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Review

Antibiotics in severe pancreatitis: the current status

C Bassi, C Falconi, L Casetti, A Valerio, E Caldiron, G Butturini and P Pederzoli

Surgical and Gastroenterological Department — Pancreatic Unit, Hospital Borgo Roma, University of Verona, Italy

Background

Mortality in severe pancreatitis is as high as 40% if infected pancreatic necrosis supervenes. Whenever possible prevention of infection has become the relevant end point for pancreatologist researchers. The 'ideal' drug should be characterised by a specific activity against the bacteria known to be responsible for infected pancreatic necrosis and be able to penetrate the pancreas in sufficient concentrations.

Methods

Several studies strongly suggest the rational background to antibiotic choice. To date there have been eight prospective trials and one each on selective decontamination and enteral nutrition.

Results

Three of the eight were carried out in the mid-1970s and show disappointing results but using drugs now known as not able to penetrate the gland and unsuitable against the usual flora involved. All the other studies report a significant reduction of infected necrosis and pancreatic abscess incidence during severe pancreatitis apart from the only one in which mortality seems to be significantly influenced.

Discussion

Among the several options aimed at reducing infected pancreatic necrosis and pancreatic abscess the prophylactic use of antibacterial drugs is the only one to be tested up to now in more than one prospective and randomised trial. Strong consideration should be given to treating patients with severe pancreatitis with broad-spectrum antibiotics.

Keywords

severe acute pancreatitis, infections, infected pancreatic necrosis, pancreatic abscess, antibiotics.

Identification of pancreatic and peripancreatic necrosis, and prevention and treatment of the associated infections represent the most important fields of modern experimental and clinical research in acute pancreatitis [1–26]. The concept of preventing super-infection applies only to the severe and necrotic form of acute pancreatitis. Previous prospective studies of the use of antibiotics failed to show benefit because all patients with acute pancreatitis, whether severe (< 10%) or uncomplicated (~ 90%), were enrolled [1–3].

Gram-negative pathogens isolated in infected necrosis are believed to reach the pancreas by bacterial translocation, whereas Gram-positive organisms appear to superinfect the necrotic tissues during bacteraemias from remote sites [4,5,12,16]. The most frequently involved bacteria are therefore of intestinal origin, and therefore there should be a rationale for prophylactic antibiotic treatment, or for bowel sterilisation. The ideal drug to use should be characterised by:

- Specific activity against the bacteria known to be responsible for pancreatic infections.
- Ability to penetrate into the pancreatic tissue, pancreatic exocrine secretions and peripancreatic fluid/exudate at therapeutic mean inhibitory concentrations (MIC).
- Ability to penetrate the pancreas during acute pancreatitis.
- Clear-cut clinical capacity to reduce the development of infected necrosis [4,5,7–11,13-18].

Following the recent introduction of modern antibiotic prophylaxis, the occurrence of staphylococcal species and even primary fungal infection is slowly, but steadily, increasing [5,19–21,26]. This changing bacteriologic spectrum suggests the need for continuous reassessment of the

Correspondence to: *C Bassi, Surgical and Gastroenterological Department, University Hospital Borgo Roma, 37138 Verona, Italy*

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Table 1. *Penetration of antibiotics into the human pancreas*

Good penetration	Varying degrees	Poor penetration
Fluoroquinolone	Streptomycin	Ampicillin
Metronidazole	Chloramphenicol	Moxalactam
Clindamycin	Clotrimoxazole	Tetracyclines
Mezlocillin	Cefoxitin	Aminoglycosides
Imipenem	Ceftazidime	Cephalosporins

potential roles of other specific drugs [4,13–15,21–25]. With regard to the ability of antibiotics to penetrate the pancreatic tissues, there appears to be some kind of blood–pancreatic juice barrier within the pancreas [4,13, 15,22–25].

Table 1 illustrates the overall penetration of different antibiotics in man. This paper reviews recently reported clinical.

Clinical studies

Our group was the first to address prospectively the role of an effective, broad-spectrum antibiotic (imipenem, 500 mg every 8 h) given prophylactically in patients with severe acute pancreatitis. We specifically studied only patients with documented necrotising pancreatitis (using dynamic, contrast-enhanced CT) in whom the antibiotic was begun within 72 h of the onset of pancreatitis and was continued for at least 2 weeks. This regimen decreased the incidence of development of infected necrosis (confirmed by fine-needle aspiration and/or intra-operative tissue culture), when compared with randomised patients not receiving the antibiotic (12% versus 30%; $p < 0.01$). The beneficial effects were maximal (no infections in 27 consecutive patients) when the necrosis involved < 50% of the glandular volume [7]. Likewise, Sainio and colleagues in Finland demonstrated a significant reduction in mortality rate (3% versus 23%) with cefuroxime (4.5 g day^{-1}) at onset of the attack [8]. In a letter commenting on the trial, Baudin [27] points out that the inclusion of patients dying of untreatable toxaemia in the early phases of acute pancreatitis undermines any possibility of properly assessing the benefit of antibiotic therapy aimed at preventing a different phenomenon, namely infected necrosis, which generally tends to occur later. In effect, the Finnish trial reported a statistically-significant difference in mortality between treated and untreated patients, after including two cases of fulminant pancreatitis in the control group.

Interpretation of the results of the trial is made even more difficult by the fact that three-quarters of the patients changed antibiotic during the course of the disease. There was no significant difference in the incidence of specific pancreatic infections between the two groups (nine versus 12 cases of infected necrosis or pancreatic abscess), but only a significant difference in extra-pancreatic (particularly urinary tract) infections. Broadly speaking, the study appears to support the use of the drug in question (cefuroxime, an antibiotic with poor penetration of the pancreas in therapeutic concentrations [4,13,14,23]), as the specific agent in the management of acute pancreatitis. In his reply to Baudin's comment, Sainio asserts that "to exclude patients from analysis after randomisation is not justified". While this statement may be impeccable from the theoretical standpoint, it fails to make allowance for the clinical complexity of acute pancreatitis and its pathophysiology.

Another important and elegant study on this topic was performed recently in Japan [9]. The pancreatic infection rate was 50% in the 16 patients referred > 8 days from disease onset and treated with different antibiotics (cefmetazone, $n = 5$ patients; piperacillin, $n = 4$; cefoperazone/sulphactan, $n = 2$; imipenem, $n = 2$; and cefuzonam, $n = 2$). By contrast, the incidence of pancreatic infection was lower (23%) in the 22 patients treated with i.v. imipenem within 7 days of disease onset and 0% in 15 comparable patients treated with imipenem (500 mg/12 h) by intra-arterial infusion. The mortality rate was significantly and progressively decreased in these three groups (44%, 14%, and 7%, respectively). Delcenserie and co-workers, in a smaller series, tested combinations of different antibiotics (ceftazidime, 2 g every 8 h; amikacin 7.5 mg kg^{-1} every 12 h and metronidazole, 500 mg every 8 h for 10 days). No infection occurred in treated patients, versus a 58.3% infection rate in the untreated control group of 12 patients [11].

Recently, the concept of prevention of pancreatic super-infection has been addressed by a different approach.

Luiten and colleagues reported a reduction in mortality rate (35% versus 22%) in patients with necrotising pancreatitis treated with a regimen of selective intestinal decontamination. This effect was related to a reduction in late deaths (>2 weeks) and was secondary to a decrease in Gram-negative pancreatic infections ($p < 0.05$). Unfortunately, the timing of the start of treatment in relation to the onset of the disease was not given, nor was there any standard duration of treatment, nor yet stratification of patients in regard to the extent of necrosis [10].

Finally, in a recent multi-centre study [26], we compared imipenem versus pefloxacin (400 mg twice a day). Despite its theoretical potential, pefloxacin is not a valid alternative because of the significantly lower infection rate detected in the imipenem goup [10% versus 37%].

Conclusion

Despite the fact that infectious complications are still regarded as the primary cause of death in severe pancreatitis [5], the most recent studies [6,20,21] appear to provide evidence not only for a reduction in the overall infection rate, but also for an increased number of deaths occurring in patients with sterile necrosis. These investigators claim that the reduced infection rate is, at least partly, due to the routine use of suitable antibiotics.

On the whole, the data obtained in our most recent study [26] relating to the overall low incidence of pancreatic infections (23%) and associated mortality rate (14%) confirm the trend reported in other uncontrolled series when compared with historical data from the same centres. Since the introduction of antibiotic prophylaxis protocols, Banks and co-workers [6], report that the incidence of infected necrosis has fallen from 67 to 32%, while Ho and Frey [21] register a drop from 75 to 20%. The results emerging in our series appear all the more important given the fact that patients were selected on the basis of severity or extent of necrosis, focussing precisely on those patients at greatest risk [26]. The selection of such a restricted patient sample explains the lengthy time-period taken to conduct this trial (6 years) and the relatively limited number of patients recruited. The small sample size is unquestionably a factor with a major bearing on the lack of a significant difference in mortality rates between the two treatment groups.

Assuming a 30% theoretical risk of infections in untreated patients and a 15% anticipated reduction as a result of effective prophylaxis, Barie [16] calculates that a statistically-flawless trial would need to recruit at least 188 patients. Clearly, this is not a feasible proposition, other than in the context of a study involving many more centres than those taking part in our own or other trials. On the other hand, the estimate of a 30% risk of developing pancreatic infections is acceptable from the theoretical standpoint if we consider all patients with infected necrosis ranging from < 30% to > 50% of pancreatic volume. In our previous study of imipenem versus no treatment [7], the risk of infection of the necrosis progressively increased in relation to the extent of the necrosis (25% for necrosis < 30%; 36.5% for necrosis from 30–50%; 50% for necrosis > 50%).

The choice of a maximum-risk patient sample exclusively composed of severe pancreatitis cases (extent > 50%) in our last trial at least partly offsets the drawbacks presented by the fairly limited number of patients recruited. Unfortunately, as already stressed, no precise data regarding extent of necrosis are reported in the other published trials and the time elapsing between onset of symptoms and the start of treatment is not always clearly specified, nor is the actual treatment duration [8–11].

Regardless of the criticism that each of these individual trials might attract, the sum total of these contributions prompt us to conclude that antibiotic treatment is mandatory in severe necrotising pancreatitis.

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