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Originals

Selective decontamination of the digestive tract with norfloxacin in the prevention of ICU-acquired infections: a prospective randomized study

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Abstract. The efficacy of a relatively cheap regimen of selective decontamination (SDD) was evaluated in a diverse population of ICU patients. Patients requiring prolonged ICU stay (>5 days) were randomly allocated to a treatment group or control group. Control patients (n = 52) received perioperative antimicrobial prophylaxis and antibiotic treatment was instituted only on sound clinical and bacteriological criteria. Treated patients (n = 48) received gastro-intestinal and oro-pharyngeal decontamination with polymyxin E, norfloxacin, amphotericin B and systemic antibiotic prophylaxis with trimethoprim until decontamination was achieved. The rate of gram-positive infections was not altered by SDD. The incidence of gram-negative respiratory tract, urinary tract and line infections was significantly reduced from 44%, 27% and 15% respectively in the control group to 6%, 4% and 0% in the treatment group. Mortality from nosocomial sepsis and overall mortality were also significantly reduced from 15% and 54% to 0% and 31% respectively. The ICU stay was not reduced by SDD, nor was time on the ventilator or use of therapeutic antibiotics. The reduction in morbidity and mortality was achieved at a relatively low cost.

Key words: Nosocomial infections – Antimicrobial prophylaxis – Infection control – Selective decontamination

Infection rates of over 80% have been reported in patients requiring prolonged ICU stay of more than 5 days [1, 2, 3, 4]. Most of these infections are endogenous with the patient's own oropharynx and digestive tract as the main source of infection [5]. Nosocomial infections are preceded by colonization of the oropharynx and digestive tract with aerobic gram-negative hospital bacteria [2, 6]. This pattern of colonization and subsequent infection may be influenced by selective decontamination of the digestive tract (SDD). The objective of SDD is to eliminate gram-negative aerobic bacteria and yeasts in the mouth, throat and gut by means of non-absorbable antibiotics [7]. The anaerobic microflora is unaltered and the colonization resistance patterns are left intact, thereby preventing overgrowth with resistant strains [8].

The first clinical use of SDD in ICU patients was reported in 1984. Stoutenbeek et al achieved an impressive reduction of ICU-acquired infections from 81% to 16% in patients with multiple trauma [2]. Selective decontamination was performed with the topical use of a mixture of polymyxin E, amphotericin B and tobramycin. Systemic cefotaxime was administered until decontamination occurred.

The beneficial effects of such a regimen of infection prevention in ICU patients have been demonstrated by a number of studies [9, 10, 11]. In 1986 however, the subject was still highly controversial. In order to establish whether SDD would be effective in a general ICU with a wide variety of general medical, surgical, neurological and neurosurgical patients a prospective randomized study was undertaken. At that time, SDD with the above antibiotics was very expensive so we used a modified regime with a cheaper alternative as suggested by Vollaard et al [12]. (Norfloxacin was used instead of tobramycin and systemic prophylaxis was achieved with trimethoprim).

Patients and methods

Study design

All patients admitted to the ICU who were expected to stay for more than five days were divided into several diagnostic groups and randomly allocated to a treatment group or control group. Control patients received the appropriate perioperative antimicrobial prophy-

laxis. Antibiotic treatment was instituted only on sound clinical criteria preferably supported by bacteriological evidence. Treated patients received gastro-intestinal decontamination with a suspension of polymyxin E 100 mg, norfloxacin 50 mg and amphotericin B 500 mg instilled through the nasogastric tube four times daily. The oropharyngeal cavity was decontaminated with an ointment containing 2% of the same antibiotics, applied to the oral mucosa four times daily. On top of antibiotic treatment of established infections, or short term prophylaxis perioperatively, these patients received systemic antibiotic prophylaxis with trimethoprim 500 mg per day. This prophylaxis was discontinued when potentially pathogenic micro-organisms could no longer be isolated from the oropharynx, respiratory tract or digestive tract. If colonization of the respiratory tract occurred in spite of the selective decontamination, antimicrobial treatment was started even in the absence of clinical evidence of infection.

Clinical screening

All patients were examined daily for clinical signs of infection. Haematological and biochemical data were collected at least once daily. Chest X-rays were taken almost daily, or more frequently when indicated.

Bacteriological screening

Cultures from the oropharynx, of sputum or tracheal aspirate, urine and faeces were taken on admission (inventory cultures) and thereafter twice weekly (surveillance cultures). The first rectal sample was usually not obtained before seven days. Cultures of blood, intravascular catheters, wounds and drains were taken as clinically indicated (indication cultures).

Definitions

Micro-organisms isolated from inventory cultures were considered to be admission flora. Micro-organisms isolated from surveillance cultures were considered to be ICU acquired, unless already present in the cultures on admission. Colonization was defined as the repeated isolation of the same micro-organism in cultures from the same site.

Lower respiratory tract infections were defined as clinical and radiological signs of pulmonary infiltration, with fever and leucocytosis and dense growth in cultures of sputum or tracheal aspirate. Urinary tract infections were diagnosed as the presence of more than 10^5 micro-organisms per ml, with or without clinical signs of infection. Wound infections were diagnosed as purulent discharge from inflamed wounds with a positive culture. Abdominal sepsis was diagnosed as peritonitis, localized abscess, or purulent discharge from drains. Septicaemia was defined as fever, leucocytosis and a positive blood culture. Intravascular line infections were diagnosed as positive cultures of the same micro-organism from a catheter tip and blood or as a resolution of fever within 24 hours after removal of a catheter (with a positive culture of the tip) in the absence of other signs of infection.

Statistical analysis

The data from both groups were analysed with Fisher's exact test. A p level of <0.05 was considered to be significant.

Results

In the period from October 1986 to September 1987 112 patients were admitted to the study. Twelve patients were excluded because they died within 24 hours after admission to ICU. The remaining 100 patients were analysed. The control and treatment groups were comparable in terms of their characteristics (Table 1) and their diagnostic categories on admission (Table 2). All patients had indwelling urinary catheters and naso-gastric tubes. Arterial and central venous catheters were routinely used. The majority of patients were mechanically ventilated. One treated patient was on chronic haemodialysis. Two treated patients developed renal failure, one due to sepsis and the other following aortic aneurysm surgery. Renal failure requiring haemodialysis occured in four control patients (due to sepsis) and in two control patients (following circulatory failure).

Table 1. Patient characteristics

	Control	Treatment
No. of patients	52	48
Sex M/F	32/20	26/22
Mean age, years (SD)	60.0 (18.2)	64.3 (16.3)
ASA score II	14	11
III	22	25
IV	14	12
V	2	0
Mean SAPS, points (SD)[a]	12.4 (5.3)	11.5 (4.8)
Mean ISS, points (SD)[b]	38.6 (16.9)	39.0 (11.1)
Ventilatory support		
no. of patients	43	37
mean time, days (SD)	7.8 (8.0)	10.7 (16.4)
range	1–57	1–70
Haemodialysis		
no. of patients	6	3
Mean ICU-stay, days (SD)	13.4 (12.1)	16.9 (16.7)
Mean antibiotic use, units (SD)	11.1 (10.3)	10.6 (11)

[a] Simplified Acute Physiology Score (20)
[b] Injury Severity Score (21)

Bacteriological assessment

Oropharynx (Fig. 1). On admission gram-negative bacteria were isolated from approximately 40% of patients in both groups. After 7 days 85% of control patients had gram-negative bacteria, compared to 3% of

Table 2. Primary diagnosis of patients

	Control	Treatment
polytrauma	9	5
abdominal sepsis	9	10
other sepsis	3	3
SAH (GCS < 8)	7	4
other neurological disorders	4	7
ruptured aortic aneurysm	5	5
major abdominal and thoracic surgery (ASA ≥ 3)	9	7
cardiac insufficiency	4	5
respiratory insufficiency	2	2
Total	52	48

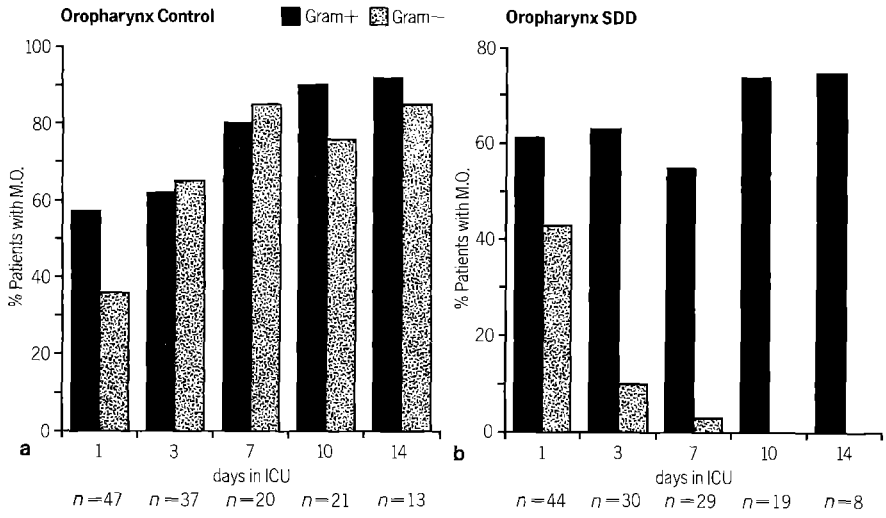

Fig. 1a, b. Isolation rates in oropharynx. *M. O.* = micro-organisms

treated patients. The isolation rate remained at 85% in control patients during the rest of their stay and was reduced to 0% in treated patients. Gram-positive micro-organisms were isolated in approximately 60% of patients in both groups at the time of admission. This level was maintained in treated patients but slightly increased to 80% in control patients. *Streptococcus faecalis* and *Staphylococcus epidermidis* predominated in both groups.

Sputum or tracheal aspirate (Fig. 2). On admission gram-negative bacteria were isolated in 24% of patients in the control group and in 41% of treatment group patients. After 7 days 67% of control patients harboured gram-negative bacteria compared to 26% of treated patients. Gram-positive bacteria were isolated in 38% of the inventory cultures of control patients and in 37% of those from treated patients. The number of patients who had gram-positive bacteria gradually increased in both groups. Predominantly *Streptococcus faecalis* and *Staphylococcus epidermidis* were isolated. The isolation rate of yeasts fell to zero in treated patients and remained at about 20% in control patients.

Digestive tract (Fig. 3). Inventory cultures of the faeces were not performed routinely because they did not influence the antimicrobial regimen. Nevertheless 18 faecal samples were taken randomly on admission *E. coli* was isolated in the faeces of approximately 80% of patients in both groups and other aerobic gram-negative bacteria were found in about 50%. In the control group the isolation rate of *E. coli* remained at the same level and the isolation rate of other gram-negative bacteria gradually increased to 70%. In the treatment group the isolation rate of *E. coli* gradually fell to zero over 14 days and the isolation rate of other gram-negative bacteria at the same time fell to about 20%. Gram-positive bacteria were isolated in the stools of virtually all patients in both groups on ad-

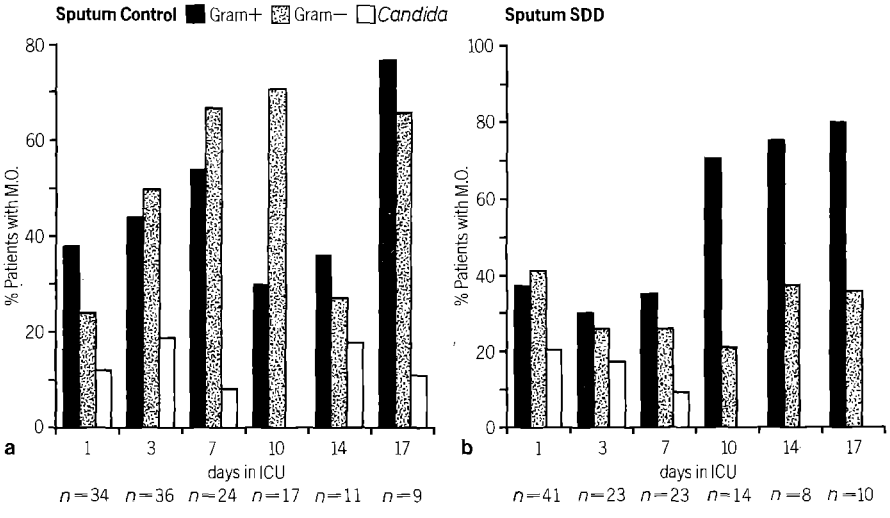

Fig. 2a, b. Isolation rates in sputum or tracheal aspirate. *M. O.* = micro-organisms

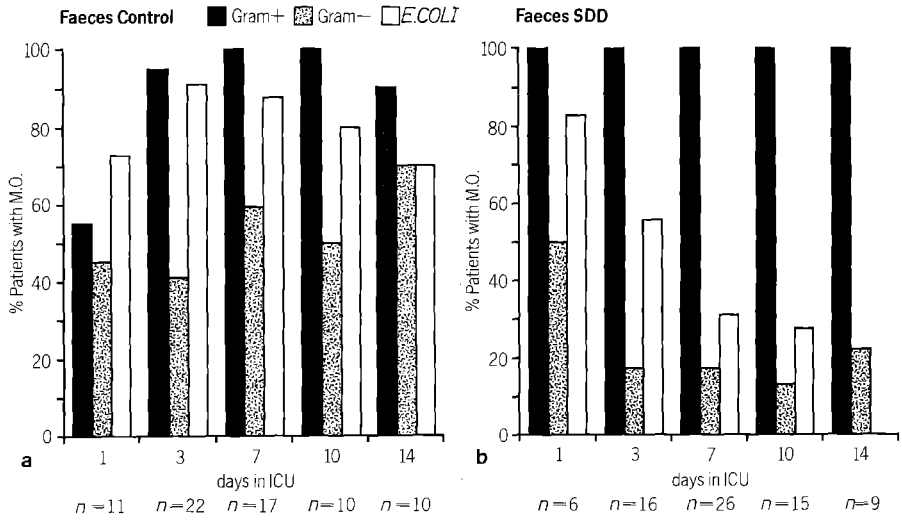

Fig. 3a, b. Isolation rates in the faeces. *M. O.* = micro-organisms

Table 3. Infections on admission

	Control $n = 52$	Treatment $n = 48$
No. of patients with infection (%)	18 (34.6%)	25 (52%)
No. of infections	20	36
– intra-abdominal	6	8
– wound	3	5
– respiratory tract	6	15
– urinary tract	4	5
– CNS	0	1
– septicaemia	1	2
gram-positive infections	2	5
gram-negative infections	6	11
mixed-infections	11	14
candida infections	0	2
not documented	1	4

Table 4. ICU-acquired infections

	Control $n = 52$	Treatment $n = 48$
No. of patients with infection (%)	40 (77%)	25 (52%)[a]
No. of infections	112	51
– intra-abdominal	8	0
– wound	6	4
– respiratory tract	29[b]	7
– urinary tract	26	11
– intravascular lines	23[b]	18[b]
– septicaemia	18[b]	11[b]
– miscellaneous	2	0
gram-positive infections	44	41
gram-negative infections	30	5
mixed infections	31	4
candida infections	7	1

[a] $p < 0.01$
[b] Several patients had more than one infection

mission and throughout the whole stay in the ICU, the most frequent isolates were *Staphylococcus epidermidis* and *Streptococcus faecalis.*

Urine. On admission gram-negative bacteria were isolated in 6 patients (13%) of the control group and 5 patients (11%) of the treatment group. Gram-positive bacteria were isolated in 7% and *Candida* in 4% of patients in both groups.

The isolation rate of gram-negative bacteria during the ICU stay was about 10% in treated patients and 20% in control patients. After 14 days gram-positive bacteria were isolated in the urine of 8% of control patients compared to 67% of treated patients.

Incidence of infections on admission. On admission 20 infections were diagnosed in 18 patients (35%) of the control group and 36 infections in 25 patients (52%) of the treatment group (Table 3).

Incidence of ICU-acquired infections. In the control group 40 patients (77%) suffered 112 episodes of infection. In the treatment group 25 patients (52%) acquired 51 infections (Table 4).

The incidence of gram-positive infections was the same in both groups. The incidence of gram-negative lower respiratory tract infections, urinary tract infections and intravascular line infections was significantly reduced in the treatment group (Table 5).

Eight control patients developed intra-abdominal sepsis. In 5 patients (infected ascites, ischemic colitis, acalculous cholecystitis, peridiverticulitis) there was no obvious causal relationship with their primary condition. Two patients developed peritonitis following gastro-intestinal surgery and in one patient a subphrenic abscess was drained after recent surgery for colonic perforation.

Table 5. Incidence of ICU-acquired infections

	Control ($n = 52$) No. patients	Treatment ($n = 48$) No. patients	p-value
Respiratory tract infections			
gram-positive	2	3	NS
gram-negative and mixed	23 (44%)	3 (6%)	$p<0.00001$
Candida	1	1	NS
Total	26	7	$p<0.001$
Urinary tract infections			
gram-positive	9	9	NS
gram-negative and mixed	14 (27%)	2 (4%)	$p<0.001$
Candida	3	0	NS
Total	26	11	$p<0.005$
Intravascular line infections			
gram-positive	10	15	NS
gram-negative and mixed	8 (15%)	0	$p<0.005$
Total	18	15	NS
Septicaemia			
gram-positive	9	9	NS
gram-negative and mixed	3	1	NS
Total	12	10	NS

Bacteriology of ICU-acquired infections

In the control group 96 gram-positive micro-organisms were isolated from the site of infection against 51 in the treatment group. *Staphylococcus epidermidis* and *Streptococcus faecalis* were the most frequently isolated micro-organisms in both groups. Although the presence of *Staphylococcus aureus* in the oropharynx and sputum was suppressed by SDD (44 isolations in the surveillance cultures of the control group versus 13 in the treatment group) and the number of isolations in respiratory tract infections fell from 5 to 2, the overall isolation rate of *Staphylococcus aureus* from infections did not differ between the control group (8) and treatment group (10), largely as a result of line infections.

Ninety-five gram-negative bacteria were isolated from the site of infection in the control group against 9 in the treatment group. *Pseudomonas aeruginosa* (25), *E. coli* (23), *Enterobacter* (16), *Klebsiella* (9), *Proteus* (7) and *Acinetobacter* (6) were most frequently isolated in the control group. In the treatment group *Pseudomonas aeruginosa* (6), *Klebsiella* (2) and *Bacteroides fragilis* (1) were isolated from infections.

Table 6. Mortality

	Control	Treatment	
acquired sepsis	8	0	$p<0.004$
primary sepsis	3	2	ns
cardiac failure	5	4	ns
respiratory failure	2	3	ns
CNS failure	4	1	ns
multiple organ failure	6	5	ns
Total mortality	28	15	$p<0.02$

Mortality (Table 6)

Mortality from acquired sepsis occurred in 8 control patients but did not occur in the treatment group ($p<0.004$). Four patients died of pneumonia with irreversible pulmonary insufficiency. Three patients died of general sepsis including acquired intra-abdominal sepsis. One patient died of post-operative peritonitis. The overall mortality rate was significantly reduced from 54% (28/52) in the control group to 31% (15/48) in the treatment group ($p<0.02$).

Antibiotic resistance

Table 7 shows the susceptibility to norfloxacin of micro-organisms isolated from the inventory cultures of oropharynx, sputum, urine and faeces of all patients in both groups and compares the sensitivity of the micro-organisms isolated in the surveillance cultures of the control group and the treatment group. Only a few gram-negative micro-organisms were not sensitive to the drug. A resistant *Pseudomonas maltophilia* was isolated from 4 cultures in 2 treated patients.

Economical assessment

The use of parenteral antibiotics did not differ significantly between the groups. The mean parenteral antibiotic consumption per patient was 11.1 units (SD 10.5) in the control group versus 10.6 units (SD 11.0) in the treatment group (one unit = use of one antimicrobial agent for one day). The systemic antibiotic prophylaxis with trimethoprim was withdrawn after an average of 8.4 days. Including the systemic trimethoprim prophylaxis and the SDD-suspension the mean antibiotic use in the treatment group was 36.5 units (SD 31.4). The total costs of the selective decontamination regimen (systemic antibiotic prophylaxis, SDD-suspension and SDD-paste) averaged Dfl. 500,– per patient.

As expected, the costs of the bacteriological monitoring were higher in the control group. In this group 663 inventory and surveillance cultures were taken. In 508 positive cultures 1158 micro-organisms were isolated. In the treatment group 646 cultures resulted in 458 positive cultures with 884 isolated micro-organisms.

Discussion

The data we have presented, recording the isolation and infection rates in the control group of our study are in concert with the literature. Colonization of the

Table 7. Sensitivity to norfloxacin

	Inventory cultures Control + Treatment			Surveillance cultures Control			Surveillance cultures Treatment		
	+	−	0	+	−	0	+	−	0
Staph. aureus	21			53	1	3	12		1
Staph. epidermidis	34	8	3	85	77	2	34	183	4
Strept. viridans	1		5			12			10
Strept. haem.		1	19	4		28	1		12
Strept. pneum.			6	1		2			2
Strept. faecalis	12	18	1	80	143	10	31	227	9
Neisseria			6		1	1			
Haem. influenzae			16	1		24			3
E. coli	38			134		4	44		
Klebsiella	13	1		34	2	2	11		
Enterobacter	8			46	2	1	3		
Proteus	16			34			8		
Pseudomonas	13	2		127	2	2	56	4	1
Citrobacter	1			20	1		4		
Acinetobacter	2			9	1		6		
Achromobacter					1				
Clostridium			3			11			17
Total	159	30	59	628	231	102	210	414	59

+ susceptible; − resistant; 0 not tested

oropharynx, trachea and digestive tract with aerobic gram-negative micro-organisms increases with the duration of ICU stay and the relationship between colonization and subsequent infection has been demonstrated in several studies [2, 6, 9] Selective decontamination of the digestive tract (SDD) can prevent this process. Stoutenbeek et al. [2] were the first to use this method of prevention of infection in ICU patients. The oropharynx and gut were selectively decontaminated with a mixture of the non-absorbable antibiotics polymyxin E, tobramycin and amphotericin B. Systemic cefotaxime was given to prevent early infections until decontamination was achieved. The infection rate in trauma patients was reduced from 81% to 16%. This significant and favourable result was marred only by the fact that the control group was, although carefully monitored, a retrospective one.

Ledingham et al. [11] used the same regimen in a prospective study with consecutive control and treatment groups. They achieved a consistent reduction in colonization of the digestive tract with aerobic gram-negative bacilli and a substantial reduction in the incidence of acquired infections from 24% to 10%. Kerver et al. [10] were the first to demonstrate the efficacy of the aforementioned regimen in a prospective randomized study. The incidence of unit acquired infections was significantly reduced from 81% to 39%. In the meantime Unertl et al. [9] had demonstrated a reduction in the incidence of respiratory infections from 70% to 21% in long term ventilated patients with a modification of the topical regimen (gentamicin instead of tobramycin) and without systemic antibiotic prophylaxis.

In the present study several components of the original regimen were replaced by cheaper alternatives. Systemic trimethoprim was used instead of cefotaxime. In the topical mixture of antibiotics norfloxacin was substituted for tobramycin. Norfloxacin, a quinolone, is effective against aerobic gram-negative bacilli. Although absorbable, high faecal concentrations can be achieved [13].

The results of our prospective randomized study show that the concept of SDD is valid. The colonization of oropharynx, respiratory tract and digestive tract with aerobic gram-negative micro-organisms was considerably reduced and subsequently resulted in a significant reduction of gram-negative lower respiratory tract infections, urinary tract infections and intravascular line infections. In five instances SDD failed to prevent a gram-negative infection. In 3 patients who were on prolonged mechanical ventilation a lower respiratory tract infection was preceded by a breakthrough of *Pseudomonas aeruginosa* in the sputum after initially successful decontamination. The pseudomonas strains were not resistant to the drugs used and were not recovered in the oropharynx. The reason for the latter was not fully understood. Niederman et al. [14] reported a tendency of pseudomonas to stick to the tracheal epithelium rather than the oropharyngeal mucosa, suggesting the possibility of causing lower respiratory tract infections while "bypassing" the oropharynx. Another explanation might

be that these three patients had tracheostomies, which was where the same micro-organisms were cultured. Infections could possibly have been prevented by the application of the SDD-paste to the tracheostomies as well.

The gram-positive microflora is obviously not altered by SDD. *Streptococcus faecalis* and *Staphylococcus epidermidis* are often considered as normal inhabitants of oropharynx and digestive tract and therefore not included in the colonization rates reported by other authors [2, 10, 11]. Unertl [9] found *Staphylococcus epidermidis* in 84% and *Streptococcus faecalis* in 53% of cultures of the oropharynx in treated patients compared to 95% and 75% respectively in control patients. In the present study the isolation rates of these micro-organisms were almost identical in both groups, apart from the urine where isolation rates were considerably higher in treated patients. According to the definition of an urinary tract infection ($\geq 10^5$ micro-organisms/ml) *Streptococcus faecalis* particularly was responsible for a disappointingly high number (9) of such infections in both groups. There was a tendency for the development of multiresistance in *Staphylococcus epidermidis* in both groups, whilst *Streptococcus faecalis* was usually only sensitive to ampicillin. It is doubtful whether these micro-organisms can be considered harmless. They were responsible for urinary tract infections, line infections and septicaemia, including one case of endocarditis. In the presence of cardiac valvular disease and vascular prosthesis gram-positive bacteraemia must be taken seriously.

It is notoriously difficult to prove that nosocomial infections contribute to the mortality risk in critically ill patients. Death in the absence of severe underlying disease is rare [15]. In one study however nosocomial pneumonia did increase the likelihood of a fatal outcome in patients whose condition was not terminal on admission [16]. The demonstration of causality may be a matter of definition, when a patient develops pneumonia and subsequently progressive respiratory failure, the latter may be irreversible and eventually lead to death even when the initial infection has been cured. It seems fair to attribute such an event to infection rather than to organ failure. Nevertheless confusion will remain unless overall mortality is influenced. In our series mortality due to acquired sepsis and overall mortality were reduced significantly. Other studies have been unable to demonstrate a reduction of the overall mortality [9, 10, 11], although Ledingham et al. [11] did achieve a significant reduction of mortality in acute trauma patients. In the study by Kerver et al. [10] infection-related mortality was also significantly reduced.

The present study shows that norfloxacin is an effective component of the SDD regimen. Although serum levels were not measured the dosage used is too small to expect any beneficial systemic effect. One might even expect resistance to develop with such a sub-therapeutic dose of an absorbable drug, but this did not occur in our series. The relative merits of norfloxacin and tobramycin need further investigation. Tobramycin may be more effective in preventing a breakthrough of *Pseudomonas aeruginosa* but is much more expensive than norfloxacin.

Stoutenbeek et al. have shown that the addition of systemic cefotaxime to the SDD regimen was necessary to prevent early respiratory tract infections [17]. There is little doubt that cefotaxime is a more powerful drug than trimethoprim, but only three of the respiratory tract infections in the treatment group were caused by gram-positive micro-organsims that could have been prevented if cefotaxime had been used instead of trimethoprim. It is doubtful whether this benefit outweighs the extra costs involved.

The price of SDD is often mentioned as a disadvantage. In this study a full cost-benefit analysis was not performed but SDD did not result in shorter ICU stay, shorter time on the ventilator or less frequent use of antibiotics. A possible explanation for the latter is that as a consequence of our protocol colonization of the respiratory tract with gram-negative micro-organisms was agressively treated with systemic antibiotics even in the absence of clinical signs of infection. In other studies a slightly decreased overall use of antibiotics and a significant reduction of antibiotic use for acquired infections has been reported [10, 11, 18]. Antibiotic costs account for only a small percentage of the total costs involved in ICU care [19]. A substantial though not significant reduction of ICU stay of approximately three days per patient was reported in two studies [2, 10].

In conclusion, the results of this study show that SDD is a useful method of preventing nosocomial infections in ICU patients. The components of the original recipe appear to be interchangeable and further studies including careful cost-benefit analysis are required to determine which drugs are preferable. The greatest benefit of SDD is the reduction of lower respiratory tract infections in mechanically ventilated patients. On top of that SDD seems to permit the prolonged use of systemic antibiotic prophylaxis without the usual penalty of colonization and overgrowth of drug resistant micro-organisms. In one centre, where the regimen has been used since 1982, problems with resistance have not yet been encountered [18].

As the ultimate goal of ICU treatment is survival, it would be desirable to indentify groups of patients who will benefit from SDD in terms of reduced mortality, at least from an economical point of view. It is however difficult to predict in an individual patient

whether the prevention of infection will influence the final outcome and in the meantime it seems fair to settle for the reduced risk of morbidity. We strongly recommend more widespread use of SDD in the general ICU.

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