

Early antibiotic treatment in acute necrotising pancreatitis

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Summary

Despite improvements in surgical treatment and intensive care, mortality from severe acute pancreatitis remains high. We have carried out a randomised study of 60 consecutive patients with alcohol-induced necrotising pancreatitis to find out whether early antibiotic treatment can improve outcome.

30 patients were assigned cefuroxime (4.5 g/day intravenously) from admission. In the second group, no antibiotic treatment was given until clinical or microbiologically verified infection or after a secondary rise in C-reactive protein. The inclusion criteria were C-reactive protein concentration above 120 mg/L within 48 h of admission and low enhancement (<30 Hounsfield units) on contrast-enhanced computed tomography. There were more infectious complications in the non-antibiotic than in the antibiotic group (mean per patient 1.8 vs 1.0, $p=0.01$). The most common cause of sepsis was *Staphylococcus epidermidis*; positive cultures were obtained from pancreatic necrosis or the central venous line in 14 of 18 patients with suspected but blood-culture-negative sepsis. Mortality was higher in the non-antibiotic group (seven vs one in the antibiotic group; $p=0.03$). Four of the eight patients who died had cultures from pancreatic necrosis positive for *Staph epidermidis*.

We conclude that cefuroxime given early in necrotising pancreatitis is beneficial and may reduce mortality, probably by decreasing the frequency of sepsis.

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See Commentary page 652

Introduction

Despite advances in the treatment of severe acute pancreatitis, mortality remains high. Lower mortality has been achieved as a result of improvements in operative treatment and intensive care.^{1,2} Treatment with pancreatic enzyme inhibitors has been disappointing and there have been few investigations of prophylactic antibiotic therapy.^{3–7} An early report suggested that prophylactic antibiotics conferred no benefit.³ Adequate assessment of the severity of pancreatitis has been a substantial difficulty in the past, and comparison of the results of different studies has been almost impossible. New radiological and laboratory methods now, however, allow analysis of the degree of severity with acceptable accuracy.^{8–14}

Although the overall mortality rate of pancreatitis has decreased, infectious complications have been reported to indicate a poor outcome.^{15,16} Among patients treated in intensive-care units, the species reported to cause most cases of sepsis are *Escherichia coli* and *Staphylococcus aureus*.^{17,18}

Prophylactic antibiotic treatment has not been routinely used in our hospital for patients with alcohol-induced necrotising pancreatitis. Antibiotics are given only to patients with clinically or microbiologically verified infection or when there is strong suspicion of infectious complications. When we started this study in July, 1989, there had been no controlled clinical study of patients with severe necrotising pancreatitis that indicated benefit from prophylactic antibiotic therapy.

Our aim was to find out whether clinical outcome for patients with acute alcohol-induced necrotising pancreatitis can be improved by antibiotic treatment with cefuroxime started early on admission.

Patients and methods

Between July, 1989, and November, 1993, 820 patients with acute pancreatitis were treated at the Second Department of Surgery, Helsinki University Central Hospital. We studied 60 consecutive patients with severe necrotising alcohol-induced pancreatitis admitted during this period. Inclusion criteria for randomisation were C-reactive protein concentration above 120 mg/L within 48 h of admission and low contrast enhancement of the pancreas (below 30 Hounsfield units [HU]) on contrast-enhanced computed tomography (CE-CT). If CE-CT could not be done because of impaired renal function or allergy, early extrapancreatic scores were recorded and patients with scores of 4 or more points were included in the study.¹⁹ Reasons for exclusion were treatment elsewhere for more than 2 days before admission to our hospital, continuing antimicrobial treatment, a previous severe episode of pancreatitis, and aetiology other than alcohol and no history of alcohol intake before admission.

All patients with alcohol-induced pancreatitis suspected to have the necrotising form of the disease underwent dynamic CE-CT within 24 h of admission. A rapid intravenous injection of meglumine iohalamate (400 mg iodine per mL at a dose of 400 mg iodine per kg body weight) or iohexol (300 mg iodine per mL; 400 mg iodine per kg) was given, half to each cubital vein.

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Characteristic	Antibiotic group (n=30)	Non-antibiotic group (n=30)
Demography		
Men/women	27/3	26/4
Mean (SD) age in years	43.0 (11.3)	38.7 (8.4)
Pancreatitis		
Mean (SD) duration of symptoms in days	2.0 (1.6)	1.8 (1.0)
Number with first episode	24	21
Number with relapse	6	9
Mean (range) maximum C-reactive protein (mg/L) in first 48 h	308 (141-548)	343 (140-496)
Mean (SD) early prognostic signs positive/studied	5.3 (1.6)/10.8	5.7 (1.9)/10.3
Hospital stay		
Number (%) of patients operated on	7 (23%)	14 (47%)
Mean (SD) hospital stay	33.2 (22.1)	43.8 (43.1)
Mean (SD) duration of intensive-care treatment	12.7 (10.7)	23.6 (28.7)

*Ranson's criteria.⁴

Table 1: Patients' characteristics at study enrolment

The pancreas was scanned at a preselected level for 60 s in a Siemens Somatom 2, Somatom DR2, or DRH. Enhancement values below 30 HU indicated necrotising pancreatitis. Early extrapancreatic changes were scored¹⁹ (oedema around part of or the entire pancreas, the mesenteric fat, or the perirenal fat, peritoneal exudate, bowel distension, and pleural effusion: 1 point for each). Preliminary CT analysis was done by the radiologist on call at the hospital and later verified by an experienced senior radiologist.

C-reactive protein concentrations and modified early prognostic signs were examined by our hospital routine.

Blood samples were cultured twice a week for each patient. When signs of sepsis with high fever and low blood pressure occurred without any other apparent cause, extra blood samples were taken for culture and repeated after half an hour. Bacteriological culture of urine samples was done twice a week. Central venous lines were changed every 14 days or earlier if the line was thought to be the cause of the unexplained fever. The tips of all removed lines were cultured bacteriologically. Gram staining and bacterial cultures were also done weekly from CT-guided or ultrasound-guided biopsy samples of peripancreatic fluid from patients suspected to have infected necrosis²⁰ (n=72) because of persistent fever, rise in C-reactive protein, or fluid collections detected by CT. Further samples from drains were cultured at least twice a week after surgery by the standard methods used in our clinic. Blood-culture-positive sepsis, pneumonia and/or adult respiratory distress syndrome, urinary infection, and intra-abdominal abscess or infected necrosis were recorded as infectious complications.

Patients were assigned on admission to two treatment groups by means of numbered envelopes. In the antibiotic group three doses of 1.5 g cefuroxime per day intravenously was started on admission and continued until clinical recovery and fall to normal of C-reactive protein concentrations. In cases of full clinical recovery but moderately raised C-reactive protein concentrations, antibiotic treatment was continued with cefuroxime by mouth (two doses of 250 mg per day) for 14 days. In the non-antibiotic group, no antibiotic treatment was given before infection had been clinically, microbiologically, or radiologically verified, or until there was a secondary rise in C-

reactive protein of more than 20% after the acute phase. The choice of antibiotic in this group depended on the type of infection and was based on bacterial cultures when available. In both groups, antibiotic treatment was changed if necessary according to positive cultures or suspicion of inadequate antimicrobial efficacy. C-reactive protein was measured daily after admission, and blood cultures were done at least twice a week and immediately when sepsis was clinically suspected. CT scans were repeated if there was deterioration or if the course of disease was long.

Conservative treatment of the patients in the intensive-care unit in the acute phase consisted of adequate fluid replacement by central venous catheter, with monitoring of central venous pressure, and assistance of respiratory or renal function when needed. A decision to operate was based on clinical criteria: development of an acute abdomen requiring immediate surgery; verified infected necrosis; generalised sepsis; shock; or persisting or increasing organ dysfunction despite maximum intensive care for at least 3 days. The standard procedures were debridement of devitalised tissue with preservation of vital pancreatic tissue and, in some cases, postoperative lavage.²¹

The primary endpoint was survival. Secondary endpoints included length of hospital stay, duration of treatment in the intensive-care unit, and rate of infectious complications. Multiple regression analysis with a log-linear regression model and analysis of covariance were done for duration of symptoms before admission, age, first or recurrent disease, positive early prognostic signs, and maximum C-reactive protein in 48 h to find unexpected confounding influences for continuous outcomes. Statistical analysis and comparisons between the groups were by Student's unpaired *t* test for parametric analysis and Fisher's exact test for non-parametric analysis.

Results

The groups were similar in mean age, sex distribution, and duration of symptoms before admission (table 1). Six patients in the antibiotic group and nine in the non-antibiotic group had relapsing pancreatitis.

CE-CT showed low enhancement (<30 HU) in at least a third of the pancreatic tissue in 48 patients. 25 patients (13 antibiotic group, 12 non-antibiotic group) had low enhancement of the whole gland, and three patients in each group had low enhancement involving only the tail of the pancreas. Five patients in the antibiotic group and seven in the non-antibiotic group had plain CT only, with similar mean extrapancreatic scores.

The mean C-reactive protein concentrations within 48 h of admission were similar in the two groups, as was the mean number of prognostic signs (table 1).

The total number of recorded infectious complications was 30 in the antibiotic group and 54 in the non-antibiotic group (table 2). None of the tested covariates had any significant effect on the number of infectious complications. The mean number of infections per patient was significantly lower in the antibiotic group (table 2; $p=0.01$, 95% CI 0.20-1.40). When infectious complications were analysed separately only the difference in urinary-tract infections was significant ($p=0.0073$).

	Antibiotic group	Non-antibiotic group
Blood-culture-positive sepsis	4	8
Urinary-tract infection	6	17*
Pneumonia/ARDS	11	17
Abscess or infected necrosis	9	12
Number of subjects with any of these complications	20 (67%)	25 (83%)
Mean number of complications per patient	1.0 (0.9)	1.8 (1.3)†

* $p=0.0073$. † $p<0.01$. ARDS=adult respiratory distress syndrome.

Table 2: Infectious complications

Infection	Species cultured	Days after admission
Sepsis	<i>Streptococcus pneumoniae</i>	3
Sepsis	<i>Pseudomonas aeruginosa</i>	3
Sepsis	<i>Staph epidermidis</i>	8
Sepsis	<i>Staph aureus</i>	6
Urinary infection	<i>Ent faecalis</i>	3
Urinary infection	<i>Klebsiella pneumoniae</i>	5
Urinary infection	<i>Staph epidermidis</i>	15
Urinary infection	<i>Staph epidermidis</i>	3

Table 3: Positive bacterial cultures in non-antibiotic group before start of antimicrobial treatment

	Antibiotic group	Non-antibiotic group
<i>Ent faecalis</i>	0	1
<i>Klebsiella</i> sp	1	0
<i>Ps aeruginosa</i>	0	1
<i>Candida albicans</i>	1	0
<i>Staph epidermidis</i>	1	4
<i>Staph aureus</i>	1	2
Total	4	8

Table 4: Bacterial findings in patients with verified sepsis

Antibiotic treatment was changed in 20 patients in the antibiotic group at a mean of 9.2 (range 2–28 days). 23 non-antibiotic group patients were given antibiotic at a mean of 6.1 (2–16) days from admission. In the non-antibiotic group the reason for starting antibiotic treatment was culture-verified sepsis or strong clinical suspicion of sepsis in 13 patients. In the antibiotic group, therapy was changed for these reasons in only three patients, none of whom had culture-verified sepsis. Changes of antibiotic treatment were necessary because of urinary-tract infection in three antibiotic-group and four non-antibiotic-group patients and because of a secondary rise in C-reactive protein in two patients in each group.

In the non-antibiotic group, antibiotic treatment was started because of suspected infection in 14, preoperatively in one, and because of positive bacterial cultures in eight (four sepsis, four urinary-tract infections; table 3). Only seven (23%) of the 30 patients in this group did not receive any antibiotic treatment at all.

Samples of peripancreatic necrosis were taken from 21 patients in the antibiotic group (41 samples) and from 18 in the non-antibiotic group (31 samples). Because of the design, no samples could be taken before antibiotic treatment in the antibiotic group. In the non-antibiotic group, 17 samples were taken before antibiotic treatment; all were negative. Of the 14 samples taken in that group after initiation of antibiotic treatment, 2 were positive. Of the 21 surgically treated patients, ten had positive cultures before or at the time of the operation. Eleven patients had negative cultures preoperatively, but ten of these had positive cultures from drains postoperatively.

12 patients (four antibiotic group, eight non-antibiotic group) had blood-culture-positive sepsis (table 4). In two cases the sepsis was due to bacteria normally associated with the colonic flora, one of them postoperatively; the other patient also had gram-positive cocci of unknown species. *Staph epidermidis* was found in cultures from either the peripancreatic necrosis or the tip of the central venous catheter in 14 of the 18 patients with suspected but not blood-culture-positive sepsis.

Both the mean total hospital stay and the mean stay in the intensive-care unit were longer in the non-antibiotic than in the antibiotic group (43.8 vs 33.2 days; 23.6 vs 12.7 days) but the differences were not significant ($p=0.24$, $p=0.06$, respectively). When two non-antibiotic-group patients with fulminant disease were excluded from this analysis, the difference in stay in the intensive-care unit was significant (25.2 [29.1] vs 12.7 [10.7] days; $p=0.0393$, 95% CI 0.64–24.4). Of the tested covariates only age had a significant effect on the time needed in the intensive-care unit (p adjusted for age=0.0258). Operative intervention was needed in seven patients in the antibiotic group (two additional late abscesses were drained percutaneously) and 14 patients in the non-antibiotic group. The difference between the groups in the total number of operations was significant (8 vs 36; $p=0.012$, 95% CI 0.20 to 1.60).

	Antibiotic group	Non-antibiotic group
Fulminant course with irreversible shock	0	2
Verified <i>Staph aureus</i> sepsis	0	1
Verified <i>Ent faecalis</i> sepsis	0	1
Multiorgan failure and cultures of pancreatic necrosis positive for <i>Staph epidermidis</i>	1	3
Total deaths	1	7*

* $p=0.0284$, Fisher's exact test.

Table 5: Cause of death and mortality

One antibiotic-group patient and seven patients in the non-antibiotic group died (table 5); this difference was significant ($p=0.028$). All these patients were in their first episode of pancreatitis. The death of the patient in the antibiotic group was presumably due to sepsis and multiorgan failure with positive postoperative cultures of *Staph epidermidis*. Similar findings were recorded in three patients in the non-antibiotic group who died. Two others in that group died 2 and 4 days after fulminant disease and irreversible shock, which may have been caused or worsened by sepsis. The remaining two patients in the non-antibiotic group died from blood-culture-positive sepsis due to *Staph aureus* or to *Enterococcus faecalis*. Mortality of all patients in this study was 13.3%.

Discussion

Although the mortality of patients with sterile necrosis and systemic complications is high,²² when respiratory and renal failure are accompanied by infectious complications and infected pancreatic necrosis mortality is even higher.²³ Reduction in overall mortality is due partly to adequate fluid resuscitation and effective intensive care combined with the correct timing and type of operative intervention.^{24–26} The frequency of cholangitis in patients with gallstone-induced pancreatitis is about 30%.²⁷ In our clinic, these patients have routinely been given prophylactic antibiotics on the assumption that bile stasis may lead to cholecystitis or cholangitis. The participants in this study all had extremely severe alcohol-induced pancreatitis. Of 820 patients with acute pancreatitis, only 60 were accepted for the study. Antibiotic treatment of patients with alcohol-induced necrotising pancreatitis has not been routine in our hospital.

In some previous studies, reliable verification of the severity of pancreatitis has been difficult. We have previously shown a strong correlation between low enhancement of contrast medium and reduced blood flow in the diseased pancreas.¹³ In this study, the severity of the disease was verified by CE-CT, and the extent of necrosis and of enhancement of contrast medium in the two groups were similar. We excluded patients referred from other hospitals who had been treated there for longer than 2 days. High C-reactive protein concentrations, although unspecific, increase the reliability of assessment of the severity of the pancreatitis; values were high in both groups, without significant differences between them.

This study was prompted by the high frequency of complicated infections caused by *Staph aureus* in patients treated in the intensive-care unit, and the susceptibility of this bacterium to cefuroxime. Methicillin-resistant strains of *Staph aureus* are very rare in our hospital. *E coli*, the most commonly reported cause of infected pancreatic necrosis,^{15,20} is seldom resistant to cefuroxime in our hospital.

In previous studies of symptomatic patients, early surgical debridement was shown to be beneficial despite

bacterial findings.²⁸ In our study, many of the patients had sterile necrosis with negative bacteriological cultures on peroperative samples but, in all except one patient, cultures from drains became positive postoperatively. We suggest that in many cases infection of the necrotic pancreatic tissue is ascending and may even have been caused by the operation. We therefore do not recommend operative treatment for these patients in the early course of the disease.²⁹ Peroperative damage to the intestine may bring about infections caused by colonic bacteria. Moreover, antimicrobial treatment may reduce the reliability of bacterial cultures taken peroperatively and also mask blood cultures despite clinically imminent sepsis.

The frequency of *Staph epidermidis* both in verified sepsis and in patients with subclinical sepsis suggests that this micro-organism is more important than has previously been recognised in the progression of fatal complications in necrotising pancreatitis. The choice of cefuroxime as prophylactic antibiotic in our study was based on the susceptibility of *E coli* and *Staph aureus*, common causes of sepsis, to this drug. It has been suggested that high concentrations of antibiotics in the pancreatic necrosis are important in the treatment of necrotising pancreatitis, but we found that cefuroxime given intravenously early in the course of the disease reduced mortality, even though possibly only moderate concentrations may be reached in the necrotic pancreatic tissue.^{7,15} Although most of the *Staph epidermidis* strains cultured at our clinic are resistant to cefuroxime, this drug seems to be effective enough to protect the patient against severe infectious complications during the first week of treatment. If a patient develops severe pancreatitis with progressively spreading necrosis of the gland and peripancreatic tissue, ischaemia may lower the resistance of these patients to *Staph epidermidis* and other bacteria that do not normally cause sepsis. Cefuroxime seems able to reduce severe infectious complications and also to prevent secondary *Staph epidermidis* infections.

In our study, ten of 21 surgically treated patients had infected necrosis verified by positive bacterial cultures of samples taken before or during the operation. Nevertheless, when the pancreas is totally necrotic and infected, no antibiotic treatment alone is sufficient and surgical intervention is then the treatment of choice. We believe, however, that infected necrosis is only one source of recurrent sepsis, although an important one. The origin of bacteria causing systemic septic complications may vary among patients treated in intensive-care units and may be difficult or impossible to trace, especially in patients who are receiving antimicrobial therapy. A broad-spectrum antibiotic administered prophylactically might be even more effective, but imipenem failed to reduce mortality significantly.³⁰

More effective drugs should be considered as a reserve for severe and life-threatening complications. In our study, cefuroxime was safe, and no severe side-effects related to the drug were observed. If the signs of infection, high C-reactive protein concentrations, and deterioration or lack of improvement persist after the first week, in the absence of positive bacterial cultures we routinely discontinue cefuroxime and start intravenous treatment with vancomycin, imipenem, and fluconazole to cover infections caused by pseudomonas, enterococcus, cefuroxime-resistant staphylococci, and candida. Because of the low cost and other apparent advantages of

antibiotic treatment, we believe that such treatment should be started early in all patients with necrotising pancreatitis. Selection and dosage of antibiotics should, of course, be adjusted in relation to clinical circumstances and microbiological studies.

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Driving ability in cancer patients receiving long-term morphine analgesia

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Summary

When given in single doses to healthy volunteers, opioid analgesics impair reaction time, muscle coordination, attention, and short-term memory sufficiently to affect driving and other skilled activities. Despite the increasing use of oral morphine daily, little is known about the effect of long-term opioid therapy on psychomotor performance. To examine the effects of continuous morphine medication, psychological and neurological tests originally designed for professional motor vehicle drivers were conducted in two groups of cancer patients who were similar apart from experience of pain. 24 were on continuous morphine (mean 209 mg oral morphine daily) for cancer pain; and 25 were pain-free without regular analgesics.

Though the results were a little worse in the patients taking morphine, there were no significant differences between the groups in intelligence, vigilance, concentration, fluency of motor reactions, or division of attention. Of the neural function tests, reaction times (auditory, visual, associative), thermal discrimination, and body sway with eyes open were similar in the two groups; only balancing ability with closed eyes was worse in the morphine group.

These results indicate that, in cancer patients receiving long-term morphine treatment with stable doses, morphine has only a slight and selective effect on functions related to driving.

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See Commentary page 652

Introduction

When opioids are prescribed for severe cancer pain, good analgesia is often obtained at the expense of sedation, dizziness, and mental clouding.¹ These effects interfere with activities that demand alertness—especially driving. Drugs affecting the central nervous system are generally judged hazardous in motorists² and in many countries carry warning stickers.

In opioid-naïve healthy volunteers, clinical doses of both sublingual and intramuscular buprenorphine are reported to impair reaction time, muscle coordination, attention, and short-term memory.^{3,4} Likewise single oral doses of methadone increase reaction times and impair ocular coordination; yet in drug addicts receiving methadone maintenance, reaction times and overall cognitive functioning seem to be normal,^{5,6} and the driving safety record of narcotic users is hardly worse than average, the relative risk of an accident being 1.1.⁷

What is known about morphine and its effects on complex tasks? Sjögren and Banning⁸ measured simple reaction times to auditory stimuli in 14 cancer patients receiving constant doses (130-400 mg). When oral treatment was switched to epidural they were able to reduce median morphine dose from 210 mg to 80 mg; yet no significant differences were found in reaction times in the two treatment phases. Bruera and co-workers⁹ used four simple bedside memory tests, before and 45 minutes after the morning dose, in 40 patients receiving long-term analgesia. In those with stable dosage morphine had no effect; but, in patients whose dose had been increased by 30% or more in the past two days, cognitive performance

	Morphine mean (SD)	Control mean (SD)
Morphine dose mg/day	209 (221)	0 (0)
Female/male	12/12	15/10
Age	53 (9.4)	51 (11.2)
Primary site of cancer		
Breast	7	10
Lung	3	3
Gastrointestinal	5	6
Urogenital	7	3
Other	2	3
Karnofsky grade (100-0)	80 (8.5)	80 (6.8)
Duration of disease (weeks)	31 (33)	53 (71)
Time on morphine (days)	96 (137)	0 (0)
Education		
Basic	11	12
Trade school	5	5
Intermediate	4	5
University	3	3

None of the differences were significant.

Table 1: Characteristics of morphine and control groups

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