



Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study

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Summary

Background Previously, we assessed selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) on survival and prevention of bacteraemia in patients in intensive-care units. In this analysis, we aimed to assess effectiveness of these interventions for prevention of respiratory tract colonisation and bacteraemia with highly resistant microorganisms acquired in intensive-care units.

Methods We did an open-label, clustered group-randomised, crossover study in 13 intensive-care units in the Netherlands between May, 2004, and July, 2006. Participants admitted to intensive-care units with an expected duration of mechanical ventilation of more than 48 h or an expected stay of more than 72 h received SOD (topical tobramycin, colistin, and amphotericin B in the oropharynx), SDD (SOD antibiotics in the oropharynx and stomach plus 4 days' intravenous cefotaxime), or standard care. The computer-randomised order of study regimens was applied by an independent clinical pharmacist who was masked to intensive-care-unit identity. We calculated crude odds ratios (95% CI) for rates of bacteraemia or respiratory tract colonisation with highly resistant microorganisms in patients who stayed in intensive-care units for more than 3 days (ie, acquired infection). This trial is registered at <http://isrctn.org>, number ISRCTN35176830.

Findings Data were available for 5927 (>99%) of 5939 patients, of whom 5463 (92%) were in intensive-care units for more than 3 days. 239 (13%) of 1837 patients in standard care acquired bacteraemia after 3 days, compared with 158 (9%) of 1758 in SOD (odds ratio 0.66, 95% CI 0.53–0.82), and 124 (7%) of 1868 in SDD (0.48, 0.38–0.60). Eight patients acquired bacteraemia with highly resistant microorganisms during SDD, compared with 18 patients (with 19 episodes) during standard care (0.41, 0.18–0.94; rate reduction [RR] 59%, absolute risk reduction [ARR] 0.6%) and 20 during SOD (0.37, 0.16–0.85; RR 63%, ARR 0.7%). Of the patients staying in intensive-care units for more than 3 days, we obtained endotracheal aspirate cultures for 881 (49%) patients receiving standard care, 886 (50%) receiving SOD, and 828 (44%) receiving SDD. 128 (15%) patients acquired respiratory tract colonisation with highly resistant microorganisms during standard care, compared with 74 (8%) during SDD (0.58, 0.43–0.78; RR 38%, ARR 5.5%) and 88 (10%) during SOD (0.65, 0.49–0.87; RR 32%, ARR 4.6%). Acquired respiratory tract colonisation with Gram-negative bacteria or cefotaxime-resistant and colistin-resistant pathogens was lowest during SDD.

Interpretation Widespread use of SDD and SOD in intensive-care units with low levels of antibiotic resistance is justified.

Funding None.

Introduction

Respiratory tract infections acquired in intensive-care units have been associated with high rates of morbidity and mortality and increased health-care costs, especially when they are caused by highly resistant microorganisms (table 1).^{1–3} Reductions in the rates of respiratory tract infections have been achieved through prophylactic antibiotic regimens such as selective digestive tract decontamination (SDD)^{4,5} and selective oropharyngeal decontamination (SOD).^{6,7} However, prophylactic use of antibiotics might increase selection for antibiotic-resist-

ant pathogens, which is the main drawback of such interventions. SDD aims to prevent colonisation by Gram-negative bacteria, *Staphylococcus aureus*, and yeasts in patients in intensive care through application of non-absorbable antimicrobial treatments in the oropharynx and gastrointestinal tract. This intervention also preemptively treats possible infections with commensal respiratory tract bacteria through systemic administration of cephalosporins during the first 4 days in intensive-care units, and maintains anaerobic intestinal flora through selective use of antibiotics (both topically and

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systemically).^{8,9} SOD is oropharyngeal decontamination only, without any specific recommendations for systemic antibiotic use.

We previously reported primary and secondary clinical outcomes, including rates of survival, bacteraemia, antibiotic use, length of stay, and duration of mechanical ventilation, from a multicentre study¹⁰ comparing SOD and SDD with standard care. Both interventions were associated with improved day-28 survival and reduced incidence of acquired bacteraemia in 13 Dutch intensive-care units with low rates of antibiotic resistance. In the paper¹⁰ and a subsequent analysis¹¹ we reported the ecological effects of SDD and SOD on the overall intensive-care-unit population including short-staying patients who were not enrolled in the study. Compared with standard care, SDD and SOD were associated with decreased mortality and reduced need for systemic antibiotics.¹⁰ Moreover, SDD was also associated with a reduction in occurrence of candidaemia and bacteraemia with Gram-negative microorganisms as compared with SOD.

However, neither publication reported the effects of SDD and SOD on bacteraemia and respiratory tract colonisation with highly resistant microorganisms or bacteria resistant to the SOD and SDD antibiotics that were acquired while patients were in intensive-care units. We aimed to assess such outcomes in this study.

Methods

Study sites and patients

Our group did a pragmatic, open-label, clustered group-randomised, controlled, crossover study in 13 intensive-care units between May, 2004, and July, 2006. The participating intensive-care units differed in size and teaching status, covering all levels of intensive care in the Netherlands. Because the interventions included ecological changes in the intensive-care units, an

individualised, randomised design would have led to interference between treated and untreated patients. Therefore, cluster randomisation was needed and all three study regimens (SDD, SOD, and standard care) were to be applied to all eligible patients during 6 months with the order of regimens randomly assigned. The study periods were preceded by a wash-in and/or wash-out month during which newly admitted patients were treated according to the centre-specific allocation treatment for the following period, but actual inclusion started after the wash-in period (see supplementary online appendix of de Smet and colleagues¹⁰). Patients admitted to intensive-care units with an expected duration of mechanical ventilation of more than 48 h or an expected stay of more than 72 h were eligible for inclusion. Expected stay was assessed by doctors responsible for care of patients in each unit.¹⁰

The study protocol was approved by institutional review boards at all participating hospitals. Because SDD and SOD were regarded as common practice in the Netherlands and not harmful to patients, and because only a unit-wide approach would allow reliable estimation of the true effect of the interventions, the institutional review boards waived, after review, the need for informed consent. We obtained permission to use patient-specific medical data for analysis from patients or their representatives.¹⁰

Randomisation and masking

A clinical pharmacist, who was not involved in care of patients at any of the participating units, did the randomisation and was masked to intensive-care unit identity. The order of the three study regimens provided to patients was randomly generated by computer software and allocated to the wards in consecutive order of study start.

	ESBL*	Quinolones	Aminoglycosides	Carbapenems	Co-trimoxazole	Ceftazidime	Piperacillin	Penicillins	Glycopeptides	Oxacillin	Meticillin
Enterobacteriaceae											
<i>Escherichia coli</i>	A	B	B	A
<i>Klebsiella</i> spp	A	B	B	A
Other	A	B	B	A	B
Glucose non-fermenting Gram-negative rods											
<i>Acinetobacter</i> spp	..	B	B	A	..	B
<i>Stenotrophomonas</i> spp	A
Other (including <i>Pseudomonas aeruginosa</i>)	..	C	C	C	..	C	C
Gram-positive bacteria											
<i>Streptococcus pneumoniae</i>	A	A
<i>Enterococcus</i> spp	B	B
<i>Staphylococcus aureus</i>	A	A

Resistance to one antibacterial agent in category A, to two or more in category B, or to three or more in category C is required to define the microorganism as highly resistant. ESBL=extended-spectrum β-lactamase. *During the study, determination of ESBL was not standardised and multiple different methods were used in participating laboratories; therefore, resistance to any third-generation cephalosporins (eg, cefotaxime, ceftazidime, and ceftriaxone) was used as proxy for presence of ESBL in *Escherichia coli*, *Klebsiella* spp, and *Proteus* spp.

Table 1: Definitions of highly resistant microorganisms

Procedures

The SDD regimen was 4 days of intravenous cefotaxime and topical application of tobramycin, colistin, and amphotericin B in the oropharynx and stomach. Use of antibiotics that impair colonisation resistance, such as amoxicillin, penicillin, amoxicillin-clavulanic acid, and carbapenems was discouraged during SDD. Surveillance cultures of endotracheal aspirates and oropharyngeal and rectal swabs were done on admission and then twice every week. The SOD regimen was oropharyngeal application of the same paste as used for SDD, with surveillance cultures of endotracheal aspirates and oropharyngeal swabs done on admission and twice every week, without restrictions in doctors' choices of systemic antibiotic therapy. During standard care, participating intensive-care units were free to follow their own guidelines and surveillance cultures were not done in all units. There were no restrictions on the choice of systemic antibiotic therapy. By contrast with the protocols for endotracheal aspirate surveillance cultures, there were no differences between the three groups in terms of indication for taking blood cultures.

In this analysis, we used all microbiological culture results from blood and endotracheal aspirate samples obtained from patients in the study. We use the term colonisation to mean bacterial growth in respiratory tract samples. For patients with more than one endotracheal aspirate culture in 1 day, we interpreted the results as one culture. We regarded bacterial growth in endotracheal aspirate samples obtained on the day of admission or the 2 days after as colonisation on admission. We regarded bacterial growth in samples obtained after the third day, and with documented absence in previous cultures, as acquired in the intensive-care unit. Microbiological procedures were identical for respiratory tract samples that were obtained for clinical reasons (ie, as in standard care, but also potentially SOD and SDD) as for surveillance reasons (ie, just SOD and SDD).

In all three study periods, we obtained blood cultures on clinical indication, as assessed by the treating doctors. For patients with more than one blood culture in 1 day, results were pooled as results for one blood culture. We regarded bacterial growth in blood cultures obtained on the day of admission or the 2 days after as bacteraemia on admission. We defined growth from blood cultures collected after the third day or later, with documented absence in cultures during the first 3 days, as bacteraemia acquired in the intensive-care unit. We excluded coagulase-negative staphylococci from this analysis.

Susceptibility testing was done according to the national guidelines.¹² Only the first culture results with an acquired microorganism were analysed; further positive culture results with the same microorganism were regarded as part of the same event.

We defined highly resistant microorganisms according to the national guidelines (table 1),¹³ and established three main groups: Enterobacteriaceae, Gram-negative

non-fermenters, and Gram-positive bacteria. Resistance to any third-generation cephalosporin (eg, cefotaxime, ceftazidime, and ceftriaxone) was used as proxy for the presence of extended spectrum β -lactamase in *Escherichia coli*, *Klebsiella* spp, and *Proteus* spp.

Statistical analysis

We calculated crude odds ratios (ORs) and 95% CI for rates of acquisition of bacteraemia and respiratory tract colonisation in intensive care units between the three groups, as well as rate reductions, absolute risk reductions, and numbers needed to treat. We did a time-to-first-event analysis Kaplan-Meier survival analysis with follow-up until 40 days (or discharge from the intensive-care unit if this was before 40 days). We tested differences between groups with the log-rank test (significance defined as $p < 0.05$).

Patients who had the same species of highly resistant microorganism isolated during the first 3 days of stay and after the third day were not included as an event in the analysis. The same rule was applied for patients with cefotaxime-resistant and tobramycin-resistant Gram-negative rods. All analyses were done with SPSS version 15.0.

This trial is registered at <http://isrctn.org>, number ISRCTN35176830.

Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

5939 patients were enrolled and data for 5927 patients were available for analysis (table 2). Baseline characteristics differed between treatment groups (webappendix).¹⁰ Patients in the SDD and SOD groups had higher acute

See Online for webappendix

	Standard care (n=1989)	SOD (n=1904)	SDD (n=2034)
Patient-days	26 908	25 006	27 068
Patients with length of stay >3 days	1837 (92%)	1758 (92%)	1868 (92%)
Blood cultures			
Patients with ≥ 1 blood culture	1125 (57%)	1194 (63%)	1102 (54%)
Days with ≥ 1 blood culture	2988	3180	2887
Blood-culture-days per patient-day	0.11	0.13	0.11
EACs			
Patients with ≥ 1 EAC in first 3 days in ICU	688 (35%)	1044 (55%)	1025 (50%)
EAC-days in first 3 days in ICU	762 (5919)	1184 (5653)	1125 (6053)
EAC-days per patient-day in first 3 days in ICU	0.13	0.20	0.19
EAC-days after day 3 in ICU	4422 (20 989)	5651 (19 353)	6260 (21 015)
EAC-days per patient-day after day 3 in ICU	0.21	0.29	0.30

Data are n (%) or n (patient-days), unless otherwise stated. SOD=selective oropharyngeal decontamination. SDD=selective digestive tract decontamination. EAC=endotracheal aspirate culture. ICU=intensive-care unit.

Table 2: Population of patients and microbiological sampling

	Standard care (n=1837)	SOD (n=1758)	SDD (n=1868)	Crude odds ratio (95% CI)		
				SDD vs standard care	SOD vs standard care	SDD vs SOD
Any microorganism, apart from coagulase-negative staphylococci	239 (13%)	158 (9%)	124 (7%)	0.48 (0.38–0.60); ARR 6.4%; NNT 16	0.66 (0.53–0.82); ARR 4.0%; NNT 25	0.72 (0.56–0.92); ARR 2.4%; NNT 43
<i>Candida</i> spp and other yeasts*	18 (1%)	20 (1%)	6 (<1%)	0.33 (0.13–0.82); ARR 0.7%; NNT 152	1.16 (0.61–2.21)	0.28 (0.11–0.70); ARR 0.8%; NNT 127
HRMO†	19 (1%)	20 (1%)	8 (<1%)	0.41 (0.18–0.94); ARR 0.6%; NNT 170	1.10 (0.59–2.07)	0.37 (0.16–0.85); ARR 0.7%; NNT 145

Data are n (%), unless otherwise stated. SOD=selective oropharyngeal decontamination. SDD=selective digestive tract decontamination. ARR=absolute risk reduction. NNT=number needed to treat. HRMO=highly resistant microorganism. *One case of *Saccharomyces cerevisiae* in the standard-care group. †One patient in the control group had two episodes of bacteraemia with HRMOs (one episode on day 9 with *Enterobacter cloacae* and *Escherichia coli* and one on day 30 with *Acinetobacter baumannii*).

Table 3: Patients with bacteraemia and candidaemia acquired in intensive-care units

	Standard care (n=1837)	SOD (n=1758)	SDD (n=1868)
Bacteraemia			
<i>Acinetobacter</i> spp	2	..	1
<i>Enterobacter cloacae</i>	5	8	..
<i>Escherichia coli</i>	6	6	2
<i>Klebsiella</i> spp	3	3	3
<i>Pseudomonas aeruginosa</i>	2	..	1
<i>Stenotrophomonas maltophilia</i>	1
<i>Serratia marcescens</i>	..	2	..
<i>Hafnia</i> spp	..	1	..
<i>Staphylococcus aureus</i>	1
Respiratory tract colonisation			
<i>Acinetobacter</i> spp	14	3	7
<i>S maltophilia</i>	8	6	7
<i>P aeruginosa</i>	29	9	10
Other glucose non-fermenting Gram-negative organisms	3	5	20
<i>Enterobacter</i> spp	18	19	9
<i>E coli</i>	23	9	4
<i>Klebsiella</i> spp	22	21	9
<i>Citrobacter</i> spp	4	3	0
<i>Morganella</i> spp	1	0	1
<i>Proteus</i> spp	2	0	2
<i>S marcescens</i>	3	9	3
<i>S pneumoniae</i>	1	2	0
<i>S aureus</i>	0	2	2

SOD=selective oropharyngeal decontamination. SDD=selective digestive tract decontamination.

Table 4: Acquired highly-resistant microorganisms

physiology and chronic health evaluation (APACHE) II scores than did patients in standard care, and were more often mechanically ventilated and admitted to intensive-care units for non-surgical reasons. Patients in the SDD group were older than were patients in the standard care and SOD groups.¹⁰

5463 (92%) of 5927 patients remained in an intensive-care unit for more than 3 days (table 2). Blood cultures were obtained from 3421 (58%) of 5927 patients, at an average frequency per patient-day of 0.11 cultures in

standard care, 0.13 in SOD, and 0.11 in SDD (table 2). Bacteraemia occurred in 305 patients in the first 2 days after admission to intensive-care units.

Bacteraemia acquired in an intensive-care unit was more common in standard care than it was in SDD or SOD, and was more common in SOD than SDD (table 3). Candidaemia acquired in an intensive-care unit was more common in standard care and SOD than it was in SDD (table 3). 47 episodes of acquired bacteraemia were caused by highly resistant microorganisms (tables 3 and 4). One patient had more than one episode (table 3). Development of bacteraemia acquired in intensive-care units caused by highly resistant microorganisms was 59% less frequent with SDD than with standard care and 63% less frequent for SDD than with SOD (tables 3 and 4).

We did 19404 microbiological cultures from endotracheal aspirates. When divided between the time of analysis, frequencies of microbiological cultures from endotracheal aspirates were lowest during standard care (table 2). Frequency of respiratory tract cultures was about 30% lower during standard care than it was in SOD or SDD.

We obtained endotracheal aspirate cultures on admission for 688 (35%) of 1989 patients in the standard-care group, 1044 (55%) of 1904 patients in the SOD group, and 1025 (50%) of 2034 in the SDD group (table 2). Distribution of species isolated was much the same between groups. Prevalence of highly resistant microorganisms at the time of admission to intensive-care units was low, ranging from 2.4% during SDD to 3.9% during SOD, and did not differ between study groups. Endotracheal aspirate cultures were obtained from 2595 (48%) of 5463 patients who stayed in an intensive-care unit for more than 3 days: cultures were obtained for 881 (49%) of 1837 patients in standard care, 886 (50%) of 1758 in SOD, and 828 (44%) of 1868 in SDD.

After day 3 in the intensive-care unit, colonisation of all groups of Gram-negative bacteria that were acquired in intensive-care units was highest in patients receiving standard care. Acquisition rates of *Acinetobacter* spp and *Stenotrophomonas maltophilia* (gathered as one group) and of other glucose non-fermenting Gram-negative rods

	Patients with length of stay >3 days and EACs			Crude odds ratio (95% CI)		
	Standard care (n=881)	SOD (n=886)	SDD (n=828)	SDD vs standard care	SOD vs standard care	SDD vs SOD
Any microorganism	867 (98%)	862 (97%)	800 (97%)	0.46 (0.24–0.88)	0.58 (0.30–1.13)	0.80 (0.46–1.38)
<i>Acinetobacter</i> spp and <i>Stenotrophomonas maltophilia</i>	123 (14%)	92 (10%)	92 (11%)	0.77 (0.57–1.03)	0.71 (0.53–0.95)	1.08 (0.79–1.46)
Other glucose non-fermenting Gram-negative rods*	215 (24%)	149 (17%)	167 (20%)	0.78 (0.62–0.98)	0.63 (0.50–0.79)	1.25 (0.98–1.60)
<i>Escherichia coli</i> and <i>Klebsiella</i> spp	300 (34%)	185 (21%)	63 (8%)	0.16 (0.12–0.21)	0.51 (0.41–0.63)	0.31 (0.23–0.42)
Other Enterobacteriaceae	323 (37%)	230 (26%)	130 (16%)	0.30 (0.26–0.41)	0.61 (0.49–0.74)	0.53 (0.42–0.68)
Other Gram-negative microorganisms†	133 (15%)	60 (7%)	14 (2%)	0.10 (0.06–0.17)	0.41 (0.30–0.56)	0.24 (0.13–0.43)
<i>Enterococcus</i> spp‡	37 (4%)	32 (4%)	93 (11%)	2.89 (1.95–4.29)	0.85 (0.53–1.39)	3.38 (2.23–5.11)
<i>Candida</i> spp and other yeasts	393 (45%)	476 (53%)	465 (56%)	1.59 (1.31–1.93)	1.44 (1.20–1.74)	1.10 (0.91–1.33)
<i>Aspergillus</i> spp and other fungi	28 (3%)	43 (5%)	47 (6%)	1.83 (1.14–2.96)	1.55 (0.96–2.52)	1.18 (0.77–1.80)
<i>Staphylococcus aureus</i> §	174 (20%)	111 (13%)	95 (11%)	0.53 (0.40–0.69)	0.58 (0.45–0.75)	0.90 (0.68–1.21)
<i>Streptococcus pneumoniae</i>	15 (2%)	18 (2%)	5 (<1%)	0.35 (0.13–0.97)	1.20 (0.60–2.39)	0.29 (0.11–0.79)
HRMO	128 (15%)	88 (10%)	74 (9%)	0.58 (0.43–0.78); ARR 5.5%; NNT 18	0.65 (0.49–0.87); ARR 4.6%; NNT 22	0.89 (0.64–1.23)

Data are n (%), unless otherwise stated. EAC=endotracheal aspirate culture. SOD=selective oropharyngeal decontamination. SDD=selective digestive tract decontamination. ARR=absolute risk reduction. NNT=number needed to treat. HRMO=highly resistant microorganism. *Such as *Pseudomonas aeruginosa*. †*Haemophilus* spp, *Neisseria* spp, and *Pasteurella* spp. ‡Vancomycin-resistant enterococci were not cultured. §Two patients in the SOD group and two patients in the SDD group acquired methicillin-resistant *Staphylococcus aureus*.

Table 5: Patients with respiratory tract colonisation acquired in intensive-care units

(predominantly *Pseudomonas aeruginosa*) were much the same in patients receiving both SDD and SOD. However, the rate of acquired colonisation with Enterobacteriaceae was lower with SDD than with SOD (table 5).

For Gram-positive bacteria, acquired colonisation with enterococci occurred more frequently in patients receiving SDD than standard care and SOD (table 5). Acquired colonisation with yeasts and fungi was more common with SDD than with standard care (table 5).

After day 3, we noted acquired colonisation with highly resistant microorganisms in 290 patients. Such colonisation was most common during standard care with 128 (15%) patients, compared with 88 (10%) during SOD and 74 (9%) during SDD (tables 4 and 5). Compared with standard care, SDD reduced the rate of acquired highly resistant microorganisms by 38% and SOD by 32% (tables 4 and 5). Gram-negative bacteria accounted for 98% of all such microorganisms (tables 4 and 5). Four patients acquired respiratory tract colonisation with methicillin-resistant *Staphylococcus aureus* in two centres; two patients were receiving SOD and two were receiving SDD. No patients acquired vancomycin-resistant enterococci (tables 4 and 5).

Tobramycin and colistin were used as topical antibiotics in all patients during SOD (in oropharyngeal paste) and SDD (in oropharyngeal paste and enteral suspension). Cefotaxime was given intravenously during the first 4 days to all patients receiving SDD. Gram-negative bacteria resistant to either of these antibiotics were rarely found during the first 3 days of admission to an intensive-care unit. During standard care, 13 (2%) of 688 patients in an intensive-care unit with one or more culture in the first 3 days after admission were colonised with a Gram-negative bacterium that was resistant to tobramycin at admission, compared with 42 (4%) of 1044 during SOD

and 30 (3%) of 1025 during SDD. We analysed the presence of cefotaxime resistance only for Enterobacteriaceae; prevalence at admission was nine (1%) during standard care, 20 (2%) during SOD, and 30 (3%) during SDD.

Colonisation with Gram-negative bacteria acquired in the intensive-care unit and resistant to tobramycin occurred with much the same frequency and time to acquisition during all three interventions (figure). Although acquisition with tobramycin-resistant Enterobacteriaceae was lowest during SDD, this reduced acquisition was compensated for by the highest acquisition rate of tobramycin-resistant non-fermenting Gram-negative rods (table 6). Acquired colonisation with cefotaxime-resistant Enterobacteriaceae occurred less frequently and later during SDD than it did in the other treatment groups (figure). SDD was associated with a 62% reduction in acquisition rate of cefotaxime-resistant Enterobacteriaceae compared with SOD and standard care (table 6).

Incidence of intensive-care-unit acquired respiratory tract colonisation with Gram-negative bacteria that were intrinsically resistant to colistin (ie, *Proteus* spp and *Serratia* spp) was lower during SDD than it was in standard care and SOD, with rate reductions of 55% for SDD compared with standard care and 48% for SDD compared with SOD (table 6). Differences between the three interventions were not caused by clustering of patients in a minority of the participating intensive-care units (webappendix).

We also investigated the effects of less frequent respiratory tract culture sampling during standard care by comparing ORs for acquired colonisation with Enterobacteriaceae, non-fermenter species, and *Candida* species for the units with comparable culture frequencies in all three study periods and the units with lower

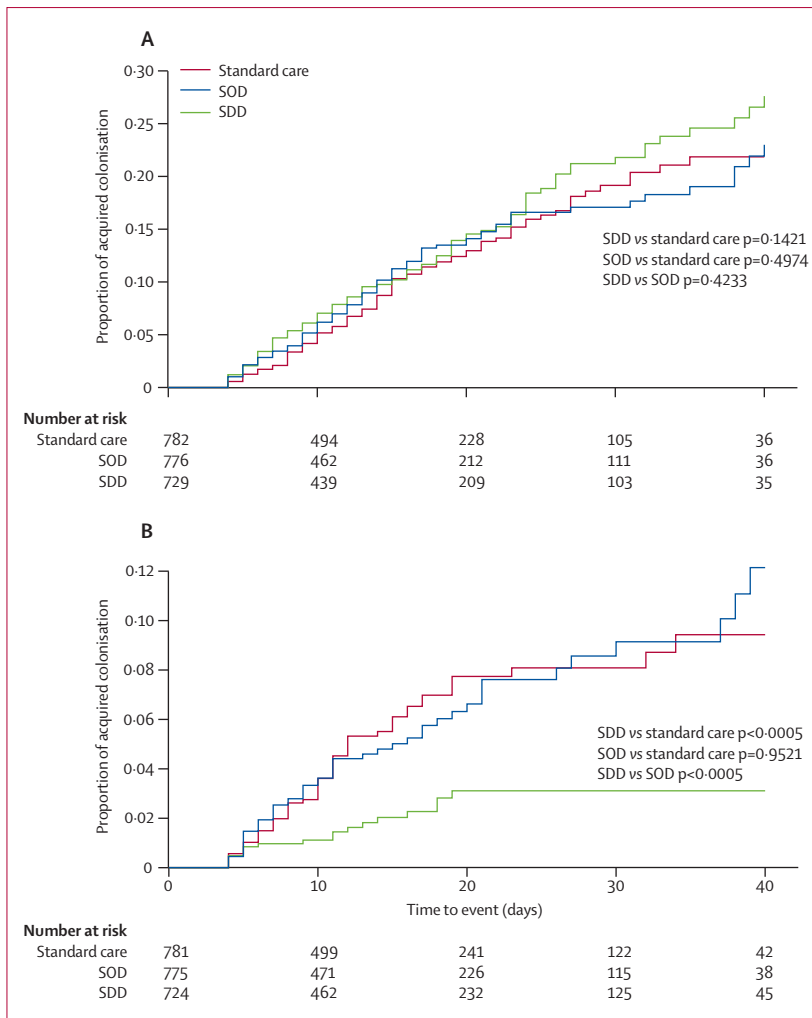


Figure: Kaplan-Meier analysis of time to event of acquisition of tobramycin-resistant Gram-negative rods (A) and cefotaxime-resistant Enterobacteriaceae (B)
SDD=selective digestive tract decontamination. SOD=selective oropharyngeal decontamination.

frequencies during standard care. The average respiratory tract culture frequencies were 0.30 per day during standard care, 0.31 during SOD, and 0.32 during SDD in centres with equal culture frequencies, and 0.18, 0.30, and 0.30, respectively, in those with less frequent culture sampling during standard care. Compared with standard care, ORs for acquisition of Enterobacteriaceae were 0.19 (95% CI 0.12–0.30) during SDD for the three centres with equal culture frequencies in all study periods and 0.17 (0.12–0.24) for ten centres with lower culture frequencies during standard care, and 0.52 (0.36–0.75) and 0.64 (0.50–0.82), respectively, during SOD. For SDD compared with SOD, odds ratios were 0.36 (0.22–0.60) in those centres with equal culture frequencies and 0.26 (0.18–0.39) in those with lower culture frequencies during standard care. ORs were also much the same for the other groups of pathogens (data not shown).

Discussion

In intensive-care units with low rates of antibiotic resistance, the use of SDD was associated with a reduction in acquired bacteraemia and respiratory tract colonisation caused by highly resistant microorganisms compared with standard care. SOD reduced rates of acquired respiratory tract colonisation with highly resistant microorganisms compared with standard care, but rates of bacteraemia from highly resistant microorganisms did not differ. Daily use of topical tobramycin and colistin was not associated with higher acquisition rates of resistant Gram-negative bacteria. Intravenous administration of cefotaxime for 4 days as part of SDD, which is generally regarded as a risk factor for increasing resistance, was associated with a large reduction in the acquisition rate of cefotaxime-resistant Enterobacteriaceae in the respiratory tract compared with standard care and SOD.

Our study was the largest prospective assessment of topical antimicrobial prophylaxis in patients in intensive care, with an estimated overall inclusion rate of 89% in 13 Dutch centres from a cluster-randomised design (panel). Nevertheless, there were slight differences in the baseline characteristics between the study groups, suggesting that patients receiving SDD or SOD were more severely ill than were those receiving standard care.¹⁰ As a result, reductions in day-28 mortality were apparent only after adjustment for these baseline differences. In the present analysis of microbiological outcomes, no adjustments were made for these baseline characteristics and the reported differences in resistance between standard care and both intervention periods should, therefore, be considered as conservative estimates.

Surveillance of respiratory tract colonisation was done in all study groups, whereas surveillance of digestive tract colonisation was done only in the SDD group. Therefore comparison of colonisation of the digestive tract with resistant microorganisms between the three groups was not possible. However, respiratory colonisation usually reflects colonisation of the patient.

Another imbalance between the standard-care population and both intervention groups was the culture frequency of respiratory tract samples. Respiratory tract samples were obtained twice every week during SDD and SOD, as per protocol, but this was not included in the protocol for standard care. As a result, culture frequency was 30% lower during standard care, which might have introduced a negative detection bias for intensive-care-unit acquired colonisation. Potentially, endotracheal cultures were done most frequently in the more severely ill patients in standard care, which could have introduced a positive selection bias. However, when we compared intensive-care units that had the same routine and frequencies of respiratory tract sampling for all three groups with those units in which sampling occurred less frequently for standard care, we noted equivalent ORs for

	Patients with length of stay >3 days and EACs			Crude odds ratio (95% CI)		
	Standard care (n=881)	SOD (n=886)	SDD (n=828)	SDD vs standard care	SOD vs standard care	SDD vs SOD
Tobramycin resistance						
<i>Escherichia coli</i> and <i>Klebsiella</i> spp	31 (4%)	19 (2%)	9 (1%)	0.30 (0.14–0.64)	0.60 (0.34–1.07)	0.50 (0.23–1.11)
Other Enterobacteriaceae	25 (3%)	41 (5%)	15 (2%)	0.63 (0.33–1.21)	1.66 (1.00–2.76)	0.38 (0.21–0.69)
<i>Acinetobacter</i> spp and <i>Stenotrophomonas maltophilia</i>	40 (5%)	45 (5%)	49 (6%)	1.32 (0.86–2.03)	1.13 (0.73–1.74)	1.18 (0.78–1.78)
Other glucose non-fermenting Gram-negative rods*	18 (2%)	20 (2%)	49 (6%)	3.02 (1.74–5.20)	1.11 (0.58–2.11)	2.56 (1.51–4.35)
Gram-negative rods (total)	104 (12%)	112 (13%)	115 (14%)	1.21 (0.91–1.60)	1.08 (0.81–1.44)	1.11 (0.84–1.47)
Cefotaxime resistance						
<i>E coli</i> and <i>Klebsiella</i> spp	13 (1%)	12 (1%)	2 (<1%)	0.16 (0.04–0.72)	0.92 (0.41–2.02)	0.18 (0.04–0.79)
Other Enterobacteriaceae	44 (5%)	42 (5%)	18 (2%)	0.42 (0.24–0.74)	0.95 (0.61–1.46)	0.45 (0.25–0.78)
Enterobacteriaceae (total)	56 (6%)	56 (6%)	20 (2%)	0.36 (0.22–0.61); ARR 4%; NNT 26	0.99 (0.68–1.46)	0.37 (0.22–0.62); ARR 4%; NNT 26
Colistin resistance						
<i>Proteus</i> spp and <i>Serratia</i> spp	130 (15%)	112 (13%)	55 (7%)	0.41 (0.29–0.57); ARR 8%; NNT 12	0.84 (0.64–1.10)	0.49 (0.35–0.69); ARR 6%; NNT 17

Data are n (%) unless otherwise stated. EAC=endotracheal aspirate culture. SOD=selective oropharyngeal decontamination. SDD=selective digestive tract decontamination. ARR=absolute risk reduction. NNT=number needed to treat. *Such as *Pseudomonas aeruginosa*.

Table 6: Respiratory tract colonisation with Gram-negative bacteria resistant to tobramycin, cefotaxime, or colistin acquired in intensive-care-units

acquisition of pathogens. Furthermore, microbiological procedures were identical for samples obtained for clinical reasons or as part of surveillance, suggesting the effect of detection bias was small.

Baseline characteristics and culture frequencies did not differ between patients receiving SDD or SOD. Our data, therefore, allow investigation of the effects of enteral decontamination in combination with intravenous administration of cefotaxime during the first 4 days on acquisition of respiratory tract colonisation. SDD was associated with a substantial reduction in acquired respiratory tract colonisation with Enterobacteriaceae, but not with that of non-fermenting Gram-negative rods, such as *Acinetobacter* species, *S maltophilia*, and *P aeruginosa*. As most non-fermenting bacteria are intrinsically resistant to cefotaxime, intestinal colonisation seems to be a relevant source for Enterobacteriaceae, but not for non-fermenters.

As previously reported,¹⁰ clinical outcomes (eg, day-28 mortality) were comparable between patients receiving SDD and SOD, and therefore a preference for either regimen was difficult to make. Another study¹⁴ showed that respiratory tract decolonisation was associated with a 33% reduction in occurrence of bacteraemia with Gram-negative bacteria acquired in intensive-care units; intestinal tract decolonisation was associated with a 45% reduction in this study. This effect can explain why we reported large and significant relative reductions in bacteraemia in both interventions. The clinical significance of these findings can best be expressed in numbers needed to treat. Compared with SOD, 43 patients would have to be treated with SDD to prevent one episode of bacteraemia, 127 patients to prevent one episode of candidaemia, and 145 patients to prevent one episode with bacteraemia with highly resistant microorganisms.

However, we calculated these numbers needed to treat on the basis of patients with a minimum length of stay in an intensive-care unit of more than 3 days. In an intention-to-treat analysis, including the 8% of the patients with less than 3 days' stay (equally distributed over the three study groups), the number needed to treat would be higher. The attributable effects of such episodes on survival and length of stay will establish whether these figures justify a preference for SDD over SOD. In our study, with 1904 patients receiving SOD and 2034 receiving SDD, differences in bacteraemia rates did not produce significant differences in outcomes.¹⁰

By comparison with SOD, the number needed to treat with SDD to prevent one episode of acquired respiratory tract colonisation was 26 for cefotaxime-resistant Enterobacteriaceae and 17 for intrinsically colistin-resistant Enterobacteriaceae. However, this beneficial effect on the acquisition with cefotaxime-resistant Enterobacteriaceae is, at least partly, balanced by higher acquisition rates of non-fermenting bacteria that are intrinsically resistant to this antibiotic. Overall, rates of acquired respiratory tract colonisation with highly resistant microorganisms did not differ significantly between SDD and SOD.

Selection for antibiotic-resistance is an important threat associated with SDD and SOD.¹⁵ The results of our study suggest the opposite. SDD was associated with a 48% reduction in the rate of bacteraemia with highly resistant microorganisms, and both interventions yielded reductions in acquired respiratory tract colonisation with highly resistant microorganisms of 32% for SOD and 38% for SDD. Moreover, compared with standard care, SOD was not associated with higher rates of acquired colonisation with tobramycin-resistant or colistin-resistant Gram-negative bacteria and SDD

Panel: Research in context**Systematic review**

We searched the PubMed database without language restrictions for papers published up to Feb 15, 2011 with the search terms "ICU" AND "antibiotic resistance" AND "SOD" OR "selective oropharyngeal decontamination" AND "SDD" OR "selective digestive decontamination". Of 639 search results, no studies compared effects of selective digestive decontamination (SDD) with selective oropharyngeal decontamination (SOD), or SOD with standard care with regard to emergence of antibiotic resistance in patients in intensive-care units. One study⁵ compared the effects of SDD with standard care on incidence of antibiotic resistance, and had an equivalent study design to our analysis (unit-wide implementation of intervention).

Interpretation

We report a novel study quantifying the effects of SDD, SOD, and standard care on occurrence of bacteraemia and respiratory tract colonisation with highly resistant microorganisms acquired in intensive-care units. SDD was associated with a 59% rate reduction of highly resistant bacteraemia compared with standard care in this setting, and a 63% rate reduction compared with SOD. SOD was associated with a rate reduction in acquired respiratory tract colonisation with highly resistant microorganisms of 32% compared with standard care, and SDD was associated with a 38% reduction compared with standard care.

was even associated with reduced acquisition rates of bacteria resistant to cefotaxime and colistin. These findings confirm the results from a single-centre study⁵ in the Netherlands, in which SDD was also associated with smaller proportions of patients colonised with resistant pathogens in the respiratory tract.

Our patient-based analysis supports the results of our previous ecological analysis,¹¹ in which we reported unit-wide reductions in prevalence of antibiotic-resistant Gram-negative bacteria in the respiratory tract during treatment with SDD or SOD. Nevertheless, in that analysis we also reported a unit-wide increase in ceftazidime resistance after SOD and SDD were discontinued, which seems to contradict our present findings. However, there are two important differences between the analyses. In the ecological analysis,¹¹ we used point-prevalence surveys in which all patients in the unit (whether or not enrolled in the trial) were included and resistance trends were analysed over time. Many of these patients were in the intensive-care unit for a very short amount of time (≤ 3 days), and did, therefore, not receive SDD or SOD and were not included in the present patient-based analysis. Furthermore, as we did not have control units without SDD and SOD, we could not establish to what extent the reported increase of resistance in time developed independent of either intervention.

The ecological effects of SOD and SDD need to be established in more detailed and longer studies.

Results from the Extended Prevalence of Infection in Intensive Care (EPIC) II study confirmed a strong relation between infection rate and mortality, and 62% of participating patients had infections with Gram-negative bacteria and 17% with *Candida* species; 71% of patients received antibiotics as prophylaxis or treatment.³ New approaches for control of infections and antimicrobial resistance in intensive-care units are needed.

The benefits of prophylactic antibiotic use need to be balanced against the inevitable risks of selection of antibiotic-resistant bacteria. As such, widespread use of topical antimicrobial prophylaxis in patients in intensive-care units has been the subject of debate for years. The beneficial effects of SDD and SOD on outcomes, together with the favourable results for infection and colonisation with antibiotic-resistant pathogens reported in this study, justify the extended use of these interventions in settings with low rates of antibiotic resistance. However, the long-term effects on development of resistance, especially with presently reported increase in infections caused by extended-spectrum β -lactamase-producing bacteria and carbapenemase-producing bacteria, should be carefully monitored. Our results warrant further studies in settings with higher baseline rates of resistance than in our study.

Contributors

AMGAdS, JAJWK, and MJMB designed and managed the study. MCJB, EMM, ATB, EJK, MALvH, BMDJ, SFTT, and JAK critically reviewed the study design for intellectual content. AMGAdS, JAJWK, EMM, RFJB, ATB, EJK, MALvH, ARJ, BMDJ, GJvA, IHMEF, SFTT, SC, JAK, JPA, and PDJS collected data. AMGAdS, JAJWK, MCJB, HEMB, and MJMB did the data analysis. AMGAdS, JAJWK, and MJMB wrote the first draft of the report. All authors reviewed and revised the report.

Conflicts of interest

JAJWK has been a consultant to 3M, Destiny Pharma, Cepheid, and Phico Therapeutics and has received grants from Pfizer and Cepheid. MJMB has participated in advisory boards of 3M, Aventis, and Novartis and has received lecture fees from 3M, Novartis, Pfizer, and Kimberly Clark. All other authors declare no conflicts of interest.

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