benefit from prophylactic antibiotic use. It significantly reduces the number of infections, reduces sepsis and reduces mortality related to acute pancreatitis.

Con: No, antibiotics are not important in the management of patients with pancreatitis with evidence of pancreatic necrosis

Lorne H Blackbourne and Stephen M Cohn

Limiting prophylactic antibiotic use in severe pancreatitis minimizes the development of resistance and superinfections in vulnerable hosts, and also avoids unnecessary costs. Nearly three decades ago in small, prospective, randomized trials (totaling 192 patients), the use of antibiotics for routine pancreatitis was shown to be of no apparent benefit [9–11]. At this juncture there is no definitive, level one, data supporting the use of intravenous antibiotics in the treatment of patients with severe pancreatitis, even in the setting of pancreatic necrosis. The few prospective studies that exist investigating antibiotic use in severe pancreatitis have been nonblinded trials with small patient populations [1,2].

Pederzoli and colleagues, in the most often quoted trial to support the routine use of antibiotics in pancreatitis, prospectively randomized 74 patients with severe necrotizing pancreatitis in a nonblinded fashion (secondary to either alcoholism or gallstones) to receive imipenem–cilastin or no antibiotics [1]. They found no significant differences in organ dysfunction or mortality (antibiotics, 29% and 7% versus no antibiotics, 39% and 12%; $P=$not significant) or mortality (antibiotics, 7% versus no antibiotics, 12%; $P=$not significant). The frequency of operation for debridement of pancreatic necrosis was also unaffected, but Pederzoli and colleagues did note that there was a decrease in the number of positive pancreatic cultures (percutaneously and intraoperatively).

Sainio and colleagues randomized 60 patients with alcoholic necrotizing pancreatitis to receive cefuroxime versus no antibiotic treatment in a nonblinded trial [2]. They reported a significant decrease in mortality in the patient group receiving antibiotics when compared with those not receiving antibiotics (3% versus 23%, $P=0.03$). This study has been criticized because of its small size and because of the large percentage of patients (50%) who apparently succumbed from infections caused by *Staphylococcus epidermidis* (which were often associated with catheter sepsis).

Lutien and colleagues more recently used intravenous and enteral antibiotics (including amphotericin) to achieve decontamination of the gastrointestinal tract for the purpose of possibly decreasing bacterial inoculation of the necrotic pancreatic tissue via translocation [8]. One hundred and two patients were randomized to gut decontamination or to standard treatment. They reported a nonsignificant decrease in mortality (22% gut decontamination versus 35% controls, $P=0.19$) in patients undergoing the antibiotic regimen. Other large trials utilizing gastrointestinal decontamination in groups of critically ill patients have failed to demonstrate a decrease in mortality or intensive care days. This extensive protocol, however, requires significant resource utilization and costs, and also carries a potential risk of the development of bacterial resistance.

While there is inconclusive data supporting the use of prophylactic antibiotics in the setting of severe pancreatitis, there is some evidence suggesting that misuse of antibiotics leads to devastating superinfections. Isenmann and

colleagues have shown a significant increase in *Candida* infections in patients with pancreatic necrosis with prolonged exposure to antibiotics [12]. Among 92 patients with infected pancreatic necrosis, 22 had *Candida* infections and this subgroup had a major increase in mortality (64%) compared with those patients without *Candida* (19%, $P<0.01$). Certainly, critically ill patients developing superinfections tend to be those with more severe disease, with longer antibiotic courses and with longer hospital stays.

We need to identify the subset of patients who are most likely to benefit from prophylactic antibiotics in the setting of severe pancreatitis. An adequately powered, randomized, double-blind, multicenter trial involving a suitable antibiotic regimen compared with placebo in a homogeneous group with severe pancreatitis is required. The primary endpoints should be clinically relevant, such as defined organ dysfunction, length of intensive care unit stay, and 30-day and 60-day mortality. Until such a study is completed, we cannot recommend routine prophylactic antibiotics in the setting of severe pancreatitis.

Pro's response

Graham Ramsay and Paul Breedveld

We agree with Blackbourne and Cohn that all systemic antibiotic use carries a risk of increasing selection pressure for resistance, and that antibiotic use should be minimized where appropriate. We also agree that the early trials they cite were inconclusive. As we said, the trials used inappropriate antibiotics and did not focus on necrotizing pancreatitis.

The discussion should focus on the relative benefit in terms of infection, morbidity and mortality against the risk of increased resistance to antimicrobials, based on the current literature.

While we agree that confirmatory studies are desirable (they are in progress), we still conclude that patients with necrotizing pancreatitis should receive antibiotic prophylaxis.

The study of Luiten and colleagues on selective decontamination of the digestive tract for prophylaxis deserves special attention. It suggests we can achieve the benefits of prophylaxis without the risk of increasing resistance, through the use of systemic antibiotics [8].

Con's response

Lorne H Blackbourne and Stephen M Cohn

"Meta-analysis is to statistical data analysis what metaphysics is to theoretical physics!"

Utilizing meta-analyses of tiny, inconclusive and, in some instances, flawed clinical trials to justify the use of a modality (broad-spectrum antibiotics) with known adverse impact (microbial resistance, superinfection, drug toxicity and cost) appears unfounded. We believe that a multicenter, double-blind, prospective, randomized trial is warranted prior to the use of antibiotics in the setting of necrotizing pancreatitis. We presently use antibiotics in this population only when computed tomography-guided aspiration biopsy of pancreatic necrosis reveals bacterial pathogens.

References

1. Pederzoli P, Bassi C, Vesentini S, Campedelli A: **A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem.** *Surg Gynecol Obstet* 1993, **176**:480-483.
2. Sainio V, Kemppainen E, Puolakkainen P, Taavitsainen M, Kivisaari L, Valtonen V, Haapiainen R, Schroder T, Kivilaakso E: **Early antibiotic treatment in acute necrotising pancreatitis.** *Lancet* 1995, **346**:663-667.
3. Delcenserie R, Yzet T, Ducroix JP: **Prophylactic antibiotics in treatment of severe acute alcoholic pancreatitis.** *Pancreas* 1996, **13**:198-201.
4. Schwarz M, Isenmann R, Meyer H, Beger HG: **Antibiotic use in necrotizing pancreatitis. Results of a controlled study.** *Dtsch Med Wochenschr* 1997, **12**:356-361.
5. Bosscha K, Vos A, Visser MR, Berger P, van Dullemen H, Ploeg R: **Reduced risk of complications associated with severe acute (necrotizing) pancreatitis by administration of antibiotics; results from a literature review.** *Ned Tijdschr Geneeskd* 2001, **145**:1982-1985.
6. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ: **Assessing the quality of reports of randomized clinical trials: is blinding necessary?** *Control Clin Trials* 1996, **17**:1-12.
7. Golub R, Siddiqi F, Pohl D: **Role of antibiotics in acute pancreatitis: a meta-analysis.** *J Gastrointest Surg* 1998, **2**:496-503.
8. Luiten EJT, Hop WCJ, Lange JF, Bruining HA: **Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis.** *Ann Surg* 1995, **222**:57-65.
9. Craig, RM, Dordal E, Myles L: **The use of ampicillin in acute pancreatitis.** *Ann Int Med* 1975, **83**:831-832.
10. Finch, WT, Sawyres JL, Schenker S: **A prospective study to determine the efficacy of antibiotics in acute pancreatitis.** *Ann Surg* 1976, **183**:667-671.
11. Howes, R, Zuidema GD, Cameron J: **Evaluation of prophylactic antibiotics in acute pancreatitis.** *J Surg Res* 1975, **18**:197-200.
12. Isenmann R, Schwarz M, Rau B, Trautmann M, Schrober W, Beger H: **Characteristics of infection with candida species in patients with necrotizing pancreatitis.** *World J Surg* 2002, **25**: 372-376.