SEVERE ACUTE PANCREATITIS and SELECTIVE DECONTAMINATION
(Results of a multicenter controlled clinical trial)

ERNSTIGE ACUTE PANCREATITIS en SELECTIEVE DECONTAMINATIE
(Resultaten van een multicentrische gecontroleerde klinische studie)

Nip the danger in the bud/gut
(metaphor)

A United States Air Force F-117 "Stealth Fighter" of the 37th Tactical Fighter Wing performs a **precision attack** on an Iraqi air **defense sector headquarters** during **early stages** of Operation Desert Storm. January 17, 1991. The dark spot at the upper right quadrant of the sighting cross is the entry point of a bomb dropped moments earlier by a preceding aircraft.

This "Official Department of Defense Photo" was kindly put at my disposal by the Office of the Assistant Secretary of Defense (Public Affairs) of The Pentagon, Washington, D.C., United States of America.

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PROEFSCHRIFT

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Ernest Johan Theodoor Luiten

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Acute pancreatitis is the most terrible of all calamities that occur in connection with the abdominal viscera. The suddenness of its onset, the illimitable agony which accompanies it, and the mortality attendant upon it, all render it the most formidable of catastrophies.
Moynihan, 1925

Aan Joy, Jacky Denise en Kevin Alexander

CONTENTS

CHAPTER 1

INTRODUCTION

TREATMENT OF ACUTE PANCREATITIS: AN ONGOING DEBATE BETWEEN MEDICAL AND SURGICAL THERAPY

From a mild self-limiting disease, development of multiple organ failure and frequently septic complications towards a fulminant course resistant to any type of treatment, acute pancreatitis is a disorder that has numerous causes, an obscure pathogenesis and an often unpredictable outcome.

Following anecdotal reports[1-3], acute pancreatitis first became widely recognized as a clinical and pathologic condition through an exhaustive review and systematic analysis of the course of the disease of 53 patients, reported more than a century ago by Reginald Fitz, Professor of Pathological Anatomy at the Harvard University[4]. In contrast to Senn[5], a Chicago surgeon, he initially considered early operative intervention ineffective and hazardous in these patients. Here the debate between medical and surgical therapy for acute pancreatitis originates and has continued ever since.

Because acute pancreatitis was usually diagnosed at operation or at autopsy during the beginning of the 20th century and a significant proportion of those diagnosed at surgery survived, Fitz waived from this conservative stance stating that operative intervention would be 'more helpful the earlier in the course of the disease it is performed'[6]. Moynihan further delineated the surgical approach to pancreatitis in 1925 and today his principles of lesser sac debridement and drainage remain very nearly the state of the art when it comes to surgery in these patients[7-9]. However due to the introduction of methods for measurements of serum amylase and its elevated levels in case of acute pancreatitis, which decreased the number of diagnoses made at surgery, as well as to reports of Mikkelson in 1934 and Paxton and Payne in 1948, emphasizing a decrease in survival after operative management, early surgical intervention was widely regarded as unnecessary or harmful[10-12].

Developments in intensive care allowing to safely correct circulatory volume and electrolyte disturbances, relief pain, maximize renal perfusion, support respiration and provide adequate nutrition, enabled more patients to survive the initial critical phase of the disease and further contributed towards this conservative treatment. However medical therapies attempting to 'put the pancreas at rest' by inhibiting acinar cell secretion with regimens involving nasogastric suction[13-15], cimetidine[15-18], atropine[19], glucagon[18,20-22], calcitonin[23,24], and somatostatin or its analog octreotide[25-27] have met with almost uniformly disappointing results. Controlled trials with inhibitors of proteolytic enzymes, e.g. aprotinin (Trasylol)[20,28], gabexate mesilate[29,30], and phosphlipase inhibitors[31], have

similarly been ineffective in ameliorating the disease so far. Because few patients with severe disease were enrolled in many of these studies, the possibility of not reaching statistical significance may have biased the conclusions (type II error)[32]. Triple ostomy a surgical procedure-comprising cholecystostomy, gastrostomy and jejunostomy-to relieve the load on the pancreas was recommended by Lawson et al.[33]. However although a jejunostomy proved useful for quick resumption of enteral feeding[34] this procedure to rest the inflamed gland, which also included closed drainage of the lesser sac, failed to prove its efficacy and gave rise to high incidence of septic complications[34,35]. Also peritoneal lavage was not found to improve the prognosis[36,37]. In anticipation of future therapies, directed at inhibition of intracellular pathological events (e.g. lysosomal enzyme activity/synthesis, colocalization of liposomes and zymogen granules)[38], which may possibly become available, treatment of patients with acute pancreatitis to day remains largely custodial in trying to control presenting symptoms as much as possible.

In about 20% to 30% of patients with acute pancreatitis a severe clinical course arises with development of multiple organ failure and variable amounts of necrosis of peri- and pancreatic tissues[39]. With improvement in the early medical management of severe acute pancreatitis, secondary infection of the (peri) pancreatic necrosis became the leading cause of death in severe acute pancreatitis[40-43]. During the mid-seventies three controlled clinical trials, using ampicillin, failed to prove efficacy in patients with acute pancreatitis[44-46].

Since conservative management failed to decrease the high mortality rate due to septic complications in patients with necrotizing pancreatitis, early surgical removal of necrosis once again was recalled during the early eighties[47-50]. In 1986 Beger et al, who performed a prospective bacteriological analysis of necrotic tissues obtained at surgery from 114 patients with acute necrotizing pancreatitis, demonstrated that infection of (peri)pancreatic necrosis occurs early and frequently, causing a significant increase in morbidity and mortality as compared to sterile necrosis[51]. Infection of (peri)pancreatic necrosis develops in 40% to 60% of patients with severe acute pancreatitis[51-57]. Chances to develop infection of necrosis increase with larger amounts of necrosis[41,58]. In accordance with the adage 'ubi pus, ibi evacua', infected necrosis was recognized as an absolute indication for surgical intervention. A significant contribution has been made by Gerzof et al. by introducing the computer tomography-guided percutaneous fine-needle aspiration and subsequent culture of (peri)pancreatic necrosis and fluid collections enabling early diagnosis of pancreatic infection[52]. However the role of surgery has been controversial with regard to sterile necrosis. Since patients with sterile necrosis

can do well even without surgery, operative intervention in these patients nowadays is limited to those who do not respond to maximal intensive care[59-61].

Despite surgical treatment of necrosis of infected (peri)pancreatic necrosis the prognosis remained worse as compared to patients in whom necrosis remained sterile. Prophylactic measures, i.e. antibiotics, once again gained interest when attention shifted from surgical removal-i.e. necrosectomy-of infected necrosis towards prevention of infection of necrotic (peri)pancreatic tissues. Although the role of bacteria in the *induction* of experimental acute pancreatitis had been extensively examined, little was known about the pathogenesis of *secondary* infection of (peri)pancreatic necrosis. Webster et al., who firstly demonstrated that postinduction bacteremia is an important phenomenon in experimental acute pancreatitis, suggested that local infectious complications originate from hematogenous seeding[62]. Because microbiological analysis of infected (peri) pancreatic necrosis, both experimentally and clinically, revealed mostly gram-negative aerobic micro-organisms which showed a resemblance with the intestinal flora, the gut was postulated as their possible origin[8,9,51-53,62-65]. Raised titres of antibodies against enterobacterial common antigen, which indicate the humoral antibody response against enteric bacteria, further supported the hypothesis that these micro-organisms may possibly originate from the intestine from which they translocate towards the necrosis[66].

In 1987 Lange et al. showed in a controlled study of experimental acute pancreatitis in rats, that reduction of intestinal flora, by means of either subtotal colectomy or intestinal lavage and intraluminal instillation of kanamycin both resulted in a reduction of mortality. However in the colectomized rats gram-negative bacteraemia was not prevented, suggesting incomplete reduction of intestinal flora as compared to the lavaged rats in which gram-negative micro-organisms were absent both in blood as well as ascites[67].

A pilot study was conducted in patients with severe acute pancreatitis using intestinal lavage. However the application of this technique did impose us with severe logistic problems and resulted in undesirable dyscomfort for the patient (Lange JF, unpublished data).

A clinical feasible way to effectively reduce the aerobic gram-negative intestinal flora was reported for the first time in 1984 by Stoutenbeek et al. with their use of selective decontamination of the digestive tract[68]. In this technique non-absorbed antibiotics are employed to eliminate or greatly reduce the number of aerobic gram-negative bacilli and yeasts in the gastrointestinal tract (thus reducing the risk of endogenous infection), whilst retaining the normally predominant anaerobic flora (thereby preventing colonization or overgrowth with drug-resistant strains,

a phenomenon termed colonization resistance)[69,70]. The prophylactic strategy combined three distinct components: SDD applied to the patients throughout their ICU stay, systemic cefotaxime administered for the first few days only and intensive microbiological surveillance. SDD was supplemented with cefotaxime for *a few days* to provide additional broad-spectrum cover for the early period of admission when SDD is only partially established. Cefotaxime has negligible effects on the anaerobic flora of the gastrointestinal tract and is thus unlikely to hamper resistance to colonization[71].

Since infection of (peri)pancreatic necrosis emerged as the principal determinant for survival in the patient with severe acute pancreatitis surviving the early phase of the disease and aerobic gram-negative micro-organisms, possibly originating from the digestive tract based on resemblance, are most frequently isolated, selective decontamination of the digestive tract was investigated as a prophylactic strategy. After all, increasing the proportion of patients in whom (peri)pancreatic necrosis is precluded from secondary infection may lead to reduction of mortality as depicted in the hypothesis given below.

HYPOTHESIS

Severe acute pancreatitis

↓

Selective decontamination of the digestive tract

↓

Elimination and prevention of acquisition of
aerobic gram-negative intestinal micro-organisms

↓

Preservation of *sterile* (peri)pancreatic necrosis

↓

Reduction of mortality?

AIM OF THE STUDY

Selective decontamination of the digestive tract was used as an prophylactic strategy in a multicenter controlled clinical trial in patients with severe acute pancreatitis in order to evaluate the following issue:

1) Does the use of selective decontamination reduce mortality in patients with severe acute pancreatitis?
2) Does the use of selective decontamination reduce aerobic gram-negative infection of (peri)pancreatic necrosis in patients with severe acute pancreatitis?
3) Does aerobic gram-negative colonization of the digestive tract lead to an increased risk of aerobic gram-negative pancreatic infections and is this event time related?
4) Does the difference in the quantity and quality of micro-organisms, colonizing the digestive tract, influence morbidity and mortality of severe acute pancreatitis?
5) Does the use of selective decontamination reduce intestinal colonization with aerobic gram-negative micro-organisms in patients with severe acute pancreatitis?
6) Is the prognosis dependent on the different bacteriological status of (peri) pancreatic necrosis, i.e. development of gram-negative and/or gram-positive infection as compared to preservation of sterile necrosis?
7) Is there a reduction in morbidity when infection of the necrosis can be prevented?

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CHAPTER 2

CONTROLLED CLINICAL TRIAL OF SELECTIVE DECONTAMINATION FOR THE TREATMENT OF SEVERE ACUTE PANCREATITIS

Ernest J.T. Luiten, Wim C.J. Hop, Johan F. Lange, Hajo A. Bruining

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ABSTRACT

Secondary infection of (peri)pancreatic necrosis is the major cause of death in patients with severe acute pancreatitis. Controlled clinical trials to study the effect of selective decontamination in such patients are not available. A randomized controlled multicenter trial was undertaken in 102 patients with objective evidence of severe acute pancreatitis to evaluate whether selective decontamination (SD) reduces mortality.

Between April 22, 1990 and April 19, 1993, 102 patients with severe acute pancreatitis were admitted to 16 participating hospitals. Patients were entered into the study if severe acute pancreatitis was indicated, on admission, by multiple laboratory criteria (Imrie score ≥ 3) and/or computed tomography criteria (Balthazar grade D or E). Patients were randomly assigned to receive standard treatment (control group) or the same standard treatment plus selective decontamination (SD group). All patients received full supportive treatment and surveillance cultures were taken in both groups.

Fifty patients were assigned to the SD group and 52 were assigned to the control group. There were 18 deaths in the control group (35%), compared with 11 deaths (22%) in the SD group. (adjusted for Imrie score and Balthazar grade: $p=0.048$). This difference was mainly caused by a reduction of late mortality (>2 weeks) due to significant reduction of gram-negative pancreatic infection ($p=0.003$). The average number of laparotomies per patient was reduced in patients treated with SD ($p<0.05$). Failure of SD to prevent secondary gram-negative pancreatic infection with subsequent death was seen in only three patients (6%) and transient gram negative pancreatic infection in one (2%). In both groups of patients, all gram-negative aerobic pancreatic infection was preceded by colonization of the digestive tract by the same bacteria.

Reduction of gram-negative colonization of the digestive tract, preventing subsequent pancreatic infection by means of selective decontamination, significantly reduces morbidity and mortality in patients with severe acute pancreatitis.

INTRODUCTION

DESPITE improvement in surgical strategies, the mortality of patients with acute necrotizing pancreatitis remains high, between 20 to 70 %[1-8]. Infection of pancreatic necrosis is the most important cause of late mortality in severe acute

pancreatitis[3,7,9-13]. The value of prophylactic antibiotics has not been clearly demonstrated in patients with severe acute pancreatitis and possibly is due to patient selection, inadequate spectrum, insufficient doses or tissue penetration[12,14-17]. Intravenous antibiotics, which penetrate the pancreas-blood barrier, may not protect the necrotic nonperfused areas in and around the inflamed pancreas against infection.

The route by which sterile pancreatic necrosis becomes infected is not yet known. Experimental studies and clinical observations have suggested that translocation of bacteria toward the pancreas occurs hematogenously[18,19], transmurally through the colon[20-22], via lymphogenous routes[20,23], via ascites[19,23], and through bile[24], and duodenal chyme reflux[25]. Because gram-negative bacteria-predominantly isolated from the pancreatic necrosis-are of enteric origin, it seems probable that the source of the translocating bacteria is the intestine[2,7,9,10,14,22,23,26,27]. Prevention of translocation by intraluminal elimination of aerobic gram-negative micro-organisms in the intestinal tract may be an effective method to prevent pancreatic necrosis from becoming infected. In a controlled experimental study on rats with bile-salt-induced pancreatitis Lange et al. demonstrated a significant reduction of mortality in rats treated with intestinal lavage and intraluminal instillation of kanamycin[19]. Isaji et al. recently demonstrated in mice fed a choline-deficient, ethionine-supplemented diet to induce pancreatitis that oral antibiotics caused a three-fold reduction of infected necrosis and a significantly improved survival[28].

Several clinical studies have demonstrated that selective decontamination effectively eliminates aerobic gram-negative bacteria from the intestinal tract and sometimes reduces gram-negative septic complications in intensive care unit patients. However, results regarding reduction of mortality are conflicting[29-34]. This randomized, controlled clinical trial was undertaken to evaluate whether selective decontamination reduces mortality in patients with objective evidence of severe acute pancreatitis.

PATIENTS AND METHODS

Patients

Between April 22, 1990 and April 19, 1993, 102 patients with objective clinical signs of severe acute pancreatitis were admitted to 16 participating hospitals. The diagnosis of acute pancreatitis had been established on the basis of clinical

examination and elevated plasma levels of amylase (>1000 IU per liter), or at diagnostic laparotomy (ten patients). All patients were scored according to a multiple laboratory criteria score (Imrie score)[35] and contrast-enhanced computed tomography (CE-CT) examinations were used to classify disease severity (Balthazar grades)[36] (Table 1) within 48 hours of hospital admission.

Table 1. Prognostic Systems Used to Select Patients for Inclusion in the Trial

Multiple Laboratory Criteria (Imrie score)*	
Age	> 55 years
Serum uncorrected calcium	< 2.00 mmol/l
Serum urea	> 16 mmol/l
Lactate dehydrogenase	> 600 U/l
Blood glucose (no diabetes)	> 10 mmol/l
White cell count	> 15 10^9/l
Serum albumin	< 32 g/l
PaO_2	< 60 mm Hg (7.5 kPa)

Degree of disease severity according to Balthazar classification†	
grade A	normal pancreas
grade B	focal or diffuse enlargement of the pancreas (including contour irregularities, nonhomogeneous attenuation of the gland, dilatation of the pancreatic duct, and foci of small fluid collections within the gland, as long as there is no evidence of peripancreatic disease)
grade C	intrinsic pancreatic abnormalities associated with haziness and streaky densities representing inflammatory changes in the peripancreatic fat
grade D	as C plus single ill-defined fluid collection (phlegmon) in or adjacent to the pancreas
grade E	as C plus two or multiple, poorly defined fluid collections or the presence of gas in or adjacent to the pancreas

* : The Imrie score equals the number of separate criteria present (minimum : 0 ; maximum : 8).
† : CT scan with use of oral (1/2 hr before) and intravenous contrast (rapid iv drip). PaO_2 = arterial oxygen concentration.

Patients were included in the study if the following criteria were met: severe acute pancreatitis was indicated by 3 or more points according to the Imrie score and/or CT findings corresponding with Balthazar grade D or E. Findings at diagnostic laparotomy were not accepted as an inclusion critera.

Exclusion criteria were defined as follows: allergy to one of the antibiotics of the SD regimen; younger than 18 years of age; postoperative pancreatitis after pancreatic surgery; and bacteriologically proven infected necrosis at the time of randomization. The attending clinician obtained informed consent from the patient or relatives.

Patients who satisfied the criteria were randomly assigned to receive standard treatment (control group) or the same standard treatment plus selective decontamination (SD group). A 24-hour randomization service was available to randomize patients with stratification per center. Follow-up CT scans were repeated every week until discharge or death. The study was approved by the ethics committees of the participating hospitals.

Control Group: Standard Treatment

A nasogastric tube was always inserted. Intravenous crystalloid solutions were given according to clinical requirements. Oxygen therapy, based on arterial blood gas analysis, was administered by face mask and was replaced by assisted ventilation if the patient developed respiratory insufficiency. Cultures from the oropharynx, rectum, sputum, gastric content, and urine were taken on admission to the hospital and twice a week until discharge . If fever (≥39°C) was present, blood cultures were taken. Except for urine, qualitative semiquantitative bacteriologic analysis was performed routinely on all cultures. Cultures of (peri)pancreatic necrosis and ascites were obtained at laparotomy or by means of ultrasonographic or CT-guided percutaneous puncture, as described by Gerzoff et al.[10], if there was clinical suspicion of infected pancreatic necrosis. Patients underwent surgery if an ultrasonographic or CT-guided puncture showed presence of bacteria or if the condition was deteriorating despite aggressive supportive treatment. Surgery was performed either by transverse or median laparotomy. If repeated laparotomies were foreseen, a laparostomy, i.e. a ventral open packing of the abdominal cavity, was created[2]. Antibiotics were prescribed according to the antibiogram only in the presence of concurrent infection. Enteral feeding was replaced by total parenteral nutrition only if recurrent gastric retention was present.

SD group: Standard Treatment with Adjuvant Selective Decontamination

Patients randomized to the SD group received the same treatment as the control group with the addition of selective decontamination (SD). The SD regimen

consisted of oral administration of colistin-sulfate (200 mg), amphotericin (500 mg) and norfloxacin (Noroxin^R 50 mg) every 6 hours. A sticky paste containing 2% of the three SD drugs was smeared along the upper and lower gums every 6 hours and at the tracheostomy, if present. The aforementioned daily dose also was given in a rectal enema every day. A short-term systemic prophylaxis (mean 7.4 days) of cefotaxim sodium (Claforan^R 500 mg) every 8 hours was given until gram-negative bacteria were eliminated from the oral cavity and rectum. SD was discontinued as soon as the risk of aquiring a new infection was absent-i.e., the patient was extubated and without supplementary oxygen therapy or infusions, on regular oral diet, and mobilized on the ward.

Statistical Analysis

Power calculations at the phase of trial design, assuming a decrease in mortality from 50% to 25%, led to a total number of 154 patients to be included (alpha=0.05 (two-sided) and beta=0.10).

Because the annual accrual rate was much less than expected, after 2 years it was decided to limit the size of the trial to 100 evaluable patients, thereby reducing the power to 80% at one-sided testing. This decision was made without consideration of the accumulating outcomes.

Percentages were compared by the Fisher exact test or the chi square test, if appropriate. Continuous data were compared by the Mann-Whitney *U* test. For mortality, which was the major end-point in this study, multivariate analysis (logistic regression[37]) at entry into the study, allowing for Imrie score and Balthazar grade, was performed to obtain a higher level of precision in comparing treatment groups. Two-sided p values of 0.05 or less were considered statistically significant. Follow-up was continued until death or discharge from the hospital.

RESULTS

Inclusions, Exclusions, and Withdrawals

Of the 109 patients randomized into the study 2 (SD: n=1 ; control: n=1) were excluded because of peroperatively proven infected necrosis immediately (<1hr) after randomisation and before treatment was started. In addition, five patients (SD: n=3; control: n=2) were withdrawn from the study because the clinical diagnosis was found to be erroneous (one patient with streptococcal sepsis, one

patient with an acute aortic occlusion immediately after coronary bypass surgery, one patient with a ruptured pancreatic pseudocyst, one patient with chronic pancreatitis and one patient with an ERCP-induced choledochus perforation).

Table 2. Baseline characteristics of Patients with Severe Acute Pancreatitis

	SD group (n=50)	Control group (n=52)
Mean age (range)	56 (26-91)	55 (20-88)
Sex		
Male	31	29
Female	19	23
Etiology		
Alcohol	19	12
Gallstones	17	19
Hyperparathyroidism	0	2
Blunt abdominal trauma	1	0
Postoperative	2	2
ERCP+ - induced	1	3
Unknown	10	14
Imrie score		
0	5	4
1	8	7
2	2	10
3	10	6
4	12	13
5	9	6
6	3	2
7	1	4
8	0	0
Balthazar degree of disease severity		
grade A	0	0
grade B	0	0
grade C	3	4
grade D	21	20
grade E	26	27
day 1 unavailable	0	1*

+ : ERCP = endoscopic retrograde cholangiopancreatography

* : CT-scan was performed on day 5 : grade D

Of the remaining 102 patients, 50 had been assigned to the SD group and 52 to the control group. Inclusion scores are listed in Table 2. Selective decontamination was started within 24 hrs of randomization. Ten patients (SD: n=8 ; control: n=2) with severe acute pancreatitis had to be randomized only on the basis of the multiple laboratory criteria (Imrie score ≥3) as their condition did not permit transport from the intensive care unit to the CT scanner at that time. Of these patients, fluid collections in or adjacent to the severely inflamed pancreas (personal communication with the atttending surgeon immediately post-operatively) were demonstrated on the first day of the study during laparotomy in eight patients and with abdominal ultrasound in one patient. Because of these results, the Balthazar grade was classified as grade E. In the other patient (control group; Imrie score=3), a CT scan was performed only after five days of treatment and it demonstrated a peripancreatic fluid collection. The latter patient also underwent surgery on the first day after randomization; however, the pancreatic loge was left untouched. The Balthazar grade at the time of randomization was unavailable for this patient.

Comparability of Control and SD group

Both treatment groups appeared well matched for age, sex, etiologic factors, Imrie score, and Balthazar grade. Characteristics for both groups are listed in Table 2. The mean Imrie score was 3.2 for both groups. Patients with an Imrie score of 8 were not encountered in this study.

Mortality

Eleven patients (22%) in the SD group died as compared to 18 patients (35%) in the control group. This difference is not significant (p=0.19). The 95% confidence limits of the difference (control group minus SD group) in mortality ranges from less than 4% to more than 30%. Survival according to treatment group is shown in Figure 1. All deaths occurred within 80 days. In each of both groups 6 patients died of multiple-organ failure with documented sterile pancreatic necrosis. Ten patients in the control group died of a gram-negative pancreatic sepsis syndrome compared with only three such patients in the SD group (p=0.07). In each of both groups one patient died of sepsis due to a solitary gram-positive pancreatic infection. Gram-positive sepsis of unknown origin, without pancreatic infection, was the cause of death in one patient in each of both groups.

The Imrie score at entry into the study appeared to correlate very strongly with mortality (Figure 2). Mortality was 0% for an Imrie score of 0 or 1, and gradually increased to 100% for patients with an Imrie score of 7 (p_{trend}<0.001). Mortality also increased with increasing Balthazar grade, although these differences were less pronounced (p_{trend}=0.04) (Figure 2). The worsening of prognosis with increasing Imrie score and Bathazar grade was apparent in each separate treatment group. Overall mortality in the SD group *versus* the mortality in the control group appeared to be significantly lower (p=0.048), using multivariate analysis allowing for Imrie score and Balthazar grade (Table 3). This analysis also demonstrates the importance of the Imrie score in predicting mortality. There was no significant relation between mortality and the Balthazar grade.

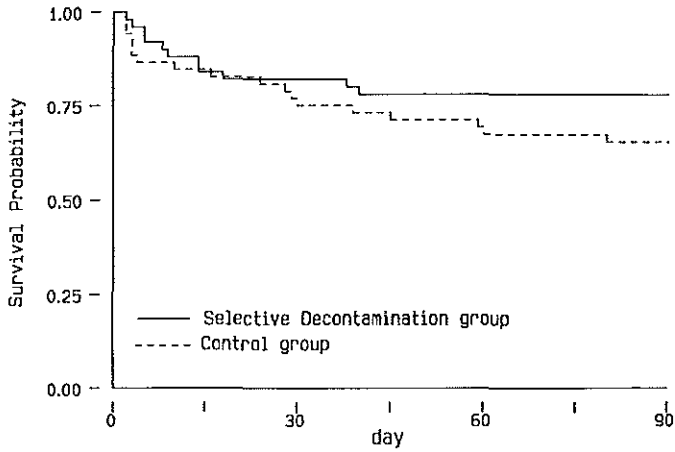

Figure 1. Overall survival according to treatment. Overall mortality rates at 90 days: SD group=22% ; control group=35%. Adjusted for Imrie score and Balthazar grade, p=0.048. Difference in mortality rates equals 13% (95% confidence limits: -4%, +30%).

Bacteriologic analysis

Secondary pancreatic infection occurred in 20 patients (38%) in the control group and in 9 patients (18%) of the SD group (p=0.03). Gram-negative pancreatic infection occurred in 17 patients (33%) in the control group and in only 4 patients (8%) in the SD group (p=0.003). Pancreatic necrosis was not infected in 11 of 16 patients who died early in contrast to only 3 of 13 patients who died after 2 weeks

(p=0.03). This difference is similar for both groups. Qualitative bacteriologic analysis of (peri) pancreatic necrosis for both groups is demonstrated in Table 4. Of 74 bacterial colonies isolated from 20 patients of the control group 61% were aerobic gram-negative pathogens. Of 28 colonies isolated from nine patients of the SD group 21% were aerobic gram-negative. Any case of gram-negative pancreatic infection was preceded by intestinal colonization with identical gram-negative flora in both groups, as learned from surveillance cultures of the digestive tract.

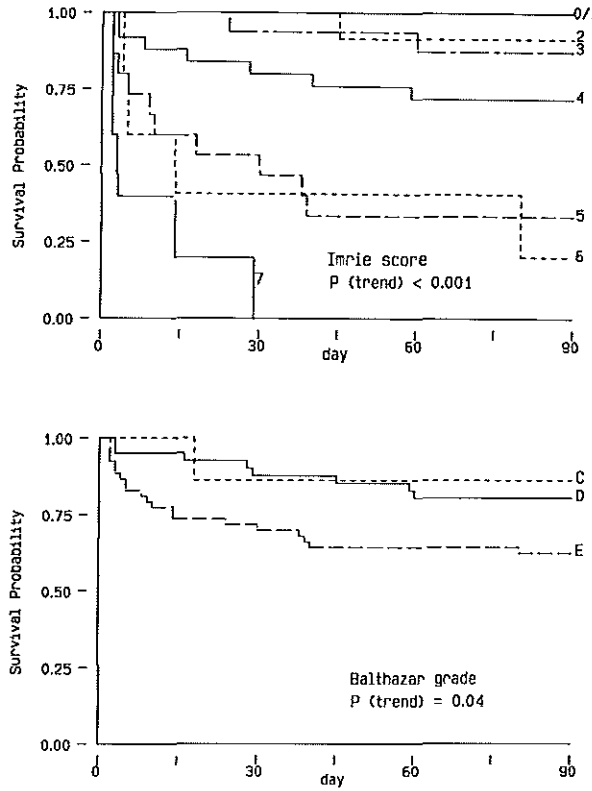

Figure 2. Survival according to an Imrie score of 0/1 (n=24), 2 (n=12), 3 (n=16), 4 (n=25), 5 (n=15), 6 (n=5), and 7 (n=5), respectively (upper panel) ; Survival according to Balthazar grade C (n=7), D (n=41), or E (n=53), respectively (lower panel) ; Both as assessed at entry into the study, *for both treatment groups combined.* Severe acute pancreatitis was defined according to Imrie score ≥ 3 points and/or CT findings according to Balthazar's degree of disease severity grade D or E.

Table 3. Multivariate analysis of mortality in relation to treatment, Imrie score, and Balthazar grade

Factor	Odds-ratio		p-Value	
Treatment				
control	1*		-	
SD	0.3	(0.3)	0.048	(0.049)
Imrie score	3.7+	(3.9)	<0.001	(<0.001)
Balthazar grade				
C/D	1*		-	
E	1.8	(-)	0.354	(-)

* : reference category. + : relative to patients who have an Imrie score of 1 point less. Data given are odds-ratios for mortality. (Odds-ratios > 1 indicate an increased mortality; < 1 indicate a decreased mortality.) Data between parentheses denote results when only treatment and Imrie score are analysed regarding mortality.

SD regimen: complications and failure of SD

There were no noticeable allergies in the SD regimen, and none of the deaths in the SD group were attributable to the SD regimen. SD was started within 24 hours from randomization in all patients in the SD group, except one patient (day 4). The average length of SD treatment was 19 days. Oral paste and rectal enemas were well tolerated. Gram-negative colonization of the digestive tract was successfully prevented or reversed in 46 of 50 patients (92%) of the SD group. However, failure of SD to prevent gram negative colonization of the digestive tract with subsequent infection of pancreatic necrosis with the same gram negative bacteria was seen in 4 of 50 patients (8%). Three of these patients died after 9, 37, and 40 days due to infection with *Pseudomonas aeruginosa* (2 pts.) and *Klebsiella* (1 pt.). *Escherichia coli* (<1+) was isolated only once from pancreatic necrosis in one of these patients at the end of the first week because of initial persistance of intestinal *E. coli*. Transient gram-negative pancreatic infection during SD treatment was seen in one patient-i.e., *Pseudonomas aeruginosa* (<3 days) followed by *Serratia marescescens* (<18 days)-who was later discharged after 106 days.

Table 4. Bacteriologic Analysis of Infected (Peri)Pancreatic Necrosis. Presence of Micro-organisms*

Species	SD group (n=9)	Control group (n=20)
Gram negative aerobic		
Acinetobacter spp.	-	3
Citrobacter spp.	-	3
Escherichia coli	1	12
Enterobacter spp.	-	5
Klebsiella spp.	1	5
Pseudomonas spp.	3	10
Proteus spp.	-	2
Morganella spp.	-	4
Serratia maresc.	1	-
Alcaligenes spp.	-	1
Gram positive aerobic		
Staphylococci spp.	-	1
Staph. aureus	4	4
Staph. epidermidis	9	12
Streptococci	2	-
Enterococci	7	12
Yeasts		
Candida albicans	2	10

*: micro-organisms may occur in combinations in each separate patient

Surgery and surgery-related morbidity

In the control group, an average of 3.1 laparotomies was performed per patient in contrast to only 0.9 in the SD group ($p<0.05$; Table 5). A laparostomy, whenever repeated necrosectomy was foreseen, was created in 50% of the patients in both groups. In the control group surgical complications were seen in nine patients compared with four patients of the SD group, who had undergone surgery less frequently ($p=0.50$, N.S.).

Median hospital stay in patients who survived was 30 days (range 10-106) in the SD group compared with 32 days (range 6-241) in the control group ($p=0.65$, N.S.).

Table 5. Surgery and Surgical Morbidity

	SD group (n = 50)		Control group (n = 52)	
Laparotomy	16	(32%)	24	(46%)
Laparotomies/pt (range)	0.9*	(0-17)	3.1*	(0-29)
Patients with surgery-related complications	4	(8%)	9	(17%)
Complications†:				
Small bowel resections	0		5	
Large bowel resections	1		7	
Enteric fistulas	2		6	
Pancreatic fistulas	2		2	
Splenectomy	0		3	

* : $p < 0.05$; † : complications may occur in combinations in each separate patient.
Laparostomies were created in 8 out of 16 patients in the SD group and in 12 out of 24 patients in the control group. Data given are numbers of patients (percentages) or mean (range).

DISCUSSION

The division of severe acute pancreatitis into an early vasoactive toxic phase and a late phase dominated by septic complications is widely accepted[9,38-40]. Systemic complications during the initial phase of circulatory depression, such as myocardial depression, acute renal and respiratory failure, are thought to be mediated by activated pancreatic enzymes and other vasoactive and toxic agents released from the pancreas and the peritoneal exudate[38,41,42]. Intensive treatment has improved the prognosis with regard to these complications, which previously were the major cause of death during the early phase of severe acute pancreatitis[38,43,44].

Secondary infection of pancreatic necrosis currently is the most lethal complication of severe acute pancreatitis, particularly during the later stages of the disease[2,9-13,17,20,38,45]. Gram-negative (facultative) aerobic bacteria, originating from the digestive tract, are predominantly isolated from infected pancreatic necrosis[9,14,19,23,26]. Recently, Medich et al. reported that acute pancreatitis in rats promotes translocation of gastrointestinal organisms to the inflamed pancreas and peripancreatic region[27]. Widdison et al. reported striking results from a feline

model, suggesting gut-derived pancreatic infection by showing that labeled intestinal *E. coli* were not recovered from the site of acute necrotizing pancreatitis when the colon was enclosed in an impermeable bag that prohibited translocation[22].

Until now, the beneficial effect of prophylactic antibiotics in acute pancreatitis has been debated[12,15,16]. Recently, Pederzoli et al. reported that prophylactic treatment with intravenous imipenem significantly reduced the incidence of infected necrosis (12.2%) as compared with placebo (30.3%). However, no significant reduction in mortality could be demonstrated[46]. If increased bacterial translocation from the digestive tract is the mechanism leading to pancreatic infection, selective decontamination should, in theory, be useful in preventing pancreatic infection[27]. McClelland et al. reported a significant reduction in clinical signs of sepsis in patients with acute pancreatitis and acute respiratory failure who were treated with SD[31]. No significant reduction in mortality, however, was demonstrated from this retrospective analysis comprising only six SD patients in a 3-year period, who were compared with nine historic control patients from an earlier 3-year period. Reduction of mortality in ICU patients treated with adjuvant SD is still a matter of debate[29-34], and randomized controlled clinical trials of selective decontamination in the treatment of patients with severe acute pancreatitis are not available. In the prospective clinical trials reported to date, only a few patients had severe acute pancreatitis or developed pancreatic infection. In the present study, SD significantly (p=0.003) reduced the incidence of gram-negative pancreatic infection. Consequently, a significant reduction in the number of laparotomies having fewer surgery-related complications occurred in patients treated with SD.

Because infection of originally sterile pancreatic necrosis is a secondary phenomenon, effective antibiotic prophylaxis may result mainly in reduction of late mortality. Early mortality, rather dominated by effects of vasoactive and toxic agents released from the pancreas and peritoneal exudate than by septic complications, may consequently be less reduced by antibiotics[38-42]. This may explain why SD, reducing total mortality, did not affect early mortality (within 2 weeks) as appeared on further analysis (SD: 16%; 8/50 patients; control: 15%; 8/52 patients)(p=0.71). Late mortality, on the other hand, was significantly reduced by SD (SD: 7%; 3/42 patients; control: 23%; 10/44 patients). In both groups all gram-negative pancreatic infections, if present, were preceded by colonization of the digestive tract with the same gram-negative bacteria. If pancreatic necrosis was infected despite successful SD, only gram-positive aerobic bacteria were isolated as has also been noted by others[47]. If SD fails, however,

mortality increases sharply, which has has been recognized earlier in surgical intensive care patients[48].

Severity scoring of acute pancreatitis immediately after admission has previously been strongly advocated to identify patients at risk[35,36,49-51]. It also enables clinicians to compare treatment results more accurately. Scoring systems should be accurate but easy to use. The Imrie score proved to be very valuable in identifying patients with acute pancreatitis with increased risk of death. Computed tomography findings, according to Balthazar's degree of disease severity, were less accurate in predicting prognosis. Total mortality of patients who were found to have severe acute pancreatitis according CT findings alone (Balthazar grade D or E, but Imrie score <3) was less than 5% in each group. These data suggest that the use of SD in such patients may not result in additional benefit and is cost-inducing.

CONCLUSIONS

We conclude that SD is especially indicated for patients with severe acute pancreatitis with an Imrie score ≥3, regardless of the CT findings[36] on admission. Treated as such, in this study total mortality was reduced from 55% (17/31 patients) to 31% (11/35 patients) with a 95% confidence interval for the difference in mortality ranging from 0% to 48%.

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CHAPTER 3

DIFFERENTIAL PROGNOSIS OF GRAM-NEGATIVE VERSUS GRAM-POSITIVE INFECTED, AND STERILE (PERI)PANCREATIC NECROSIS

Results of a randomized trial in patients with severe acute pancreatitis treated with adjuvant selective decontamination

Ernest J.T. Luiten, Wim C.J. Hop, Johan F. Lange, Hajo A. Bruining

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ABSTRACT

Results of a previous randomized multicenter trial involving 102 patients with severe acute pancreatitis treated with or without adjuvant selective decontamination (SD) were analyzed additionally with regard to the bacteriologic status of (peri)pancreatic necrosis.

The incidence of gram-negative pancreatic infection was significantly reduced in patients treated with SD ($p=0.004$). Once such an infection develops, mortality increases 15-fold ($p<0.001$) in comparison with that for patients with sterile necrosis. Among patients in whom only gram-positive infection of (peri)pancreatic necrosis was found, there was no significant increase in mortality. These results were similar in both treatment groups. In addition, the hospital stay was significantly longer in cases of gram-negative infected necrosis. The incidence of gram-positive infected necrosis in patients treated with SD did not increase.

Gram-negative pancreatic infection can be prevented with adjuvant SD, thereby reducing mortality among patients with severe acute pancreatitis.

INTRODUCTION

As infectious complications have become the leading cause of mortality and morbidity in cases of acute necrotizing pancreatitis, patients in whom devitalized pancreatic and peripancreatic tissues remain sterile have to be distinguished from others in whom secondary infection of (peri)pancreatic necrosis develops (i.e. sterile vs. infected necrosis).

Sterile (peri)pancreatic necrosis, especially in the absence of systemic complications, has a favorable prognosis, with a reported mortality rate of zero to 11%[1-4]. Mortality, which increases sharply with increasing Ranson or Imrie score on admission, is related to systemic complications resulting in multiple organ failure, occurring most frequently during the first two weeks of illness[5-10].

Infected necrosis on the other hand, occurs later during the course of the disease, often proves fatal, and is generally agreed to represent an absolute indication for surgery in an effort to reduce mortality[2,11-14].

Cultures in cases of infected necrosis yield most frequently a polymicrobial flora, with a preponderance of gram-negative aerobic bacteria in 50%-70% of cultures, suggesting an enteric origin[2,5,12,15-19]. Gram-positive aerobes (mainly enterococci and staphylococci) are isolated in only 5%-20% of cultures[2,5,12,15-19].

Patients with severe acute pancreatitis in whom infected necrosis exists are usually dealt with as one group, irrespective of the specific flora cultured. However, because of varying intrinsic pathogenic potential, the prognosis of patients with infected (peri)pancreatic necrosis may differ according to the bacteria cultured. In accordance with results of bacteriological analyses of infected (peri)pancreatic necrosis, two major groups of patients can be distinguished: those with gram-positive infected necrosis and those with gram-negative infected necrosis. This distinction between patients with infected (peri)pancreatic necrosis has not been studied prospectively to date.

In a recent controlled clinical trial, selective decontamination (SD) was shown to effectively reduce mortality among patients with objective signs of severe acute pancreatitis[5]. However, SD does not prevent gram-positive infection. Subsequent intestinal overgrowth with *Enterococcus* species, resulting in an increase in gram-positive infections, has been suggested to be a limitation of SD[20].

An additional analysis of the results of this prospective, controlled clinical study was performed to evaluate for both treatment groups (i.e., the SD group and control group) a possible difference concerning mortality between (1) patients with either gram-positive infected necrosis or gram-negative (peri)pancreatic infection during the course of the disease and (2) patients in whom (peri)pancreatic necrosis remained sterile.

PATIENTS AND METHODS

Patients

Between April 22, 1990 and April 19, 1993, 102 patients with objective signs of severe acute pancreatitis were admitted to 16 participating hospitals. The diagnosis of acute pancreatitis had been established on the basis of clinical examination and elevated plasma levels of serum amylase (>1,000 IU/L; normal range, 0-300 IU/L (Phadebas)), or at diagnostic laparotomy (10 patients). All patients had severe acute pancreatitis, according to a multiple laboratory criteria score (Imrie score≥3) and/or grade D or E (Balthazar grades) determined by contrast-enhanced CT[7,21]. Bacteriologically proven infected necrosis at the time of randomization was defined as an exclusion criterion.

The patients were randomly assigned to receive standard treatment (control group: n=52) or the same treatment plus selective decontamination (SD group: n=50). A 24-hour randomization service was available to randomize patients, with

stratification per center. Informed consent was obtained from the patient or relatives by the attending clinician.

The SD regimen consisted of oral administration of colistin sulfate (200 mg), amphotericin (500 mg) and norfloxacin (Noroxin^{R}; 50 mg) every 6 hours. A sticky paste containing 2% of the three SD drugs was smeared along the upper and lower gums every 6 hours and at the tracheostomy, if present. The aforementioned daily dose also was given in a rectal enema every day. A short-term systemic prophylaxis of cefotaxime sodium (Claforan^{R}; 500mg) was given every 8 hours until gram-negative bacteria were eliminated from the oral cavity and rectum (average, 7.4 days). SD was discontinued as soon as the risk of acquiring a new infection was absent, i.e., the patient was extubated receiving no supplementary oxygen therapy or infusions, on regular oral diet, and ambulatory on the ward. A more elaborate outline has been reported in chapter 2.

Microbiology

An ultrasonography or CT-guided fine-needle aspiration (FNA) with subsequent culture was performed if there was clinical suspicion of infected (peri)pancreatic necrosis[11]. Clinical suspicion of (peri)pancreatic infection was based on the occurrence of fever and leukocytosis (usually lasting at least 2-3 days, during which other sources of infection were excluded), associated with CT-findings demonstrating (peri)pancreatic necrosis.

The microbial flora of the infected pancreas was carefully monitored. Culture specimens of pancreatic and peripancreatic devitalized tissues (i.e., necrosis) were obtained at every laparotomy and from drainage. They were sent directly to the laboratory and cultured semiquantitatively. If fever ($\geq 39^{0}$C) was present, blood cultures were performed. Identifications were made following routine microbiological procedures.

Pancreatic necrosis, peripancreatic devitalized tissues and fluid collections were considered sterile in those patients with a nonseptic course and in those with negative cultures.

Surgery

Besides severe intraabdominal hemorrhage or presence of enteric fistulas, reasons for surgery included (1) aspirate cultures that demonstrated development of infected necrosis and (2) rapid deterioration of the patient's condition toward multiple-organ failure that was resistant to exhaustive intensive treatment (SD

group, 16 patients; controls 24). Results of surveillance cultures of the digestive tract were not taken into account in the decision to perform a reintervention. The decision to perform either percutaneous drainage or relaparotomy was based on ultrasonographic and CT findings as well as findings from the previous laparotomy.

Access to the pancreas was obtained through a median or (preferably) transverse laparotomy. If repeated laparotomies were foreseen, a laparostomy (i.e., ventral open packing of the abdominal cavity) was created, ensuring a rapid and easy access to the upper abdominal cavity[12]. Removal of necrotic tissue was mainly performed by means of finger or clamp fraction (i.e., necrosectomy). Infected necrosis is mostly solid, in contrast with a pancreatic abcess, which represents a localized collection of fluid, often encapsulated, that occurs after the pancreatitis has subsided.

Statistical Analysis

Percentages and continuous data were compared between groups by means of Fisher's exact test and Mann-Whitney's test, respectively. Cumulative percentages of patients developing gram-negative or gram-positive infected necrosis, taking account of the length of survival, were assessed by the actuarial Kaplan-Meier method and log-rank-test. Cox regression was used to evaluate various factors simultaneously regarding mortality[22]. This method was also used to assess the relation between the occurrence of pancreatic infections (only gram-negative, only gram-positive or mixed gram-negative/gram-positive) and mortality[23]. P-values given are two-sided, and $p=0.05$ was considered the limit of significance.

RESULTS

Of 102 patients with objective signs of severe acute pancreatitis (Imrie score$\geq$3 and/or Balthazar CT score grade of D or E), 50 patients were assigned to the SD group and 52 to the control group. The groups were well matched with regard to Imrie score (mean for both: 3.2) and Balthazar grade as is demonstrated in chapter 2.

Microbiology

Twenty-nine of 102 patients (28%) developed infected (peri)pancreatic necrosis. *Pseudomonas aeruginosa* (13 patients), *Escherichia coli* (13), *Staphylococcus epidermidis* (21) and enterococci (19) were most frequently isolated; anaerobes (3) were found to play only a minor role and were not further analyzed.

Infected necrosis occurred in 9 of 50 patients (18%) of the SD group in comparison with 20 of 52 patients (37%) of the control group (p=0.03), because of a significant reduction of gram-negative infected necrosis (SD group, 4/50 (8%); controls, 17/52 (33%)). Three patients who developed infected necrosis had not undergone surgery. Infected necrosis was demonstrated at autopsy (two patients) or by percutaneous drainage (one).

Figure 1 shows the increasing percentage of patients over time who developed gram-negative pancreatic infection. The incidence of gram-positive infection of (peri)pancreatic necrosis did not significantly differ between treatment groups (SD, 9/50 (18%); controls, 16/52 (31%)) (Figure 1).

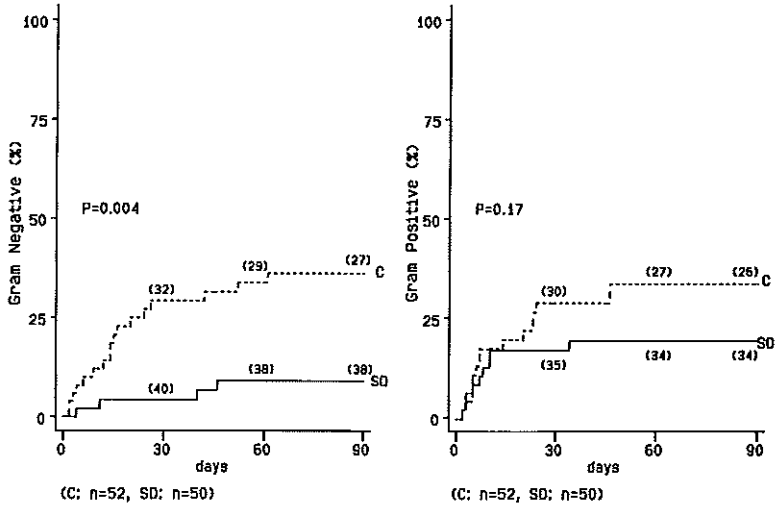

Figure 1. Cumulative percentage over time of patients with infection due to gram-negative bacteria (left panel) and with gram-positive infection of (peri)pancreatic necrosis (right panel) according to treatment group. In parentheses are numbers of patients at risk. ---- = control group (n=52); ——— = Selective Decontamination group (n=50 pts.)

The Imrie score at enrollment in the study appeared to correlate very strongly with the incidence of gram-negative (peri)pancreatic necrosis over time, especially in the control group ($p<0.001$) (Figure 2). The Balthazar grade at enrollment in the study also correlated with the incidence of gram-negative pancreatic infection, although this correlation was less pronounced (Grade C/D, 6/48 (12%); Grade E, 14/53 (26%)) (with adjustment for treatment group, p=0.03).

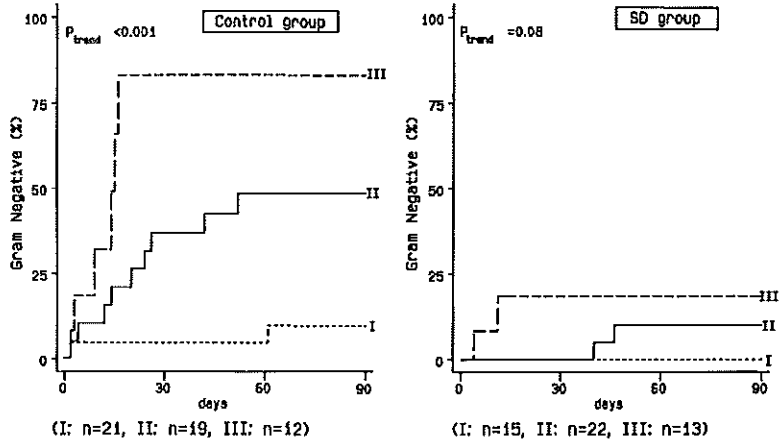

Figure 2. Cumulative percentage over time of patients with gram-negative infection of (peri)pancreatic necrosis in the control group (left panel) and SD group (right panel), according to Imrie score (I, 0-2; II, 3-4; III, >4) at enrollment in the study. Control group scores: I, 21 patients; II, 19; III, 12; p_{trend} <0.001. SD group scores: I, 15 patients; II, 22; III, 13; p_{trend}=0.08.

Fourty FNAs were performed in 25 patients (range, 1-4 per patient). Twenty-one of these FNAs (17 patients) were done without treatment with intravenous antibiotics at the time of aspiration. Only 4 of these aspirations (19%) showed presence of bacteria (*E. coli* 1, *S. epidermidis*, 3). Nineteen FNAs (16 patients) were done during simultaneous treatment with intravenous antibiotics. Eight of these (42%) showed infection of (peri)pancreatic necrosis (*Enterobacter* species, 1; *Klebsiella* species, 1; *S. epidermidis*, 4; enterococci, 4; *Staphylococcus aureus*, 1). Some aspirates contained more than one type of bacteria.

Mortality

Mortality is significantly reduced among patients treated with adjuvant SD[5]. Among patients who survived (n=73), the percentage of cases in whom infected necrosis had occurred was 19% (14 patients), which is significantly (p=0.002) lower than the 52% (15) of non-survivors (n=29) (Table 1).

To evaluate the impact on mortality of infected (peri)pancreatic necrosis developing during treatment, patients were classified each day according to whether pancreatic necrosis was still sterile, or whether only a gram-positive, only a gram-negative or a mixed gram-negative/gram-positive pancreatic infection had occurred. All patients started in the sterile condition in accordance with the enrollment criteria. With the use of Cox regression for both groups, it emerged that in comparison with patients with sterile necrosis, those who acquired only a gram-positive pancreatic infection had a 1.6-fold increased death rate (p=0.52) . Patients who developed only a gram-negative pancreatic infection had a 14.4-fold increased death rate (p<0.001) in comparison with the rate for those with sterile necrosis. A similar increased mortality of 15.8-fold (p< 0.001) was found for those with mixed gram-negative/gram-positive infected necrosis.

Table 1. Bacteriologic classification of (peri)pancreatic necrosis during the course of the disease. Analysis with regard to survivors and non-survivors.

	No. (%) of patients			
Classification	Survivors (n=73)		Non-survivors (n=29)	
Sterile	59	(81 %)	14	(48 %)
Only gram-positive	6	(8 %)	2	(7 %)
Only gram-negative	-	(-)	4	(14 %)
Mixed gram-positive/negative	8	(11 %)	9	(31 %)

Data given are numbers of patients with percentages between parentheses. The percentage of patients with infected (peri)pancreatic necrosis among non-survivors (15/29 ; 52%) is significantly higher as compared to survivors (14/73; 19%) : p=0.002.

Table 2. Results of multivariate analysis of mortality in relation to development of infection of (peri)pancreatic necrosis during treatment, baseline Imrie-score, baseline Balthazar grade and randomized treatment. All patients start in the sterile category in accordance with the entry criteria.

Factor	No. of death*	Relative death rate		Significance◇		95% Confidence limits of relative death rate
Infected pancreatic necrosis						
Sterile	14/5,209	1★		...		...
Only G+	2/615	1.2		.86		0.2, 5.5
Only G−	4/103	8.0§		.001		2.4, 27.1
Mixed G+/G−	9/508	7.0§		.002		2.1, 24.5
Imrie score						
0-2	1/36	1★	(1)	...	(...)	...
3-4	9/41	7.4	(10.6)	.06	(.03)	0.9, 60.3
5-7	19/25	31.2	(56.8)	.001	(.001)	3.9, >100
Balthazar grade						
C/D	9/48	1★	(1)	...	(...)	...
E	20/53	0.9	(1.3)	.76	(.38)	0.3, 2.3
Treatment group						
Controls	18/52	1★	(1)	...	(...)	...
SD	11/50	0.8	(0.4)	.56	(.03)	0.3, 1.8

(G+: gram-positive; G-: gram-negative; SD: selective decontamination). Parentheses around data denote results obtained without allowance for the factor infections (infectious status). Upon enrollment, CT (Balthazar grade) was not available for one patient as explained in chapter 2.

* number denotes the number of patient-days (up to day 80, i.e. the day number of the last death) after the first occurrence of the infection specified, or the number of patients for Imrie score, Balthazar grade or treatment.

◇ comparison with reference category

★ reference category

§ not significantly different from each other, but both significantly greater in comparison with "Only G+" category value

Table 2 shows results of multivariate analysis of the relationship between mortality and the type of pancreatic infection, taking into account the Imrie score, Balthazar grade, and randomized treatment. This analysis demonstrates that development of a gram-negative infection of (peri)pancreatic necrosis during the

course of the disease is an important and ominous sign, while there was no significant increase in mortality due to gram-positive pancreatic infection. With these infections taken into account, there is still an increased death rate of patients with a higher Imrie multifactorial initial assessment. No additional prognostic value was found for the Balthazar grade. The data between parentheses (Table 2) also show that SD decreases mortality when analyzed without consideration of infectious status.

There was no mortality difference between treatment groups for patients without gram-negative infected necrosis (i.e. sterile or only gram-positive) as demonstrated in Figure 3 (left panel). After the occurrence of a gram-negative pancreatic infection mortality was high (13/21; 62%). As shown in Figure 3 (right panel) survival in these patients did not significantly differ between treatment groups. However a gram-negative pancreatic infection occurred in only four patients in the SD group.

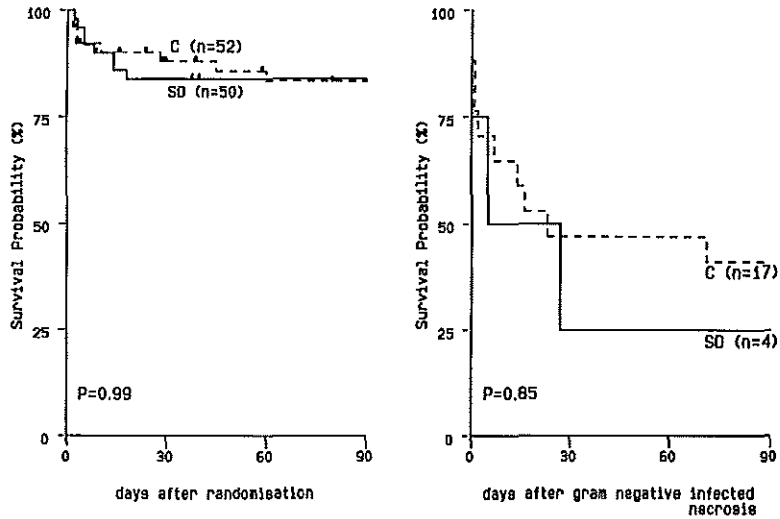

Figure 3. *Left*, survival from the time of enrollment in the study, counting only deaths of patients with sterile or only gram-positive infected (peri)pancreatic necrosis, according to treatment group. Tick marks (X) denote deaths after gram-negative infection of (peri)pancreatic necrosis. *Right*, survival after the occurrence of gram-negative infection of (peri)pancreatic necrosis, according to treatment group. (C=control group; SD=selective decontamination group)

Hospital stay

The average hospital stay of survivors with gram-negative infected (peri)pancreatic necrosis (8 patients) was 135 days (range, 56-241 days), which is significantly higher than the mean values of 55 days (range, 26-82 days) ($p=0.01$) and 30 days (range, 10-71 days) ($p<0.001$) for survivors with only gram-positive (6 patients) or sterile necrosis (59), respectively. Although smaller, the difference between hospital stay of survivors with only gram-positive infected and sterile necrosis is also significant ($p=0.004$). These results were similar in both treatment groups (SD group and controls).

DISCUSSION

This study demonstrates that mortality increases dramatically once gram-negative infection of (peri)pancreatic necrosis occurs in patients with severe acute pancreatitis. However if (peri)pancreatic necrosis becomes infected with only gram-positive aerobic bacteria, mortality is not significantly increased and is comparable with that among patients in whom pancreatic necrosis remains sterile throughout the course of the disease. This is probably because *S. epidermidis* or enterococci, most frequently isolated in cases of infected necrosis due to a solitary gram-positive organism, are less pathogenic in these patients.

The overall incidence of secondary infection of (peri)pancreatic necrosis is 28%. In the control group infected necrosis occurred at a rate of 38%, which has also been described by others[1,15,24]. In patients treated with SD, the overall incidence of infected necrosis (18%) was significantly reduced because of a marked reduction of gram-negative infected necrosis (only 8%, vs. 33% in the control group). The occurrence of a gram-negative infection of (peri)pancreatic necrosis is an ominous sign. Mortality among these patients increases significantly, irrespective of coexistence of a gram-positive infection, as shown in this study. Mortality with regard to the bacteriologic status of (peri)pancreatic necrosis was comparable for the SD group and the control group, i.e., once gram-negative infection of (peri)pancreatic necrosis occurred, mortality increased considerably in both treatment groups. However, mortality in the treatment group was significantly reduced among patients treated with adjuvant SD (Table 2), a finding that was also published previously[5].

Consequently, SD reduces mortality among patients with severe acute pancreatitis because of a significant reduction in the development of gram-

negative infection of (peri)pancreatic necrosis. This is accomplished by reduction of gram-negative intestinal colonization, leading to reduced gram-negative bacterial translocation into the (peri)pancreatic necrosis. However, SD is not useful for patients in whom gram-negative pancreatic infection already exists or develops during SD administration, as is demonstrated in this study.

It has been suggested that overgrowth and translocation of gram-positive bacteria, i.e., enterococci or staphylococci, may be a drawback of SD[20,25]. Our results do not support this hypothesis. Neither intestinal overgrowth nor increased incidence of gram-positive infected necrosis has been found in our study. Deaths due to unexplained gram-positive sepsis along with positive blood cultures (two patients) and otherwise-documented sterile necrosis at time of death were equally divided among the SD group and the controls. However, these possible hazards demand strict indications and careful bacteriologic surveillance, as is the case for any kind of antibiotic regimen.

CONCLUSIONS

The development of gram-negative infection of devitalized tissues in and around the pancreas is, apart from the Imrie score, the most important parameter determining outcome. Gram-negative pancreatic infection can be minimized with adjuvant SD, thereby reducing mortality among patients with severe acute pancreatitis.

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CHAPTER 4

PROGNOSTIC IMPORTANCE OF GRAM-NEGATIVE INTESTINAL COLONIZATION PRECEDING PANCREATIC INFECTION IN SEVERE ACUTE PANCREATITIS

Results of a controlled clinical trial of selective decontamination

Ernest J.T. Luiten, Wim C.J. Hop, Hubert Ph. Endtz, Hajo A. Bruining

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ABSTRACT

Secondary gram-negative pancreatic infections are the major cause of morbidity and mortality in patients with severe acute pancreatitis. Several experimental studies have indicated that the microbial flora causing these infections is gut-originated, however clinical results of gram-negative intestinal colonization in patients with pancreatic infections have not been reported to date.

A prospective analysis of 2159 semi-quantitive cultures from the oropharynx, rectum and pancreatic tissues taken from 90 patients revealed that all gram-negative pancreatic infections were preceded by intestinal colonization with the same micro-organisms. The risk of developing a pancreatic infection following gram-negative intestinal colonization (15/42 pts.) was significantly increased as compared to patients without gram-negative colonization (0/18 pts.)($p<0.001$) or to patients in whom *E. coli* was the only intestinal micro-organism cultured (0/30 pts.) ($p<0.001$). The occurrence of intestinal *E. coli* did not increase the risk of pancreatic infection. Gram-negative colonization of the rectum and oropharynx significantly correlated with later development of pancratic infection: relative risks 73.7 ($p<0.001$) and 13.6 ($p<0.001$) respectively. However, when both areas were evaluated simultaneously, the rectum was more significant ($p<0.001$). The severity of intestinal colonization until the moment of pancreatic infection showed an increase in time in all 15 patients. In 11 of 15 patients (73%) these infections occurred within 1 week following the first isolation from the digestive tract. Gram-negative intestinal colonization was associated with a 3.7 fold increased mortality risk ($p=0.004$).

Gram-negative intestinal colonization, *E. coli* excepted, is an early prognostic parameter in patients in whom pancreatic infection has not yet occurred and represents a significantly increased risk of pancreatic infections and mortality.

INTRODUCTION

Since advances in critical care have greatly reduced the incidence of death caused by the early cardiopulmonary sequelae of severe acute pancreatitis, secondary infections of (peri)pancreatic necrosis have emerged as the leading cause of mortality and morbidity in these patients[1-5].

The microbiology of pancreatic infections in patients with severe acute pancreatitis, which reveals mainly aerobic gram-negative bacteria, provides indirect evidence that these pathogens originate from the digestive tract[1,5-10].

Colonization of the digestive tract is thought to be the initial step of endogenous infection of other major organ systems (e.g. pancreas)[11,12]. Several experimental studies have demonstrated that acute pancreatitis promotes bacterial translocation, leading to infection of the inflamed pancreas and surrounding tissues[13-20].

The development of gram-negative infection of (peri)pancreatic necrosis significantly increases the risk of mortality in patients with severe acute pancreatitis[21]. As attention has rightly turned to prevention of pancreatic infection, early identification of patients who are at risk of developing a gram-negative pancreatic infection during the course of the disease is crucial to improving the outcome of severe acute pancreatitis. To date, prognostic scores on admission, using laboratory parameters (e.g. Imrie score) or contrast-enhanced CT findings (e.g. Balthazar grades) are the only clinical available tools for early identification of patients who are at risk of future pancreatic infection[21-23], and fine needle aspiration of pancreatic necrosis with subsequent gram-staining and culture of the aspirate is the only means of the early detection of patients in whom infection has already developed[24]. Early identification, using microbiological criteria, of patients who are at risk of developing a life-threatening gram-negative pancreatic infection during treatment has not been published so far. As several experimental studies have already indicated that the gut is the principal source of infection, analysis of the intestinal flora of patients with severe acute pancreatitis may reveal valuable prognostic data. However, clinical investigations concerning gram-negative intestinal colonization which may precede pancreatic infection in patients with severe acute pancreatitis have not been reported to date.

In this study the results of systematic semi-quantitive cultures of several body areas taken from patients with severe acute pancreatitis, during a controlled multicenter trial of adjuvant selective decontamination (SD), were analyzed to address the following questions: 1) Does gram-negative (re)-colonization of the gut lead to an increased risk of gram-negative pancreatic infection and is this event time-related? 2) Does the difference in the quantity and quality of micro-organisms colonizing the digestive tract influence the morbidity and mortality of severe acute pancreatitis?

PATIENTS AND METHODS

The microbial flora of patients with objective signs of severe acute pancreatitis was carefully monitored during a controlled clinical trial of adjuvant selective decontamination (control group n=52 patients, selective decontamination group

n=50 patients). All patients suffered from severe acute pancreatitis according to a multiple laboratory criteria score (Imrie score≥3) and/or grade D or E disease severity (Balthazar grades) using contrast-enhanced computerized tomography (CE-CT)[25,26]. An elaborate outline has been reported previously[27]. The study was conducted according to the principles established in Helsinki.

Microbiology

Surveillance cultures from the oropharynx and rectum were taken on admission and repeated twice weekly. If fever (≥39^{0}C) was present, blood cultures were taken

An ultrasonographic- or CT-guided fine needle aspiration with subsequent culture was performed if there was clinical suspicion of infected pancreatic necrosis[24]. Clinical suspicion of pancreatic infection was based on fever and leucocytosis (usually lasting at least 2-3 days during which time other sources of infection were excluded) associated with CT-findings demonstrating (peri)pancreatic necrosis. Surveillance cultures of the (peri)pancreatic devitalized tissues (i.e. necrosis) were obtained at every relaparotomy and from drainage. They were sent directly to the laboratory and cultured semi-quantitatively (1+,2+,3+,4+)[28]. Samples from the oropharynx and rectum were taken with a sterile cotton-tipped swab and cultured semi-quantitatively.

Identification was performed following routine microbiological procedures. Pancreatic necrosis, peripancreatic devitalized tissues or fluid collections were considered sterile in those patients pursuing a nonseptic course and in patients with negative cultures.

Analysis of gram-negative intestinal colonization

For each patient, a time-based qualitative microbiological profile, including the date of first occurrence as well as the duration of colonization of specific gram-negative micro-organisms was recorded (oropharynx, rectum and pancreas). For all sites, a time-based semi-quantitative microbiological profile was created for each patient in order to analyse the severity of gram-negative intestinal colonization. The maximum semi-quantitative growth was recorded and used in this analysis. Another similar semi-quantitative profile was made excluding *E. coli*. The (resident) *E. coli* is considered separately in order to facilitate the determination of nosocomial gram-negative intestinal colonization without interference of the host's own *E. coli*[29]. For every patient, monomicrobial,

polymicrobial or absence of gram-negative intestinal colonization was also recorded during the course of the disease.

Patients in whom insufficient surveillance cultures had been taken to perform a reliable analysis, i.e. more than one week without surveillance cultures, were exluded from this analysis.

Follow up was continued until either death or the risk of development of a pancreatic infection was considered negligible-i.e. the patient was extubated and without supplementary oxygen therapy or infusions, on a regular oral diet, and mobilized on the ward. Selective decontamination was also discontinued at that same time.

Statistical Analysis

The relation between the occurrence of gram-negative intestinal colonization and the risk of developing a gram-negative pancreatic infection with time was investigated using Cox regression with time-dependent variables[30]. The same technique was used to evaluate the relation between gram-negative intestinal colonization and mortality. The cumulative risk of gram-negative pancreatic infection after the first occurrence of gram-negative intestinal colonization was assessed using the actuarial Kaplan-Meier method. Two-sided p-values of 0.05 or less were considered statistically significant.

RESULTS

Of 102 patients who entered the study, 12 were excluded from this analysis because insufficient intestinal surveillance cultures had been taken. A total of 2159 surveillance cultures (90 patients) were analyzed, including 430 cultures taken from devitalized (peri)pancreatic tissues (43 patients). Of the 90 patients, 15 (17%) developed a gram-negative pancreatic infection during the course of the disease, 3 of 49 patients receiving adjuvant selective decontamination and 12 of 41 control patients.

Qualitative analysis of cultures from the digestive tract (i.e. oropharynx and rectum) and (peri)pancreatic tissues are presented in Table 1. Only 6 of 62 patients (10%) in whom *E.coli* was found in the rectum (mostly present from the onset of the disease) developed pancreatic infection, which is remarkably low when compared to other gram-negative bacteria isolated from the lower intestine (Table 1).

Table 1. Qualitative Analysis of Gram-negative Intestinal Colonization, and Gram-negative Infected Pancreatic Necrosis. Incidence of Micro-organisms in 90 patients[a]

	Oropharynx (no. patients)		Rectum (no. patients)		Pancreas[a] (no. patients)	
	SD	C	SD	C	SD	C
Escherichia coli	3	8	31[b]	31[b]	-	6[b]
Pseudomonas aeruginosa	5	10	4	13	2	9
Klebsiella spp.	1	2	3	10	-	4
Citrobacter spp.	-	4	-	3	-	2
Enterobacter spp.	-	4	-	5	-	2
Morganella morganii	2	2	3	3	-	2
Proteus spp.	-	1	-	6	-	-
Serratia marescescens	1	-	1	-	1	-
Acinetobacter spp.	-	2	-	3	-	3

SD: selective decontamination group, C: control group. Gram-negative intestinal colonization during treatment did not occur in 18 patients and in 30 of 64 patients E. coli was the only micro-organism isolated from the digestive tract. *a*: micro-organisms may occur in combinations in each separate patient. (Pseudomonas: 2, Pseudomonas + Acinetobacter + Citrobacter: 1, E.coli + Acinetobacter: 1, Pseudomonas + E.coli + Morganella: 1, Pseudomonas + Klebsiella: 1, Pseudomonas + E.coli + Klebsiella: 2, Pseudomonas + Enterobacter: 1, Acinetobacter: 1, Pseudomonas + E.coli: 1, Pseudomonas + Citrobacter: 1, Klebsiella + Morganella: 1, Pseudomonas + E.coli + Enterobacter: 1, Serratia: 1. *b*: incidence of gram-negative pancreatic infection following rectal isolation of *E. coli* is noticeably lower when compared to other gram-negative micro-organisms. A monomicrobial pancreatic infection with *E. coli* did not occur.

A monomicrobial pancreatic infection with *E. coli* did not occur. An analysis was therefore performed separating (resident) *E. coli* from other gram-negative bacteria, in order to facilitate the determination of intestinal colonization with gram-negative nosocomial micro-organisms, acquired during the hospital stay, and their relation to the development of pancreatic infection.

Gram-negative intestinal colonization and pancreatic infection

Of 48 patients in whom either intestinal colonization did not occur (n=18 patients) or in whom *E. coli* was the only micro-organism cultured during the course of the disease (n=30 patients), none developed a gram-negative pancreatic infection (Table 2).

However, of the 42 patients in whom gram-negative intestinal colinization occurred (with or without additional *E. coli*) during the course of the disease, 15 (36%) developed a gram-negative pancreatic infection. Using Cox regression analysis, the risk of developing a gram-negative pancreatic infection following intestinal colonization is significantly increased ($p=0.003$ and $p<0.001$) and intestinal *E. coli* is clinically unimportant (Table 2). The same significant differences were found when only patients were considered who did not receive SD (i.e. control group). As there were only 3 patients in the SD group with gram-negative pancreatic infection, no separate reliable statistical evaluation of this group was possible.

Table 2. Risk Analysis of Gram-negative Pancreatic Infection following Gram-negative Intestinal Colonization in 90 Patients with Severe Acute Pancreatitis

	Secondary gram-negative pancreatic infection				
	Present (%)		Absent (%)		p value (Cox regression)
Intestinal colonization:					
Absence of gram-negative intestinal colonization	0	(0%)	18	(100%)	#
Only *E. coli* cultured	0	(0%)	30	(100%)	n.s.
Gram-negative micro-organism(s) without additional *E. coli*	4	(44%)	5	(56%)	0.003[a]
Gram-negative micro-organism(s) with additional *E. coli*	11	(33%)	22	(67%)	<0.001[ab]

#: Reference category. a: Both P-values ≤ 0.001 when compared to "only *E. coli* cultured". b: Occurrence of additional intestinal *E. coli* in patients with gram-negative intestinal colonization does not increase ($p=0.91$) the risk to develop a gram-negative pancreatic infection as compared to patients in whom gram-negative intestinal colonization occurred without additional *E. coli*.

The time lag between gram-negative intestinal colonization (*E. coli* excluded) and subsequent (peri)pancreatic infection is shown in Figure 1. In all patients gram-negative pancreatic infection (n=15) was preceded by intestinal colonization with the same micro-organisms. The majority of these infections (11/15, 73%) occurred within 1 week following the first isolation from the digestive tract. In four

patients, the same micro-organisms (*Pseudomonas aeruginosa*: 2, *Enterobacter spp.*: 1, *Citrobacter spp.*: 1) were also isolated from blood samples taken because of fever during the interval between gram-negative intestinal colonization and the development of gram-negative pancreatic infection. In 9 (33%) of 27 patients without gram-negative pancreatic infection, gram-negative intestinal colonization (*E. coli* excluded) occurred with more than one species (polymicrobial) which is comparable to 6 (40%) of 15 patients with gram-negative pancreatic infection. Using Cox regression analysis, no significant relation was found between the occurrence of polymicrobial versus monomicrobial gram-negative intestinal colonization and the later development of gram-negative pancreatic infection.

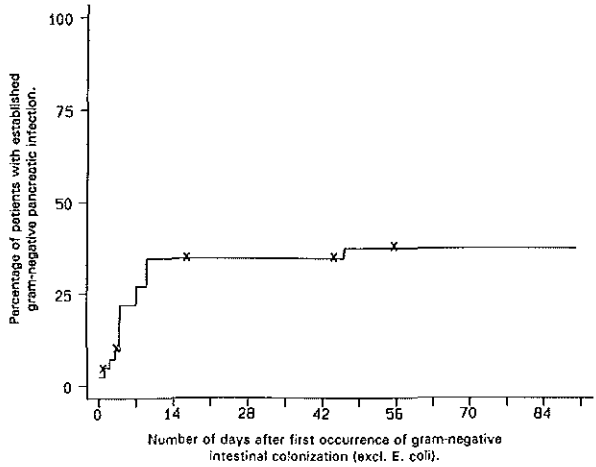

Figure 1. Time lag between first day that gram-negative intestinal colonization (excl. *E. coli*) was demonstrated and establishment of secondary gram-negative pancreatic infection in 42 patients. Tick marks (X) denote length of survival of patients dying without gram-negative pancreatic infection.

Analysis of the rectum and oropharynx revealed that gram-negative pancreatic infection (n=15) was preceded by rectal colonization in five, oropharyngeal colonization in one and colonization of both areas in nine patients. In 27 patients without gram-negative pancreatic infection despite gram-negative intestinal colonization, rectal or oropharyngeal colonization was found in 13 and 6, respectively, and in both areas in 8 patients. Colonization of either area (i.e. rectum, oropharynx), when evaluated separately using Cox regression,

significantly correlated with the later development of gram-negative pancreatic infection: the relative risks for rectum and oropharynx were 73.7 ($p<0.001$) and 13.6 ($p<0.001$), respectively. These results, when only patients of the control group were analyzed, were 24.3 ($p=0.003$) and 6.8 ($p=0.002$), respectively. However, when both areas were evaluated simultaneously, colonization of the rectum was more important ($p<0.001$), while no additional predictive value was found for colonization of the oropharynx ($p=0.34$, n.s.). Figure 2 shows the degree of severity (semi-quantitative) of gram-negative rectal colonization until the moment of gram-negative pancreatic infection. An increase with time was found in all 15 cases except one (14/15). In the remaining patient gram-negative pancreatic infection was preceded by only oropharyngeal colonization, which also increased with time. Colonization persisted for more than one week in only 4 of 21 (19%) patients with rectal colonization without gram-negative pancreatic infection.

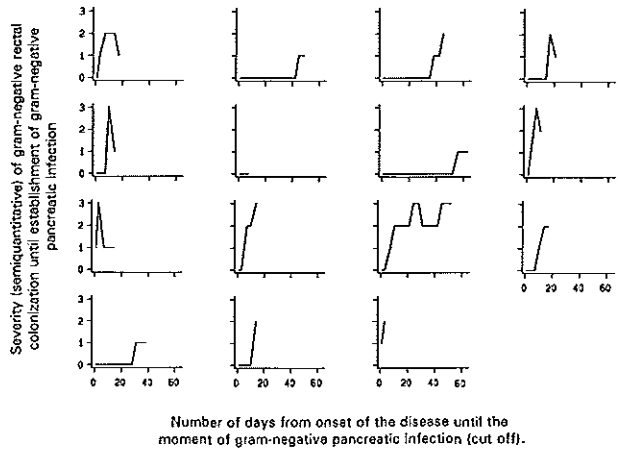

Figure 2. Severity (semiquantitative) of gram-negative intestinal colonization with time in 15 patients with gram-negative pancreatic infection. Rectal colonization is presented until the first day that gram-negative pancreatic infection was demonstrated.

Gram-positive intestinal colonization and pancreatic infection

No correlation was found between gram-positive intestinal colonization and the later development of gram-positive pancreatic infection. Gram-positive intestinal

colonization preceding gram-positive pancreatic infection was found in only 4 of 21 (19%) patients (6 colonies isolated from 4 patients: *Enterococci* 4, *Staphylococcus epidermidis* 1 and *Streptococcus* 1). In the remaining 17 cases (81%), intestinal gram-positive micro-organisms were either absent (n=9) or only found after gram-positive pancreatic infection had already developed (n=8).

Gram-negative intestinal colonization and mortality

Twenty-two patients (22/90 patients, 24%) died. Multiple organ failure with documented sterile (peri)pancreatic necrosis was the cause of death in nine patients. Nine patients died due to a gram-negative pancreatic infection. Two patients died due to solitary gram-positive pancreatic infection. Gram-positive sepsis of unknown origin with documented sterile pancreatic necrosis was the cause of death in two other patients.

Table 3. Risk Analysis of Mortality following Gram-negative Intestinal Colonization in 90 Patients with Severe Acute Pancreatitis

	Non-survivor		Survivor		p value
	n	(%)	n	(%)	(Cox regression)
Intestinal colonization:					
Absence or only *E. coli* cultured	8	(17%)	40	(83%)	
Gram-negative micro-organism(s) (with or without additional *E. coli*)	14	(33%)	28	(67%)	0.004[a]

Mortality risk is not influenced by intestinal *E. coli*. a: Gram-negative intestinal colonization is associated with a 3.7 fold increased mortality risk (p=0.004).

Of 42 patients with gram-negative intestinal colonization, 14 (33%) died: 9 due to gram-negative pancreatic infection. Of the remaining 48 patients without gram-negative intestinal colonization, 8 (17%) died. None of these eight patients died due to a gram-negative pancreatic infection. Table 3 shows that, when using Cox regression analysis, gram-negative intestinal colonization was associated with a 3.7 fold (p=0.004) increased mortality risk. This increase of mortality risk was 7.4 (p=0.02) in the control group, and 2.2 (p = 0.23) in the SD group. These relative risks for the two treatment groups did not significantly differ from each other

(p=0.24). Presence of intestinal *E. coli*, as the only micro-organism cultured or as an additional finding in patients colonized with other gram-negative flora, did not increase the mortality risk.

DISCUSSION

Several experimental studies have demonstrated that the intestinal tract is the origin of secondary pancreatic infection and have suggested possible routes of translocation[13-20,31,32]. Until now clinical studies have restricted the microbiological analysis to cultures of (peri)pancreatic necrosis obtained by percutaneous aspiration or specimens taken during operation. Since predominantly gram-negative bacteria have been found, reflecting the flora of the intestinal tract of ICU-patients, it has been suggested that these micro-organisms originate from the gut, from which they translocate during the course of the disease[1,2,5-10].

This prospective analysis of the occurrence of gram-negative intestinal colonization during the course of the disease in patients with severe acute pancreatitis, provides direct clinical evidence that aerobic gram-negative pancreatic infections do originate from the gut.

Besides anaerobes and enterococci, the normal colonic flora frequently consists of *Enterobacteriaceae*, predominantly *E. coli*. The colonization rate of *E. coli* remained the same during hospital stay as has also been reported by other investigators[29]. However, other gram-negative micro-organisms (e.g. *Pseudomonas spp.*, *Acinetobacter spp.*), referred to as nosocomial micro-organisms, are acquired during hospitalization and colonize the digestive tract of more than 80% of ICU-patients within two weeks of admission[12,29,33-35]. They are replaced by resident flora after recovery and discharge. Therefore the analysis was performed with *E. coli* considered separately, in order to facilitate determination of colonization with nosocomial bacteria, acquired during hospital stay, and their relation to the development of secondary gram-negative pancreatic infection[29]. The presence of intestinal *E. coli* did not increase the risk of pancreatic infection and mortality. Colonization with nosocomial gram-negative bacteria, however, significantly increases the risk of developing a secondary endogenous gram-negative pancreatic infection, as shown in this study. Moreover, when the same analysis was made for two treatment groups separately (subgroup analysis), results were similar to those of the whole group of patients, i.e. once gram-negative intestinal colonization occurs, the risk of developing a gram-negative pancreatic infection is increased, irrespective of SD treatment.

When *E. coli* were isolated from the pancreatic tissues (only 10% of patients with rectal E. coli), it was always found in a mixed infection with other gram-negative micro-organisms which had already caused infection at an earlier stage. In a clinical study on bacterial translocation in trauma patients, macrophages within mesenteric lymph nodes were found positive for *Escherichia coli* β-galactosidase, which suggested that most of these micro-organisms were ingested and killed by macrophages[36]. This might explain why presence of intestinal *E.coli* did not increase the risk of development of gram-negative pancreatic infections in our study.

Multiple organ failure due to gram-negative infected pancreatic necrosis is the major cause of later death in patients with severe acute pancreatitis. The development of gram-negative pancreatic infection increases the risk of mortality significantly[21]. The occurrence of gram-negative intestinal colonization leading to an increased risk of the development of gram-negative pancreatic infection, therefore, causes a significant increased risk of mortality in these patients, as shown in this study.

Gram-positive pancreatic infections are mostly not gut-derived, i.e. exogenous, as is shown in this study. Infection of pancreatic necrosis with gram-positive micro-organisms does not increase the risk of mortality[21].

Approximately 40% of the patients in whom colonization of the digestive tract with gram-negative bacteria occurred, developed a pancreatic infection. More than 70% of these pancreatic infections developed within 1 week following the first isolation from the digestive tract. In an elegant experimental study on rats Wang et al. described a significant increase of gut-originated bacteria in the pancreatic tissues in 20% of the animals 24 hours after the induction of severe acute pancreatitis[20].

Analysis of surveillance cultures of the digestive tract showed that colonization of the rectum is more predictive than colonization of the oropharynx. Surveillance cultures from the stomach were taken in too small numbers to perform a reliable analysis. However gastric gram-negative colonization showed a resemblance to that of the oropharynx in patients in whom both sites had been cultured. These findings suggest that the the lower intestinal tract. i.e. small intestine, colon and rectum, serve as the most important reservoir from which translocation occurs towards the (peri) pancreatic tissues. Widdison et al. already showed, in experimental studies, that pancreatic infections are reduced when the colon is enclosed in an impermeable bag[32].

The evolution of the severity of rectal gram-negative intestinal colonization until the moment of gram-negative pancreatic infection showed an increasing

magnitude with time, suggesting that an increase in the number of micro-organisms is necessary for the break down of mucosal barriers and defense mechanisms before translocation towards distant organs can take place. This study shows that polymicrobial gram-negative intestinal colonization did not have an additional predictive value with regard to the risk of developing a gram-negative pancreatic infection, as compared to patients in whom only one species was found in the digestive tract, suggesting that the quantity is more important than the quality. Several investigators found a direct relationship between the quantitative increase of intestinal gram-negative micro-organisms and the magnitude of translocation, again implying intestinal bacterial overgrowth as an important promotor of translocation[19,20,37-39]. This is in agreement with the finding that gram-negative rectal colonization was only incidental or transient in almost all our patients who did not develop a gram-negative pancreatic infection. This may also be attributed to a difference of severity of the disease causing different grades of gut failure and impairment of immunological defense mechanisms (average Imrie score on admission in this study: 4.5 with rectal colonization and infection in comparison to 2.7 without infection despite rectal colonization)[40].
To date, prognostic data with regard to patients with severe acute pancreatitis who are at risk of developing a gram-negative pancreatic infection have been restricted to non-microbial parameters, i.e. high multiple laboratory scores (Imrie score) as well as extensive (peri)pancreatic necrosis demonstrated by contrast-enhanced CT[21-23]. Our results demonstrate that gram-negative pancreatic infections are preceded by intestinal colonization approximately one week earlier.

CONCLUSIONS

The appearance of intestinal colonization with gram negative micro-organisms, increasing with time, is an early ominous predictive sign indicating that a serious, often fatal, gram negative pancreatic infection can probably be expected usually 1 week after the first intestinal occurrence. The presence of intestinal *E. coli* was not found to be of clinical importance with regard to the development of pancreatic infection, as well as with regard to mortality.
Gram-negative intestinal colonization is an early prognostic parameter in patients in whom pancreatic infection has not yet occurred; it entails a significantly increased risk of pancreatic infections as well as higher mortality. Therefore increased efforts to free the digestive tract of nosocomial gram-negative micro-organisms seems warranted.

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CHAPTER 5

EFFECTIVE REDUCTION OF GRAM-NEGATIVE INTESTINAL COLONIZATION WITH SELECTIVE DECONTAMINATION IN PATIENTS WITH SEVERE ACUTE PANCREATITIS

Results of a prospective colonization study with separate analysis of *E. coli*

Ernest J.T. Luiten, Wim C.J. Hop, Hubert Ph. Endtz, Hajo A. Bruining

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ABSTRACT

Since the presence of gram-negative intestinal flora significantly increases the risk to develop an aerobic gram-negative pancreatic infection, prophylaxis should be focused on eliminating this flora from the digestive tract. Investigations concerning effective antibiotics however have mainly been focused on the target organ, i.e. the inflamed pancreas

Results from 1729 surveillance cultures of the digestive tract taken from 90 patients with severe acute pancreatitis, during a randomized multicenter trial of selective decontamination (SD), were analyzed prospectively in order to evaluate the effect of SD on gram-negative intestinal colonization.

The cumulative incidence of intestinal colonization with aerobic gram-negative noscomial micro-organisms in the SD group (15 of 49 patients, 31%) was significantly decreased as compared to the control group (27 of 41 patients, 66%) (p=0.005). Also, the prevalence of gram-negative nosocomial pathogens in the SD group was significantly decreased as compared to the control group at nearly all days from day 10 until day 28. *Escherichia coli*, which was analyzed separately, was eliminated within 1 week in all patients from the SD group and the prevalence remained more or less stable in the rectum (30-40%) and oropharynx (0-10%) in the control group.

Although establishment of selective decontamination was not achieved in 3 of 49 patients in the SD group, emergence of resistance to the drugs used in the SD regimen was not found.

Selective decontamination can both effectively prevent and reverse gram-negative intestinal colonization in patients with severe acute pancreatitis. Successfull reduction of gram-negative pancreatic infections and mortality in patients with severe acute pancreatitis with SD is achieved through effective reduction of intestinal colonization.

INTRODUCTION

Antibiotic prophylaxis in the treatment of patients with severe acute pancreatitis has gained new interest. In the search of effective prophylaxis, the new broad-spectrum antimicrobial agents have been investigated with regard to their pancreas-specific pharmocokinetics and activity against the bacteria most frequently isolated from infected (peri)pancreatic necrosis[1,2,3]. In order to reach the

inflamed pancreas and surrounding tissues antibiotics are administered intravenous, although regional arterial perfusion has been reported also[4].

Aerobic gram-negative infection of (peri)pancreatic necrosis, which is the determinant with regard to morbidity and mortality, occurs through translocation of microbes which originate from the gut[5,6]. Development of gram-negative intestinal colonization of the digestive tract is an ominous sign predicting a significant increased risk of secondary infection of pancreatic necrosis as was dicussed in chapter 4.

Instead of focusing on protection of the target, i.e. the inflamed pancreas, antimicrobial prophylaxis may be more effective when primarily directed against the organ system from which the danger originates, i.e. the gut[7-9]. Intravenous broad-spectrum antibiotics currently investigated in patients with severe acute pancreatitis-e.g. imipenem, cefuroxime, ceftazidime, ofloxacin, or pefloxacin-do not prevent gram-negative colonization of the digestive tract. Selective decontamination of the digestive tract (SD) however, is an enteral antimicrobial prophylaxis designed to prevent or eradicate, if initially present, oropharyngeal and gastrointestinal colonization with aerobic gram-negative potentially pathogenic micro-organisms, leaving the indigenous flora, which are thought to play a role in the resistance to colonization, predominantly undisturbed[10,11].

Several authors have reported about the effect of SD on intestinal colonization in ICU patients[12-17]. The successfull reduction of gram-negative pancreatic infections and mortality in patients with severe acute pancreatitis with SD, as reported recently[18], should find its explanation through the effect of SD on intestinal colonization. However, apart from experimental studies[19-21], the latter has not yet been examined prospectively in patients with severe acute pancreatitis.

In this controlled prospective colonization study results of systematic semi-quantitative cultures of the digestive tract, taken from patients with severe acute pancreatitis, were analyzed to evaluate the effect of SD on intestinal colonization with aerobic gram-negative micro-organisms.

PATIENTS AND METHODS

The microbial intestinal flora of patients with objective signs of severe acute pancreatitis was prospectively monitored during a randomized clinical trial of adjuvant selective decontamination (Control group n=52 pts., Selective Decontamination group n=50 pts.). All patients suffered from severe acute pancreatitis according to a multiple laboratory criteria score (Imrie score ≥3) and/or grade D

or E disease severity (Balthazar grades) using Contrast-Enhanced Computerized Tomography (CE-CT)[22,23].

The SD regimen consisted of oral administration of colistin sulfate (200 mg), amphotericin (500 mg) and norfloxacin (50 mg) every 6 hours. A sticky paste containing 2% of the three SD drugs was smeared along the upper and lower gums every 6 hours and at the tracheostomy, if present. The aforementioned daily dose also was given in a rectal enema every day.

Short-term (average 7.4 days) systemic prophylaxis with cefotaxime sodium (500 mg) was given every 8 hours until SD was established. i.e. elimination of nosocomial gram-negative micro-organisms from the oral cavity and rectum.

Microbiology

Surveillance cultures from the oropharynx and rectum were taken on admission and repeated twice weekly according to the original protocol. Samples were taken with a sterile cotton-tipped swab and cultured semi-quantitatively (1+,2+,3+,4+)[24]. Identification was performed following routine microbiological procedures.

Occurrence of gram-negative intestinal colonization of the digestive tract (oropharynx and rectum) was noted for each patient separately by recording the date of first isolation as well as duration of colonization of specific micro-organisms. Colonization was defined as the presence of the same micro-organism in two or more consecutive cultures of samples, taken from the same site. The effect of SD on intestinal (resident) *E. coli* and gram-negative intestinal colinization with other aerobic gram-negative, hospital-acquired, potential pathogenic micro-organisms, here referred to as "gram-negative nosocomial micro-organisms", was studied separately in accordance with reports from others[6,12,15,16,25].

Patients in whom surveillance cultures had not been taken sufficiently to perform a reliable analysis were excluded from this analysis. Follow up was continued until death or until the risk of development of a pancreatic infection was considered absent-i.e. the patient was extubated and without supplementary oxygen therapy or infusions, on a regular diet, and mobilized on the ward. Selective decontamination was discontinued at that same time.

Statistical analysis

Percentages were compared using Fisher's exact test. The cumulative incidence of gram-negative intestinal colonization, taking account of individual periods of

observation, was calculated using the Kaplan-Meier method. Comparison of these curves was done using the logrank-test, or the logrank-test for trend if appropriate. P-values ≤ 0.05 (two-sided) were considered significant.

RESULTS

Of 102 patients who entered the study, 12 were excluded from this analysis as intestinal surveillance cultures had been taken insufficiently. A total of 1729 surveillance cultures (control group: 41 patients, SD group: 49 patients) were analyzed. Qualitative analysis of surveillance cultures is presented in Table 1.

Table 1. Qualitative Analysis of Gram-negative Intestinal Colonization. Incidence of Micro-organisms in 90 patients[a]

	SD (no. patients)	control (no. patients)
Escherichia coli	33	31
Nosocomial micro-organisms:	15	27[b]
Pseudomonas aeruginosa	8	16
Klebsiella spp.	4	10
Citrobacter spp.	-	5
Enterobacter spp.	-	6
Morganella morganii	3	4
Proteus spp.	-	6
Serratia marescescens	1	-
Acinetobacter spp.	-	4

SD: selective decontamination group(n=49 patients), control: control group (n=41 patients).
a: micro-organisms may occur in combinations in each separate patient. b: p=0.005.
Gram-negative intestinal colonization did not occur in 18 patients (SD: 13 patients, control:5 patients). In 30 of 64 patients *E. coli* was the only micro-organism isolated from the digestive tract (SD: 21 patients, control:9 patients). In the SD group rebound-colonization (only 2 consecutive cultures) with *Pseudomanos aeruginosa* (1 patient) and *Klebsiella* (1 patient) occurred after discontinuation of SD.

The isolation of gram-negative nosocomial micro-organisms differed consistently between the control and the SD group. To compare prevalences after start of treatment, results of surveillance cultures have been grouped at three-day intervals. The results from oropharynx (Figure 1a) and rectum (Figure 1b) showed the same pattern. Initially (day 1), these gram-negative micro-organisms were isolated from these sites in a small proportion (3-14%) of the patients in both groups. In the SD group the prevalence of positive samples in both oropharynx and rectum decreased to 0-2 % within 10 days of treatment. This proportion increased in the control group during the first week, then remained stable at 20-40%. From day 10 until day 28 the differences between the SD and control group were significant at all days with regard to the rectum (Figure 1b), and at all days but one (day 14: p=0.09) with regard to the oropharynx (Figure 1a). On day 1 gram-negative nosocomial pathogens were isolated in 13 patients (SD: 9 pts, control: 4 pts.) These micro-organisms were absent within 3 days in 6 out of 9 patients (78%) from the SD group as compared to 1 out of 4 patients (25%) in the control group (p=0.22, n.s.).

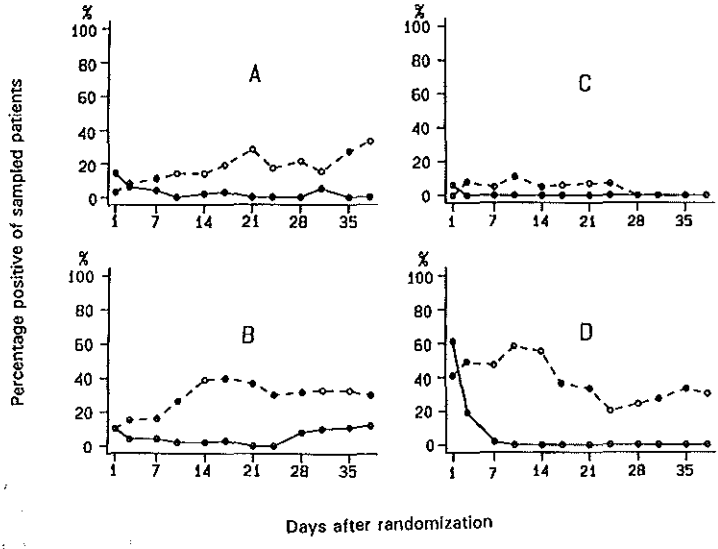

Figure 1. Results from surveillance cultures along time: Prevalence of aerobic gram-negative micro-organisms (except *E. coli*) from oropharynx (1a) and rectum (1b); the differences between control and SD group from day 10 until day 28 are significant at all days for rectal and all days but one (day 14: p=0.09) for oropharyngeal cultures. Prevalence of *E. coli* isolated from oropharynx (1c) and rectum (1d). ----: control group, ——: SD group.

E. coli was initially isolated from two or more consecutive cultures in 33 of 49 patients receiving SD (Table 1). In all of these patients *E. coli* was eliminated within 7 days SD treatment without later recurrence (Figure 1c/d). In the control group the proportion of positive cultures from the oropharynx remained stable at more or less 10% (Figure 1c). Rectal isolation of E. coli in the control group remained at high levels (30-40%) with a temporary (borderline significant, p=0.057) increase up to 58% at the beginning of the second week (Figure 1d).

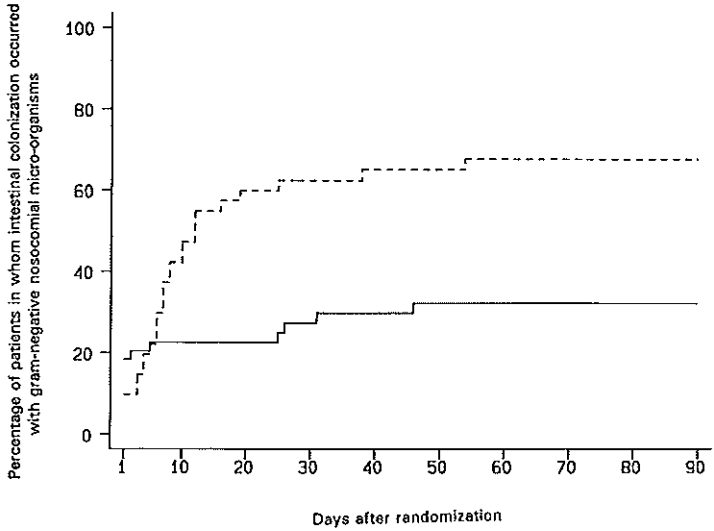

Figure 2. Cumulative incidence along time of gram-negative intestinal colonization according to treatment group : p=0.005. ----: control group, ———: SD group.

Gram-negative intestinal colonization in the control group occurred in 27 of 41 (66%) patients. In 22 of these 27 patients (81%) colonization occurred within two weeks of admission. The cumulative incidence of gram-negative intestinal colonization with gram-negative nosocomial micro-organisms according to treatment group is shown in Figure 2. In the SD group gram-negative intestinal colonization occurred in 15 of 49 (31%) patients, who are discussed in the undermentioned (p=0.005). One of these patients died after 4 days. In nine patients colonization was found during the first week only, followed by establishment of selective decontamination. In two other patients short-term rebound colonization (2 consecutive cultures) occurred after discontinuation of SD during the 4th week

(Figure 2). In another patient, in whom colonization during the first week with *Pseudomonas aeruginosa* was eliminated only after 18 days, recolonization with *Pseudomonas aeruginosa* was found on the 31th day and persisted until death after 38 days. The *Pseudomonas* strain was susceptible to norfloxacin on both occasions. In the remaining two patients initial presence of *E. coli* was eliminated by SD. In both patients selective decontamination was established for a few weeks. However in one of them, who survived, transient colonization after the 6th week was followed by transient pancreatic infection with *Serratia marcescens* resistant to the components of the SD regimen when first isolated. In the other patient, in whom intially selective decontamination was established, intestinal colonization with *Pseudomonas aeruginosa*-susceptible to norfloxacin-occurred after 31 days was followed by a fatal pancreatic infection.
The Imrie score at enrollment in the study appeared to correlate very strongly with the incidence of gram-negative intestinal colonization along time, especially in the control group (p=0.001) (Figure 3).

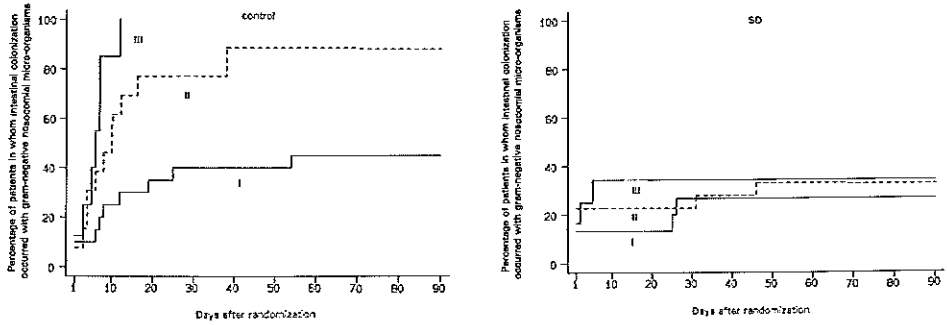

Figure 3. Cumulative incidence along time of gram-negative intestinal colonization in the control group (left) and selective decontamination (SD) group (right), according to Imrie score (I, 0-2; II, 3-4; III, >4) at enrollment in the study. Control group scores: I, 20 patients; II, 13 ; III, 8; P_{trend}=0.001, SD group scores: I, 15 patients; II, 22; III, 12; P_{trend}=0.53.

DISCUSSION

Gram-negative pancreatic infection, which appars a very important factor with regard to mortality in patients with severe acute pancreatitis, is gut-originated[6].

This study demonstrates that SD can both effectively prevent and reverse gram-negative intestinal colonization in patients with severe acute pancreatitis. The total number of patients in whom gram-negative intestinal colonization occurred (cumulative incidence) of 66% in control group patients is comparable to results reported by Aerdts et al. and Saunders et al. however higher than reported by Tetteroo et al.[14,26,27]. The actual number of patients or samples containing gram-negative nosocomial pathogens (prevalence) increased along time to a lower level than the rates (greater than 80% at seven days) as found by Stoutenbeek-who however used a historic control group-and others[12,25]. Differences probably reflect a difference of disease and severity of illness. The latter is underlined by our study which showed that the probability of occurrence of gram-negative intestinal colonization increases with higher Imrie scores on admission. A lower cumulative incidence in the SD group reflects effective prevention of gram-negative intestinal colonization whereas the prevalence is also affected by reversal by SD of gram-negative intestinal colonization after its occurrence. When comparing differences between percentages of patients with gram-negative intestinal colonization, the measure of prevalence probably is of less clinical importance as compared to the cumulative incidence. This is due to the fact that the first measure is greatly influenced by the composition of the patient groups which are sampled at the various time points.

Ledingham et al. only found an increasing prevalence of colonization in the upper gastrointestinal tract, i.e. throat and stomach, which can be explained by the fact that results from rectal colonization included the presence of (resident) *E. coli*[13]. Presence of intestinal E coli was found not to be of clinical importance with regard to development of pancreatic infection in contrast to intestinal colonization with other gram-negative nosocomial micro-organisms as has been reported previously[6]. Because administration of SD is aimed to prevent development of gram-negative pancreatic infection, the effect of SD on presence of intestinal (resident) E. coli was therefore studied separately from other gram-negative nosocomial micro-organisms similarly as reported by others [12,15,16,25].

Approximately 1 week was required to free the intestine from gram-negative nosocomial micro-organisms as was also reported by Ledingham et al.[13]. However, we did not find a difference between establishment of selective decontamination of the upper and lower intestinal tract which can be explained by additional rectal administration of SD medication in our study. As colonization of the rectum has been demonstrated to be of major importance with regard to later development of a gram-negative pancreatic infection[6], rectal administration of SD drugs is essential in patients with severe acute pancreatitis. After 3 days already 78% of the

patients, who presented with intestinal gram-negative pathogens on day 1 and who received SD, were without these pathogens as compared to 25% of the patients in the control group. However this difference did not reach statistical significance, possibly due to small numbers. Rebound colonization after withdrawal of SD-medication, as found occasionally in two patients, did not offer a problem as was observed by Tetteroo et al.[27].

In order to provide additional cover before SD was fully established, cefotaximesodium was used as a short-term (average 7.4 days) systemic prophylaxis, as it had been used most often in SD trials[12,17,26,28]. The question has been raised whether efficacy is actually conferred by the parenteral agent rather than the regimen of oral antibiotics[29,30]. Although Widdison et al. demonstrated that early administration (12 hrs from onset) of intravenous cefotaxime or levamisole in cats was indeed effective in treating-however already *established*-pancreatic infection[31,32], until now however none of the four prospective clinical trials[33-36] using only adjuvant systemic intravenous antibiotic *prophylaxis* has demonstrated both reduction of development of gram-negative pancreatic infection as well as reduction of mortality in patients with severe acute pancreatitis. (Results from these studies using intravenous antibiotic prophylaxis are discussed in detail in chapter 6[33-36].) Moreover, van Saene reported emergence of resistance-after 4 days intravenous administration-against cefotaxime, although higher dose of 50-100 mg/kg/day, of several aerobic gram-negative micro-organisms, which are frequently found in infected pancreatic necrosis, e.g *Pseudomonas* species, *Acinetobacter* species, *Enterobacter cloacae* and *Citro-bacter* species[37]. Although Büchler et al. calculated that cefotaxime reached sufficient concentrations in vital pancreatic tissue of patients undergoing mainly elective pancreatic surgery[1], Foitzik et al. however found that concentrations of antibiotics in the pancreas, e.g. cefotaxime, are low during the early phase of experimental acute necrotizing pancreatitis, depending on changes in pancreatic tissue morphology and capillary blood flow[3]. They also showed that prophylactic use of cefotaxime or oral antibiotics alone were not able to reduce pancreatic infection in rats in contrast to the combination of both[20].

Failure of SD to eliminate and prevent gram-negative intestinal colonization may be due to: 1) insufficient intestinal concentration (below the MIC) due to insufficient administration, intestinal absorption or inactivation by faeces, 2) selection of resistant organisms in the gastro-intestinal tract, 3) aquisition and colonization of resistant micro-organisms from the hospital environment, 4) de novo emergence of antimicrobial resistance during SD.

Norfloxacin is absorbed incompletely from the digestive tract and therefore reaches high faecal concentrations: at an oral dose of 200 mg daily Aerdts maesured concentrations of 100 microgram per gram faeces exceeding the MIC of even the least suseptible aerobic gram-negative micro-organisms[38]. Colistin was given in a relatively large amount (800 mg daily) because of the marked inactivation of polymyxins in the digestive tract[39,40]. When combined with other oral antibiotics even lower doses have been reported to reach sufficient intestinal concentrations[40]. Therefore inadequate administration causing insufficient intestinal concentration may have been the cause of SD-failure in two patients dying of gram-negative pancreatic infection caused by a *Pseudomonas* strain susceptible to the components of the SD regimen.

Acquisition of resistant hospital strains, as occurred in one patient, endanger every patient admitted, especially on an ICU. Although interpreted as failure of any prophylactic antimicrobial regimen, i.e. SD, it reflects the selective pressure of antibiotics and the appropriateness of (previous) antibiotic use. Moreover, local infection control practices are important in the transmission of nosocomial pathogens in an ICU[41]. A major problem in the prophylactic use of antibiotics is the risk of selection of resistant microbes and fungi. With SD, selection or de novo emergence of resistance is at least theoretically ruled out once the aerobic gram-negative micro-organisms have been eliminated: if complete intestinal elimination is achieved no resistance potential is present. An overall increase in antibiotic resistance amongst the aerobic gram-negative micro-organisms by the use of SD is either rare or absent[14,15,42-44].

Since de novo emergence of resistance to the quinolones during SD is incidental and with absence of possible systemic hazardous side-effects when absorbed as well as their low costs, they appear to be suited for SD[38,45-47].

CONCLUSIONS

Since acute pancreatitis induces intestinal bacterial overgrowth and secondary pancreatic infections are gut-originated, prophylaxis should be focused on prevention of gram-negative intestinal colonization[6,48]. Selective decontamination, including rectal administration of the same drugs, has been shown both to effectively prevent acquisition of gram-negative nosocomial micro-organisms as well as to rapidly reverse occasional initial gram-negative intestinal colonization in patients with severe acute pancreatitis thereby reducing the risk to develop a life-threatening gram-negative infection of (peri)pancreatic necrosis.

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CHAPTER 6

INFECTION OF NECROSIS IN ACUTE PANCREATITIS - ROLE OF PROPHYLACTIC ANTIBIOTICS / SD

Ernest J.T. Luiten, Hajo A. Bruining

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HISTORY

The use of antibiotics in acute pancreatitis has been continously debated for more than half a century. In 1950 Lewis and Wangensteen reported reduced mortality in dogs with acute hemorrhagic pancreatitis treated with penicillin[1]. Persky et al. demonstrated that aureomycin, given orally, resulted in 100 per cent survival after bile-induced necrotizing pancreatitis in mongrel dogs[2]. Cultures of pancreatic necrosis from non-surviving dogs treated without antibiotics, showed an increase of secondary pancreatic infection, especially with *Clostridia*. Subsequently, they found a moderate reduction of mortality with polyvalent clostridial toxoid, neomycin and polymyxin B[3].

Byrne and Joison, however discussing the primary role of bacteria in the pathogenesis of necrotizing pancreatitis, found that neomycin, tetracyclin, penicillin and sulfonamide instilled in a closed duodenal loop, prevented the onset of necrotizing pancreatitis[4]. Thal et al. mentioned increased survival when *Escherichia coli*-induced necrotizing pancreatitis was treated with aureomycin[5]. Similar results were also reported when antibiotics were used in germ-free dogs with necrotizing pancreatitis, casting some doubt on the essential role of bacteria in the pathogenesis[6].

While many investigators supported the clinical use of antibiotics in acute pancreatitis, Kodesch and DuPont in 1973 probably were the first to express sceptiscism about the protection against infectious complications[7-10]. A few years later three controlled clinical trials with ampicillin in patients suffering from, mild, acute pancreatitis showed no benefit[11-13].

Since advances in critical care have greatly reduced the incidence of death caused by the early cardio-pulmonary sequelae of severe acute (necrotizing) pancreatitis, secondary pancreatic infections currently have emerged as the leading cause of mortality and morbidity[14-18].

After a decade of nihilism in the face of infected pancreatic necrosis, there is now optimism that infection may be preventable due to results of recent controlled clinical trials based on knowledge of penetration of different antibiotics into the pancreatic tissues and on data regarding the microbial flora most frequently isolated from pancreatic necrosis[14,17-30].

INCIDENCE

Secondary infections (i.e. infected necrosis, pancreatic abscess or infected pseudocyst) complicate 3-12% of the cases with acute pancreatitis[17,21,29-34]. It is estimated that severe acute (necrotizing) pancreatitis develops in 10-20% of patients with acute pancreatitis and secondary infection of (peri)pancreatic necrosis occurs in 40-70% of these patients[14,22,26,29,30,33-42]. Gram-negative aerobic micro-organisms are isolated in 50-70% from cultures of infected (peri)pancreatic necrosis suggesting an enteric origin[14,27-30,34,37,40]. Development of gram-negative infection of (peri) pancreatic necrosis is, apart from the Imrie score, the most important parameter determining outcome as compared to patients in whom infection does not (i.e. sterile necrosis) occur[43]. Infection of necrosis with only gram-positive micro-organisms has the same prognosis as necrosis remaining sterile[43]. Gram-negative infection of pancreatic necrosis has been found to be preceded by intestinal colonization with identical gram-negative micro-organisms both experimentally and clinically[44-52].

Beger et al. showed that infection of pancreatic necrosis increases with time during the course of the disease[14]. However, only data of patients who were operated, were analyzed. We also found that the incidence of infected necrosis, when analyzing the bacteriologic status at the first laparotomy, increased with time, from 9% during the first week to 50% during the second and third week, as has also been reported by others[23,26,53]. Mortality due to infection of pancreatic necrosis is significantly increased from 31% within two weeks to 77% thereafter[23].

ROLE OF ANTIBIOTICS

Since infection of pancreatic necrosis is a secondary phenomenon, prophylactic antibiotics should be administered at an early stage of tissue injury before infection has developed, i.e. from the onset of the disease. Antibiotics should probably only be used in patients with severe acute pancreatitis (three or more positive Imrie signs), since mild acute pancreatitis is a self-limiting disease irrespective of the type of medical treatment[54-57]. It is currently unknown whether antibiotics are more useful in acute pancreatitis due to gallstones or from alcohol abuse.

Three early controlled clinical trials using prophylactic ampicillin in patients with mild mostly alcohol-induced pancreatitis showed no benefit[11-13]. However, ampicillin is a poor antibiotic choice for acute pancreatitis as it does not penetrate

the pancreas and, perhaps more importantly, does not cover the gram-negative micro-organisms most frequently isolated from infected pancreatic necrosis, i.e. *Escherichia coli, Peudomonas, Klebsiella species* and *Enterobacter species* (Chapter 2: Table 4)[14,22-24,26,27]. Above all the patients recruited only had mild disease not bearing the risk of pancreatic infection.

Based on pharmacokinetic data on several antibiotics from human pancreatic juice or pancreatic tissues from animals, several investigators have speculated about appropriate antibiotics to treat patients with acute pancreatitis[17, 58-61].

An important contribution towards better understanding of antibiotic penetration into human pancreatic tissue was made by Büchler and co-workers in 1992[25]. They calculated the potential clinical effectiveness of ten different bactericidal antibiotics, taking into account a) type and frequency of bacteria commonly involved in human pancreatic infections, b) pancreatic tissue concentrations of these antibiotics 120 minutes after intravenous infusion and c) the percentage of inhibited bacteriological strains, in 89 patients undergoing elective pancreatic surgery for acute pancreatitis, chronic pancreatitis or pancreatic cancer. Three groups of antibiotics were established: group A, substances with low pancreatic tissue concentrations (netilmycin, tobramycin), which were below the MIC of most bacteria; group B, with pancreatic tissue concentrations which were sufficient to inhibit some but not all bacteria (mezlocillin, piperacillin, ceftizoxime, cefotaxime); group C, antibiotics with high pancreatic tissue concentrations as well as high bactericidal activity against most micro-organisms found in pancreatic infections (ciprofloxacin, ofloxacin, imipenem). Metronidazole showed good penetration into the pancreas, but was not included in the efficacy analysis because of its small bactericidal spectrum almost exclusively against anaerobes.

It was recommended to be included in treatment regimes with antibiotics which are not effective against anaerobes, i.e. group B antibiotics. However, only 9% of the samples (8/89) were taken from patients with acute pancreatitis analyzing only 3 different antibiotics, i.e. mezlocillin, netilmycin and metronidazole. Because pancreatic tissue concentrations for these antibiotics were not different from patients with chronic pancreatitis or pancreatic cancer it was concluded that there were no significant differences in the pancreatic tissue concentrations with respect to the underlying disease for the other seven antibiotics analyzed. However, Foitzik et al. demonstrated that antibiotic tissue concentrations may not be consistent from one agent to another, because of changes in pancreatic tissue morphology and capillary blood flow in experimental acute pancreatitis, and that efficacy cannot be estimated solely on the basis of their pharmacology and microbiological properties[62].

Bassi et al. examined whether antibiotics excreted by the normal pancreas (imipenem, mezlocillin, gentamycin, amikacin, pefloxacin and metronidazole) are also excreted in necrotic pancreatic tissue[63]. Following parenteral administration of antibiotics, serum and samples of pancreatic necrosis, obtained by computed tomography (CT)-guided needle aspiration, intraoperatively, and from surgical drains, were collected simultaneously at different time intervals from twelve patients suffering from severe acute pancreatitis. Although all of the antibiotics reached the necrotic tissue, only pefloxacin and metronidazole concentrations consistently exceeded the MICs for the micro-organisms most commonly isolated from infected necrosis. Mezlocillin and imipenem inconsistently attained levels greater than the MICs, although the concentration of imipenem seemed to enhance by repeated administration. Aminoglycosides levels were always inadequate.

Controlled clinical trials of intravenous antibiotics

When choosing a prophylactic antibiotic in order to prevent secondary infectious complications in patients with severe acute pancreatitis, the ideal drug should be characterized by a) effectiveness against commonly involved micro-organisms, b) ability to penetrate into pancreatic tissue and pancreatic exocrine secretions, c) ability to reach therapeutic mean inhibitory concentrations (MIC) in pancreatic tissue, (peri)pancreatic necrosis and peripancreatic fluidcollections during severe acute pancreatitis, d) demonstrated clinical capacity of reducing the development of pancreatic infection and, e) cost-effectiveness and low adverse reactions.

Based on the results reported by Büchler et al.[25], a controlled multicenter trial of imipenem prophylaxis in patients with necrotizing pancreatitis was conducted Pederzoli et al.[24]. During a two-and-a-half year period 74 patients were included, based on presence of detectable pancreatic necrosis demonstrated by contrast-enhanced computed tomography (CE-CT) within 72 hours of onset of symptoms. Patients were randomized to receive standard medical treatment without (n=33 patients) or with adjuvant imipenem (41 patients) for 2 weeks (500mg every 8 hours intravenously). Ranson scores, which were not used as an inclusion criterium, ranged from 3 to 6 (mean 3.7). Almost fifty percent of the patients only had mild necrosis (less than 30%) as found on CE-CT, bearing a lesser risk of infection, and of the sixteen patients with severe pancreatic necrosis (more than 50%) only two were randomized to the control group. Nevertheless a significant reduction of pancreatic sepsis (12.2% versus 30.3%) and non-pancreatic sepsis (14.6% versus 48.5%) was observed. Unfortunately separate results with regard to reduction of the total number of patients with aerobic gram-negative infection

of necrosis, which is the determinant of mortality, can not be fully evaluated from the data reported. However mortality (7.3% versus 12.1%) was not different, but overall mortality (9.4%) was rather low probably reflecting the incidence of less severe disease.

Based on their own results regarding behaviour of antibiotics in human pancreatitis, Bassi and co-workers performed a prospective trial during a 6-year period in 60 patients with severe acute pancreatitis who were administered either pefloxacin (400mg every 12 hr) or imipenem (500mg every 8 hr) for 2 weeks. Patients were included if C-reactive protein (CRP) values were above 100mg/l and more than 50% pancreatic necrosis was confirmed by contrast-enhanced computed tomography (CE-CT) (Bassi et al., submitted for publication, with permission). The incidence of infected pancreatic necrosis, which mainly occurred after the second week when antibiotic treatment was already stoppped, in the pefloxacin group (34%) was higher as compared to the imipenem group (10%) ($p<0.05$). Mortality also was higher in the pefloxacin group (24%) as compared to the imipenem group (10%), although not statistically significant,. Despite its theoretical potential, pefloxacin was not found to be a valid alternative to imipenem in severe acute pancreatitis, which once again stresses the necessity of proven efficacy by prospective clinical trials before antibiotics are widely adopted as prophylaxis in this disease.

Sainio et al. reported a significant reduction of mortality in 60 patients, recruited during a 4-year period, with acute necrotizing pancreatitis using cefuroxime (4.5g/day)[64]. This was not associated with a reduction of pancreatic sepsis. Unfortunately the authors were forced to change from cefuroxime to alternative antibiotics in two-thirds of the patients after 9 days (2-28) and to initiate antibiotic therapy after 6 (2-16) days, on the basis of presumed or documented infection, in 23 of the 30 patients initially randomized to no therapy. The incidence of urinary sepsis was significantly decreased in the group of patients treated initially with cefuroxime. Confounding factors may have been responsible for the reported statistically significant reduction of mortality as was already noted by others[65-69]. In contrast to third generation cephalosporins, which achieve adequate pancreatic tissue levels, the pancreatic pharmocokinetics of cefuroxime are unknown and its failure to reduce infection of pancreatic necrosis in this study may indicate that pancreatic penetration is poor. However cefuroxime was chosen because of the susceptibility of *Escherichia coli* and *Staphylococcus aureus*, the latter which is a common cause of sepsis in their intensive care unit, thereby acknowledging the possibly of a lesser degree of penetration in pancreatic necrosis.

A small but well-designed controlled study of 26 patients, enrolled during a 4-year period, conducted by Schwarz et al. using ofloxacin and metronidazole reported no prevention of pancreatic infection[70]. Interestingly, the total number patients who developed an aerobic gram-negative pancreatic infection was lower in the treatment group (1/13 patients, 7%) as compared to the control group (6/16 patients, 46%) (p=0.07). However, because of the few patients recruited in this study, the possibility of not reaching statistical significance may have biased the conclusions (type II error).

A controlled study by Delcenserie and colleagues, which recruited 23 patients with alcohol-induced severe acute pancreatitis during a 5-year period, using ceftazidime, metronidazole and amikacine for only 10 days, reported a reduction of overall episodes of sepsis[71]. However, reduction of pancreatic infections, particularly reduction of aerobic gram-negative pancreatic infection was not achieved. Conclusions from this study should also be interpreted with caution due to the very small number of patients included and because amikacin, an aminoglycoside, is from a class of drugs that does not adequately penetrate the pancreas.

Clinical study of intra-arterial antibiotics

Takeda and colleagues studied reduction of pancreatic infection by continuous regional arterial infusion (CRAI) with antibiotics, which were combined with nafamostat, a protease inhibitor in an uncontrolled non-randomized study[72]. During a five-year period 53 patients with severe acute pancreatitis were referred from elsewhere and divided in three groups: Group I, 16 patients who were referred >8 days after disease onset, received intravenous nafamostat and antibiotics (5 different drugs); Group II, 22 patients referred within 7 days, during the first three-and-a-half year, received nafamostat via CRAI for 3 to 5 days and intravenous antibiotics (antibiotics not specified); Group III, 15 patients referred within 7 days during the last one-and-a-half year of the study, received both nafamostat and imipenem (500mg every 12 hr) via CRAI for 3 to 5 days. The incidence of infection of pancreatic necrosis in group III (0%) was significantly lower than those in group I (50%) and group II (23%). Although mortality rates in group II (14%) and group III (7%) were significantly reduced, as compared with that in group I (44%), both are not significantly different from each other. However, the design of the study, the different antibiotics used, the short period during which CRAI was performed and, the simultaneous use of nafamostat, a protease inhibitor, may have interfered with the results and the clinical applicabili-

ty of this technique may have its drawback. Hayashi and colleagues reported significant improved survival rate, prevention of pancreatic infection and decreased serum levels of phospholipase A_2 activity and endotoxin in an experimental study of CRAI using flomoxef in dogs with acute pancreatitis, as compared to intravenous use or a control group[73]. Moreover, they found only a little beneficial effect of intravenous administration as compared to animals treated without antibiotics, suggesting that the intravenous route may be less sufficient. However, the importance of these results is limited due to the very short follow up (only 36 hours).

Controlled clinical trial of enteral antibiotics: selective decontamination

Following better knowledge about infected necrosis, its prevalent flora suggesting an origin in the gut, experimental evidence concerning the protective effect of reduction of intestinal flora and successful clinical reduction of gram-negative intestinal flora from the digestive tract, a multicenter controlled randomized clinical trial using selective decontamination in 102 patients with severe acute pancreatitis, enrolled in a 3-year period, was conducted in the Netherlands[14,23,74-82]. All patients had severe acute pancreatitis defined by Imrie score ≥3 and or Balthazar grade D or E (Chapter 2: Table 1)[75,83]. The selective decontamination regimen consisted of oral, and rectal (enema containing daily dose), administration of colistin sulphate (200mg), amphotericin (500mg) and norfloxacin (50mg) every 6 hours. Also a sticky paste with the three drugs was smeared along the gums and tracheostomy, if present. A short term systemic prophylaxis (mean 7.4 days), using cefotaxime, was given until the digestive tract was successfully selectively decontaminated. Selective decontamination was discontinued as soon as the risk of acquiring an infection was negligible-i.e. extubated and without supplementary oxygen therapy or infusions, on regular diet and mobilized on the ward.

Selective decontamination (SD) significantly reduced overall mortality through its significant effect on gram-negative pancreatic infection and late mortality (Chapter 2: Figure 1, Table 3). The Imrie score proved to be very valuable in identifying patients with increased risk of development of gram-negative pancreatic infection and also at risk of dying[23,43]. CT-findings using Balthazar grades were less accurate as they tend to overestimate the severity of severe acute pancreatitis (Chapter 2: Figure 2, Table 3). SD reduced mortality in treated patients with three or more positive Imrie signs from 55% to 31% with a 95% confidence interval for the difference in mortality ranging from 0% to 48%. Failure of SD to successfully maintain clearance of gram-negative nosocomial

flora from the digestive tract was seen in four patients, followed by development of a pancreatic infection. Suggested SD-induced overgrowth of gram-positve flora was not found[84,85].

There is general agreement that infected (peri)pancreatic necrosis is an absolute indication for operation, which may need to be repeated[14,26,37,39,86-88]. Even after surgery, infected necrosis carries a threefold higher mortality rate (range 15-82%) in contrast to sterile necrosis[34,87,89]. A significant lower number of repeated laparotomies and lower surgery-related complication rate were achieved in patients treated with SD through a significant reduction of gram-negative pancreatic infections[23]. More than 70% of these infections occurred within 1 week of first isolation from the digestive tract[52].

Persky and collegues in 1951 were way ahead of their time when they found a much greater effectiveness of the oral as compared to intravenous aureomycin and postulated that the micro-organisms responsible for secondary infection of the pancreas in dogs originated from the intestine[2]. Favourable effects have been reported on the outcome of experimental necrotizing pancreatitis in rats, reducing the intestinal flora by means of colectomy, caecostomy , intestinal lavage with addition of oral kanamycine or colonic irrigation[81,90]. Two recent experimental studies with selective decontamination reported reduction of pancreatic infection[47,91].

Since acute pancreatitis induces intestinal bacterial overgrowth and secondary pancreatic infections are gut-derived, the gut serves as the "motor" of pancreatic sepsis[50-52,92]. Intravenous antibiotic prophylaxis, i.e. imipenem, does not affect the colonic pool of bacteria[47]. In order to nip the danger of secondary pancreatic infection in the bud, early elimination of gram-negative micro-organisms from the digestive tract by means of SD seems the most logical and effective step to reduce morbidity and mortality in severe acute pancreatitis.

OTHER PROPYHLACTIC STRATEGIES

Initial enthousiasm for peritoneal lavage was dampened by a large controlled clinical trial showing no effect on the outcome of severe acute pancreatitis[93-97]. However, inspiring results were reported by the late J.H.C. Ranson, comparing long (7 days) versus short (2 days) peritoneal lavage[98]. The operative technique advocated by Beger et al. consists of necrosectomy and continuous closed postoperative lavage of the lesser sac[33]. Currently an overall mortality rate of 15.4% is reported in case of infected pancreatic necrosis[34]. Initially a lower

mortality rate of 8.4%[99] was reported including results of patients operated for sterile necrosis. The very impressive results in case of sterile necrosis necrosis may be partly due to the excessive lavage, initially with more than 24 liters per day, preventing secondary pancreatic infection.

RECOMMENDATIONS FOR TREATMENT

Only patients with severe acute pancreatitis (i.e. three or more positive Imrie signs) will benefit from antibiotic therapy. As infection can occur already during the first week after onset of the disease, prophylactic antibiotics should be given as soon as possible after admission and diagnosis. Antibiotic prophylaxis should be continued until the risk of pancreatic infection is absent.

Up to now selective decontamination of the digestive tract (colistin, amphotericin and norfloxacin) combined with a short term (average 7 days) systemic prophylaxis of cefotaxime, until selective decontamination is established, is most effective in reducing morbidity as well as mortality.

The intravenous prophylactic antibiotics used, should adequately penetrate (peri)pancreatic tissues and should be effective against the prevalent flora found in infected necrosis. However imipenem, which meets these criteria, has only proven its efficacy with regard to reduction of pancreatic infection but not mortality.

Further controlled multicenter trials with adjuvant antibiotic prophylaxis, including large numbers of patients with severe acute pancreatitis after proper severity stratification, are warranted in order to answer the many open questions.

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CHAPTER 7

SELECTIVE DECONTAMINATION FOR SEVERE ACUTE PANCREATITIS: SUMMARY

Ernest J.T. Luiten, Hajo A. Bruining

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INTRODUCTION

Acute pancreatitis is an acute inflammatory process of the pancreas, with variable involvement of peripancreatic tissues or remote organ systems. Despite a wide variety of etiology, gallstones and alcohol represent more than 75% of all etiologic causes[1].

According to the Atlanta *clinically based* classification of acute pancreatitis, 75% of all patients only suffer from a *mild* acute disease with minimal organ dysfunction with an uneventful recovery irrespective of the type of medical treatment[2]. However, during the initial 24 to 48 hours after onset of symptoms about 20%-30% of all patients with acute pancreatitis develop a severe clinical course. *Severe* acute pancreatitis is associated with organ failure and/or local complications, such as necrosis, abscess, or pseudocyst. This severe acute disease is further characterized by 3 or more Imrie/Ranson criteria, or 8 or more APACHE II points[2]. The rapid development of organ dysfunction and (peri)pancreatic necrosis is initiated by "premature" intrapancreatic activation of pancreatic enzymes which trigger a systemic inflammatory response evoked by host-derived inflammatory mediators. With agressive intravenous fluid replacement and intensive care more patients pass through these critical early stages and later secondary infection of (peri)pancreatic necrosis currently is the major cause of death in patients with severe acute pancreatitis.

INFECTION OF (PERI)PANCREATIC NECROSIS

Infection of (peri)pancreatic necrosis occurs in 40-70%[3-6] and the incidence increases with larger amounts of necrosis[3,7]. Beger et al.[3] performed a microbiological analysis of (peri)pancreatic necrosis obtained during the first necrosectomy from 114 patients who were operated on because of development of necrosis. They demonstrated that the incidence of infected (peri)pancreatic necrosis increased with time from 24% during the first week up to more than 70% during the third week[3]. A similar analysis performed in only 24 patients from the control group of our study, who were operated on because of clinical deterioration despite intensive care or because of proven infection of (peri)pancreatic necrosis, showed a more or less comparable (small numbers of patients) increase from 12% during the first week up to 50% during the third week. However, patients who are found to have sterile necrosis at first necrosectomy may develop infection of (peri)pancreatic necrosis later during the course of the disease which is not taken into account in

this incidence analysis. Moreover, patients whose deteriorating condition demands a (first) surgical intervention, however, later during the course of the disease are likely to have developed an infectious complication during hospital stay. A lower incidence of infected necrosis at first laparotomy during the first week is also influenced by the number of patients who were operated on despite sterile necrosis, which used to be an indication for surgical intervention during the last decade. An analysis of all 52 patients who were not administered selective decontamination in our study (control group), thus including also the remaining patients who did not need surgery, showed that the true incidence of gram-negative infection of (peri)pancreatic necrosis remained stable at approximately 9% (range, 10%-7%) during the first, second, third, and fourth week, respectively, and 18% when infection occurred after the fourth week. Mortality due to the development of a gram-negative pancreatic infection occurred more than 2 weeks later (average 15 days, range 0-71 days). If patients survived despite a gram-negative pancreatic infection, hospital stay was significantly longer (*chapter 3*).

In 1986 Beger et al.[3] underlined to distinguish patients with infected from sterile necrosis because of different morbidity and mortality. Ever since, patients with infected necrosis have been dealt with as one group, regardless of the specific flora cultured. However, the prognosis for patients with infected necrosis differs according to the bacteria isolated, as shown in *chapter 3*. Cultures in cases of infected (peri)pancreatic necrosis most frequently yield a polymicrobial flora, with a preponderance of aerobic gram-negative micro-organisms, suggesting an enteric origin[3-6]. Mortality is significantly higher once aerobic gram-negative infection occurs as compared to development of infection with only gram-positive micro-organisms (*chapter 3*).

CLINICAL TRIALS WITH PROPHYLACTIC *SYSTEMIC* ANTIBIOTICS

Since infection of pancreatic necrosis, especially aerobic gram-negative, is of major importance with regard to morbidity and mortality, attention currently is focused on prevention. However once infected it represents an absolute indication for surgical intervention.

Results of four recently reported clinical trials with *intravenous* antimicrobial *prophylaxis* are discussed in detail in *chapter 6*. In summary, an Italian randomized multicenter study, with prophylactic imipenem, demonstrated a significant reduction of infected pancreatic necrosis[8]. However, mortality was not reduced. In a Finnish study, cefuroxime did not reduce the overall incidence of pancreatic

infection[9]. Confounding factors may have been responsible for the reported reduction of mortality[10,11]. A French study using ceftazidime, amikacine and metronidazole, reporting a reduction of overall episodes of sepsis did neither achieve a reduction of overall nor gram-negative pancreatic infection[12]. A well-designed German study, using ofloxacin and metronidazole, did not demonstrate efficacy with regard to prevention of infection of pancreatic necrosis[13]. Conclusions from the two aforementioned studies have to be interpreted with caution due to the small sample size.

Recently, a Japanese clinical study demonstrated reduction of pancreatic infection by continuous regional *arterial* infusion with imipenem combined with nafamostat, a protease inhibitor[14]. However, the simulaneous use of nafamostat, a protease inhibitor, may have interfered with the results and the clinical applicability of this technique may have its drawback.

Although results of the four clinical trials with intravenous antimicrobial prophylaxis are not all identical[8,9,12,13], antibiotics that achieve adequate pancreatic tissue levels, such as the third generation cephlosporins, piperacillin, 4-quinolones, imipenem and metronidazole, may be considered as prophylaxis against secondary infectious complications in severe acute pancreatitis[15].

SELECTIVE DECONTAMINATION TO PREVENT PANCREATIC INFECTION: THE RATIONALE

The microbiology of pancreatic infections in patients with severe acute pancreatitis, which yields predominantly aerobic gram-negative micro-organisms, provides indirect evidence that these pathogens originate from the digestive tract[3-6]. Colonization of the digestive tract is thought to be the initial step of endogenous infection of other major organ systems (e.g. (peri)pancreatic necrosis)[16,17]. During hospitalization, the digestive tract of more than 60% of the patients with severe acute pancreatitis is colonized with nosocomial gram-negative flora, usually *Pseudomonas aeruginosa* and *Klebsiella species*, as shown in *chapter 5*. Bacterial translocation from the gut towards the pancreas is promoted by acute pancreatitis as demonstrated experimentally[18-25].

Direct clinical evidence demonstrating that aerobic gram-negative infections of (peri)pancreatic necrosis are gut-originated is reported in *chapter 4*, which shows that the appearance of gram-negative intestinal colonization (*E. coli* excepted) entails a significantly increased risk of pancreatic infections as well as higher mortality.

In *chapter 5* is shown that selective decontamination of the digestive tract can both effectively prevent and reverse gram-negative intestinal colonization in patients with severe acute pancreatitis. Reduction of gram-negative intestinal colonization decreases the risk to develop a secondary pancreatic infection (*chapter 4*). The development of gram-negative pancreatic infection is the determinant of mortality in contrast to patients in whom infection of necrosis does not occur (i.e. preservation of sterile necrosis) or to dose who develop an infection with only gram-positive bacteria during the course of the disease as shown in *chapter 3*. Mortality is decreased through this reduction of gram-negative infection of (peri)pancreatic necrosis as shown in *chapter 2*. Figure 1 displays these established relations with regard to use of selective decontamination.

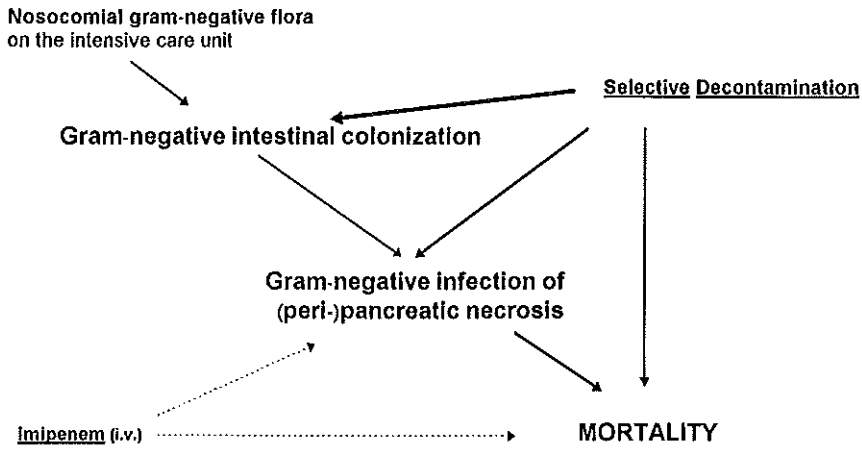

Figure 1. Clinical sequence of development of aerobic gram-negative infection, following intestinal colonization, of (peri)pancreatic necrosis in patients with severe acute pancreatitis including the effect of antibiotic prophylaxis with either selective decontamination or intravenous antibiotics, i.e. imipenem. Solid arrows refer to significant relations. Dotted arrows refer to possible relations.

ANTIMICROBIAL PROPHYLAXIS IN SEVERE ACUTE PANCREATITIS: INTRAVENOUS OR ENTERAL?

Since various possible routes of translocation towards the pancreas are suggested, intravenous antibiotics may not effectively combat translocating bacteria on all pathways[26]. Moreover intravenous antibiotics neither prevent the occurrence of gram-negative intestinal colonization nor do they always penetrate sufficiently into pancreatic tissue during acute pancreatitis. Although adequate pancreatic tissue penetration was demonstrated, imipenem does not always exceed the minimal inhibitory concentrations of the most frequently isolated micro-organisms in non-perfused necrotic (peri)pancreatic tissues as demonstrated by Bassi and co-workers[27]. In accordance with these findings, Foitzik and co-workers demonstrated that imipenem, which has a good water solubility but moderate liposolubility, accumulates in oedematous perinecrotic tissue during the early phase of the disease however that the concentration tends to decrease, already after 48 hours, with resolution of the oedema and the progression of acinar cell necrosis later in the course of the disease[28]. The latter can also be learned from the results of Pederzoli et al., which show that imipenem did not reduce pancreatic infection in patients with substantial amounts of (peri)pancreatic necrosis[8].

Widdison and colleagues demonstrated that early (12 hours from onset) administration of intravenous cefotaxime or levamisole in cats was indeed effective in treating however already established pancreatic infection[29,30]. Mithöfer and colleagues reported reduction of early (7 days) pancreatic infection in experimental acute pancreatitis in rats, which received prophylactic intravenous ciprofloxacin or imipenem as compared to a control group[31]. Early mortality was reduced only with ciprofloxacin. In human acute pancreatitis however, pancreatic infection only plays a minor role with regard to early mortality. Mortality at 21 days, the end point of the study, was reduced for both treatment groups. However, late pancreatic infection was not reduced probably because of the low number of control animals alive. Moreover, the high percentage of anaerobic pancreatic infection (43%) after 3 weeks does not correspond with findings in human pancreatitis and presumably can not be explained by translocation. Araida and co-workers demonstrated that intravenous ciprofloxacin reduced the incidence of pancreatic infection and 24-h mortality[32]. However the antibiotic was given simultaneously with the induction of pancreatitis and follow up was very short (24 hour).

Drewelow and colleagues confirmed the ability of necrotic pancreatic tissue to take up intravenously administered ceftazidime in three patients with acute

pancreatitis[33]. Intravenous pefloxacin, which in theory should have better pharmocologic properties with regard to concentrations in pancreatic tissue and necrosis was not found to be more effective, in fact worse, when compared with imipenem in a clinical trial (Bassi et al., submitted, with permission). Similarly, the clinical efficacy of other 4-quinolone class of antibiotics (e.g. ciprofloxacin and ofloxacin), as well as third generation cephalosporins (e.g. cefotaxime, ceftriaxone, ceftazidime) has not been proven yet in large scale prospective clinical studies. However, appropriate studies to define the ideal antibiotic and optimal length of prophylaxis would require the enrollment of approximately 200-300 or more patients and are difficult to undertake[15,34].

Finally, these broad spectrum antibiotics may also cause an increase of fungal complications as well as selection of resistant nosocomial micro-organisms, as was found by Pederzoli and colleagues in the group treated with imipenem in which two infections caused by *Citrobacter* and one caused by *Serratia* occurred, which were not found in the control group[8,35].

Lange and colleagues reported reduced gram-negative septicaemia and mortality in experimental acute pancreatitis in rats treated with intestinal lavage combined with enteral administration with kanamycin[36]. Similarly, Isaji and co-workers reported reduced pancreatic infection and mortality in mice treated with enteral antibiotics[37]. Marotta and collaegues demonstrated in rats with acute pancreatitis that treatment with a daily rifamixin enema significantly reduced pancreatic infection and mortality[38]. These results were even better when lactitol, a cathartic, was added. However, treatment was started already before inducing acute pancreatitis. Gianotti and collaegues have evaluated different regimes of enterally administered antibiotics including selective decontamination, the latter which consisted of polymyxin B, amphotericin B and amikacin, 12 hours after onset of experimental acute pancreatitis[39]. The survival rate between days 2 and 7 was significantly better in the selective decontamination group, but had disappeared at day 10. Although after 3 days aerobic gram-negative flora in the caecum was reduced in all groups, selection of *Pseudomonas* occurred in the group that received an antibiotic regimen, which was also used as prophylaxis in colorectal surgery. Translocation towards the pancreas was only reduced in the rats treated with selective decontamination or the same antibiotic combination without amphotericin B. However in this latter group intestinal overgrowth and increased pancreatic infection with fungi occurred.

It has been suggested that the beneficial effects of selective decontamination do not solely arise from the elimination of pathogenic gram-negative bacteria from

the digestive tract but also because of its restorative actions on the intestinal mucosa associated immune system, i.e. secretory immunoglobulin A (sIgA)[40]. The rationale of administration of enteral antibiotics, i.e. selective decontamination, through which reduction of pancreatic infection and reduction of mortality is achieved was already discussed above. Since the development of gram-negative intestinal colonization significantly increases the risk of secondary infection of (peri)pancreatic necrosis, prevention and/or elimination of intestinal gram-negative pathogens by means of enteral administration of antibiotics, i.e. selective decontamination of the digestive tract, seems the most logic measure to *nip the danger in the bud.* Figure 1 displays these established relations with regard to the use of selective decontamination as compared to possible relations with regard to the use of intravenous antibiotics, e.g. imipenem.

The triple regimen of selective decontamination also comprises, however, a short-term, systemic prophylaxis, using cefotaxime, to provide additional cover during establishment of decontamination of the digestive tract with enteral antibiotics. This initial administration of intravenous cefotaxime can not be attributed to for the observed differences in morbidity and mortality (*chapter 2*) as was questioned by Johnson[41] because, also in the control group, more than 70% of the gram-negative pancreatic infections developed after the first week. Moreover Foitzik et al. showed that concentrations of intrapancreatic cefotaxime are inadequately low during the early phase (96 hr) of acute experimental pancreatitis[28]. They also demonstrated that early pancreatic infections were reduced only when intravenous cefotaxime and enteral antibiotics were combined, i.e. selective decontamination (SD)[21]. Once the gut - the "motor of pancreatic sepsis" - is cleared from aerobic gram-negative pathogens by continuous administration of enteral antibiotics, i.e. establishment of selective decontamination, additional use of intravenous antibiotics is not neccessary anymore and can be stopped.

TIMING AND STRATIFICATION

Since infection of necrosis may occur already during the first week of the disease antibiotic prophylaxis should be administered *as soon as possible* after admission and stratification of severity.

No firm clinical data exist with regard to the optimal length of antimicrobial prophylaxis in these patients. It may be advocated to continue selective decontamination until the risk of development of infection of pancreatic necrosis

is negligible, i.e., extubated and without supplementary oxygen therapy or infusions, on a regular oral diet and mobilized on the ward.
Only patients with *severe* acute pancreatitis will benefit from antimicrobial prophylaxis, because mild disease has an uneventful course and recovery regardless of the type of medical treatment. Early stratification of all patients with acute pancreatitis, by means of a multifactorial prognostic score (e.g. Ranson, Imrie or APACHE II) as well as contrast-enhanced CT scan, is therefore strongly advocated[42-44]. The Imrie (Glasgow) score, identifying severe acute pancreatitis in patients with 3 or more positive prognostic signs, proved to be vary valuable in this respect. Increasing scores were associated with increased incidence of gram-negative intestinal colonization (*chapter 5*), increased risk to develop a gram-negative pancreatic infection (*chapter 3*), and increased mortality (*chapter 2*).

The Imrie score correlates very strongly with mortality. Mortality was 0%, for an Imrie score of 0 or 1. and gradually increased to 100%, for patients with an Imrie score of 7, as shown in *chapter 2*. Mortality in patients who were found to have severe acute pancreatitis according CT criteria alone (Balthazar grades D or E, but Imrie score <3) was less than 5% in both groups (SD and control). Selective decontamination may not result in additional benefit in such patients. On the other hand most patients who presented with Imrie score >6 died very rapidly due to a fulminant course frequently resistant to any type of treatment. Infection of pancreatic necrosis also only plays a minor role in case of early death mostly due to acute multiple organ failure (*chapter 2*). Therefore application of selective decontamination of the digestive tract will be most useful in patients with intermediate scores (3-6) who sustain the initial critical phase of the disease. However since the course of the individual patient with severe acute pancreatitis may be unpredictable, the aforementioned does not suggest that selective decontamination should be withheld from patients with very high Imrie scores on admission.

CONCLUSIONS AND RECOMMENDATIONS

The development of secondary gram-negative infection of (peri)pancreatic necrosis in patients with severe acute pancreatitis, which can be expected following the appearance of gram-negative intestinal colonization, is the determinant with regard to outcome. Rectal surveillance cultures proved to be an early prognostic parameter in this respect.

SD reduces gram-negative intestinal colonization, leading to decreased gram-negative bacterial translocation into the pancreatic necrosis. Consequently, SD reduces mortality in patients with severe acute pancreatitis due to a significant reduction of the development of gram-negative infection of pancreatic necrosis. However SD is not useful in patients in whom gram-negative pancreatic infection already exists before, or in whom gram-negative infection develops during SD administration.

In summary, *early* administration of selective decontamination to patients with *severe* acute pancreatitis, stratified according a multifactorial prognostic score (e.g. Imrie score ≥3), currently is the most effective prophylaxis to reduce both infection of (peri)pancreatic necrosis as well as mortality in patients with severe acute pancreatitis.

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CHAPTER 8

SELECTIEVE DARMDECONTAMINATIE BIJ ERNSTIGE ACUTE PANCREATITIS: SAMENVATTING

INTRODUCTIE

Acute pancreatitis is een acute ontsteking van de alvleesklier (pancreas), die gepaard gaat met een variabele weerslag op de omliggende weefsels en organen gelegen op afstand (bv. longen, nieren). Ondanks een veelvoud aan oorzaken, vertegenwoordigen galsteenlijden en overmatig alcoholgebruik meer dan 75% van alle oorzakelijke factoren.

Volgens de "Atlanta-classificatie" voor acute pancreatitis, is er bij ruim driekwart van de patiënten sprake van een *milde vorm* waarbij de functie van organen op afstand niet of nauwelijks is aangetast. Het ziektebeloop bij deze patiënten is meestal ongecompliceerd en zij genezen vrijwel allemaal zonder dat specifieke maatregelen, b.v. speciale medicijnen, nodig zijn. Echter gedurende de eerste 24 a 48 uur na het omstaan van de symptomen welke wijzen op het optreden van een acute pancreatitis ontwikkelt zich bij ongeveer 20-30% van de patiënten een zeer ernstige ontsteking van het pancreas. Deze *ernstige vorm* gaat gepaard met ernstige functiestoornissen van diverse andere orgaansystemen (Multipel OrgaanFalen (MOF)) en/of met locale complicaties zoals het omstaan van weefselversterf (necrose), pus- en afgekapselde vochtcollecties (abcessen en pseudocysten). Om de ernst van de aandoening in kaart te brengen worden laboratorium resultaten en de bevindingen van afbeeldend Röntgen-onderzoek (b.v. CT-scan) getoetst aan speciaal hiervoor ontwikkelde prognostische scores. Indien gebruik wordt gemaakt van een score welke opgebouwd is uit klinisch chemische parameters, wordt gecontroleerd of specifieke "lab-uitslagen" de drempelwaarde, aangegeven door de criteria, welke samen een prognostisch scoresysteem vormen, al of niet overschrijden. De Imrie score, welke gebruikt werd in deze studie, bestaat uit 8 afzonderlijke criteria waarop de patiënt wel (1 punt) of niet (0) kan scoren. Hoe zieker de patiënt, des te hoger is de score (maximum score=8). Er is sprake van een ernstige acute pancreatitis indien de patiënt voldoet aan 3 of meer criteria.

INFECTIE VAN PANCREASNECROSE

Met ontwikkelingen op het gebied van de intensive care geneeskunde, waarbij de functie van falende orgaansystemen kunstmatig kan worden ondersteund, overleven meer patiënten de eerste kritieke fulminante fase van de ziekte. Aangezien de natuurlijke weerstand van de patiënt ernstig is aangetast door de heftige ontsteking van het pancreas dreigt in tweede instantie het gevaar van het

optreden van infecties. De (groten)deels afgestorven alvleesklier vormt immers een ideale voedingsbodem voor bacteriën die volop aanwezig zijn op de intensive care afdeling. Bij meer dan 80% van de patiënten die langer dan 1 week opgenomen liggen op deze afdeling wordt het spijsverteringskanaal (over)bevolkt door deze (hoofdzakelijk gram-negatieve) intensive care bacteriën (nosocomiale flora), die binnen dringen via natuurlijke openingen (bv. mond of anus), of via infuuslijnen, of beademingsbuizen.
Infectie van afgestorven weefsels in en rond het pancreas ((peri)pancreatische necrose), welke optreedt in 40-70% van de gevallen, is op dit moment de hoofdoorzaak van sterfte bij patiënten met ernstige acute pancreatitis.

HYPOTHESE

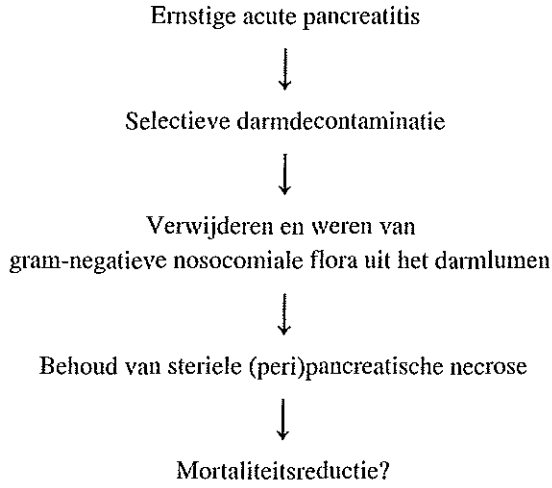
Het klinisch belang van het onderscheid tussen patiënten met ernstige acute pancreatitis waarbij de (peri)pancreatische necrose al of niet (steriel) geïnfecteerd is, werd voor het eerst benadrukt door de collega Beger en medewerkers in een publicatie daterend uit 1986. Aan de hand van kweekresultaten van operatief verwijderde necrose, werd aangetoond dat het sterftecijfer in geval van geïnfecteerde necrose significant hoger was in vergelijking met patiënten bij wie sprake was van steriele necrose. Kwalitatieve analyse van de kweekuitslagen toonde aan dat in ± 70% gram-negatieve bacteriën werden aangetroffen welke, zoals reeds hierboven gesteld, vaak voorkomen op de intensive care afdeling en ook in het spijsverteringskanaal van ernstige zieke patiënten tijdens ziekenhuisopname, met name gedurende verblijf op de intensive care unit.

Selectieve darmdecontaminatie is een antibiotische profylaxe waarbij met behulp van een combinatie van een drietal antibiotica, toegediend via mond en anus, gram-negatieve nosocomiale flora (incl. gisten) selectief worden verwijderd uit het darmlumen en waarbij de "eigen" darmflora wordt gespaard. Deze laatste vormt een onderdeel van een complex aan factoren welke bij gezonde personen weerstand (kolonisatie resistentie) biedt tegen overbevolking door nosocomiale flora. Aangezien het enkele dagen kan duren voordat het darmlumen volledig selectief is gedecontamineerd wordt bij aanvang een kortstondige aanvullende profylaxe met intraveneuze (per infuus) antibiotica (systemische profylaxe) toegediend.

Naar aanleiding van de overeenkomst tussen de bacteriële flora zoals aangetroffen in necrose enerzijds en het darmlumen van intensive care patiënten anderzijds, werd gepostuleerd dat infectie van (peri)pancreatische necrose zou kunnen

optreden doordat deze bacteriële flora eerst het spijsverteringskanaal binnendringt (kolonisatie) en vervolgens van hieruit migreert (bacteriële translokatie), bv. via het bloed, lymfebanen, of rechtsreeks door de darmwand via de vrije buikholte, naar (peri)pancreatische necrose.

Door middel van het continu schoonspoelen met een zoutoplossing van darmen (intestinale lavage) met daarin een antibioticum bij ratten met ernstige acute pancreatitis bereikte collega Lange en medewerkers een belangrijke mortaliteitsreductie.



Figuur 1. Hypothese

In tegenstelling tot intestinale lavage is selectieve darmdecontaminatie klinisch wel goed toepasbaar bij ernstig zieke patiënten. Mede naar aanleiding van resultaten van bovengenoemd dierexperimenteel onderzoek, werd gepostuleerd dat indien gram-negatieve nosocomiale flora, middels toepassing van selectieve darm-decontaminatie, verwijderd en geweerd kan worden uit het darmlumen van patiënten met ernstige acute pancreatitis, reductie van infectie van (peri) pancreatische necrose zou kunnen worden bereikt. Indien gram-negatieve infectie van necrose inderdaad een belangrijke factor zou zijn met betrekking tot de prognose zou bovenstaande uiteindelijk moeten leiden tot mortaliteitsreductie bij deze groep patiënten (Figuur 1). Deze hypothese is onderzocht in een multicenter trial waaraan 16 ziekenhuizen in Nederland hebben deelgenomen.

RESULTATEN

In *hoofdstuk 2* worden de resultaten van deze multicentertrial beschreven waarbij middels een gecontroleerde studie (vergelijking met een controle groep) de waarde van selectieve darmdecontaminatie (SD) bij 102 patiënten met ernstige acute pancreatitis is onderzocht. SD als toevoeging aan een standaard optimale en intensieve behandeling, resulteerde in een significante reductie van gram-negatieve pancreasinfecties alsook mortaliteit. Patiënten die behandeld werden met SD hoefden minder vaak opnieuw te worden geopereerd voor het verwijderen van (geïnfecteerde) necrose. In 8% van de patiënten trad ondanks behandeling met SD toch een gram-negatieve pancreasinfectie op.

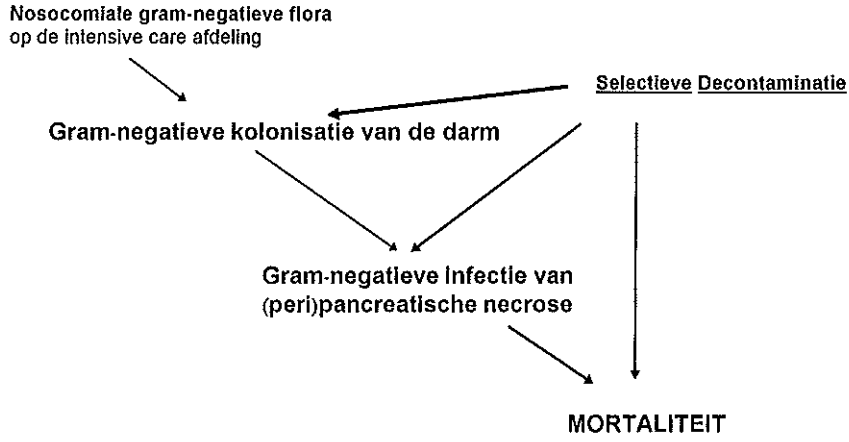
In *hoofdstuk 3* wordt het sterfterisico berekend afhankelijk van de soort pancreasinfectie; gram-positieve, gram-negatieve, en gemengde in vergelijking met patiënten bij wie geen infectie van (peri)pancreatische necrose (steriele necrose) optreedt. Los van het feit dat geïnfecteerde (peri)pancreatische necrose chirurgisch moet worden behandeld geeft de ontwikkeling van gram-negatieve pancreasinfectie tijdens het beloop van een ernstige acute pancreatitis een sterk verhoogd mortaliteitsrisico ten opzichte van louter gram-positieve infectie of steriele necrose. Het omstaan van een pancreasinfectie met louter gram-positieve bacteriën, waaronder zgn. huidflora, geeft op zichzelf geen aanleiding tot een verhoogd sterfterisico ten opzichte van steriele necrose. Een door anderen geopperd nadeel als zou SD aanleiding geven tot een verhoogde incidentie van gram-positieve infecties wordt in dit onderzoek weerlegd.

In *hoofdstuk 4* wordt beschreven dat gram-negatieve pancreasinfecties hun oorsprong vinden in de darm die gekoloniseerd wordt door nosocomiale gram-negatieve flora. Het optreden van kolonisatie van de darm tijdens een ernstige acute pancreatitis, geeft een significant verhoogd risico op het aansluitend, meestal 1 week later, ontstaan van een gram-negatieve pancreasinfectie en dientengevolge een verhoogd mortaliteitsrisico. Het ontstaan van gram-positieve pancreasinfecties worden meestal niet voorafgegaan door kolonisatie van de darm.

In *hoofdstuk 5* wordt aangetoond dat SD bij patiënten met een ernstige acute pancreatitis effectief gram-negatieve nosocomiale flora elimineert en weert uit de darm.

CONCLUSIES

Het gebruik van SD bij patiënten met ernstige acute pancreatitis, direct na het stellen van de diagnose, resulteert in een reductie van kolonisatie van de darm met gram-negatieve nosocomiale flora. Hierdoor treden minder gram-negatieve pancreasinfecties op wat, aangezien dit een zeer belangrijke prognostische parameter is, leidt tot reductie van morbiditeit en mortaliteit (Figuur 2).



Figuur 2. Ontwikkeling van gram-negatieve infectie van (peri)pancreatische necrose, volgend op intestinale kolonisatie, bij patiënten met ernstige acute pancreatitis. De pijlen naar rechts, welke samen een cascade vormen, duiden achtereenvolgens op een verhoogd risico op de daaropvolgende gebeurtenis. Selectieve decontaminatie (pijlen naar links) resulteert in een reductie van gram-negatieve kolonisatie van de darm (dikste pijl), waardoor reductie van respectievelijk pancreasinfectie en mortaliteit wordt bewerkstelligd.

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Rita Stege heeft als trial-secretaresse bergen werk verzet.

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CURRICULUM VITAE

De auteur werd op 11 oktober 1960 geboren te 's Gravenhage. Hij bezocht het Rythovius College te Eersel (NB) en behaalde het VWO diploma (Atheneum B) in 1979.

Vanwege uitloting voor de studie Geneeskunde, als gevolg van de numerus fixus, week hij uit naar België. Vanaf 1979 volgde hij de studie Geneeskunde aan de Katholieke Universiteit van Leuven, waarvan het eerste jaar te Kortrijk. Het co-assistentschap Heelkunde (maart t/m juni 1985) volgde hij aan de University of Colorado (Prof.Dr. E.E. Moore) te Denver (USA) en aan de Thomas Jefferson University (Prof.Dr. R. Rosato) te Philadelphia, Pennsylvania (USA).
Op 26 juni 1986 behaalde hij het diploma in de Genees-, Heel-, en Verloskunde (artsexamen) te Leuven met Grote Onderscheiding.

In juli 1986 behaalde hij het Examination of Medical Sciences (amerikaans artsexamen; Medical Doctor) te Brussel onder auspiciën van de Educational Committee for Foreign Medical Graduates.

Vanaf juli 1986 was hij arts-assistent Heelkunde in opleiding in het ziekenhuis Gasthuisberg verbonden aan de Katholieke Universiteit Leuven (Prof.Dr. J.A. Gruwez). In verband met toelating tot de opleiding Heelkunde na het doorlopen van een selectieprocedure onder auspiciën van de Nederlandse Vereniging voor Heelkunde te Utrecht werd de opleiding in Leuven in december 1986 beëindigd. Vanaf 1 januari 1987 tot en met 31 december 1992 werd hij opgeleid tot chirurg; de eerste drie jaar in het St. Claraziekenhuis te Rotterdam (opleider: Dr. T.I.Yo), gevolgd door drie jaar in het Academisch Ziekenhuis Dijkzigt te Rotterdam (hoofd: Prof.Dr. J. Jeekel; opleider: Prof.Dr. H.A. Bruining). Met ingang van 1 januari 1993 werd hij geregistreerd als chirurg en was hij als junior-staflid verbonden aan de afdeling Heelkunde van het Dijkzigt ziekenhuis te Rotterdam waar hij zich toelegde op de oncologische chirurgie (Prof.Dr. H.W. Tilanus).

Vanaf 1 januari 1994 is hij als vrijgevestigd chirurg werkzaam in het St. Anna ziekenhuis te Geldrop (NB) in associatie met P.R.M. De Bevere, Dr. C.R. van den Hoogenband, T.A. Weber, F.Th.P.M. van der Linden, en R.F.T.A. Assmann, chirurgen. In december 1996 ontving hij de "Schoemakerprijs 1995" voor de publicatie van de onderzoeksresultaten in de Annals of Surgery. Vanaf juni 1994 is hij teamarts van het Nederlandse Waterpoloteam Heren, en sedert mei 1998 bij de Grand Prix Formule-1 autorace te Monte Carlo (Monaco).