Original article

Antibiotic prophylaxis in acute pancreatitis

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INTRODUCTION

Acute pancreatitis is a common disease with a continuously increasing incidence.[1,2] The great majority of all attacks of acute pancreatitis have a relatively benign course which is resolved by standard conservative therapy.[3,4] However about 10 to 25% of patients have severe disease.[1,4-7] Although the overall mortality rate from acute pancreatitis has decreased as a result of improvements mainly in supportive care and surgical treatment the mortality of patients with acute necrotizing pancreatitis remains high (20-60%).[1,3,5,7-15] Today few patients die from cardiopulmonary or renal complications alone. The major cause of death in these patients is the superinfection of pancreatic and peripancreatic necrosis.[1,3,6,7,10,12,16,17] Major pancreatic infection occurs in 8-10% of patients with acute pancreatitis and is responsible for more than 80% of deaths in these patients.[1,4,6,18,19] Early in the course of the disease the necrotic tissue is sterile[3,18,20,21] but the incidence of infection increases with time.[3,18,21,22,23] This means that infection is a secondary phenomenon and necrotic areas are a haven where organisms multiply, resulting in infected pancreatic necrosis. The prophylactic use of antibiotics might be a useful treatment option at an early stage of the disease before necrotic areas become infected because they are capable to penetrate pancreatic tissue and to achieve M.I.C. (Maximum Inhibitory Concentrations) levels in serum and pancreatic juice.[18] However the efficiency of prophylactic antibiotics in acute pancreatitis is still a matter of debate.[6,7,18,23-28]

The purpose of this review is to present the past and current knowledge concerning the prophylactic use of antibiotics in acute pancreatitis.

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MATERIAL AND METHODS

Inclusion criteria for this review were prospective randomized trials on the prophylactic use of antibiotic in acute pancreatitis. A search of the medical literature (MEDLINE) indentified 10 studies dealt with this topic. The three early trials by Howes,[29] Craig[30] and Finch[31] performed in 1970s on patients with mild pancreatitis all involved received ampicillin. The five recent studies conducted between 1993 and 1998 by Pederzoli,[32] Sainio,[33] Delcenserie,[34] Schwarz[35] and Bassi[36] on patients with acute necrotizing pancreatitis who were treated with broad-spectrum antibiotics. One study conducted by Luiten[37] on patients with a severe form of disease but the treatment modality was selective decontamination of the gastrointestinal tract plus cefotaxime. And finally one study performed by Golub[38] was a meta-analysis of eight previously reported studies.

Prospective studies

In the study by Howes et al, 104 patient with acute pancreatitis were randomly allocated into antibiotic and non-antibiotic treatment groups which were comparable with no statistically significant differences in age, race, sex. Nine of these patients were excluded because of physician noncompliance. The remainder with even history numbers (n=48) were placed on ampicillin and those with odd history numbers (n=47) were given no antibiotics. The ampicillin was initially given 1gr every 6h parenterally but when the patient began oral intake it was given by mouth, for a total of 5 days, unless a septic complication developed. All patients received stadard supportive care (i.v. fluids, nasogastric suction, analgesics and anticholinergics).

There were no deaths in the 104 consecutive patients during the period of clinical protocol and no statistically

Table 1. Prospective trials on antibiotic prophylaxis on acute pancreatitis

Authors	Severity	Inclusion criteria	Number of patients Control	Antibiotic	Type of antibiotics	Dosages	Duration
Howes	mild	Clinical pancreatitis+ amylase >160U/ml	95	47	Ampicillin	1gr qid	5 days
Craig	mild	Clinical pancreatitis	46	23	Ampicillin	1gr qid	7 days
Finch	mild	Clinical pancreatitis+ amylase >160 U/ml	58	31	Ampicillin	500mg- 1 gr qid	7 days
Pederzoli	necrotizing Ranson score 3.7	Necrosis on CT or U/S	74	41	Imipenem	500 mg/8h	14 days
Sainio	Ranson score 5.5	CRP>120mg/l Necrosis on CT	60	30	Cefuroxime	1.5gr/8h	14 days
Luiten	Imrie score 3.2 Baltazar grade D and E	Imrie score >3 CT scan grade D or E	102	50	SD (Colistin +Amphotericin +Narfloxacin) +Cefotaxime	(200mg+500mg +50mg qid) 500mg/8h	Until patient extubated and on oral diet Mean 7.5 days
Delcenserie	Ranson score 2.3	Two or more collections on CT	23	11	Ceftazidime +"Amikasine +Metronidazole	2g/8h +7.5mg/kg/12h	10 days
Schwarz	Ranson score 4.5	Clinical pancreatitis +Necrosis on CT	26	13	Ofloxacin +Metronidazole	200mg/12h +500mg/12h	10 days
Bassi	Ranson score 4.6 APACHE II 11.5	CRP>100mg/l Necrosis >50% of gland on CT	60*	30	Imipenem, Pefloxacin	500mg/8h, 400mg/12h	14 days

*comparison between two antibiotics without control group

significant differences in either group regarding days of fever (3 days), days of hyperamylasemia (2 days), days of hospitalization (9 in antibiotic versus 12 in non antibiotic group). Among 95 patients who were included in the study, 11 patients (12%) developed septic complications, 5 patients in the antibiotic group (10%) and 6 patients in the non antibiotic group (13%), which is not statistically significant.

In conclusion, this study showed that antibiotics were of no value and possibly might even be harmful as prophylaxis in acute pancreatitis.

Craig et al, in a randomized blind study evaluated the role of ampicillin in patients with acute pancreatitis. Thirty-nine men with 47 episodes of acute pancreatitis entered the study and were divided into groups (16 placebo and 15 ampicillin treated group) and started on the trial within 24 hours of admission. Each patient was placed on nasogastric suction and i.v. fluids until asymptomatic for 48 hours. Ampicillin 1gr or placebo was given i.v. every 6 hours until the nasogastric tube was removed and clear fluids begun. The ampicillin was administered orally (1gr every 6 hours) to complete a 7-day course of therapy. The ampicillin and placebo group each comprised 23 episodes of pancreatitis (43 were propably alcoholic pancreatitis, two had choledocholithiasis and one had idiopathic pancreatitis).

There were no deaths in either group, nor any difference between the groups regarding duration or severity of abdominal pain (3 days both), leukocytosis (1.8 days vs 2.3), hyperamylasemia (6 days vs 5) or fever (3 days both). There were no other serious complications of acute pancreatitis except that one patient receiving ampicillin had three positive culture for E. coli resistant to ampicillin that required i.v. cephalothin, and two patients in the placebo group had pericardial friction rubs during the early phase of their illness.

The authors concluded that ampicillin is ineffective as prophylactic therapy in patients with alcohol-related acute pancreatitis.

Finch et al[31], in a double-blind prospective study, evaluated the efficacy of ampicillin in the treatment of acute alcohol-induced and idiopathic pancreatitis. Fifty-eight patients with acute pancreatitis were randomly divided into antibiotic (n=31) and non-antibiotic (n=27) treatment groups. All patients received identical medical therapy (nasogastric suction, i.v. fluids, analgesics, anticholinergics). In the antibiotic group 19 patients received 500mg ampicillin every 6h i.v. and 11 patients received 1gr ampicillin every 6h. the average duration of antibiotic treatment was 7 days.

There were no septic complications in either treatment group and only one death in the antibiotic group, caused by aspiration pneumonia. Also there were no statistically significant differences between the two groups regarding the length of hospitalization, the number of days required to return to a normal serum amylase level, the number of days required to become afebrile and the complication rates, except for the recurrence rate (6 patients in the antibiotic vs 2 in the non antibiotic group).

Pederzoli et al[32], in a prospective randomized multicenter clinical study evaluated the efficacy of prophylactic use of antibiotic in patients with acute necrotizing pancreatitis. There were 74 patients observed at 6 centers with necrotizing acute pancreatitis which was diagnosed on the basis of standard clinical criteria, ultrasonographic and computer tomographic scans within 72h of onset. The patients were randomly assigned into two groups. Group 1 was the control group, consisting of 33 patients, who received only medical treatment (nasogastric suction, H_2-blockers, antiprotease drugs, total parenteral nutrition and analgesics), and group 2, consisting of 41 patients who received medical treatment plus 0.5gr imipenem i.v. every 8h for 10 days beginning from CT demonstration of necrosis. The mean Ranson score was 3.7. Pancreatic sepsis was always detected by means of cultures.

Table 2. Results of prospective trials on mortality

	Mortality		
References	Control	Antibiotics	p
Howes	0/47	0/48	0.99
Craig	0/23	0/23	1
Finch	0/27	1/31	0.56
Pederzoli	4/33 (12.1%)	3/41 (7.3%)	0.41
Sainio	7/30 (23.3%)	1/30 (3.3%)	0.028
Luiten	18/52 (34.6%)	11/50 (22%)	0.19[1]
Delcenserie	3/12 (25%)	1/11 (9%)	0.38
Schwarz	2/13 (15.3%)	0/13	0.27
Golub	34/237 (14.3%)	17/247 (6.8%)	0.016
Bassi	7/30 (24%)[2]	3/30 (10%)	0.18

[1]Adjusted for Imrie score and Balazar grade p:0.048

[2]Comparison pefloxacin vs imipenem

The overall incidence of pancreatic sepsis was 20.3% (10 patients in group 1 and 5 patients in group 2 – 30.3% vs 12.2%) which is statistically significant ($p<0.01$). Worthy of note was that no pancreatic sepsis occurred in patients with imipenem when the necrosis was less than 50% of the pancreatic volume, whereas in the placebo group even necrosis less than 30% did not prevent sepsis from occurring. The overall incidence of non-pancreatic sepsis was 29.7% (16 patients in group 1 and 6 patients in group 2) which is statistically significant. On the other hand there was no difference between the two groups regarding the incidence of multiple organ failure (13 patients in group 1 vs 12 in group 2) and mortality (4 patients in group 1 and 4 in group 2).

Sainio et al[33], carried out a randomized prospective study of 60 consecutive patients with alcohol-induced necrotizing pancreatitis to find out whether early antibiotic treatment can improve outcome. Inclusion criteria were CRP concentration above 120mg/l and low contrast enhancement of the pancreas on contrast-enhanced CT scan within 48h of admission. Patients were assigned on admission to one of two groups. in the antibiotic group (30 patients) 1.5gr cefuroxime three times daily was given i.v. whereas in the non-antibiotic group only conservative medical treatment was given. The mean Ranson score was 5.5.

There were more infectious complication in the non-antibiotic group than in the antibiotic group (mean per patient 1.8 vs 1 – $p<0.01$) but without difference in the incidence of pancreatic absess or infected necrosis (9 patients vs 12 patients) as well in the incidence of pneumonia, bacteremia and acute respiratory failure. However cefuroxime prophylaxis reduced overall mortality (1 patient died in the antibiotic group and 7 in the non-antibiotic group -3% vs 23% which is statistically significant $p=0.028$). There was no statistical difference between the two groups regarding the length of stay in the hospital or the ICU.

Delcenserie et al[34], in a prospective randomized study evaluated the necessity for prophylactic antibiotic treat-

ment in patients with severe acute alcoholic pancreatitis. In his study twenty-three consecutive patients suffering from acute alcoholic pancreatitis with computed tomography scans demonstrating two or more fluid collections within 48h of onset were randomly assigned to two groups receiving either non-antibiotic treatment or prophylactic antibiotics. All patients underwent standard intesive medical treatment (TPN+Analgesics). Group I, consisting of 12 patients received only medical treatment whereas group II consisted of 11 patients received medical treatment plus i.v. antibiotics (ceftazidime 2gr every 8h; amikacin 7.5mg/kg every 12h; and metronidazole 0.5 gr every 8h for 10 days). Sepsis was always diagnosed by positive culture.

Seven episodes of severe sepsis occurred in group I (incidence 58.3%) and no infection occurred in the antibiotic group (incidence 0%) ($p<0.03$). There was no difference between the two groups regarding length of stay, number of days of fever, incidence of multiorgan failure. Mortality also failed to achieve statistical significance (3 in group I vs 1 in group II).

Schwartz et al[35], in a prospective randomized trial evaluated the effect of prophylactic administration of antibiotics in patients with acute necrotizing pancreatitis. Twenty-six patients with acute necrotizing pancreatitis and sterile necrosis quantified by contrast-enhanced CT entered the study and were divided into two groups. In the antibiotic group, consisting of 13 patients, ofloxacin (200mg) and metronidazole 500mg were given twice daily intravenously for 10 days. The results were compared to those in a control group of patients (n:13) who had not received antibiotics. Sepsis was always detected by FN biopsies and positive cultures performed on days 1, 3, 5, 7, 10. Mean Ranson score was 4.5 and the extent of the necrosis was 40% in both groups.

Antibiotic prophylaxis neither prevented nor delayed sterile necrosis from becoming infected, which occurred at a median of 9.5 days in the antibiotic group and 10 days in the control group. However the clinical course documentated by the APACHE II score showed significant improvement under antibiotic treatment (day 1, score: 15 – day 10, score:9.5) whereas in the control group the clinical condition deteriorated significantly (day 1, score: 11.5 – day 10, score: 16.0) $p<0.01$. There was a trend toward lower mortality in the antibiotic group (none of the patients died in the antibiotic group within the first 3 weeks compared to 2 deaths in the control group) but this was not statistically significant.

Luiten et al[37] in a randomized controlled multicenter trial evaluated the efficacy of selective decontamination to reduce mortality in patients with severe acute pancreatitis. In his study 102 patients with severe acute pancreatitis were admitted to 16 participating hospitals on the basis of clinical examination and multiple laboratory criteria (Imrie score >3) and/or computer tomography criteria (Balthazar grade D or E) within 48h of admission. Patients were randomly assigned to receive standard treatment (control group, n:50) or the same standard treatment plus SD (SD group, n:50). Standard treatment consisted of nasogastric tube, i.v. fluids and oxygen ther-

Table 3. Results of prospective trials on infection complications

	INFECTION COMPLICATIONS				
References	Control		Antibiotics		P
Howes	6/47 (12.7%)		5/48 (10.4%)		N.S.
Craig	0/23		1/23 (4.2%)		N.S.
Finch	0/27		0/31		N.S.
	P.S.	N.P.S.	P.S.	N.P.S.	
Pederzoli	10/33 (30.3%)	16/33 (48.5%)	5/41 (12.2%)	6/41 (14.6%)	0.01
Sainio	12/30 (40%)	25/30 (83%)	9/30 (30%)	20/30 (67%)	N.S.
Luiten	20/52 (38%)	-	9/50 (18%)	-	0.03[1]
Delcenserie	7/12 (58.3%)	-	0/11	-	0.03
Schwarz	13/13	-	13/13	-	N.S.
Bassi[2]	10/30 (34%)	13/30 (43.3%)	3/30 (10%)	6/30 (20%)	0.059

[1]Gram (-) pancreatic infections p:0.003 (17/52 vs 4/50 patients)

[2]Comparison pefloxacin vs imipenem

P.S.: Pancreatic sepsis. N.P.S.: Non pancreatic sepsis

apy whereas SD regimen consisted of oral administration of colistin sulfate 200mg, amphotericin (500mg) and norfloxacin (50mg) every 6h. The aforementioned daily dose was also given in a rectal enema every day. A short-term systemic prophylaxis mean duration 7.4 days) of cefotaxime sodium (500mg) every 8h was given intravenously until gram (-) bacteria were eliminated from the oral cavity and rectum. The mean Imrie score was 3.2 for both groups.

There were 18 deaths in the control group (35%) compared with 11 deaths (22%) in the SD group, which is not significant (p=0.19). The Imrie score at entry into the study appeared to correlate very strongly with mortality. In patients with an Imrie score>3 mortality fell from 55% (11/31) to 31% (11/35) which is statistically significant (p=0.048). SD significantly reduced (p=0.003) the incidence of gram negative pancreatic infection which consequently results in a significant reduction in the number of laparotomies (3.1 laparotomies per patient in conrol vs 0.9 in SD group, p<0.05) and surgery-related complications (9 patients in control group vs 4 patients in SD group, p=0.5 N.S.). Mean hospital stay was similar in both groups (32 days in control group vs 30 days in SD group).

As there were concerns about the role of antibiotic prophylaxis in reducing mortality Golub et al[38], performed a meta-analysis of the eight previously published trials on prophylactic use of antibiotics in acute pancreatitis.

Although only the study by Sainio et al[33] showed significant decrease in mortality with antibiotics, a meta-analysis of four randomized prospective trials revealed a positive benefit of prophylactic antibiotics in reducing mortality p<0.016. Also the probability of dying was 6.6% in the antibiotic treated patients as compared with 13.3% in the control subjects. Meta-analysis of the three early studies that used ampicillin showed no benefit in reducing mortality in contrast to the meta-analysis of four recent trials that used broad-spectrum antibiotics in patients with severe pancreatitis where there was a reduction in overall mortality p<0.008. However if the study by Sainio was removed for consideration, the treatment effect is no longer significant. Authors concluded that all patients with severe pancreatitis should be treated with broad-spectrum antibiotics.

Bassi et al[36], in a multicenter prospective randomized trial including centers from Italy and Greece (Agia Olga Hospital) investigated the usefulness of pefloxacin vs imipenem in patients with severe acute pancreatitis. In this trial 60 patients with severe acute pancreatitis with necrosis affecting at least 50% of the gland as detected by contrast-enhanced computer tomography and confirmed by CRP values above 100mg/l, were randomly assigned into two groups. In group I (n=30) patients were allocated to receive imipenem 500mg three times daily i.v. and in group P (n=30) patients received pefloxacin 400mg twice daily for two weeks. All patients received standard supportive therapy. Suspected infected necrosis was diagnosed by FNA and culture examinations. The mean Ranson score was 4.6 and the mean APACHE II score was 11.5.

Ten of 30 patients in group P developed infected necrosis (34%) compared with three of 30 patients in group I (10%) which is statistically significant (p=0.034). The incidence of extrapancreatic infections was also greater in group P (44%) vs group I (20%) though not significant (p=0.059). Mortality was not different in the two groups (24% vs 10%, p=0.18). All deaths were caused by septic shock syndrome. The mean hospital stay was similar in the two groups (31 vs 29 days).

The authors concluded that although pefloxacin was considered an alternative regiment, imipenem remains the antibiotic of choice in acute pancreatitis.

DISCUSSION

Although in most patients acute pancreatitis has a relative benign course which is resolved with conservative medical treatment, in a few instances patients suffer from a severe form of the disease with necrosis of pancreatic and peripancreatic tissue resulting in high morbidity and mortality. it is well known that pancreatic infection and multiorgan failure is the principal cause of death[1,3,6,7,18,39] in patients who survive the initial phase of the acute pancreatitis and become infected in the following weeks.

It was believed that infection of necrotic areas developed late in the course of the disease since Beger[40] demonstrated that bacterial contamination can occur early and frequently. A prospective clinical study revealed a contamination rate 23,8% in patients operated on during the first week although the contamination rate rose to 71.4% in the third week. The predominance of gram negative species of enteric origin[3,7,40-42] indicates that bacteria translocate from the bowel and infect necotic tissue.[18,21,22,40,43-48]

In an attempt to prevent bacteria and fungal colonization of necrotic areas, a number of randomized pro-

spective trials examined the role of antibiotic prophylaxis. The first three trials[29,30,31] which were conducted in the 1970's using ampicillin failed to show a beneficial therapeutical effect. These studies included patients with a mild form of the disease as evidenced by a zero mortality rate in the control groups. Furthermore ampicillin is a drug which cannot penetrate pancreatic tissue and achieve therapeutic consentration in pancreatic juice and the spectrum of activity is limited against organisms most commonly found in infected necroses.[18,41,49]

However during recent years new knowledge has been gained about infected pancreatic necrosis, [21-26,40,43,44] prevalent microorganisms in acute pancreatitis,[22,40-42] blood pancreas barrier[50] and antibiotic penetration into the pancreas,[18,22,27,40,51,52] the therapeutical M.I.C. of these in acute pancreatitis[18,51] and the role of bacterial translocation in superinfection of pancreatic necrosis.[18,21,22,43-46,53]

The recent trials, conducted in the 1990's, included patients with a severe form of the disease who were treated with broad-spectrum antibiotics. Pederzoli[32] using imipenem found a significant decrease in pancreatic and peripancreatic sepsis without differences in mortality or in the incidence of multiorgan failure and need for surgery. Sainio[33] using cefuroxime found a significant decrease in mortality rates and in the number of infections per patient. Delcenserie[34] also showed significant derease in septic complication without difference in mortality and multiorgan failure using ceftazidime, amikacin and metronidazole. Schwarz[35] using ofloxacin and metronidazole found that antibiotics could not prevent sterile necrosis from becoming infected although clinical conditions deteriorated in the control group compared to the antibiotic treatment group in which there was a trend to lower mortality. Bassi[36] showed that imipenem proved significantly more effective in prevention of pancreatic infection than pefloxacin without difference in mortality. Luiten[37] showed that SD of the gastrointestinal tract significantly reduced the incidence of gram negative pancreatic infection, late mortality and the need for surgery. Finally Golub[38] because of the small size of previously reported trials and conflicting effects of mortality performed a meta-analysis and showed a positive benefit for antibiotics in reducing mortality.

These recent trials confirm the results of experimental[22,27,28,44,54-57] and retrospective[16,53,57] studies which have shown that antibiotic prophylaxis is beneficial in acute pancreatitis.

Based on this evidence, thirty-one specialists in pancreatic disease from a wide range of disciplines met in Santorini in a consensus conference[58] and agreed that prophylactic treatment is strongly recommended in severe pancreatitis. Appropriate antibiotics are those that are active against a wide variety of organisms, in particular gram negative pathogens; antibacterial therapy should be started as early as possible after identification of severe attack. When applying antibiotics in acute necrotizing pancreatitis the possible risk of Fungal suprainfection should be kept.[59]

In conclusion the use of antibiotics in the treatment of acute pancreatitis depends on the severity and propably the cause of the disease. In mild forms of acute pancreatitis antibiotics are not clinically useful because these attacks have a relatively benign course without secondary pancreatic infection, and are resolved by conservative treatment. On the other hand, in the severe form of the disease, where pancreatic and peripancreatic necroses become infected in about 40-60% of cases, the use of broad-spectrum antibiotics, such as imipenem and cinolones, early in the course of the disease have proven beneficial in reducing septic complications and mortality.

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