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Prevention of bacterial infection and sepsis in acute severe pancreatitis

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Between 1984 and 1986 six patients with acute respiratory failure (requiring ventilation for at least 3 days) complicating acute pancreatitis were managed on the intensive care unit (median ventilation period 6 days; range 3–41 days). Between 1987 and 1989 nine similar patients were managed (median ventilation period 35 days, range 4–69 days), and a regimen of enteral tobramycin, polymyxin and amphotericin to selectively decontaminate the digestive tract (SDD) was introduced. Five of six patients treated before 1987 had serious infections (three Gram-negative, one fungal), compared with only one of nine patients treated with SDD ($P<0.05$). Clinical signs of sepsis were evident for 62% of the pre-SDD period, compared with 39% of the period during SDD therapy ($P<0.001$). Systemic antibiotic prescribing was reduced in the SDD group; however, mortality remained unaffected with only two patients surviving pre-SDD and three during SDD treatment.

SDD reduces infection rates and sepsis in patients with acute pancreatitis and may help to improve the prognosis of this life-threatening condition.

Infection is common in acute severe pancreatitis and is associated with a threefold increase in mortality *(1)*. When respiratory failure complicates acute pancreatitis, the risk of infection increases as mechanical ventilation lowers host resistance *(2)*.

Gram-negative aerobic bacteria account for the majority of these infections *(3,4)* and are designated as hospital acquired, although it may be more precise to label them as endogenous infections, as they arise from organisms which first colonise the patient's own gastrointestinal tract. This phenomenon frequently occurs during the hospital admission but is related to physical illness rather than the hospital environment.

Since 1987 we have been using a combination of non-absorbable enteral antibiotics to selectively decontaminate the digestive tract (SDD). This regimen was designed to decontaminate the digestive tract of aerobic Gram-negative bacteria and yeasts, as respiratory infections in ventilated patients were thought to originate from the oropharynx and the gastrointestinal tract, once colonised by such organisms *(5)*.

This paper presents data concerning the septic and infective complications of patients with acute pancreatitis requiring ventilation in the 3-year period before and after the introduction of SDD.

Patients and methods

Between 1984 and 1986 eight patients with acute pancreatitis and respiratory failure requiring ventilation were managed on the intensive care unit. In the 3 years 1987 to 1989 after the introduction of SDD, a further 13 patients were managed. Two patients from each group were not studied because they died within 48 h of admission and a further two patients in the SDD group were successfully weaned from ventilation within 24 h and were not studied. Patient details are summarised in Table I.

SDD was initiated upon starting mechanical ventilation, which was the indication for admission to the

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Table I. Patient details

	Age (years)	*Sex*	*Study (days)*	*Aetiology*	*Ranson*	*Apache*	*Outcome*
1984–1986							
LL	75	F	5	U	10	27	Died
YT	22	F	41	GS	2	8	Died
FC	67	M	6	A	7	20	Died
AG	75	F	25	U	5	21	Alive
JY	55	M	6	GS	6	21	Died
JC	39	M	3	A	4	14	Alive
1987–1989							
JH	58	M	22	A	7	22	Died
FK	69	F	69	U	6	26	Alive
DL	30	M	57	A	5	15	Died
MA	34	M	31	A	9	26	Alive
BC	50	M	41	A	8	25	Alive
AP	41	M	9	A	7	28	Died
DH	36	M	35	A	7	23	Died
ER	62	M	4	GS	10	30	Died
BT	40	M	46	GS	5	14	Died

U, Unknown; GS, Gallstone; A, Alcohol

intensive care unit. Clinical and microbiological data were collected until either the patients were successfully weaned from the ventilator or they died.

SDD has three components:

(a) Cefotaxime 1 g 6 hourly, intravenously for the first 4 days;
(b) An oropharyngeal paste applied by a gloved finger to the buccal mucosa and oropharynx 6 hourly, containing tobramycin 2%, polymyxin 2%, and amphotericin B 2%
(c) A nasogastric instillation containing tobramycin 80 mg polymyxin 100 mg and amphotericin B 500 mg given 6 hourly.

Nasogastric suction was discontinued for 1 hour after each instillation.

Surveillance swabs were taken routinely from the oropharynx and rectum for culture, and additional cultures performed when indicated clinically. All specimens were cultured aerobically using standard microbiological techniques for bacteria and yeasts and anaerobically when indicated clinically *(6)*. Infection in this study was defined as a microbiologically proven clinical diagnosis. A bacteraemia was confirmed by two consecutive sets of positive blood cultures. Urine infections were diagnosed by culture of more than 5×10^7 organisms/l. Chest infections and infections at other sites were diagnosed by dense growth of micro-organisms with 3+ leucocytes from the tracheal aspirate or swab on microscopy. Patients were defined as being septic with a core temperature greater than 38.5°C for 2 h or more in the day along with any two of the following clinical or laboratory features: haemodynamic instability requiring an increase in inotropic therapy, deterioration in respiratory function as measured by arterial blood gases, an increase in peripheral blood leucocyte count by 10×10^9/l, or a doubling of the serum C-reactive protein level.

Antibiotics were prescribed when pathogens appeared on culture and when indicated on clinical grounds. All patients routinely received H_2 antagonists as prophylaxis against upper gastrointestinal haemorrhage.

Assessment of other major organ failure was made on the following criteria: cardiac, a need for inotropic support; renal, requiring renal replacement therapy; hepatic, plasma bilirubin >75 μmol/l in the absence of a dilated common bile duct. The severity of pancreatitis was assessed by the Ranson scoring system *(7)* on admission and Apache II scores were also calculated *(8)* at this time (Table I).

The details of the surgical procedures are summarised in Table II. The main indications for surgery were determined clinically and manifest as either overwhelming sepsis or haemorrhage, though on five separate occasions CT scan correctly identified abscess collections or pancreatic necrosis requiring surgical intervention. CT-guided aspiration of the pancreas for evidence of infection was not performed.

The incidence of sepsis and infection was analysed using the χ^2 test.

Results

The infections of both groups are shown in Table III. Between 1984 and 1986 five of six patients developed serious infection, by contrast to only one of nine patients treated by SDD, despite the longer mean study period of this group. In the non-SDD or conventionally treated group, Gram-negative organisms were the cause of infection in three patients, *Candida albicans* in one and

Table II. Summary of surgical details

	Nature of operation	*Timing of operation*	*Necrosis*	*Collections*	*Haemorrhage*
1984–1986					
LL	em (1)	1 (1)	BT+	+	2
YT	em (4)	13 (5), 23 (15)	+++	+++	36
	el (1)	31 (23), 48 (40)			
FC	em (1)	30 (−7)	—	+++	2
AG	—	—	—	—	3
JY	em (2)	7 (1), 17 (11)	B++	+++	9
JC	—	—	—	+	—
1987–1989					
JH	em (2)	9 (2), 29 (2)	—	++	8
FK	em (6)	15 (13), 19 (17)	BT++	++	30
	el (4)	22 (20), 36 (34)			
		48 (46), 103 (101)			
DL	em (6)	9 (3), 11 (5)	T++	++	30
1 (5)	T++	++	30		
	e (1)	42 (36), 53 (47)			
		53 (47), 61 (55)			
MA	em (6)	12 (2), 14 (4)	BT	++	22
	el (17)	18 (8), 20 (10)			
		22 (12), 28 (18)			
BC	em (5)	2 (−2), 6 (2)	BT	+++	18
	el (12)	21 (17), 33 (29)			
		47 (43)			
AP	em (4)	10 (2), 12 (4)	H	—	41
	el (2)	14 (6), 16 (8)			
DH	em (10)	3 (1), 5 (3)	BT+	+	74
	el (6)	7 (5), 9 (7)			
		6 (14), 23 (21)			
		25 (23), 32 (30)			
		37 (35), 38 (36)			
ER	—	—	HBT+	—	1
BT	em (7)	39 (−7), 46 (1)	HBT+	++++	66
	el (7)	48 (3), 50 (5)			
		64 (19), 68 (23)			
		80 (35)			

Nature of operation: Either emergency (em) or elective (el) procedure, with number of procedures carried out in parentheses. Timing of operation: Time of emergency procedures after admission with the time on intensive care in parentheses. Necrosis: Extent of necrosis to include pancreatic head (H), body (B), tail (T), peripancreatic region (+), extrapancreatic region (++) and extensive extrapancreatic necrosis (+++). Collections: Collections of pus which are pancreatic (+), extrapancreatic (++) or extensive extrapancreatic collections (+++). Haemorrhage: Number of units of blood required during the admission.

coagulase-negative staphylococcus in the remaining patient. One patient (YT) appeared to develop a disseminated Gram-negative infection with two episodes of bacteraemia despite systemic antibiotic therapy. In four patients treated by SDD, coagulase-negative staphylococci were isolated from the blood, prompting removal of the central venous catheter and confirmation of catheter-associated infection in each case. These infections were not thought to be serious as concomitant signs of sepsis were evident in only one case (DL), who responded to line removal and antistaphylococcal therapy.

The six patients studied between 1984 and 1986 were septic for 53 of 86 (62%) days compared with 122 of 314 (39%) days in the nine patients receiving selective decontamination ($P < 0.001$). Overall, only five patients had no definite infections but still died, all with evidence of sepsis for a large part of the study period. Overall, only five patients survived and all had some evidence of infection. These patients were studied for 34 ± 24 days (mean $\pm$ SD) and had evidence of sepsis for 31% of this period. The 10 non-survivors were studied for 23 ± 20 days and were septic for 53% of this period. All of the pre-SDD patients who died had evidence of sepsis at the

Table III. Summary of infections

1984–1986	
LL	*E. Coli*—Bacteraemia (1)
YT	*E. Coli*—Bacteraemia (20)
	E. Coli—Peritoneum (20)
	E. Coli—Pneumonia (34)
	E. Coli—UTI (38)
	E. Coli—Bacteraemia (38)
FC	*Candida*—Fungaemia (5)
AG	*E. Coli*—Pneumonia (14)
JY	—
JC	CNS—Pneumonia (1)
1987–1989	
JH	—
FK	*Pseudomonas*—Bacteraemia (1)
DL	CNS—Neckline (33)
MA	CNS—Neckline (8)
BC	CNS—Neckline (10)
AP	—
DH	CNS—Neckline (19)
ER	—
BT	—

UTI, Urinary tract infection; CNS, Coagulase-negative, staphylococci.

Figures in parentheses indicate days in relationship to study period.

time of death. Five SDD patients died with evidence of sepsis, three of these patients developed fatal encephalopathy and two died with uncontrollable haemorrhage from the pancreatic bed. A further patient in the SDD group became progressively unresponsive to inotropic drugs without obvious signs of sepsis. The encephalopathy we encountered was a preterminal event, preceding death by up to 1 week. It was characterised by status epilepticus, diffuse slow wave pattern on EEG and absence of focal pathology on CT scan. Post-mortem findings revealed multiple small white matter haemorrhages.

Significant reductions in anti-staphylococcal prescribing (27% *vs* 47% of the study period, $P<0.001$) were seen in the SDD group along with reductions in metronidazole (43% *vs* 71%, $P<0.001$) and ampicillin (6% *vs* 16%, $P<0.005$) prescribing. No significant differences in the prescription of other classes of antibiotic were seen, even cefotaxime, which was part of the SDD regimen, was used for the same proportion of the study in the pre-SDD period.

Emergency surgery was performed more frequently in the SDD group, though is unlikely to have been as a result of this treatment; rather that these patients were more ill as reflected by the Ranson and Apache scoring and also at this time a positive approach to surgery was adopted, with greater willingness to operate electively to lavage and débride necrotic material and pockets of pus.

Multiple-organ dysfunction was present in four of six patients pre-SDD treatment. One patient had four major organs failing and three organs had failed in a further three patients. None of the patients with multiple-organ failure in this group recovered. All of the patients in the SDD group had multiple-organ failure (four systems in six patients, three systems in three patients), which was reflected by the higher mean Ranson (7.1 *vs* 5.7) and Apache II score (23.5 *vs* 18.5) in this group. One patient survived quadruple organ failure.

Discussion

The importance of secondary pancreatic infection in determining prognosis in acute necrotising pancreatitis has been emphasised previously *(1,3,4)*. The risk of infection appears to be related to the duration and extent of the pancreatic necrosis *(9)* which may simply reflect the natural history of infection in critically ill patients *(10)*, with colonisation and subsequent infection the inevitable consequences of prolonged illness.

The organisms responsible for the majority of pancreatic infections *(1,4)* are typical of those found to colonise the gastrointestinal tract in critically ill patients *(5)*. This is no coincidence and may be due to translocation of bacteria through the gut wall or lymphatics, or haematogenous spread of organisms after uptake by the portal system. The gut wall integrity may well be compromised in the milieu of inflammatory mediators released during the acute attack of pancreatitis. Other mechanisms of 'gut leak' concern nutritional factors, particularly the amino acid glutamine *(11)* and also altered secretion of mucus or immunoglobulin A *(12)*.

Prophylactic use of systemic antibiotics does not appear to reduce the incidence of secondary infections in acute pancreatitis *(13,14)*; however, with refinements in our knowledge of the ability of antibiotics to penetrate pancreatic tissue then perhaps improvements in infection control may be seen *(15)*. Improvements in resuscitation early in the course of acute pancreatitis to improve oxygen delivery at a tissue level *(16)* may lead to limitation of pancreatic necrosis and at the same time improve both gastrointestinal and hepatic function. Aggressive surgical techniques *(17–21)* appear to have improved prognosis in severe cases, although controlled studies are lacking and mortality remains high in cases of multiple-organ failure, mainly because of infectious complications.

In this paper we have only described those patients who required mechanical ventilation. Respiratory failure occurs infrequently in acute pancreatis, associated with the most advanced cases and often in conjunction with other organ malfunction *(22)*. Although we have not demonstrated improved mortality figures in this paper, the patients treated with SDD demonstrate prolonged survival on the intensive care unit in spite of higher Ranson and Apache scores with significant reductions in both clinical signs of sepsis and defined infections. In view of the particular problems associated with acute severe pancreatitis we believe SDD represents a step forward in the management of such cases and would be well worth studying prospectively on a larger scale.

Why should SDD work and why use this particular combination of antibiotics? Any illness induces changes in the intestinal microflora *(23,24)* with a shift towards 'hospital' flora including *Klebsiella, Proteus, Enterobacter* and *Pseudomonas* species. These changes become most obvious with critical disease; even the stomach and respiratory tract may become colonised, particularly when there is a failure to maintain a normal gastric pH *(25,26)*. These 'hospital' organisms are particularly implicated in causing secondary infection in necrotising pancreatitis *(1,3)*. In such critically ill patients with multiple-organ failure, gastric failure is common with an inability to maintain an acid pH, even in the absence of H_2 blockers. We feel that this could be an important factor in the host resistance to colonisation and would now recommend the use of sucralfate rather than H_2 antagonists in the prophylaxis against upper gastrointestinal haemorrhage.

Tobramycin and polymyxin are both potent antibiotics which are not absorbed to any significant extent when given enterally and therefore do not cause toxicity. They are both bactericidal to Gram-negative organisms and have previously been demonstrated to deplete the gut of Gram-negative bacteria *(5)*. Yeasts, in particular *Candida albicans* can readily colonise the gut and this is countered by amphotericin B in the preparation. A parenteral agent is required in addition to the non-absorbable agents to treat or prevent infections on admission, which could be described as primary infections. It should be stressed that SDD is only of value in preventing secondary or hospital acquired infection. In the original studies *(5)*, cefotaxime was chosen because it covers both community and hospital flora except *Pseudomonas*. The increased frequency of coagulase-negative staphylococcal (CNS) infections in the SDD group is important as these infections can be life-threatening *(27)*. An awareness of the potential of CNS will ensure that these infections are treated promptly and efficiently, so that the reduction in highly virulent Gram-negative infections at the expense of an apparent increase in CNS infections would appear to be a fair 'trade-off'.

Marshall and Sweeney *(28)* differentiated the roles of infection as a microbial phenomenon and sepsis as a host response. These two terms have always classically been linked together, although the relationship is often obscure. They noted that the host response was more important than infection in determining outcome in a group of critically ill surgical patients. This is a finding which we can confirm as all but one patient who died had evidence of sepsis at the time of death and the surviving patients were septic for significantly shorter periods. Many of the features of sepsis can be explained by endotoxaemia which occurs in severe cases of pancreatitis *(29)*. Although a reduction in endotoxin might be expected simply as a result of decreasing the numbers of Gram-negative bacteria using SDD therapy, it is known that polymyxin, a component of the SDD regimen has specific anti-endotoxin effects *(30)*.

Surgery alone did not appear to influence outcome; however, only three patients were treated conservatively, two from the early group, one (AG) with relatively mild disease whose main problem was chronic lung disease and weaning from the ventilator, and another (JC) similarly with relatively mild disease who responded quickly to peritoneal lavage. The other patient treated conservatively from the SDD group had severe disease, but because of his underlying medical complications was not considered suitable for surgery and was managed by lavage alone. In our experience pancreatitis patients with multiple-organ failure and signs of sepsis will not survive with conservative therapy and repeated surgery is often required to remove residual necrotic material and drain abscesses. This experience is reflected in the greater number of operations performed in the SDD group of patients who tended to have more severe disease. Although we could not claim improved survival in the SDD group, these patients were surviving for some considerable periods on the intensive care unit despite fulminant disease suggesting that the infection control measures of SDD, along with aggressive drainage and débridement, were at least partially effective. It is to be stressed that we do not consider SDD to be effective on its own in this situation but it should complement surgery by preventing secondary infections.

We would conclude that SDD is a valuable adjunctive therapy for patients with acute severe pancreatitis and by reducing the associated infections and sepsis contribute to the progress being made in the management of this condition.

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Invited comment

In this paper the authors suggest that the use of selective decontamination of the digestive tract (SDD) in ventilated patients with severe acute pancreatitis will result in reduced infection rates and improved outcome. They have shown some effect of SDD in an analysis of two small groups of consecutive patients. The incidence of bacteraemia and chest infections was reduced by SDD as were the periods of 'sepsis' but the overall outcome and mortality rate was not affected.

The authors have given little information about the type of infection in the retroperitoneum, which is one of the most significant determinants of outcome, nor how SDD may have modified this. They do mention bacterial translocation from the gut but further therapeutic manoeuvres would be required to mitigate this process.

Clearly a trial of these therapies in acute pancreatitis with its protean manifestations would be difficult to mount (although some are being attempted) and those concerned with the care of these very difficult patients might view this paper with some scepticism. The reduction of Gram-negative infections was accompanied by a raised incidence of *Staph epidermidis* in the blood and this can, on occasions, be serious though not apparently so in these patients. In future, the early management of acute pancreatitis will probably involve a combination of new methods with modulation of the pathophysiological and immunological responses and the prevention of bacterial translocation from the gut. The place of SDD in this situation is as yet unproven but gaining ground and this paper provides some food for thought.

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