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Decrease in nosocomial pneumonia in ventilated patients by selective oropharyngeal decontamination (SOD)

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Abstract *Objective:* To determine the influence of selective oropharyngeal decontamination (SOD) on the rate of colonization and infection of the respiratory tract in intensive care patients requiring mechanical ventilation for more than 4 days. A financial assessment was also performed.
Design: Randomized, prospective, controlled study using amphotericin B, colistin sulfate (polymyxin E), and tobramycin applied to the oropharynx and systemic cefotaxime prophylaxis.
Setting: Anesthesiology intensive care unit (ICU) of a 1500-bed hospital.
Patients: A total of 88 patients admitted as emergencies and intubated within less than 24 h were enrolled. Fifty- eight patients received SOD and 30 patients served as controls. Randomization was in the proportion of 2 : 1 study patients to controls.
Interventions: Microbiological samples from the oropharynx and other infected sites were taken at the time of admission, then twice a week and after extubation.
Measurements and results: With the use of SOD, colonization was significantly reduced. Furthermore, the infection rate decreased from 77 % in the controls to 22 % in the study patients.
Staphylococcus aureus was the main potential pathogen causing colonization and pneumonia. Number of days in the ICU, duration of ventilation, and mortality were not significantly decreased. The total cost of antibiotics was reduced. Development of resistance was not observed.
Conclusions: The use of SOD significantly reduced the colonization and pneumonia and the total charge for antibiotics. The length of stay in the ICU, duration of ventilation, and mortality were similar. No resistance was observed. *Staphylococcus aureus* was selected by SOD in some patients and the clinical relevance needs further observation.

Key words Selective decontamination of the digestive tract (SDD) · Selective oropharyngeal decontamination (SOD) · Ventilated intensive care patients · Colonization rate · Nosocomial pneumonia · Antibiotic resistance

Introduction

Infections remain among the most dangerous complications on intensive care units (ICUs). The respiratory tract is affected most. Patients on long-term ventilation have an especially increased risk, with high rates of morbidity and mortality.

The incidence of primary pneumonias, which normally appear during the first 48 h after admission, is 27 to 50 % [1]. Primary pneumonias are caused by microor-

ganisms present in the oropharynx of the patient at the time of admission. About 30 % of the normal population are carriers of Streptococcus pneumoniae, Haemophilus influenzae, or Staphylococcus aureus [1].

The incidence of secondary pneumonias, which normally appear 48 h after admission, is 30–90 % [2]. Exogenous infections, reduced by hygienic measures, are rare. Most infections are endogenous through colonization of the oropharynx by gram-negative bacteria, acquired through micro-aspiration from the patient's own oropharynx.

In 70–75 % of all critically ill patients, the normal oropharyngeal flora changes to gram-negative bacteria within 48 h of hospital admission [3]. The microorganisms are usually *Enterobacteriaceae, Pseudomonadaceae,* and yeast. The risk of pneumonia increases with increasing colonization rates. The mortality for secondary pneumonia is reported to be 20–60 % [4].

Stoutenbeek and coworkers [1, 5] developed selective decontamination of the digestive tract (SDD) to reduce colonization and the incidence of pneumonias and other infections. SDD consists of the local use of antibiotics (oropharynx and digestive tract) and systemic administration of cefotaxime. The infection rate during a stay in the ICU was reduced from 81 to 16 %. Other authors have reported similar results [6–14].

However, the cost of SDD can be very high because the antimicrobials applied locally are very expensive. It should be possible to use only selective oropharyngeal decontamination (SOD) to eliminate potential pathogenic microorganisms and thus to reduce colonization and infection rates. This prospective, randomized, controlled clinical study set out to determine the effectiveness of SOD with respect to colonization and infection rates in ventilated intensive care patients.

Materials and methods

Study design

This prospective, randomized, controlled clinical trial was carried out with a study group and a control group. During the study period, a total of 125 patients were admitted to the anesthesiology ICU of the Munich-Schwabing City Hospital. They were included if they met the following criteria for the study: intubation within 24 h of admission, expected time on a ventilator more than 4 days, and the interval between intubation and first microbial culture less than 36 h. Not included were patients transferred from other hospitals and patients with obvious infections, prior antibiotic therapy, adult respiratory distress syndrome, leucopenia, or myelosuppression at the time of admission. Randomization was performed on the basis of a sequential list of block-randomized assignments maintained by the principal investigator. The proportion of study patients to control patients was 2 : 1. Observation began with the patient's admission to the ICU and ended after extubation, transfer, or death of the patient. All patients were examined daily for signs of respiratory infection by one of the authors. Microbial examinations were performed twice a week and hematological and biochemical data (including arterial blood gases) and chest X-rays were obtained at least once daily. The chest X-ray was read by an independent radiologist who was unaware of the patient's randomization. Prior to the study, all patients were classified on the basis of their Acute Physiology and Chronic Health Evaluation (APACHE) II score. Variables were recorded daily and scores were calculated daily. Informed consent was obtained from all patients or their relatives. The study was approved by the Ethics Commitee.

Patients

Control group

Thirty patients randomized into the control group usually did not receive any antibiotics. If they had had surgery, they got one dose of perioperative prophylaxis: mezlocillin and metronidazole for abdominal surgery and cefazolin for orthopedics, bone, or head surgery. If infections were suspected, caused by unknown bacteria, initial therapy was begun with a combination of penicillins of cephalosporins and an aminoglycoside. When microbiological data were available, they were treated specifically. Sucralfate (1 g) was administered 4 times a day as prophylaxis against gastric stress ulcers. Sucralfate was used because it normally gives adaequate protection without increasing the risk of pneumonia [15, 16]. Sucralfate is bactericidal against microorganisms and does not change the pH value of gastric fluids. This allows gastric acid to act as an important protective agent against bacterial infections starting in the gastrointestinal tract.

Study group

Fifty-eight patients randomized into the study group received oropharyngeal decontamination 4 times a day, administered as premixed paste (2 % amphotericin B, 2 % tobramycin, and 2 % polymyxin E) to the palpate and to the lower lip. The gastrointestinal tract was not decontaminated. Furthermore, systemic cefotaxime (2 g) was administered 3 times a day for 3 days. In planned or emergency surgery, they received perioperative prophylaxis consisting of one dose of cefotaxime and metronidazole for abdominal surgery or cefazolin for bone, neuro-, and orthopedic surgery. Sucralfate (1 g) was also administered 4 times a day as prophylaxis against gastric stress ulcers.

Microbiological surveillance

Specimens were collected for quantitative cultures immediately after the patient was admitted to the ICU and then twice a week from oropharyngeal and rectal swabs, endotracheal aspirates, urine, gastric aspirates and wound secretions, blood cultures, and tips of initially placed catheters. The samples were obtained in the morning before the administration of local or systemic antibiotics. They were cultured on MacConkey agar, chocolate agar, blood agar, Sabouraud agar, and Schaedler agar for anaerobic bacteria. After an incubation period of 24–48 h, standard methods for identification and sensitivity testing were used. Organisms considered potential pathogens were: *Enterobacteriaceae,* pseudomonads, glucose-nonfermenting gram-negative rods, such as *Acinetobacter* or *Stenotrophomonas,* and *S. aureus, H. influenzae, Moraxella catarrhalis, S. pneumonia,* and beta-hemolytic streptococci. *Candida* were found whenever the count was > 10^4 colony forming units (cfu)/ml and enterococci when isolated in blood cultures or at a concentra-

tion of $> 10^5$ cfu/ml from more than two body sites. To assess the importance of bacterial colonization, the quantitative culture of tracheal aspirates was expressed as the recently described "bacterial index" [17]. The bacterial index is the sum of the logarithms of the different bacteria cultured in 1 ml of tracheal aspirate. According to data in the literature, there is a good correlation between a bacterial index ≥ 5 and the incidence of pneumonia [18].

Definitions

Pneumonia was considered when a new infiltrate emerged on the X-ray, together with increasing amounts of tracheobronchial secretions containing more than 3×10^4 granulocytes/μl and at least two of three further criteria: temperature > 38.5 °C, white blood count $> 12\,000/mm^3$ or $< 4000/mm^3$, a decrease in arterial oxygen tension equiring an increase in fractional inspired oxygen. In addition, positive quantitative microbial cultures were taken into account. Tracheal aspirates yielding bacteria $> 10^4$ cfu/ml and > 10 polymorphonuclear neutrophils/field were considered positive [19, 20]. All criteria were included in a clinical pulmonary infection score (CPIS), recently described by Pugin et al. [21]. Accordingly, ventilation-associated pneumonia was diagnosed when the CPIS score reached 7 points during intubation and remained elevated for at least 3 days. Colonization was considered when only bacteriologic criteria were positive.

Statistical methods

The two-sided Fisher exact test was used for statistical analysis. Age, length of time on the ventilator, and the colonization data were tested with the Mann–Whitney U-test. The significance level was 5 % ($p < 0.05$).

Results

Patients

A total of 125 patients were examined; 37 were excluded (24 in the study group and 13 in the control group), because of early extubation (8 study, 4 control), early death (4 study, 2 control), or protocol violation (12 study, 7 control). The remaining 88 patients entered the study, 58 as study patients and 30 as control patients. Both groups were comparable in age, sex, time on the ventilator, and concomitant disease (Table 1).

Table 1 Clinical characteristics of the patients

Clinical characteristics	SOD group ($n = 58$)	Controls ($n = 30$)
Average (SD) age	39.9 (16.9)	44.7 (18.7)
Male/female	44/14	24/6
APACHE II score (SD)	16 (5.8)	18 (5.9)
Diagnosis [No. (%)]		
Head injuries	30 (52)	15 (50)
Multiple trauma	20 (34)	9 (30)
Peritonitis	8 (14)	6 (20)
Deaths [No. (%)]	11 (19)	5 (17)
Mean (SD) time on ventilation	12.9 (8.1)	14.6 (5.9)
Mean (SD) days in ICU	18 (7.8)	22 (8.8)
Mean (SD) duration of antibiotic therapy (days)	10.3 (8.5)	12.7 (7.1)

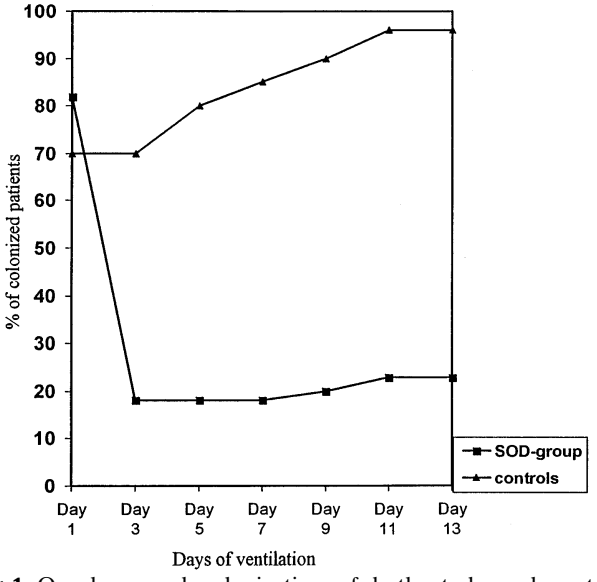

Fig. 1 Oropharyngeal colonization of both study and control groups during ventilation

Pharyngeal, tracheal, and rectal colonization

On admission, the oropharynx was colonized in 81 % of study patients (47/58) and in 70 % of controls (21/30) by various respiratory pathogens (Table 2). In study patients, colonization significantly ($p < 0.0001$) decreased within 72 h to 18 % (Fig. 1). At extubation, 22 % (13/58) of study patients were still colonized: 2 by *Pseudomonas aeruginosa* (bacterial index 5), 2 by enterococci in a significant count of 10^5 cfu/ml, and 9 by *S. aureus* (bacterial index 5). Seven of the patients who were initially colonized by *S. aureus* could not be decontaminated (proven by restriction fragment length polymorphism; RFLP). In the remaining 2 patients, strains were transmitted exogenously by another colonized patient (also proven by RFLP). *P. aeruginosa* was transmitted in both cases exogenously by severely contaminated mouthwash (proven by RFLP).

In control patients, colonization rose continuously over the first 11 days (Fig. 1). At extubation, 93 % (28/30) were colonized (Table 2). Seven patients initially colonized by *S. aureus* remained colonized (proven by RFLP). In one case, *S. aureus* was exogenously transmitted by a colonized patient (proven by RFLP), and in 2

Table 2 Spectrum of microorganisms during ventilation. Numbers are numbers of patients (*s* start of ventilation, *e* end of ventilation)

Microorganisms	Oropharynx				Tracheal aspirates				Rectum			
	SOD		Controls		SOD		Controls		SOD		Controls	
	s	e	s	e	s	e	s	e	s	e	s	e
Staphylococcus aureus	18***	9***	8	8	18***	9***	7	7	0	0	0	0
Streptococcus pneumoniae	5***	0***	2[a]	0	5***	0***	2[a]	0	0	0	0	0
Group A streptococci	0	0	1[a]	0	0	1	1[a]	0	0	0	0	0
Group B streptococci	1	0	0	0	1	0	0	0	0	0	0	0
Haemophilus influenzae	7***	0***	5[a]	0	7***	0***	5[a]	0	0	0	0	0
Klebsiella pneumoniae	3	0	1[a]	4	3	0	1[a]	4	2	2	3	3
C. diversus	1	0	0	0	1	0	0	0	1	1	0	0
Pseudomonas aeruginosa	0	2	0	5	0	2	0	5*	1	4	1	3
Proteus mirabilis	0	0	0	1	0	0	0	1	1	1	2	1
Proteus vulgaris	0	0	0	1	0	0	0	1	3	3	4	3
Morganella morganii	0	0	0	1	0	0	0	1	0	0	2	2
Escherichia coli	0	0	0	1	0	0	0	1	37	37	21	21
Enterobacter cloacae	0	0	0	2	0	0	0	2	4	4	1	1
Acinetobacter antitratus	0	0	0	1	0	0	0	1	0	0	0	0
Enterococcus faecalis	0	8	0	3	0	2	0	3	6	11	5	5
Enterococcus faecium	0	2	0	1	0	0	0	1	0	1	0	1
Coagulase-neg. staphylococci												
oxacillin-sensitive	4	4	0	3	1	2	0	3	14	5***	4	2***
multiresistant	0***	4***	0	2	0	2	0	2	0	6	2	4
Candida albicans	12*	0*	4	5	12*	0*	4	5	9	8	5	5

* $p < 0.001$; ** $p < 0.01$; *** $p < 0.05$

[a] Removal by antibiotic therapy

cases *P. aeruginosa* was transmitted by contaminated mouthwash (proven by RFLP). Thirteen patients acquired gram-negative rods from their own intestinal microorganisms (RFLP). Five patients carried enterococci $< 10^4$ cfu/ml. With regard to colonization in the trachea, we found a similar situation (Table 2). Colonization of the rectum was not influenced by oropharyngeal decontamination; colonization by pathogenic microorganisms, yeast, coagulase-negative staphylococci, and enterococci was similar before and after ventilation (Table 2).

Infection rate

Both groups started with a similar mean CPIS score of approximately 5. After 2 days of ventilation, the CPIS slightly increased in the control group, but remained stable in the study group. Significant differences ($p < 0.001$) occurred after 4 days. In the controls, the CPIS rose to a mean of 6.3 ± 0.6 because of primary pneumonia in 10 patients, while remaining stable in the SOD patients (no primary pneumonia). After 14 days of ventilation, the CPIS rose steadily to 7.66 ± 0.8 in the control group (13/30 secondary pneumonias), whereas it stayed at 5.4 ± 0.9 in the study group (13/58 secondary pneumonias). The infections in the controls were caused in 9 cases by endogenous, gram-negative rods from the intestinal tract (Table 3). Three patients initially colonized by *S. aureus* remained colonized and developed an infection; 2 patients acquired an exogenous infection, in 1 case with *P. aeruginosa* caused by a contaminated mouthwash, in the other case with *S. aureus* transmitted by a colonized patient. In addition, 4 of the controls had both a primary and a secondary pneumonia: *S. aureus* plus *P. aeruginosa, H. influenzae* plus *P. aeruginosa, H. influenzae* plus *Enterobacter cloacae,* and *S. pneumoniae* plus *Klebsiella pneumoniae* (results not shown in Table 3).

Secondary pneumonia in the study patients was caused by *S. aureus* in 9 cases and by *P. aeruginosa* in 2 cases; 2 patients developed an infection caused by enterococci. Seven of the patients infected with *S. aureus* had already been colonized on admission (proven by RFLP). In 2 cases, *S. aureus* was transferred from colonized patients. *P. aeruginosa* was transferred from a contaminated mouthwash. The clinical variables most influenced by SOD were less purulent tracheobronchial secretions ($p < 0.01$), lower incidence of localized infiltrates on X-ray ($p < 0.01$), and higher arterial oxygen tension. There was no significant difference between the two groups with regard to temperature (39.2 vs 39.5 °C) and leukocytosis (16 500/mm^3 vs 17 000/mm^3). When excluding bacteriologic data from the CPIS score, i.e., comparing only clinical and radiological data, the

Table 3 Infection rate during ventilation. Percentages in parentheses

	SOD group ($n = 58$)	Controls ($n = 30$)
Primary pneumonia	0*	10 (33)*
Staphylococcus aureus	0	2 (7)
Haemophilus influenzae	0**	5 (17)**
Klebsiella pneumoniae	0	1 (3)
Streptococcus pneumoniae	0	2 (7)
Secondary pneumonia	13 (22)***	14 (47)***
Staphylococcus aureus	9 (16)	3 (10)
Enterococcus faecalis[a]	2 (3)	0 (0)
Pseudomonas aeruginosa	2 (3)	3 (10)
Proteus mirabilis	0	1 (3)
Klebsiella pneumoniae	0***	3 (10)***
Morganella morganii	0	1 (3)
Enterobacter cloacae	0	1 (3)
Proteus vulgaris	0	1 (3)
Total	13 (22)*	23 (77)*
Gram-positive microorganisms	11 (19)	8 (27)
Gram-negative microorganisms	2 (3)	16 (53)*

* $p < 0.001$; ** $p < 0.01$; *** $p < 0.05$
[a] Sepsis not pneumonia

Table 4 Resistance during ventilation

Microorganisms	Group	No.	Antibiotics	No. resistant (%)
Entero-bacteriaceae	SOD	184	Tobramycin	4 (2)
	Controls	72	Tobramycin	2 (3)
	SOD	184	Polymyxin	0 (0)
	Controls	72	Polymyxin	4 (6)
	SOD	184	Cefotaxime	7 (4)
	Controls	72	Cefotaxime	2 (3)
Pseudomonas aeruginosa	SOD	28	Tobramycin	0 (0)
	Controls	38	Tobramycin	0 (0)
	SOD	28	Polymyxin	0 (0)
	Controls	38	Polymyxin	0 (0)
	SOD	28	Cefotaxime	2 (7)
	Controls	38	Cefotaxime	0 (0)
Coagulase-negative staphylococci	SOD	100	Tobramycin	58 (58)
	Controls	44	Tobramycin	22 (50)
	SOD	100	Oxacillin	26 (26)
	Controls	44	Oxacillin	12 (27)
Staphylococcus aureus	SOD	88	Tobramycin	0 (0)
	Controls	64	Tobramycin	0 (0)
	SOD	88	Oxacillin	0 (0)
	Controls	64	Oxacillin	0 (0)
	SOD	88	Cefotaxime	70 (80)
	Controls	64	Cefotaxime	48 (75)
Enterococcus faecalis	SOD	84	Ampicillin	0 (0)
	Controls	44	Ampicillin	0 (0)
Enterococcus faecium	SOD	9	Ampicillin	9 (100)
	Controls	4	Ampicillin	4 (100)
	SOD	9	Vancomycin	0 (0)
	Controls	4	Vancomycin	0 (0)

difference between the two groups remained significant ($p < 0.01$). The duration of mechanical ventilation and the number of days of ICU stay were similar in both groups (Table 1).

Mortality

Eleven study patients (19%) and 5 controls (17%) died during the study period ($p > 0.05$). The cause of death was severe brain injury in 10 SOD patients and in 3 control patients. Another study patient and 1 control patient died as a result of *S. aureus* sepsis, and the 5th control patient died from pneumonia caused by *Proteus vulgaris*.

Resistance

The resistance pattern of the microorganisms during oropharyngeal decontamination is shown in Table 4. Copy strains were not taken into account. No significant differences were found between the two groups for the sensitivity of the *Enterobacteriaceae* and the *Pseudomonadaceae*. *Enterococcus faecalis* showed the same sensitivity to ampicillin in both groups. Nine strains of *Enterococcus faecium*, which appeared in the SOD group, and four strains, which appeared in the control group, were multiresistant, but they were sensitive to glycopeptide antibiotics. Oxacillin-resistant strains of *S. aureus* were not isolated. *S. aureus* was resistant to cefotaxime. The values for the minimal inhibitory concentration (MIC) ranged between 2 and 8 μg/ml and did not alter during therapy. The percentage of oxacillin-resistant or multiresistant coagulase-negative staphylococci was similar in both groups (27 vs 26%). The oxacillin-resistant or multiresistant coagulase-negative staphylococci isolated in SOD patients after long-term ventilation differed in species and RFLP-pattern from the strains which were initially oxacillin-sensitive (Fig. 2).

Cost

Thirteen of the study patients (22%) needed antibiotic therapy in addition to cefotaxime prophylaxis, and 28 of the control patients (93%) had to be treated as well ($p < 0.0001$). Expenditure on antibiotics was much lower in the SOD group, even if one considers the SOD drug cost (DM 102.11 per day during the first 3 days, then DM 2.75 per day), which is cheaper than SDD, which costs DM 147.39 per day. With regard to the patients who needed antibiotics, the average duration of therapy was similar in both groups (10.29 days in the study group vs 12.73 days in the control group), but the average daily antibiotic cost per patient was signifi-

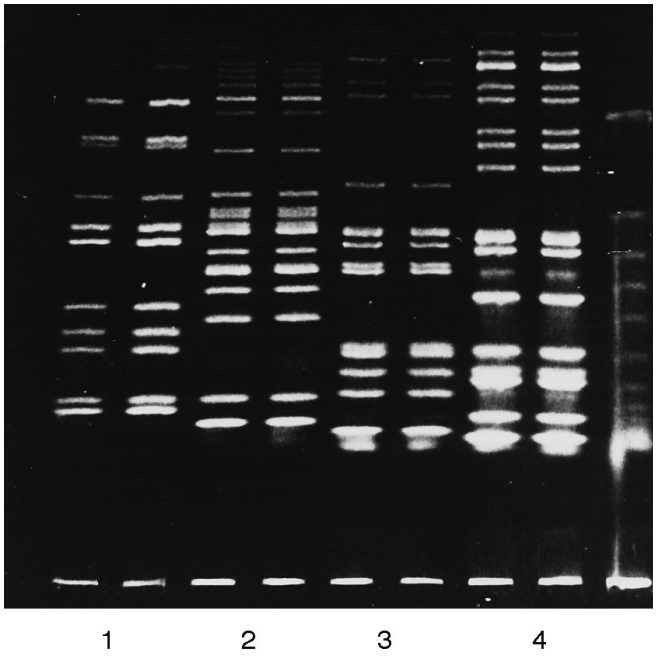

Fig. 2 Restriction fragment length polymorphism (RFLP) of coagulase-negative staphylococci. *1 Staphylococcus hominis* (oxacillin-sensitive), isolated from an SOD patient at the beginning of ventilation; *2 Staphylococcus epidermidis* (oxacillin-resistant), isolated from an SOD patient at the end of ventilation; *3 S. epidermidis* (oxacillin-sensitive), isolated from a control patient at the beginning of ventilation; *4 Staphylococcus haemolyticus* (oxacillin-resistant), isolated from a control patient at the end of ventilation

cantly lower in the SOD group (DM 76.61 vs DM 106.63) and total antibiotic cost per treated patient was lower (DM 618.74 vs DM 1357.40). The differences between the average cost per day of ventilation (DM 43,48 vs DM 80.27) and the average cost per day of antibiotic therapy (DM 50.53 vs DM 103.00) for both groups were similar.

Discussion

SDD was first described by Stoutenbeek et al. [1]. Since then, 22 of 25 studies have demonstrated the effectiveness of SDD as prophylaxis against nosocomial infections in ventilated patients [6–14, 22–32]. Most studies used nonabsorbable antibiotics, which were applied topically, plus systemic antibiotic prophylaxis; only a few used systemic antibiotics [6, 21, 27]. We refrained from local decontamination of the gastrointestinal tract because of the high cost. Instead, we carried out only local SOD with tobramycin, polymyxin E, amphotericin B, and systemic treatment with cefotaxime. We used an antibiotic paste to prevent the topical antibiotics reaching the trachea together with oropharyngeal secretions. Therefore, tracheal growth of bacteria was not inhibited by the presence of antibiotics and did not contribute to negative cultures.

As expected, the use of SOD proved to be very effective in reducing bacterial colonization of the oropharynx. The only patients for whom SOD does not offer complete protection are those heavily colonized by *S. aureus* (bacterial index > 5). At the end of ventilation, nine patients were colonized by *S. aureus*. Two had got it by transmission from another colonized patient. The other 7 patients, however, who were initially colonized by *S. aureus* at several body sites, remained colonized in spite of SOD. This is probably due to the fact that most strains of *S. aureus* were resistant to cefotaxime and polymyxin B. The tobramycin component in the SOD regimen, which is very active against *S. aureus* in such high concentrations, works well in the oropharynx but could not eradicate staphylococci in the trachea or in the lower respiratory tract. Other authors [7] who used the same or similar drugs for local decontamination also observed higher rates of staphylococcal colonization than authors who decontaminated with antibiotics, such as oxacillin, first-generation cephalosporins, or vancomycin, which are potent against staphylococci [21].

With SOD, the number of infections was significantly decreased from 77 % in the control group to 22 % in study patients. This is in accordance with other studies, including those using oropharyngeal decontamination, such as the study by Pugin et al. [21]. They were able to reduce the rate of pneumonia from 78 to 16 % by oropharyngeal decontamination with neomycin, polymyxin, and vancomycin. Rodriguez-Roldan et al. [9] also significantly reduced the pneumonia rate ($p < 0.001$) by SOD with polymyxin, tobramycin, and amphotericin B. In contrast, Laggner et al. [31] did not find a significant difference for pneumonia (12 vs 3 %) when decontaminating with gentamicin alone. In our study, 33 % of the controls developed primary pneumonia as a result of initial pharyngeal colonization by potential pathogenic microorganisms such as pneumococci or *H. influenzae*. Despite the presence of a similar count of potential pathogenic organisms in the oropharynx (71 vs 70 %), the study patients did not develop primary pneumonia. They were protected by the eradicating effect of systemic cefotaxime, which is very active against pneumococci and the other pathogens. Although systemic antibiotic prophylaxis is still controversal [32, 33], it proved to be useful in our regimen. In contrast to other studies which did not use systemic prophylaxis, we did not observe pneumonia with microorganisms causing primary pneumonias. This is in accordance with Stoutenbeek, who found in an early study a moderate effect with an enteral regimen alone and a positive effect with the addition of cefotaxime. However, the use of parenteral prophylaxis alone failed to show any beneficial effect in preventing infection [34].

Forty-three percent (13/30) of the controls developed secondary pneumonia, mainly caused by their own gram-negative intestinal microorganisms migrating to the respiratory tract (10/13). On the other hand, only 22% of study patients (13/58) developed a secondary pneumonia, but, in contrast to the controls ($p < 0.01$), this was mainly caused by gram-positive bacteria (11/13), especially *S. aureus* (9/13). Similar results have been demonstrated by others, including Gastinne et al. [29], Quinio et al. [35], and Konrad et al. [7]. A possible explanation is that cefotaxime, used as systemic prophylaxis, is not an ideal antibiotic for our patients suffering mainly from multiple trauma with open fractures or head injuries (50/58), who often develop infections caused by gram-positive bacteria including *S. aureus* and who were not only colonized in the oropharynx but at several sites, especially wounds. Because of the high MIC values of *S. aureus* against cefotaxime, the drug had only a reduced, perhaps a selective, effect on staphylococcal colonization. The tobramycin component in SOD could admittedly eradicate staphylococci from the oropharynx but not from the lower repiratory tract or from extra-oropharyngeal sites. Therefore, these sites serve as a source of recolonization followed by bacteremia, hematogenous spread, and pneumonia. In our study, heavily colonized patients with a bacterial index of ≥ 5 remained colonized by *S. aureus* at different body sites and developed an infection. Therefore, patients heavily colonized by *S. aureus* should be systemically treated with antibiotics active against staphylococci. When excluding bacteriologic data from the CPIS, i.e., comparing only clinical and radiological data, the difference between the two groups remained significant ($p < 0.01$).

The question of whether local decontamination has any effect on mortality remains unanswered. According to the meta-analysis of Kollef [23], mortality can be reduced by about 10–13% by using SDD. In our study, mortality was not affected by SOD. The number of patients who died was slightly higher (19%) in the study group than in the control group (17%), but the difference was not significant. Ten of the study patients died of brain death from severe brain lesions after multiple trauma or severe head injuries, despite the fact that their infections were successfully treated. One patient died from sepsis caused by *S. aureus*. In the control group, five patients died, three of them also from head injuries, another from sepsis caused by *S. aureus,* and the fifth from pneumonia caused by *P. vulgaris*. The study group shows slightly better results for infection mortality and noninfection mortality. However, the number of cases was too small for a definitive statement. Further studies are necessary on infection mortality only.

SOD did not alter the resistance patterns of gram-negative bacteria to the antibiotics used. This is in accordance with other results on long-term resistance behavior during SDD treatment [26, 27]. In the SOD patients, the rate of enterococcal colonization (oropharyngeal and tracheal aspirates) increased more than in the control group (20 vs 13%), probably as a result of the selection pressure of cefotaxime, polymyxin E, and tobramycin. However, the controls who received cefotaxime became colonized by enterococci also. Multiresistant strains of *E. faecium* were isolated from one control and two study patients. All patients remained colonized for a long time. Apart from two study patients who developed bacteremia which was successfully treated by ampicillin, they did not become ill or need antibiotic therapy. Although enterococci rarely cause lung infections [36], it should be kept in mind that in selected cases, such as in patients predisposed to endocarditis or immunocompromised patients, enterococci can cause severe systemic infections and pneumonia [37]. Furthermore, recent studies have identified enterococci as the second most frequent cause of nosocomial infections overall [38]. Therefore, when cephalosporins are used frequently, such as in SOD, careful microbiological monitoring is essential to find and treat resistant strains as early as possible during therapy.

The rate of colonization by oxacillin-resistant or multiresistant coagulase-negative staphylococci was the same in both groups. The strains isolated in SOD patients at the beginning and end of ventilation differed in species and RFLP-pattern. Therefore, mutations of endogenous strains do not seem probable during SOD. It is more likely that resistant strains are transmitted from exogenous sources, such as indwelling catheters, or are selected by antibiotics in the study patients and in the controls. During SOD treatment we could not isolate oxacillin-resistant strains of *S. aureus* in either group. This corresponds to published data. In only 1 of 22 centres [7] was a significant increase observed in oxacillin- (= methicillin) resistant *S. aureus* (MRSA) during SDD treatment (28.4% in the decontaminated patients vs 6.2% in the controls).

In the present study, the total cost of antibiotic use was reduced by SOD. Parenteral antibiotics had to be additionally dispensed to 22% of treated study patients compared to 93% of treated controls. This is in contrast to the frequent statement that the use of SDD increases the overall cost in terms of antibiotic usage [29] but agrees with other statements that the antibiotic cost decreases with SDD [35, 39]. Several explanations may be suggested for the low cost in this study: the decrease in the occurrence of pneumonia, the low rate of infection due to gram-negative bacteria that regime the use of expensive antibiotics, and the low cost of SOD compared to SDD.

In conclusion, our results show that SOD is an effective method of preventing nosocomial pneumonias. It proved to have the same effects as SDD in the reduction of the number of microorganisms, colonization rates,

and incidence of infections, but it reduced the total charge for antibiotics and is cheaper than SDD. The length of stay in the ICU, duration of ventilation, and mortality were not significantly reduced. Development of resistance was not observed during the study period, but *S. aureus* was selected by SOD in some patients. Other larger studies are needed to evaluate the effect of such a prophylaxis on overall cost and prognosis in critically ill patients.

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