The Role of Antibiotic Prophylaxis in the Treatment of Acute Pancreatitis

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Abstract: Acute pancreatitis is an inflammatory disorder, but it is not generally caused by infectious agents. Yet, in tertiary referral hospitals, the majority of patients who die of necrotizing pancreatitis do so as a consequence of infectious complications. These generally develop late (2–4 weeks) in the disease process. This finding prompted the hypothesis that infectious pancreatitis complications, such as an abscess or an infected necrosis which can lead to death, can be reduced by treating patients who suffer, at least initially, from a sterile inflammatory disorder, with broad-spectrum antibiotics. Here we review the experimental foundations of this hypothesis, as well as the difficulties that were encountered when clinical trials were undertaken to confirm it. At present, there is still a case for treating necrotizing pancreatitis patients with broad-spectrum antibiotics (specifically carbapenems), but the extent of the beneficial effect and the number of patients expected to profit from this approach should not be overestimated.

Key Words: acute pancreatitis, pancreatic necrosis, antibiotic prophylaxis

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Owing to a series of studies initiated by the Ulm group, it is known that infection of pancreatic necrosis is a major and life-threatening complication of acute necrotizing pancreatitis.[1] The gold standard for the differentiation between interstitial pancreatitis (about 80% of the cases) and necrotizing pancreatitis (about 20% of the cases) remains contrast-enhanced computed tomography (CT). However, this imaging procedure is not always a helpful tool for diagnosing infection. Only when air inclusions in or around the necrotic area are identified on CT is infected necrosis suspected. Otherwise, there is no specific feature on contrast-enhanced CT that is able to distinguish between infected or sterile necrosis. The gold standard for the detection of infected pancreatic necrosis is ultrasound-guided or CT-guided percutaneous aspiration of suspected pancreatic fluid collections with bacteriologic sampling. Fluid obtained by this procedure should be processed immediately for Gram staining and culture (aerobic and anaerobic bacteria, fungi).[2] A positive Gram staining has been found to be a reliable early indicator of pancreatic infection. In one retrospective study, negative Gram staining was followed by a negative culture. In almost all cases where here was a positive culture, the Gram staining also revealed organisms.[3] Gram staining is essential, as the results of bacteriologic cultures may not be available for several days. The complication rate for fine needle aspiration is low.[3,4] Rarely, bleeding or an exacerbation of acute pancreatitis will occur.[5,6] Although six published guidelines on the diagnosis and treatment of acute pancreatitis recommend fine needle aspiration for detecting infected pancreatic necrosis,[7–12] it is not mentioned in two guidelines[13,14] and the procedure is only performed in a minority of centers. In an assessment of the compliance with guidelines in Germany, for example, only one third of senior gastroenterologists said that they used the procedure.[15,16] Apparently, the majority of respondents diagnose infected pancreatic necrosis on the basis of unresolved organ failure, persisting septicemia, or both.

Infected pancreatic necrosis is still assumed to indicate that surgical debridement is necessary. However, during recent years, several studies have reported that conservative treatment such as nonsurgical drainage was successful in some patients.[17–19] Criteria to determine whether a patient with infected pancreatic necrosis will benefit from surgical or conservative treatment are currently not available.

Under these conditions, it would be helpful to prevent infection of pancreatic necrosis in the first place. The question whether antibiotics can serve this purpose and can thus improve patient survival is being controversially discussed.

Here we review the studies that have investigated whether and which antibiotics penetrate sufficiently well into pancreatic necrosis and whether prophylactic antibiotic treatment of patients with acute pancreatitis is of clinical benefit.

PENETRATION OF ANTIBIOTICS INTO HUMAN PANCREATIC FLUID AND TISSUE

At present, there are around 13 studies on the penetration of antibiotics in the human pancreas, and their results differ considerably (Table 1).[20–32] In most studies, a parenteral route of administration for the antibiotic was used, which seems appropriate for a patient with acute pancreatitis. Eight studies measured the presence and concentration of the antibiotic in pancreatic secretion, obtained either on endoscopic retrograde cholangiopancreatography (ERCP) or after stimulation via a pancreatic fistula.[20–26,32] In one study, the content of pseudocysts was used to test the penetration of the

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TABLE 1. Penetrability of Antibiotics Into Human Pancreatic Juice (Obtained During ERCP or Via a Pancreatic Fistula) and Tissue

	Route of Administration		Detection in:				
				Pancreatic Tissue			
Class	Parenteral Pseudocyst/Reference	Oral	Fluid/Reference	AP/Reference	CP/Reference	PS/Reference	
β-Lactam antibiotics							
Penicillins							
Ampicillin	+	−	−/[21,22]	−	−	−	−
Azlocillin	+	−	−/[22]	−	−	−	−
Mezlocillin	+	−	+/[20,22]	+/[27,29]	+/[29]	+/[29]	−
Piperacillin	+	−	−/[23]	−	+/[29]	+/[29]	−
Cephalosporins 1st generation							
Cephalothin	+	−	−/[24]	−	−	−	−
Cephalosporins 2nd generation							
Cefotiam	+	−	−/[22]	−	−	−	−
Cefoxitin	+	?	−/[23,24]	−	−	−	−
Cephalosporins 3rd generation							
Cefotaxime	+	−	+/[32]	−	+/[29]	+/[29]	+/[31]
Ceftazidime	+	−	−	+/[28]	+/[28]	+/[28]	−
Ceftizoxime	+	−	−	−	+/[29]	+/[29]	−
Carbapenems							
Imipenem-cilastatin	+	−	−	+/[27]	+/[29]	+/[29]	−
Other antibiotics							
Aminoglycosides							
Amikacin	+	−	−	−/[27]	−	−	
Gentamicin	+	−	−/[22]	−/[27]	−	−	−
Netilmicin	+	−	−	−/[29]	−/[29]	−/[29]	−
Tobramycin	+	−	−	−	−/[29]	−/[29]	−
Chloramphenicol	+	−	+/[22]	−	−	−	
Quinolones							
Ciprofloxacin	+	+	+/[22,26]	−	−/[29]	−/[29]	?
Ofloxacin	+	+	+/[25]	+/[30]	+/[29,30]	+/[30]	−
Pefloxacin	+	−	?	+/[27]	?	?	?
Lincomycins							
Clindamycin	+	−	+/[23]	−	−	−	−
Nitroimidazole							
Metronidazole	+	−	+/[22]	+/[27,29]	+/[29]	−	−
Tetracyclines							
Doxycycline	+	−	+/[22]	−	−	−	−

+, antibiotic detected in sufficiently bactericidal concentrations; −, antibiotic not detected or in insufficient bactericidal concentrations; AP, acute pancreatitis; CP, chronic pancreatitis; PCA, pancreatic carcinoma; PS, pseudocyst.

antibiotic. In the remaining studies, antibiotic concentrations were measured in pancreatic tissue.[31] Tissue samples were obtained from patients with different pancreatic diseases and different degrees of inflammation (acute pancreatitis, chronic pancreatitis, pancreatic carcinoma). Human studies[29] have shown that the antibiotic concentration depends on the degree of inflammation, with higher levels in acute pancreatitis compared with controls. The following results were reported in chronologic order:

Roberts and Williams[21] failed to detect the antibiotic, ampicillin in pancreatic juice obtained by ERCP, which was used in initial studies evaluating antibiotics in human acute pancreatitis.[33–35]

Benveniste and Morris[32] and Lankisch et al[31] reported sufficiently high and bactericidal concentrations of cefotaxime in both pancreatic juice and pancreatic pseudocysts.

Gregg et al[24] investigated cephalothin and cefoxitin and failed to detect them in pure pancreatic juice obtained from patients with acute relapsing or chronic pancreatitis or in controls.

Pederzoli et al found sufficiently high and bactericidal concentrations of mezlocillin,[20] ciprofloxacin,[26] and ofloxacin in pancreatic fluid.[25]

Brattström et al[23] reported sufficient bactericidal concentrations of clindamycin but not of cefoxitin or piperacillin in patients with pancreatic transplants.

Koch et al[22] tested ampicillin, azlocillin, mezlocillin, cefotiam, gentamicin, doxycycline, chloramphenicol, metronidazole, and ciprofloxacin and found sufficient bactericidal concentrations of mezlocillin, ciprofloxacin, metronidazole, doxycycline, and chloramphenicol.

Büchler et al[29] tested mezlocillin, piperacillin, cefotaxime, ceftizoxime, netilmicin, tobramycin, ofloxacin, ciprofloxacin, imipenem, and metronidazole in patients who underwent pancreatic surgery for acute or chronic pancreatitis or pancreatic carcinoma. Based on the detection of antibiotics in pancreatic tissue, three groups of antibiotics were established: Group A, substances with low tissue concentrations (aminoglycosidase, netilmicin, tobramycin) that were below the minimal inhibitory concentrations of most bacteria found in pancreatic infection; Group B, antibiotics with pancreatic tissue concentrations that were sufficient to inhibit some, but not all, bacteria in pancreatic infection (mezclocillin, piperacillin, ceftizoxime, cefotaxime); and Group C, substances with high pancreatic tissue levels, as well as high bactericidal activity against most of the organisms present in pancreatic infection (ciprofloxacin, ofloxacin, imipenem-cilastatin).

The Drewelow et al[28] and Koch et al[30] groups found sufficient bactericidal concentrations of ceftazidime and ofloxacin in the pancreatic tissue of patients with a variety of pancreatic disorders.

Bassi et al[27] tested the penetration of imipenem, mezlocillin, gentamicin, amikacin, pefloxacin, and metronidazole in cases of pancreatic necrosis. Samples were obtained by fine-needle aspiration or during operation or surgical drainage. As in the Büchler et al study,[29] gentamicin and amikacin were not detected, whereas the others were found at sufficiently high bactericidal concentrations.

ANTIBIOTIC TREATMENT IN SEVERE ACUTE PANCREATITIS: EXPERIMENTAL STUDIES

There are four experimental studies investigating the effect of prophylactic antibiotics for the prevention of pancreatic infection in acute pancreatitis (Table 2). Widdison et al[36] studied the effect of cefotaxime, administered 12 hours after the induction of acute experimental pancreatitis, using a perfusion model in cats. They found that cefotaxime reached bactericidal levels in pancreatic tissue and juice and significantly prevented pancreatic infection. Araida et al[37] studied the effect of piperacillin given immediately after the induction of acute experimental pancreatitis in the rat (duct model) and found a positive effect both on the infection and survival rate.

Foitzik et al[38] studied the effect of intravenously administered cefotaxime and imipenem plus the effect of complete gut decontamination, in a duct hyperstimulation model in the rat. Neither treatment had a positive effect on survival. Pancreatic bacterial counts, on the other hand, were significantly reduced by imipenem, but not by cefotaxime. Mithöfer et al[39] from the same group, used the identical model to investigate the effect of imipenem and ciprofloxacin but increased the antibiotic treatment from 4 to 7 days. The extended treatment probably accounts for the increased survival rate in this study. Both antibiotics reduced early and late septic pancreatic complications.

ANTIBIOTIC PROPHYLAXIS IN SEVERE ACUTE PANCREATITIS: HUMAN STUDIES

Intravenous Application

Three randomized studies were published in the 1970s, in which ampicillin or a placebo was given to less than 200 patients who had acute pancreatitis, in most cases due to alcohol abuse.[33–35] Only 1 patient in these studies died and 26 had infectious complications. All studies agreed that ampicillin had no beneficial effect on the clinical course of the disease or on serum pancreatic enzyme elevations.[33–35] For many years, this conclusion led to the erroneous impression that antibiotic prophylaxis was of no benefit in pancreatitis. However, these studies are now recognized as being flawed for several reasons. First, ampicillin has a modest spectrum of activity against Gram-negative microorganisms, which are common in pancreatic infection. Second, ampicillin achieves poor penetration in pancreatic tissue[40] and in pancreatic fluid.[21] Third, given the low severity of the disease in these studies,[33–35] they have insufficient statistical power (Type 2 error).[41]

More recently, six studies, with divergent results, have been published addressing the question of antibiotic prophylaxis in acute necrotizing pancreatitis (Table 3).

In the study by Pederzoli et al,[42] 74 patients with acute necrotizing pancreatitis, mostly of biliary origin, were selected. The mean Ranson score was 3.7 (mean value) and pancreatic necrosis had been proven by CT within 72 hours, following the onset of the disease. Patients were randomly assigned to two groups: one without antibiotic treatment and one receiving 0.5 g of imipenem every 8 hours for 2 weeks. The incidence of pancreatic sepsis was significantly reduced from 30.3% to 12.2% and that of nonpancreatic sepsis from 48.5% to 14.6% ($P < 0.01$). The rate of multiorgan failure, the need for

TABLE 2. Intravenous Antibiotic Treatment in Severe Acute Experimental Pancreatitis (AEP)

Reference	Species	Methods of AEP	Antibiotics	Start of Treatment	Less Infection	Lower Mortality Rate
Widdison et al[36]	Cat	Perfusion model	Cefotaxime	12 hr after AEP	Yes	Not studied
Araida et al[37]	Rat	Duct model	Piperacillin	Immediately after AEP	Yes	Yes
Foitzik et al[38]	Rat	Duct plus hyper-stimulation model	Imipenem Cefotaxime	6 hr after AEP	Positive effect No effect	No*
Mithöfer et al[39]	Rat	Duct plus hyper-stimulation model	Imipenem Ciprofloxacin	6 hr after AEP	Positive effect Positive effect	Yes† Yes

Duration of treatment: *4 days, †7 days.

TABLE 3. Intravenous Antibiotic Prophylaxis in Severe Acute Pancreatitis (AP): Results of Controlled Clinical Studies

Reference	Patients (n)	Dominating Cause of AP	Antibiotics	Infection				
				Less Pancreatic Infection	Less Non-Pancreatic Infection	Less Multiorgan Failure	Less Indication for Surgery	Low Mortality Rate
Pederzoli et al[42]	74	Biliary	Imipenem	Yes	Yes	No	No	No
Sainio et al[44]	30	Alcohol	Cefuroxime	Yes (not separated)		Not reported	Yes	Yes
Delcenserie et al[46]	23	Alcohol	Ceftazidime, amikacin, metronidazole	Yes	Not reported	No	Not reported	No
Schwarz et al[47]	26	Biliary	Ofloxacin plus metronidazole	No	Not reported	No	Not reported	No
Nordback et al[48]	58	Alcohol	Imipenem plus cilastatin	Not reported	Not reported	No	Yes	No
Isenmann et al[51]	114*	Alcohol	Ciprofloxacin plus metronidazole	No	No	No	No	No

*Seventy-six patients with necrotizing pancreatitis.

surgical treatment, and the mortality rate were not affected. Antibiotic prophylaxis was especially effective in patients with mild to moderate necrosis. None of the patients in the antibiotic group with less than 50% pancreatic necrosis developed septic complications. This was in contrast to those in the control group. The study has been criticized for the unequal distribution of severe necrosis. Sixteen patients had severe necrosis (>50%), of whom 14 were in the treatment group and 2 were in the placebo group. This distribution may have precluded a statistically significant effect on the indication for surgery, on the mortality and perhaps even on the development of multiorgan failure. However, infected necrosis and multiorgan failure are not necessarily parallel events in acute pancreatitis.[43]

Sainio et al[44] reported 60 patients with alcohol-induced necrotizing pancreatitis, proven by contrast-enhanced CT within 24 hours of admission. The mean Ranson score was 5.5. Thus, according to this prognostic score, patients were more severely ill than those in the study by Pederzoli et al.[42] Thirty patients were prescribed cefuroxime (1.5 g intravenously three times a day until clinical recovery and normalization of C-reactive protein [CRP] concentrations). Thirty patients were assigned to a control group. These patients did not receive any antibiotic treatment unless infection had been verified clinically, microbiologically, or radiologically or until a second rise in CRP of more than 20%, after the acute phase. In cases where there was a full clinical recovery in the antibiotic group, with moderate CRP concentrations, antibiotic treatment was continued with oral cefuroxime (250 mg/two times a day) for 14 days. Infectious complications were reduced from 1.8 in the control group to 1.0 in the antibiotic group (means, $P = 0.01$). When infectious complications were analyzed separately, only urinary tract infections were significantly reduced in the treatment group. The most common cause of infections was *Staphylococcus epidermidis.* This was also present in the cultures taken from the necrotic pancreas, in 4 of the 8 patients who had died of acute pancreatitis.

The Sainio et al study[44] has been criticized because of the strikingly high number of urinary tract infections and the high rate of *S. epidermidis* infections.[45] *S. epidermidis* is not commonly found in infected pancreatic necrosis, and the origin of this infection remains unclear.[45] Furthermore, with regard to the choice of cefuroxime, the tissue concentrations may have been suboptimal. Also, the antibiotic regimen had to be changed after a mean of 9.2 days, in 20 of the 30 patients within the treatment group. The authors had chosen cefuroxime because of the high number of *S. aureus* infections in their intensive care unit patients and because *E. coli*, a common cause of infected pancreatic necrosis, is rarely resistant to cefuroxime.

In a third study, Delcenserie et al[46] selected 23 patients with alcohol-induced acute pancreatitis, whose CT scans revealed two or more fluid collections within 48 hours, following the onset of symptoms. They were randomly assigned to two groups: one receiving placebo treatment and one receiving antibiotics (ceftazidime, amikacin, and metronidazole) for 10 days. Sepsis was diagnosed by positive blood cultures. Seven episodes of severe sepsis occurred (pancreatic infection and septic shock) in the control group, but no infections occurred in the antibiotic group ($P < 0.03$). Neither the incidence of multiple organ failure nor the mortality rate was significantly affected.

The fourth study by Schwarz et al[47] investigated 26 patients with acute necrotizing pancreatitis, mostly of biliary origin and sterile pancreatic necrosis, as proven by contrast-enhanced CT and fine-needle aspiration. These patients were randomized into two groups: a control group (initially receiving no antibiotics) and a group receiving intravenous ofloxacin (200 mg) and metronidazole (500 mg) twice a day. In both groups, fine-needle aspirations of the necrotic areas were performed on days 1, 3, 5, 7, and 10. When there was evidence of infection, antibiotics were also given to the control patients. The extent of necrosis was identical (median, 40%) in both groups. The necrotic tissue became infected within a median of 9.5 and 10 days (treatment and control

group). The clinical course, as documented by the APACHE-II score, should have significantly improved under antibiotic treatment, but this neither prevented nor delayed bacterial infection of the necrotic pancreas. Within the first 3 weeks, 2 patients in the control group died but those in the treatment group survived (statistical significance not reported).[48]

Two meta-analyses of the available data indicated that prophylactic antibiotics in patients with necrotizing pancreatitis have a positive effect on the course of the disease.[49,50] This led to a number of recent guidelines and consensus documents recommending prophylactic antibiotic treatment of all patients with acute necrotizing pancreatitis.[7–14]

As most studies included only a limited number of patients, with none of them double-blinded or placebo-controlled, Isenmann et al[51] performed a double-blinded, placebo-controlled study to investigate the effects of ciprofloxacin and metronidazole. This antibiotic combination had been shown to be effective in animal experiments.[39] A total of 200 patients were chosen to demonstrate that antibiotic prophylaxis reduces the proportion of patients with infected pancreatic necrosis from 40% in the placebo group to 20% in the ciprofloxacin and metronidazole group, with a power of 90%. After 50% of the planned sample size was recruited, an adaptive interim analysis was performed and recruitment was stopped. A total of 114 patients were included in the intention-to-treat analysis. They had been selected by 19 participating hospitals over a period of 40 months, which indicates that each center contributed 6 cases over 3.5 years. Therefore, severe acute pancreatitis was a rare event at these centers. The criteria for predicted severe acute pancreatitis were serum CRP over 150 mg/L and/or necrosis on contrast-enhanced CT. Fifty-one (44.7%) patients were chosen, on the basis of an elevated serum CRP in combination with pancreatic necrosis on CT. Nineteen (16.7%) patients had pancreatic necrosis on CT but a lower serum CRP, and 44 (38.5%) patients were chosen on the basis of an elevated serum CRP alone. In the latter group, 6 patients developed pancreatic necrosis during the subsequent course of the disease. Thus, a total of 76 patients suffered from necrotizing pancreatitis. Of these, 41 patients were in the treatment group and 35 patients were in the placebo group. A major end result of the study was a reduction in infected pancreatic necrosis, either diagnosed by intraoperative smears by CT- or by ultrasound-guided fine-needle aspiration of those necrotic areas showing bacterial infection. Other results included death, extrapancreatic infection, surgical treatment of necrotizing pancreatitis, admission to the intensive care unit, hospitalization, and systemic complications of the disease, such as shock and pulmonary and renal insufficiency. Treatment was planned to be given until day 21, after the onset of acute pancreatitis. When patients showed progressive pancreatitis, characterized by clinical deterioration and/or suspected pancreatic or extrapancreatic infection, antibiotics were switched to open label treatment. In these cases, the use of imipenem, possibly in combination with vancomycin, was recommended. Twenty-eight percent in the treatment group and 46% in the placebo group required open label antibiotic treatment. About 96 different antibiotic regimes were given in the placebo group and 68 different regimes in the treatment group. Thirty-one percent of these included a carbapenem. Data for these subgroups were not given. However, 12% of the total treatment group developed infected pancreatic necrosis compared with 9% of the placebo group (difference not significant). Mortality was 5% in the treatment group and 7% in the placebo group. This is very low for necrotizing pancreatitis but not surprising for a cohort in which the mean Ranson score on admission was between 2 and 3. To summarize, no differences were observed in the rate of infected pancreatic necrosis, systemic complications, or mortality.[51]

COMMENT

Whether the latest randomized trial suggests that antibiotic treatment in general does not prevent infected pancreatic necrosis, whether carbapenems are clearly superior to quinolones and metronidazole, or whether patients with mild pancreatitis do not benefit from antibiotic treatment has to remain an open question at this point. Recent studies suggest that imipenem and meropenem, although of equal effectiveness,[52] are superior to quinolones.[53]

There are two sides to this discussion. One group believes that early treatment with carbapenems effectively prevents infected pancreatic necrosis and reduces mortality.[42,53] The other believes that antibiotic treatment should be withheld unless the patient deteriorates.[51] For the latter, criteria for initiating antibiotic treatment in patients with predicted severe acute pancreatitis would be: the early development of sepsis or SIRS, the early failure of two or more organ systems, proven pancreatic or extrapancreatic infection, and an increase in CRP in combination with evidence of pancreatic or extrapancreatic infection (Table 4).[51]

Routine use of broad-spectrum prophylactic antibiotics has altered the bacteriology of secondary pancreatic infection in severe acute pancreatitis, from predominantly gram-negative coliforms to predominantly gram-positive organisms, without changing the rate of β-lactam resistance or fungal superinfection.[54] It is unclear whether the use of long-term prophylactic antibiotic treatment, over longer periods, promotes fungal infection.[55] Intraabdominal fungal infection was found in 37% of patients with severe acute pancreatitis and infected pancreatic necrosis.[56] Pancreatic fungal infection was found in 24% of patients with proven necrotizing pancreatitis, who had received prophylactic intravenous antibiotics.[57] Early treatment with fluconazole reduced fungal infections.[56] Whether broad-spectrum antibiotics in necrotizing pancreatitis should regularly be combined with antimycotic agents needs to be resolved in future trials.[57]

TABLE 4. Criteria to Initiate Antibiotic Treatment in Patients With a Predicted Severe Course of Acute Pancreatitis[51]

Newly developed sepsis or systemic inflammatory response syndrome (SIRS)
Newly developed failure of two or more organ systems
Proven pancreatic or extrapancreatic infection
Increase in serum C-reactive protein (CRP) in combination with evidence of pancreatic or extrapancreatic infection

TABLE 5. Antibiotic Decontamination of the Gut in Acute Experimental Pancreatitis (AEP)

Reference	Species	Methods of AEP	Method of Decontamination	Start of Decontamination	Less Infection	Less Mortality Rate
Persky et al[59]	Dog	Duct model	Oral application of aureomycin	5–10 days prior to AEP	Not studied	Yes
Lange et al[60]	Rat	Duct model	Intestinal lavage plus canamycin	Immediately prior to AEP	Yes	Yes
Isaji et al[61]	Mouse	CDE model	Oral application of bacitracin, metronidazole, neomycin	Simultaneously with AEP	No	Yes
Foitzik et al[38]	Rat	Duct plus hyper-stimulation model	Oral application of polymyxin B, tobramycin	6 hr after AEP	Yes	No
Gianotti et al[62]	Mouse	CDE model	Amphotericin B plus intravenous cefotaxime Various antibiotics	6 hr after AEP 36 hr after beginning of CDE diet	Yes Yes	No No

SELECTIVE GUT DECONTAMINATION

Selective gut decontamination with oral nonresoluble antibiotics is an alternative strategy, aimed at eliminating pathogens in the intestinal flora and reducing bacterial translocation. This would reduce the risk of pancreatic infection (Table 5).[58] This approach was tested almost 50 years ago by Persky et al,[59] who induced acute pancreatitis in dogs by injecting bile into the pancreatic duct. The mortality rate for this experimental pancreatitis was higher than 90%. Aureomycin, given orally for 5 to 10 days, until coliform microorganisms were absent in the feces on 3 consecutive days, reduced the mortality rate to zero. In another experiment, Aureomycin was given immediately after the operation; but because many capsules had not dissolved, the mortality rate was 75%. When Aureomycin was suspended in water and given by gavage immediately after the operation, the mortality rate was again zero. In contrast, Aureomycin given intravenously, immediately postoperatively, resulted in a survival rate of 40%.[59]

These early animal experiments showed for the first time that gut decontamination is beneficial in acute experimental pancreatitis. These were forgotten for many decades until Lange et al[60] induced acute experimental pancreatitis in the rat, to study the effect of gut decontamination again. Rats underwent either a subtotal colectomy or intestinal lavage plus an infusion of kanamycin. Both procedures had a significant beneficial effect on the mortality rate, thus indicating that the intestinal flora was a major factor affecting mortality in this experimental model.[60]

Isaji et al[61] studied the effect of bacterial infection in mice with diet-induced acute pancreatitis. Oral application of bacitracin, metronidazole, and neomycin increased the survival rate significantly and tended to slightly reduce infection.

Foitzik et al[38] studied different strategies of antibiotic treatment of the prevention of early pancreatic infection in an experimental model. Acute pancreatitis was induced by a combination of an intraductal injection of glycodeoxycholic acid in addition to intravenous cerulein hyperstimulation of the gland. Treatment was begun 6 hours after the induction of acute pancreatitis. Mortality was unaffected by any treatment regimen, but pancreatic infection was significantly reduced with full gut decontamination and with imipenem. It was not improved with oral antibiotics or with cefotaxime alone.

Gianotti et al[62] studied various antibiotics in mice, in which acute pancreatitis was induced by a diet deficient in choline and supplemented with ethionine. Initially, after the administration of polymyxin B, amikacin, or amphotericin B, the survival rate did improve, but this did not continue. All antibiotics used, reduced the number of bacteria in the cecum, but only some reduced the rate of translocation of gram-positive and gram-negative microorganisms to all organs.

The only controlled clinical study of selective decontamination was performed by Luiten et al[63] in a multicenter trial. This involved 102 patients who had severe acute pancreatitis. Patients were randomly assigned to a standard treatment group or to a group receiving standard treatment plus selective decontamination drugs. These consisted of an oral administration of colistin sulfate, amphotericin B, and norfloxacin given every 6 hours. In addition, a rectal enema was given every day. This contained the same three antibiotics, at the same concentration as the oral administration. This regimen was supplemented by systemic treatment with cefotaxime, which was given every 8 hours until gram-negative microorganisms were eliminated from the oral cavity and rectum. The mortality rate was 35% in the control group and 22% in the group given selective decontamination ($P = 0.048$). This difference was mainly caused by a reduction in the late mortality (>2 weeks) because of a significant reduction of gram-negative pancreatic infection ($P = 0.003$). Furthermore, in the group who were receiving selective decontamination, the average number of laparotomies per patient was reduced ($P < 0.05$).

Because this treatment combines selective gut decontamination with systemic antibiotic treatment, it is difficult to conclude which of the treatment components accounted for the beneficial effect.

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