The role of infection in acute pancreatitis

Acute pancreatitis can be a mild, transitory illness or a severe, rapidly fatal disease. About 80% of cases of the disease are acute interstitial oedematous pancreatitis which has a low morbidity and mortality rate (<1%) and roughly 20% of patients with acute pancreatitis develop necrosis of pancreatic and peripancreatic tissues. The course of severe acute pancreatitis may include an early vasoactive and toxic phase, and a late period dominated by septic complications. Improved intensive care treatment can reduce the early cardiorespiratory and renal complications related to systemic inflammatory response syndrome (SIRS).

Pancreatic infection is reported to develop in 40–70% of patients with necrotising pancreatitis and is the main life threatening complication of the disease; furthermore, consecutive sepsis and sepsis related multiple organ failure are responsible for a mortality rate of up to 50%.

In the early phase of acute pancreatitis, a broad range of specific treatment modalities have been evaluated, but all have proved ineffective. Therefore, interest has focused on the prophylactic administration of antibiotics. The use of antibiotic treatment is based on the rationale that reduction of pancreatic infection will decrease late morbidity and mortality. However, the beneficial effects of antibiotic prophylaxis are still controversial.

Possible pathways for pancreatic infection

There are several hypothetical mechanisms by which bacteria may enter pancreatic and peripancreatic necrosis (fig 1): the haematogenous route via the circulation; transmural migration through the colonic bowel wall either to the pancreas (translocation); via ascites to the pancreas, or via the lymphatics to the circulation; via the biliary duct system; from the duodenum via the main pancreatic duct.

Animal studies have shown spontaneous bacterial infection of the pancreas. In healthy animals, immunocompetent cells usually clear these contaminating organisms. However, stress, such as acute inflammation, renders the pancreas vulnerable to bacterial infection; the intestinal mucosal barrier fails, allowing these organisms to translocate to mesenteric lymph nodes, the systemic circulation, the portal venous circulation, the peritoneal cavity, and abdominal organs, with resulting supervening sepsis and critical complications. As most pathogens in pancreatic infection are gastrointestinal Gram negative bacteria, the colon seems to be the main source of pancreatitis related infections. It is, therefore, possible that bacterial translocation is the most important mechanism for contamination of pancreatic necrosis. However, considerable controversy exists about the exact pathway: do bacteria enter the pancreas after colonic translocation, through the lymphatics and circulation via contaminated ascites, or do they migrate directly to the inflamed gland because of the proximity of the transverse colon to the pancreas?

Experimental studies provide equivocal results. From their study of caerulein induced acute pancreatitis in rats, Medich et al concluded that acute pancreatitis promotes bacterial translocation leading to transperitoneal infection of the pancreas, and suggested that selective decontamination of the gut, and peritoneal lavage, may prevent pancreatic infection in acute pancreatitis. This view is supported by Marotta et al who found that ascites were the most frequently infected sample in a model of acute pancreatitis, induced by an intrabiliary injection of a trypsin/enterokinase mixture. In contrast, a recent study by Arendt et al indicated that bacteria do not spread from the peritoneal cavity in caerulein induced acute pancreatitis in rats. They showed that the peritoneal cavity could obstruct bacteria, rather than act as a source of bacterial seeding. Further experiments by Widdison et al supported the hypothesis that infection of pancreatic necrosis occurs transmurally from the colon to the pancreas; they showed that enclosing the colon in an impermeable bag prevented infection of pancreatic necrosis in a necrotising model of acute pancreatitis.

The mechanism of bacterial translocation in human necrotising pancreatitis is still a matter of considerable debate as conclusions drawn from animal studies may not be directly transferable. Additionally, human studies to evaluate translocation are difficult to perform in an ethical manner. However, many clinical studies suggest that systemic infections and multiple organ failure in critically ill or injured patients often originate from intestinal floral migration, possibly via failure of the intestinal barrier. A recent investigation of pancreatic infection by Luiten et al provided clinical evidence that aerobic Gram negative intestinal bacterial organisms are linked to a significantly increased risk of Gram negative pancreatic infections.

In summary, the most probable source of pancreatic infection seems to be the colon via bacterial translocation. However, the exact route of post bacterial transmural migration is still unknown. Possible pathways are via the lymphatics and consecutive haematogenous spread, or transmurally to the pancreas.

**Figure 1** Possible infection routes in severe acute pancreatitis.
Clinical significance of infected pancreatic necrosis

The Atlanta symposium classification of severe acute pancreatitis links it to organ failure and/or local complications, including necrosis, abscess, or pseudocysts. Usually, pancreatic infection is linked to the development of pancreatic necrosis, which is defined as either a diffuse or focal area of non-viable pancreatic parenchyma, and is typically associated with peripancreatic fatty tissue necrosis. A pancreatic abscess is a consequence of severe acute pancreatitis and is a circumscribed intra-abdominal collection of pus, usually in the proximity of the pancreas and containing little or no pancreatic necrosis. It is likely that pancreatic abscesses are a consequence of limited necrosis, with subsequent liquefaction and secondary infection during the course of severe acute pancreatitis. A postcute pseudocyst is pancreatic juice, enclosed by a wall of fibrous or granulated tissue, which may develop in severe acute pancreatitis; bacteria may be present. Several studies have examined the frequency of bacterial infection of necrotic areas in the natural course of severe acute pancreatitis, without antibiotic intervention. Beger et al showed an overall contamination rate of 24% within the first week of the onset of acute pancreatitis in patients undergoing surgery for severe acute pancreatitis, increasing to 46 and 71%, respectively, in the second and third weeks. Thus, patients with severe acute pancreatitis have the highest risk of pancreatic infection in the third week after onset of the disease. The overall infection rate in this series was 39%. Similar results were reported by Gerzof et al who performed percutaneous computed tomography (CT) guided aspiration and Gram staining, and by Bassi et al who examined smears taken intra-operatively. However, the frequency of pancreatic infection was higher in these studies, with rates of 60% and 63%, respectively.

Pancreatic necrosis usually becomes infected at a late stage in the disease, and is dependent on the extent of intra- and extra-pancreatic necrosis. Through morphological analysis by contrast enhanced CT scanning, Beger et al found a higher rate of infection in patients with extensive pancreatic necrosis. Two thirds of the patients with infected pancreatic necrosis had a total amount of necrosis of more than 30%, whereas 60% of patients with sterile necrosis had necrotic areas of less than 30% (table 1). Therefore, it seems that the presence of a significant extent of necrosis (>50% on CT scanning) is predictive of severe disease, and helps to identify patients who might develop septic complications.

The influence of bacterial infection on morbidity and mortality in severe acute pancreatitis has been analysed in surgically treated patients with infected pancreatic necrosis and in patients with sterile necrosis who have had surgery. This study looked at 170 patients with severe acute pancreatitis. Of these, 42% had infected pancreatic necrosis and 58% had sterile necrosis. Preoperative morbidity in the group with infected pancreatic necrosis was significantly higher than in patients with sterile necrosis with respect to pulmonary (56% vs 72%), renal (28% vs 45%), and cardio-circulatory (13% vs 30%) insufficiency. The mortality rate in the infected group was 20% (14 of 71 patients), a figure significantly higher than in the sterile group (11%; 10 of 99 patients).

In summary, infected pancreatic necrosis is a significant prognostic factor in severe acute pancreatitis. As infection is the leading cause of morbidity and mortality from acute pancreatitis, diagnosis and optimal treatment of infectious complications is vital.

Bacteriology in infected pancreatic necrosis

While most complicating infections in animal pancreatic studies, hospitalised patients, and in pancreatic infection are caused by a few species of bacteria (table 2), normal intestinal flora consists of more than 400 species. In the natural course of severe acute pancreatitis, cultures of infected pancreatic necroses yield monomicrobial flora in 60–87% of cases; in these studies, polymicrobial flora was confirmed in only 13–40% of cases (table 2). A preponderance of Gram negative aerobic bacteria is usually present (Escherichia coli, Pseudomonas spp, Proteus, Klebsiella spp) which suggests an enteric origin, but Gram positive bacteria (Staphylococcus aureus, Streptococcus faecalis, Enterococcus), anaerobes, and, occasionally, fungi have also been found. The incidence of fungi in long term disease may increase, especially after prolonged antibiotic treatment. In one study, candida infection was reported in 21% of patients with infected pancreatic necrosis. Luiten et al studied prospectively the difference between Gram negative and Gram positive infection in patients with infected pancreatic necrosis. They found that Gram negative infection was linked to a significantly higher mortality than Gram positive pancreatic infection.

Prevention of infection of pancreatic necrosis

Given the poor prognosis of patients with severe acute pancreatitis and infection, the possibility of prevention and/or treatment of pancreatic infection has received major attention. A summary of the options follows.

INTRAVENOUS ANTIBIOTIC PROPHYLAXIS

Infection of initially sterile pancreatic necrosis develops in the later stages of severe acute pancreatitis, and effective antibiotic treatment may reduce late mortality. Three early studies of the use of prophylactic intravenous antibiotics in the treatment of unselected patients with acute pancreatitis failed to show any favourable effect on morbidity and mortality. However, most of the patients in these studies had mild acute pancreatitis with no risk of pancreatic infection. Furthermore, later studies that focussed on pancreatic tissue concentrations of antibiotics after intravenous administration showed that ampicillin, the drug used most frequently in these early trials, failed to reach therapeutic concentrations in the infected gland, or to cover the Gram negative micro-organisms present in infected pancreatic necrosis. This altered pharmacokinetic behaviour of antibiotics is based on the observation that the pancreas has a barrier comparable to the blood–brain barrier; this blood–pancreas barrier is
responsible for the selective uptake of antibiotic drugs into the pancreas. Evaluation of the concentrations of the various classes of antibiotics has shown that the quinolones (ciprofloxacin, ofloxacin) and the carbapenem, imipenem, are substances with high pancreatic tissue concentrations and the highest bactericidal activity against most of the organisms present in pancreatic infection. In contrast, aminoglycosides are unable to penetrate human pancreatic tissue in bactericidal concentrations. The efficacy factors of some antibiotic classes are listed in table 3. This factor includes the type and frequency of bacteria found in infected pancreatic necrosis, antibiotic tissue concentrations, and the percentage of inhibited bacterial strains according to the minimal inhibitory concentration (MIC). Consequently, an ideal efficacy factor of 1 corresponds to complete inhibition of bacteria in infected pancreatic necrosis. Imipenem has an excellent efficacy factor of 0.98, whereas aminoglycosides have a very low factor (0.13). Metronidazole acts exclusively against anaerobes and is recommended only in combination with non-anaerobic antibiotics.

Prophylactic treatment with imipenem, used in a randomised controlled clinical trial by Pederzoli and colleagues, reduced the incidence of pancreatic (12.2% v 30.3%) and non-pancreatic (14.6% v 48.5%) sepsis significantly in patients with CT proved severe acute pancreatitis. However, the overall mortality rate (7.3% v 12.1%), the rate of multi-organ failure, and the necessity for surgery were all unaffected (table 4). A weakness of this study is the relatively low number of patients (74 overall); moreover, only two of 16 patients with >50% extent of necrosis were randomised to the control group (with a consequent bias in selection in the control group). Thus, overall mortality (9.4%) was low and reflected a less severe disease. These results correspond with the results of Foititz et al who found a significantly reduced rate of pancreatic infection after the application of imipenem with an unchanged mortality rate, in an animal model of severe acute pancreatitis.

Sainio et al observed a significantly reduced mortality rate in patients with severe acute alcohol induced pancreatitis treated with cefuroxime. The reduction in mortality from 23% in the control group to 3% in the treatment group was not associated with reduced pancreatic sepsis, and probably reflected a significantly decreased frequency of infectious complications. However, the number of patients was low (30 v 30), cefuroxime was changed to alternative antibiotics after a mean of 9.2 days in 20 of the 30 patients in the antibiotic group, and antibiotics were started in 23 of 30 patients in the control group at a mean of 6.1 days. Although the pancreatic pharmacokinetics of cefuroxime are unknown, failure to reduce pancreatic sepsis suggests poor pancreatic penetration similarly to other second generation cephalosporins. This is in contrast to third generation cephalosporins, which achieve adequate pancreatic tissue concentrations.

The combination of ceftazidime, amikacine, and metronidazole for 10 days decreased the incidence of sepsis in patients with severe alcoholic acute pancreatitis, but no statistical differences were found for pancreatic infection and mortality. However, conclusions from this study should be interpreted with caution because of the low number of patients recruited (n=23). Additionally, amikacine belongs to the aminoglycosides class, which do not seem to penetrate the pancreas adequately.

In a clinical controlled study using intravenous antibiotic prophylaxis with ofloxacin and metronidazole, Schwarz et al noted that the rate of Gram negative pancreatic infection in the treatment group (1/13 patients, 7%) was lower than in the control group (6/16 patients, 46%). However, no statistically significant reduction in pancreatic infection was seen because of the low number of patients in the study.

Bassi et al also studied drug concentrations of several antibiotics in serum and samples of pancreatic necrosis. In this study, necrotic sample concentrations of metronidazole and pefloxacin, which belongs to the fluoroquinolone class, exceeded the MIC for the organisms most commonly isolated in this disease. Imipenem and mezlocillin did not have consistently high MICs; aminoglycoside concentrations were also inadequate. Repeated administration of drugs seemed to encourage pefloxacin, imipenem, and metronidazole to penetrate necrotic pancreatic tissue. Pefloxacin proved inferior to imipenem in the prevention of severe pancreatic infection.

Table 3 Efficacy factors for different antibiotics in pancreatic tissue—for example, an efficacy factor of 1.0 would indicate that the antibiotic would inhibit all bacteria commonly found in pancreatic infection (adapted from 45)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Efficacy factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.14</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>0.12</td>
</tr>
<tr>
<td>Acylureidopenicillins</td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>0.71</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>0.72</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td></td>
</tr>
<tr>
<td>Cefotaxim</td>
<td>0.75</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0.76</td>
</tr>
<tr>
<td>Ceftriaxime</td>
<td>0.78</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0.79</td>
</tr>
<tr>
<td>Quinolones</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
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</tr>
<tr>
<td>Ofloxacin</td>
<td>0.87</td>
</tr>
<tr>
<td>Carbenapem</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Table 4 Prospective randomised studies of prophylactic antibiotic treatment in severe acute pancreatitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug</th>
<th>Patients (n)</th>
<th>Rate of pancreatic infection (%)</th>
<th>Rate of MOF (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luiten and colleagues</td>
<td>Oral and rectal SDD/i.v. cefotaxime</td>
<td>52  50</td>
<td>38  18†‡</td>
<td>35  22</td>
<td></td>
</tr>
<tr>
<td>Pederzoli and colleagues</td>
<td>Imipenem</td>
<td>33  41</td>
<td>30  12*</td>
<td>39  29</td>
<td>12  7</td>
</tr>
<tr>
<td>Sainio and colleagues</td>
<td>Cefuroxime</td>
<td>30  30</td>
<td>30  30</td>
<td>23  3†</td>
<td></td>
</tr>
<tr>
<td>Delcenserie and colleagues</td>
<td>Cefotaxime/amikacine/metro nitazole</td>
<td>12  11</td>
<td>58  0‡</td>
<td>25  0†</td>
<td></td>
</tr>
<tr>
<td>Schwarz and colleagues</td>
<td>Ofloxacin/metronidazole</td>
<td>13  13</td>
<td>53  61</td>
<td>15  0</td>
<td>25  0†</td>
</tr>
<tr>
<td>Bassi and colleagues</td>
<td>Pefloxacin v imipenem</td>
<td>30  30</td>
<td>34  10‡</td>
<td>24  10</td>
<td></td>
</tr>
</tbody>
</table>

SDD, oral and rectal application of colistin sulphate, amphotericin, and norfloxacin; MOF, multiple organ failure.

* p<0.01; † p=0.028; ‡ p=0.03.
infection associated with severe necrotising pancreatitis (extent of pancreatic necrosis $>50\%$), in spite of its potential for prevention. This trial included 60 patients who were given either pefloxacin or imipenem for two weeks. The incidence of infected pancreatic necrosis in the pefloxacin and imipenem groups was 34% and 10%, respectively. Imipenem proved significantly more effective in prevention of pancreatic infections ($p \leq 0.05$). Mortality was higher in the pefloxacin group (24%) compared with the imipenem group (10%), although the difference was not statistically significant (table 4).}

In summary, only the study of cefuroxime by Sainio et al showed significantly reduced patient mortality following prophylactic treatment with antibiotics. Unfortunately, all prospective studies analysing antibiotic prophylaxis in acute pancreatitis have used small sample sizes. Problems with data analysis have been compounded by the negligible incidence of mortality in the control population. Thus, Golub et al performed a meta-analysis of all prospective trials in order to see whether there is a therapeutic role for antibiotics in acute pancreatitis. The authors found that mortality was significantly reduced in a subgroup of patients with severe pancreatitis who were given broad spectrum antibiotics.

Medical experience also supports the administration of prophylactic antibiotics as the incidence of pancreatic infection seems to have over the past 10 years. With the introduction of antibiotic prophylaxis, both Banks et al, and Ho and Frey have reported a reduction in infected necrosis at a single institution from 67% to 32% and 76% to 27%, respectively. However, patient survival has stabilised or has shown a non-significant trend to decrease.

In conclusion, no sufficiently powerful randomised controlled trial proves definitively that there is a role for prophylactic antibiotic treatment. However, current evidence would seem to justify early prophylactic administration of an antibiotic concentrated by the pancreas (for example, imipenem) in patients with severe acute pancreatitis. Further trials are urgently needed to evaluate the duration of antibiotic treatment, the administration of antibiotics alone or in combination with amantadine, and the apparent shift in bacteria during the past two years.

**SELECTIVE DECONTMATION OF THE DIGESTIVE TRACT (SDD)**

Elimination or reduction of intestinal bacteria may reduce or eliminate infection in pancreatic necrosis. In 1984, Stoutenbeek et al reported that selective decontamination of the digestive tract with non-absorbable antibiotics, administered via a gastric tube, reduced the aerobic Gram negative intestinal flora in patients with multiple trauma. In combination with systemic short term cefotaxime, directed against early endogenous infection, the total infection rate decreased from 81% to 16% in their patients. Several other studies have shown that selective decontamination eliminates Gram negative bacteria from the intestinal tract, and sometimes reduces Gram negative septic complications in patients on intensive care units. However, results which show any reduction in actual mortality may be contradictory.

During their hospital stay, the digestive tract of more than 60% of patients with severe acute pancreatitis is colonised with nosocomial Gram negative flora. As the risk of infection of pancreatic necrosis increases with Gram negative intestinal colonisation, elimination of these pathogens by prophylactic selective decontamination with enterally administered antibiotics is an attractive method for prevention of infection of pancreatic necrosis. Several experimental investigations have examined the use of selective decontamination in severe acute pancreatitis.

These studies have shown that reduced intestinal flora resulted in improved survival and, possibly, reduced pancreatic infection. In an uncontrolled clinical study, SDD reduced the infection rate and sepsis in patients with acute pancreatitis complicated by acute respiratory failure, but mortality did not change. Luiten et al published a randomised controlled trial investigating SDD in patients with severe acute pancreatitis, defined by an Imrie score $\geq 3$ and or a Balthazar grade D or E. Fifty of 102 patients were treated with oral and rectal administration of colistin sulphate, amphotericin, and norfloxacin, combined with a short term systemic prophylaxis with cefotaxime until the cultures taken orally and rectally became sterile. In patients treated with SDD the overall incidence of infected necrosis ($\geq 18\%$ in the control group, $p=0.03$) and the rate of re-laparotomy (3.1 in the control group vs 0.9 in the SDD group, $p<0.05$) was significantly reduced. Potentially, these findings can be ascribed to the notable reduction in Gram negative infected pancreatic necrosis (33% in the control group vs 8% in the SDD group; $p=0.003$). Overall mortality in patients treated with selective decontamination was not significantly reduced (22% vs 35% in the control group). However, the authors suggested that SDD reduced mortality in patients with severe acute pancreatitis and an Imrie score $\geq 3$, regardless of the CT findings on admission. Nevertheless, the most important question remains unanswered: were the positive results in the treatment group achieved by topical treatment with SDD or by the short term application of intravenous antibiotics?

**INTRA-ARTERIAL ANTIBiotic PROphylaxis**

Few data exist about the efficacy of continuous regional arterial perfusion (CRAI). Habashi et al studied intravenously or intra-arterially administered antibiotics in bile induced acute pancreatitis in dogs. CRAI of antibiotics decreased the serum concentrations of endotoxin and phospholipase A2 activity, and completely prevented the occurrence of pancreatic infection; it also significantly improved the survival rate in the test animals. Unfortunately, the conclusions of this study are limited by the length of follow up (36 hours). In another study, Takeda et al examined the CRAI of nafamostat, a protease inhibitor, in combination with antibiotics. Fifty three patients were divided into three groups: group I (16 patients who were referred more than eight days after disease onset) received intravenous nafamostat and antibiotics; group II (22 patients referred within seven days) received nafamostat via CRAI, and antibiotics intravenously; group III (15 patients referred within seven days) received both nafamostat and imipenem via CRAI. The incidence of infection of pancreatic necrosis in group III (0%) was significantly lower than in groups I (50%) and II (22.8%). The mortality rates in groups II (13.6%) and III (6.7%) were significantly reduced, compared with that in group I (43.8%), but were not significantly different from each other. The major drawbacks of this study are its uncontrolled, non-randomised design, the use of different antibiotics, the short duration of antibiotic infusion, the clinically difficult technique, and the simultaneous use of a protease inhibitor, which may have complicated interpretation of the results. Therefore, further studies are necessary to evaluate the role of intra-arterial regional antibiotic treatment in severe acute pancreatitis.

**Treatment of infected pancreatic necrosis**

Local infection of necrotic areas of the pancreas influences the course of the disease, the prognosis, and the clinical management. Bacterial infection of pancreatic necrosis is usually suspected in patients who develop signs of sepsis,
and is confirmed by a bacteriologically positive fine needle aspiration. Conservative treatment will lead to almost 100% mortality in patients with signs of local and systemic septic complications of necrosis.26 27 71 Even after -26 27 71 - Early, surgically confirmed necrosis carries a mortality rate (ranging from 15 to 82%) which is three times higher than the mortality of sterile necrosis.27 71 Infected pancreatic necrosis is a clear indication for surgery, but the management of sterile pancreatic necrosis is controversial. Over the past two decades, most surgical centres have adopted a very aggressive surgical approach to severe acute pancreatitis. However, there is now a growing trend towards treating patients with sterile severe acute pancreatitis conservatively. Surgical intervention may be limited to patients with a deteriorating clinical course which does not respond to intensive care.28 40 80 In experienced hands these approaches have reduced mortality from severe acute pancreatitis to <15%.

Unproved strategies include percutaneous CT guided catheter drainage, recently described by Frey and colleagues29; transoral intrapancreatic drainage and irrigation lavage reported by Baron et al30 and laparoscopic necrosectomy.31 Further evaluation of these techniques is needed before they can be adopted into clinical practice.

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