Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effects of Decontamination of the Oropharynx and Intestinal Tract on Antibiotic Resistance in ICUs
A Randomized Clinical Trial

Evelien A. N. Oostdijk, MD, PhD; Jozef Kesecioglu, MD, PhD; Marcus J. Schultz, MD, PhD; Caroline E. Visser, MD, PhD; Evert de Jonge, MD, PhD; Einar H. R. van Essen, MD; Alexandra T. Bernards, MD, PhD; Ilse Purmer, MD; Roland Brimicombe, MD, PhD; Dennis Bergmans, MD, PhD; Frank van Tiel, MD, PhD; Frank H. Bosch, MD, PhD; Ellen Mascini, MD, PhD; Arjanne van Griethuysen, MD, PhD; Alexander Bindels, MD, PhD; Arjan Jansz, MD; Fred (A.) L. van Steveninck, MD, PhD; Wil C. van der Zwet, MD, PhD; Jan Willem Fijen, MD, PhD; Steven Thijsen, MD, PhD; Remko de Jong, MD; Joke Oudbier, MD; Adrienne Raben, MD; Eric van der Vorm, MD, PhD; Mirelle Koeman, MD, PhD; Philip Rothbarth, MD, PhD; Annemieke Rijkeboer, MD; Paul Gruteke, MD; Helga Hart-Sweet, MD; Paul Peerbooms, MD, PhD; Lex J. Winsser, MD†; Anne-Marie W. van Elsacker-Niele, MD, PhD; Kees Demmendaal, MD; Afke Brandenburg, MD, PhD; Anne Marie G.A. de Smet, MD, PhD; Marc J. M. Bonten, MD, PhD

IMPORTANCE Selective decontamination of the digestive tract (SDD) and selective oropharyngeal decontamination (SOD) are prophylactic antibiotic regimens used in intensive care units (ICUs) and associated with improved patient outcome. Controversy exists regarding the relative effects of both measures on patient outcome and antibiotic resistance.

OBJECTIVE To compare the effects of SDD and SOD, applied as unit-wide interventions, on antibiotic resistance and patient outcome.

DESIGN, SETTING, AND PARTICIPANTS Pragmatic, cluster randomized crossover trial comparing 12 months of SOD with 12 months of SDD in 16 Dutch ICUs between August 1, 2009, and February 1, 2013. Patients with an expected length of ICU stay longer than 48 hours were eligible to receive the regimens, and 5881 and 6116 patients were included in the clinical outcome analysis for SOD and SDD, respectively.

INTERVENTIONS Intensive care units were randomized to administer either SDD or SOD.

MAIN OUTCOMES AND MEASURES Unit-wide prevalence of antibiotic-resistant gram-negative bacteria. Secondary outcomes were day-28 mortality, ICU-acquired bacteremia, and length of ICU stay.

RESULTS In point-prevalence surveys, prevalences of antibiotic-resistant gram-negative bacteria in perianal swabs were significantly lower during SDD compared with SOD; for aminoglycoside resistance, average prevalence was 5.6% (95% CI, 4.6%-6.7%) during SDD and 11.8% (95% CI, 10.3%-13.2%) during SOD ($P < .001$). During both interventions the prevalence of rectal carriage of aminoglycoside-resistant gram-negative bacteria increased 7% per month (95% CI, 1%-13%) during SDD ($P = .02$) and 4% per month (95% CI, 0%-8%) during SOD ($P = .046$; $P = .40$ for difference). Day 28-mortality was 25.4% and 24.1% during SOD and SDD, respectively (adjusted odds ratio, 0.96 [95% CI, 0.88-1.06]; $P = .42$), and there were no statistically significant differences in other outcome parameters or between surgical and nonsurgical patients. Intensive care unit–acquired bacteremia occurred in 5.9% and 4.6% of the patients during SOD and SDD, respectively (odds ratio, 0.77 [95% CI, 0.65-0.91]; $P = .002$; number needed to treat, 77).

CONCLUSIONS AND RELEVANCE Unit-wide application of SDD and SOD was associated with low levels of antibiotic resistance and no differences in day-28 mortality. Compared with SOD, SDD was associated with lower rectal carriage of antibiotic-resistant gram-negative bacteria and ICU-acquired bacteremia but a more pronounced gradual increase in aminoglycoside-resistant gram-negative bacteria.

TRIAL REGISTRATION trialregister.nl Identifier: NTR1780

JAMA. 2014;312(14):1429-1437. doi:10.1001/jama.2014.7247
Published online October 1, 2014.

Editorial page 1403

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Evelien A. N. Oostdijk, MD, PhD, Department of Medical Microbiology, University Medical Center Utrecht, G04.517, PO Box 85500, 3508 GA Utrecht, the Netherlands (e.a.n.oostdijk@umcutrecht.nl).

Section Editor: Derek C. Angus, MD, MPH, Associate Editor, *JAMA* (angusdc@upmc.edu).

Reductions in the incidence of intensive care unit (ICU)–acquired respiratory tract infections have been achieved by some prophylactic antibiotic regimens, such as selective decontamination of the digestive tract (SDD) and selective oropharyngeal decontamination (SOD).[1,2] Both SDD and SOD use nonabsorbable antibiotics with activity against gram-negative bacteria, yeasts, and *Staphylococcus aureus*; these agents are applied in the oropharynx every 6 hours throughout the ICU stay. Selective decontamination of the digestive tract also includes administration of topical antibiotics in the gastrointestinal tract and systemic prophylaxis with an intravenous third-generation cephalosporin during the first 4 days of ICU stay.

In the largest study in this field, to date, SDD and SOD were compared, as a unit-wide intervention, with standard care (no SDD or SOD) in a cluster-randomized crossover study in 13 Dutch ICUs with low levels of antibiotic resistance.[3] In this study of 5939 patients, SDD and SOD, as compared with standard care, were associated with relative reductions in death at day 28 of 13% and 11%, respectively, and SDD and SOD had comparable effectiveness in reducing length of stay in the ICU and hospital and systemic antibiotic use.

Although SDD and SOD were considered equally effective in ICU patients in a study by de Smet et al,[3] questions about the effects of selection bias (inherent to an open study without individual-patient randomization) and long-term ecological effects remained. So far, there is little evidence of increased risks of antibiotic resistance in individual patients receiving SDD or SOD,[4] but outbreaks of extended-spectrum β-lactamase–producing bacteria and of Enterobacteriaceae resistant to colistin and aminoglycosides during SDD have been reported.[5,6] We therefore evaluated the effects of SDD and SOD on unit-wide bacterial ecology during a 24-month period and in addition evaluated the effects on relevant clinical end points and antibiotic resistance in individual ICU patients.

Methods

All participating ICUs were randomized to start with either SDD or SOD for 12 months (after a wash-in period of 1 month), with a crossover to the other intervention, after a wash-out, wash-in period of 1 month (**Figure**; Study Protocol in Supplement 1). In this period the new strategy (either SDD or SOD) was implemented, but patient data were not used for analysis. The first hospital started the trial in August 2009, the last hospital in January 2011 (eTable 1 in Supplement 2). Randomization was stratified into 2 strata based on presence or absence of applying selective decontamination in the unit for more than 4 months prior to the start of the study. Randomization was performed by a pharmacist not involved in the study, using a computerized randomization program. Institutional review board approval was obtained from all participating hospitals, and the need for informed consent was waived because both SDD and SOD were considered equally effective and standard of care in the Netherlands. Selective digestive tract decontamination had been used before the study in 7 ICUs, and the remaining ICUs used this study to implement SDD or SOD.

All patients admitted to the ICU with an expected ICU stay of at least 48 hours were eligible to receive SDD or SOD. To minimize inclusion bias all patients who received at least 1 dose of SDD or SOD were included, as were all patients with an ICU stay of at least 48 hours, irrespective whether they received SDD or SOD; this population is referred to as the eligible study population. Case report forms were completed by local research nurses, intensivists, or both; if possible, data were obtained via electronic patient data management systems.

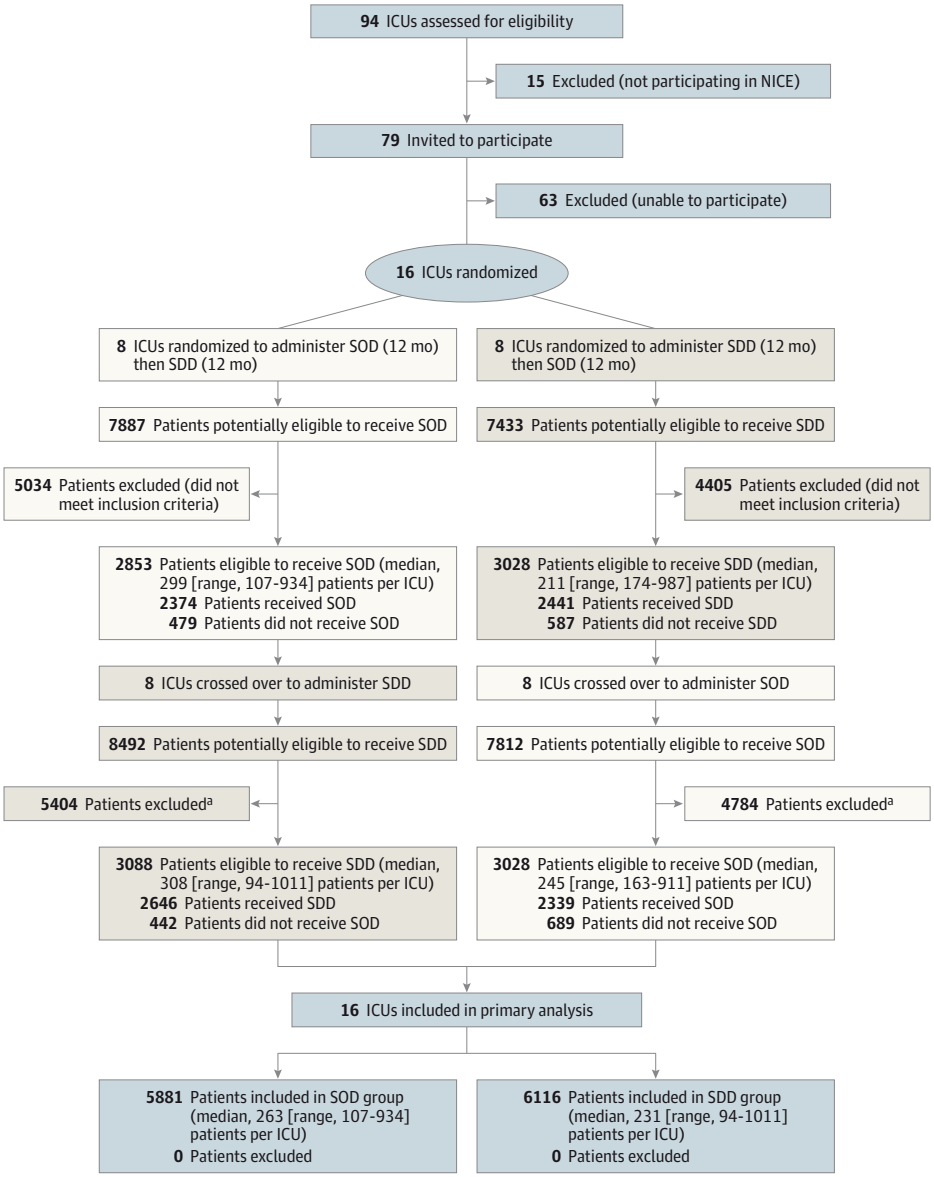
The SDD and SOD regimens have been described[2,3] and consisted of oropharyngeal application (every 6 hours) of a paste containing colistin, tobramycin, and amphotericin B, each in a 2% concentration (in patients receiving SDD and SOD), and administration (every 6 hours) of a 10-mL suspension containing colistin (100 mg), tobramycin (80 mg as sulfate), and amphotericin B (500 mg) via nasogastric tube (in patients receiving SDD). Topical antibiotics were applied until ICU discharge. In addition, a third-generation cephalosporin (either cefotaxime [1 g 4 times daily; 11 hospitals] or ceftriaxone [2 g daily; 5 hospitals]) was administered intravenously during the first 4 days in the ICU as part of SDD but not as part of SOD. (For more information on the SDD-SOD strategies see the eAppendix in Supplement 2.) Patients with clinically suspected or documented infection were treated according to standard clinical practice. Maintaining the anaerobic flora to prevent overgrowth with potential pathogens (so-called colonization resistance) is part of SDD (not of SOD). Therefore, the use of amoxicillin, penicillin, amoxicillin-clavulanic acid, and carbapenems was discouraged during the SDD period. Surveillance cultures were obtained to monitor the effectiveness of the regimen and consisted of endotracheal aspirates and oropharyngeal swabs throughout ICU stay (in patients receiving SDD and SOD) plus rectal swabs during SDD. Details of surveillance protocols are described in the eAppendix in Supplement 2.

The primary end point of the study was the unit-wide prevalence of specific antibiotic-resistant microorganisms, determined through monthly point-prevalence surveillance of rectal and respiratory samples in all patients present in the ICU (at 8 AM every third Tuesday of the month). Secondary end points included day-28 mortality, rates of ICU-acquired bacteremia, and length of ICU stay. If day-28 mortality could not be determined from hospital databases, a patient was considered to be alive at day 28. Sensitivity analysis was performed, in which all of these patients were considered to be dead at day 28.[7]

A predefined subgroup analysis was performed comparing the secondary end points in surgical and nonsurgical patients receiving either SDD or SOD. Surgical patients were defined as those who received any type of surgery in the week prior to ICU admission.

Blood cultures were obtained when bacteremia was suspected, as part of daily clinical practice. Only patients with a length of ICU stay of more than 2 days were included in the bacteremia analyses. Proportions of ICU-acquired bacteremia

Figure. Flow of 2-Group Cluster Randomized Crossover Trial



ICU indicates intensive care unit; NICE, National Intensive Care Evaluation; SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination.

[a] Reasons for exclusion not known at this stage.

were compared during SOD and SDD. Bacteremia was considered ICU-acquired if the first blood culture positive for a particular species was obtained more than 48 hours after ICU admission.

Quality control was performed throughout the study. All ICUs were visited at least 7 times to monitor completeness of point-prevalence surveillance, accuracy of data, and patient enrollment (random sample of 10%).

Data reporting was performed according to CONSORT guidelines for reporting cluster randomized trials.[8] The study was powered on the primary end point, which was the point prevalence of resistant microorganisms in rectal and respiratory tract samples. Assuming a 3% prevalence of patients colonized with multidrug-resistant gram-negative bacteria, considering a 3-fold relative reduction between both study groups (to 1%), and using an intracluster correlation coefficient of 0.010 as present in the study by de Smet et al,[3] at least 14 clusters would be needed.[9]

The primary end point was analyzed using a random-effects Poisson regression analysis. Day-28 mortality was analyzed with a random-effects logistic regression model with adjustment for all available relevant covariates (ie, age, sex, Acute Physiology and Chronic Health Evaluation [APACHE] IV score, mechanical ventilation more than 48 hours, and whether surgery was performed in the week preceding ICU admission), without further variable selection. For both analyses, the Akaike Information Criterion was used to assess the necessity of random intercepts or slopes. Other secondary end points were analyzed with Cox regression modeling.

Table 1. Baseline Characteristics

Characteristic	Regimen	
	SOD (n = 5881)	SDD (n = 6116)
Age at time of ICU admission, y		
Mean (95% CI)	63.2 (62.8-63.6)	63.0 (62.6-63.4)
Median (IQR)	66 (54-75)	65 (18-98)
Male sex, No. (%)	3513 (59.8)	3649 (59.7)
APACHE IV score		
Mean (95% CI)	79.0 (78.1-79.8)	77.4 (76.5-78.2)
Median (IQR)	75 (55-99)	73 (54-96)
Mechanical ventilation, No. (%)		
Any	4670 (79.4)	4835 (79.1)
Ventilation at least 48 h	3061 (52)	3109 (50.8)
Surgery in week before ICU admission, No. (%)	2213 (37.6)	2333 (38.2)
Specialty, No. (%)		
Surgery	1777 (30.3)	1840 (30.1)
Cardiothoracic surgery	723 (12.3)	749 (12.3)
Neurosurgery	303 (5.2)	379 (6.2)
Neurology	390 (6.6)	403 (6.6)
Internal medicine	1304 (22.2)	1269 (20.8)
Cardiology	700 (11.9)	791 (12.9)
Pulmonology	551 (9.4)	510 (8.3)
Other	120 (2.0)	168 (2.8)
Previous or preexistent condition, No. (%)		
Chronic coronary insufficiency	689 (11.7)	737 (12.1)
COPD	996 (16.9)	1003 (16.4)
Diabetes mellitus	1057 (18.0)	1136 (18.6)
Long-term dialysis	124 (2.1)	139 (2.3)
Chronic renal insuffiency	535 (9.1)	559 (9.1)
Metastasized cancer	350 (6.0)	280 (4.6)
Liver cirrhosis	132 (2.2)	155 (2.5)
Immunodepression or AIDS	551 (9.4)	685 (11.2)
Place from which patient was admitted to ICU, No. (%)		
Home	66 (1.1)	27 (0.4)
Emergency department	1801 (30.6)	1872 (30.6)
Other		
Dutch ICU	320 (5.4)	356 (5.8)
Non-Dutch ICU	14 (0.2)	10 (0.2)
Nursing home	11 (0.2)	5 (0.1)
Ward		
Same hospital	3467 (59.0)	3610 (59.1)
Other hospital	108 (1.8)	110 (1.8)
Other	91 (1.5)	120 (2.0)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination.

$P < .05$ was considered to denote statistical significance, and all reported P values are 2-sided. Data were analyzed with SPSS version 19.0 (SPSS Inc) and R version 2.14.2 (R Project for Statistical Computing [http://www.r-project.org/]).

Results

Seventy-nine ICUs participating in the National Intensive Care Evaluation were invited to participate in this open cluster-randomized crossover study (Figure), of which 16 ICUs, representing all levels of ICU care in the Netherlands (eTable 1 in Supplement 2), participated. During the 32 cluster-randomized study periods, 31 624 patients were admitted, of whom 11 997 formed the eligible study population (5881 during SOD and 6116 during SDD). The total number of eligible patients per ICU ranged from 201 to 1945 (eTable 1 in Supplement 2). The study groups were comparable regarding age, sex, and need for mechanical ventilation (**Table 1**). Yet patients in the SOD group had higher APACHE IV scores (median, 75 [interquartile range {IQR}, 55-99] vs 73 [IQR, 54-96]).

In all, 4713 of 5881 patients (80.1%) received at least 1 dose of SOD, and 5087 of 6116 patients (83.0%) received at least 1 dose of SDD. The median length of ICU stay of eligible patients who stayed in the ICU for longer than 48 hours but did not receive SOD or SDD was 4 days (IQR, 2 days) during both the SOD and SDD study periods ($P = .90$), and ICU mortality rates of these patients were 6.8% and 5.7%, respectively (odds ratio [OR], 0.82 [95% CI, 0.58-1.16]; $P = .30$) (eTable 2 in Supplement 2).

Primary and Secondary End Points

There were 384 point-prevalence surveys yielding 3776 rectal swabs. Mean numbers of patients included per survey were 156 (IQR, 13.5 [range, 133-168]) during SOD and 161 (IQR, 15 [range, 149-181]) during SDD. Prevalences of extended-spectrum β-lactamase–producing gram-negative bacteria, and gram-negative bacteria resistant to aminoglycosides, ciprofloxacin, and carbapenems and meeting definitions for highly-resistant microorganisms[10] (eTable 3 in Supplement 2) in rectal swabs, were lower during SDD (**Table 2**). Prevalence rates were less than 1% (and not statistically significantly different) for gram-negative bacteria resistant to colistin and for vancomycin-resistant enterococci. In time, the prevalence of highly-resistant microorganisms tended to increase, although slightly, during SOD and SDD. The most prominent increase was observed for aminoglycoside resistance during SDD (7% per month [95% CI, 1%-13%]), which differed from the observed increase during SOD (4% per month [95% CI, 0%-8%]; $P = .40$).

For respiratory tract colonization, 3651 patients were included in point-prevalence surveys, with a mean of 156 (IQR, 148-155) and 153 (IQR, 144-159) patients per month during SOD and SDD, respectively. The prevalence of antibiotic-resistant bacteria was markedly lower in respiratory tract samples than in rectal swabs, and there were no statistically significant differences between SOD and SDD and no significant trends in time.

Day-28 mortality was 25.4% and 24.1% during SOD and SDD, respectively (adjusted OR, 0.96 [95% CI, 0.88-1.06]), with absolute and relative mortality reductions of 0.7% and 2.8% during SDD as compared with SOD (**Table 3**). For this analysis, the status at day 28, for those discharged from the hospital alive

Table 2. Prevalence of Colonization With Resistant Bacteria During SOD and SDD

	SOD			SDD			P Value for Difference	
	Patients Colonized, No.(%) [95% CI]	Trend in Time[a] % (95% CI)	*P* Value	Patients Colonized, No. (%) [95% CI]	Trend in Time[a] % (95% CI)	*P* Value	Proportion Colonized	Slope
Rectal Samples								
Total patients cultured	n=1871 (mean per month, 156 [IQR, 150-164])			n=1928 (mean per month, 161 [IQR, 153-168])				
HRMO	237 (12.7) [11.2-14.2][b]	1.03 (1.00-1.07)	.09	140 (7.3) [6.1-8.4]	1.05 (1.00-1.10)	.05	.008	.60
ESBL	144 (7.7) [6.5-8.9][b]	1.03 (0.98-1.08)	.20	85 (4.4) [3.5-5.3]	1.06 (0.99-1.12)	.09	.02	.54
Aminoglycosides[c]	220 (11.8) [10.3-13.2][b]	1.04 (1.00-1.08)[b]	.05	109 (5.6) [4.6-6.7]	1.07 (1.01-1.13)	.02	<.001	.40
Ciprofloxacin	193 (10.3) [8.9-11.7][b]	1.01 (0.97-1.06)	.52	108 (5.6) [4.6-6.6]	1.03 (0.97-1.09)	.32	.009	.72
Carbapenems[d]	52 (2.8) [2.0-3.5][b]			30(1.6) [1.0-2.1]			.04	
Colistin[e]	13 (0.7) [0.3-1.1]			23 (1.1) [0.7-1.]			.11	
VRE	4 (0.2) [0-0.4]			11 (0.6) [0.2-0.9]				
Respiratory Samples								
Total patients cultured	n=1874 (mean per month, 156 [IQR, 148-155])			n=1840 (mean per month, 153 [IQR, 144-159])				
HRMO	61 (3.3) [2.5-4.1]	0.98 (0.91-1.06)	.64	47 (2.6) [1.8-3.3]	0.99 (0.91-1.08)	.85	.45	.89
ESBL	24 (1.3) [0.8-1.8]	0.92 (0.81-1.03)	.14	24 (1.3) [0.8-1.8]	1.01 (0.90-1.14)	.88	.31	.25
Aminoglycosides[c]	72 (3.8) [3.0-4.7]	1.02 (0.95-1.09)	.60	50 (2.7) [2.0-3.5]	1.01 (0.93-1.10)	.81	.44	.89
Ciprofloxacin	50 (2.7) [1.9-3.4]	0.97 (0.89-1.05)	.44	46 (2.5) [1.8-3.2]	0.98 (0.90-1.07)	.71	.66	.78
Carbapenems[d]	26 (1.4) [0.9-1.9]			15 (0.8) [0.4-1.2]			.01	
Colistin[e]	5 (0.3) [0.0-0.5]			12 (0.6) [0.3-1.0]			.96	

Abbreviations: ESBL, extended spectrum β-lactamase–producing bacteria; HRMO, highly resistant microorganisms; IQR, interquartile range; SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination; VRE, vancomycin-resistant enterococci.

[a] Trends in time for 12 months of SOD and 12 months of SDD. Trend data (increase or decrease) are per month. A mixed-model Poisson regression using random intercept was used to determine trends in time and to test for differences between the groups regarding proportion of patients colonized and regarding differences in slopes.

[b] Difference in slope $P < .05$ as compared with SDD.

[c] Nonsusceptible for either tobramycin or gentamycin.

[d] Nonsusceptible for either imipenem or meropenem.

[e] Enterobacteriaceae not intrinsically resistant to colistin.

before day 28 (n = 6086), could be retrieved reliably in 5504 patients (90.4%); in this group, day-28 mortality was 3.3%. Assuming that the other 582 patients had died before day 28 did not change interpretation of the absence of outcome differences between SDD and SOD. Intensive care unit mortality and in-hospital mortality were 19.8% and 27.6%, respectively, during SOD and 18.6% and 26.6% during SDD, with corresponding adjusted ORs of 0.96 (95% CI, 0.86-1.05) and 0.99 (95% CI, 0.90-1.08), respectively. Median length of stay in the ICU and hospital was determined for patients alive at day 28 and was comparable during SOD and SDD (Table 3). Hazard rates for ICU discharge and hospital discharge were not statistically different.

In the predefined subgroup analysis of surgical (37.8%) and nonsurgical (62.2%) patients, day-28 mortality for surgical patients was 19.7% during SOD and 17.7% during SDD (adjusted OR, 0.92 [95% CI, 0.78-1.09]). For nonsurgical patients, day-28 mortality was 28.8% during SOD and 28.0% during SDD, with a corresponding adjusted OR of 0.99 (95% CI, 0.88-1.11) (**Table 4**).

In total, 5442 SOD-treated and 5549 SDD-treated patients had an ICU stay longer than 2 days (**Table 5**). Mean numbers of blood cultures per patient-day were 0.13 (95% CI, 0.12-0.13) and 0.12 (95% CI, 0.12-0.12) during SOD and SDD, respectively. The proportion of patients developing ICU-acquired bacteremia with Enterobacteriaceae was lower during SDD (OR, 0.42 [95% CI, 0.29-0.60]), and the difference was most pronounced for *Escherichia coli* (OR, 0.33 [95% CI, 0.18-0.62]) (Table 5). In addition, significant reductions in ICU-acquired bacteremia were observed for aminoglycoside-resistant gram-negative bacteria (OR, 0.54 [95% CI, 0.31-0.97]), including Enterobacteriaceae and glucose-nonfermenting gram-negative rods (eg, *Pseudomonas* spp) during SDD. Proportions of patients developing ICU-acquired bacteremia with

Table 3. Mortality End Points and Length of Stay (Days)

	Regimen					
	SOD	SDD	OR or HR (95% CI)	*P* Value	Adjusted Odds (95% CI)	*P* Value
Mortality, No. (%)[a]						
No.	5881	6116				
ICU	1165 (19.8)	1138 (18.6)	0.92 (0.84-1.01)	.10	0.96 (0.86-1.05)	.43
Hospital	1625 (27.6)	1629 (26.6)	0.95 (0.88-1.03)	.22	0.99 (0.90-1.08)	.83
Day 28	1494 (25.4)	1472 (24.1)	0.93 (0.86-1.01)	.09	0.96 (0.88-1.06)	.42
Time to Discharge for Survivors at Day 28,[b] **Median (IQR), d**						
No.	4387	4644				
From ICU	6 (4-11)	6 (4-11)	0.96 (0.92-1.01)	.10		
From Hospital	19 (11-35)	19 (11-35)	0.96 (0.91-1.01)	.10		

Abbreviations: HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination.

[a] For the survival analysis, patients were censored at day 28. Patients who died before day 28 had infinitive durations to overcome informative censoring.

[b] Mixed-model regression analysis was used. Adjusted odds were corrected for age, APACHE IV score, surgery or nonsurgery, mechanical ventilation more than 48 hours (yes/no), and center.

Table 4. Subgroup Analysis of Mortality Among Surgical and Nonsurgical Patients[a]

	Regimen, No. (%)		OR (95% CI)	
	SOD	SDD	Unadjusted	Adjusted
Nonsurgical				
No.	3668	3779		
ICU	827 (22.5)	816 (21.6)	0.95 (0.85-1.06)	0.97 (0.86-1.10)
Hospital	1117 (30.5)	1130 (29.9)	0.97 (0.88-1.08)	1.01 (0.90-1.12)
Day 28	1057 (28.8)	1058 (28.0)	0.96 (0.87-1.06)	0.99 (0.88-1.11)
Surgical				
No.	2213	2333		
ICU	338 (15.3)	321 (13.8)	0.88 (0.75-1.04)	0.96 (0.80-1.16)
Hospital	508 (23.0)	498 (21.3)	0.91 (0.79-1.05)	0.98 (0.84-1.15)
Day 28	437 (19.7)	413 (17.7)	0.87 (0.75-1.02)	0.92 (0.78-1.09)

Abbreviations: ICU, intensive care unit; OR, odds ratio; SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination.

[a] Surgical patients received surgery 1 week before ICU admission. Mixed-model regression analysis was used. Adjusted odds were corrected for age, APACHE IV score, surgery or nonsurgery, and center.

colistin-resistant gram-negative organisms, vancomycin-resistant enterococci, and methicillin-resistant *Staphylococcus aureus* were below 0.2% during SOD and SDD. Time until ICU-acquired bacteremia was comparable during SOD and SDD (Table 5). Completeness of monthly point-prevalence surveillance studies among all ICU patients was 92.2% for rectal swabs and 89.5% for respiratory samples, ranging from 81.4% to 98.6% per ICU for rectal samples and from 71.4% to 98.3% for respiratory samples. The accuracy of patient inclusion was 97.5% (ranging from 91% to 100% per center), meaning that 97.5% of the patients who should have been included were included. Accuracy of case report form data was 96.0% for admission and discharge dates and 97.4% for ICU and hospital mortality. There were no statistically significant differences between SOD and SDD periods.

Both SDD and SOD were temporarily interrupted or changed as part of control programs for nosocomial outbreaks, attributable to ampicillin-resistant enterococci (6 weeks' interruption of SOD in 1 hospital) or extended-spectrum β-lactamase–producing bacteria (in 1 hospital, SOD was replaced by SDD for 4 weeks). These outbreaks occurred in different hospitals.

There were no adverse effects reported for SDD or SOD. Refusal of the mouth paste after extubation occurred most frequently, and SDD was discontinued in 1 patient because of a clinical suspicion of Stevens-Johnson syndrome, which was attributed to intravenous administration of β-lactam antibiotics.

Discussion

In this cluster randomized crossover study including 11 997 patients, the use of SDD and SOD during 24 months in 16 ICUs in the Netherlands was associated with low prevalence levels of antibiotic-resistant bacteria. Intestinal decontamination and routine intravenous treatment with third-generation cephalosporins as part of SDD resulted in a reduction in the incidence of ICU-acquired bacteremia, most pronounced for Enterobacteriaceae (OR, 0.42 [95% CI, 0.29-0.60]), including aminoglycoside-resistant gram-negative organisms (OR, 0.54 [95% CI, 0.31-0.97]), as compared with SOD. However, no additional benefits of SDD were observed for any of the other clinical end points, such as patient survival and length of stay.

Table 5. Incidence of ICU-Acquired Bacteremia for Patients With a Length of ICU Stay More Than 2 Days

	Regimen		OR, SDD vs SOD (95% CI)	*P* Value
	SOD (n = 5442)	SDD (n = 5549)		
ICU length of stay				
>2 d, No.	5442	5549		
>2 d with ≥1 blood culture, No. (%)	2662 (49)	2741 (49)		
Total No. of patient-days	54 433	56 058		
Cultures per patient-day, mean (95% CI), d[a]	0.13 (0.12-0.13)	0.12 (0.12-0.12)		
Any positive blood culture, No. (%)	319 (5.9)	253 (4.6)	0.77 (0.65-0.91)	.002
Enterobacteriaceae, No. (%)	97 (1.8)	41 (0.7)	0.42 (0.29-0.60)	<.001
Escherichia coli	39 (0.7)	13 (0.2)	0.33 (0.18-0.62)	<.001
Klebsiella spp	22 (0.4)	12 (0.2)	0.54 (0.27-1.10)	.09
Enterobacter spp	10 (0.2)	7 (0.1)	0.70 (0.27-1.83)	.47
Other Enterobacteriaceae	29 (0.5)	9 (0.2)	0.31 (0.15-0.65)	.001
GNF-GNR, No. (%)	27 (0.5)	25 (0.5)	0.92(0.54-1.60)	.78
Pseudomonas aeruginosa	20 (0.4)	23 (0.4)	1.15 (0.63-2.10)	.65
Acinetobacter spp	3 (0.1)	1 (0)	0.33 (0.04-3.20)	.38
Stenotrophomonas maltophilia	4 (0.1)	2 (0.0)	0.50 (0.09-2.73)	.45
Enterococcus spp, No. (%)	154 (2.8)	151 (2.7)	0.98 (0.78-1.23)	.85
Staphylococcus aureus, No. (%)	28 (0.5)	17 (0.3)	0.61 (0.33-1.11)	.01
Candida spp and other yeasts, No. (%)	48 (0.9)	33 (0.6)	0.69 (0.44-1.07)	.09
Resistant GNB, No. (%)[b]				
HRMO	31 (0.6)	23 (0.4)	0.74 (0.43-1.27)	.27
ESBL	8 (0.1)	5 (0.1)	0.62 (0.20-1.91)	.40
Aminoglycosides[c]	33 (0.6)	18 (0.3)	0.54 (0.31-0.97)	.04
Colistin[d]	0	4 (0.1)	NA	.13
VRE, No. (%)	3 (0.1)	0	NA	.13
MRSA, No. (%)	1 (0)	1 (0)	1.00 (0.06-15.97)	>.99
Time to bacteremia	**Median (range) [IQR]**			
Enterococcus spp	10 (3-41) [9]	10 (3-52) [10]		.52
GNB[a]	10 (3-114) [13]	11 (3-68) [17]		.64

Abbreviations: ESBL, extended-spectrum β-lactamase; GNB, gram-negative bacteria (including Enterobacteriaceae and GNF-GNR); HRMO, highly resistant microorganisms; ICU, intensive care unit; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; OR, odds ratio; SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination; VRE, vancomycin-resistant enterococci.

[a] Proportion of patient days during which a blood sample was obtained.

[b] Enterobacteriaceae and glucose-nonfermenting gram-negative rods.

[c] Nonsusceptible for either tobramycin or gentamycin.

[d] For Enterobacteriaceae not intrinsically resistant to colistin.

During SDD a lower proportion of patients was colonized in the intestinal tract with resistant microorganisms, yet there was a gradual increase observed with aminoglycoside-resistant gram-negative bacteria, which was most pronounced during the SDD study period. Long-term effects of SDD have not been studied extensively, but increasing resistance during SDD was not observed in 2 other longitudinal studies in Germany and France.[11,12] The German study was a 5-year prospective observational study in a single tertiary-care surgical ICU[11]; the French study was a retrospective case-control study, also in a single tertiary-care center, with patients studied during a 6-year period.[12] Yet both single-center studies may have been underpowered to detect the time trend as observed in our study. In another longitudinal analysis of clinical culture results from Dutch ICUs using (n = 17) or not using (n = 13) SDD or SOD during a 4-year period yielded an increasing trend of tobramycin-resistant Enterobacteriaceae, approaching statistical significance, in ICUs not using SDD or SOD. This trend was not apparent in ICUs using SDD or SOD.[13]

The increase in aminoglycoside resistance as observed in the current study is of potential importance and could result from the selective effects of tobramycin on antibiotic resistance genes in the human microbial flora, with proliferation of resistance genes in the anaerobic flora. Others have shown that the human microbiome indeed acts as a reservoir for antibiotic resistance genes.[14,15] A recent study using metagenomic approaches demonstrated an increase of antibiotic resistance genes, and especially of genes conferring resistance to aminoglycosides, in the unculturable anaerobic flora and linked to mobile genetic elements, during SDD.[16] Metagenomic approaches and studies addressing carriage with antibiotic resistant bacteria after discontinuation of SDD and SOD are needed to further investigate these hypotheses.

Furthermore, resistance to aminoglycosides increases the likelihood of acquisition of colistin resistance.[17] Colistin is becoming increasingly important as a last-resort antibiotic because of increasing infection rates with gram-negative bacteria resistant to carbapenem antibiotics in many parts of the world. The findings of the present study confirm and extend previous results reporting the epidemiology of colistin resistance in Dutch ICUs using SDD or SOD.[17] The prevalence of resistance to colistin was less than 1.1% in rectal swabs and 0.6% in respiratory samples during SDD and even lower during SOD, and only 4 episodes of bacteremia occurred with colistin-resistant gram-negative organisms (all during SDD).

Still, emergence of bacteria with acquired resistance to the antibiotics used in SDD and SOD can occur in settings with failing infection control.[6] Prophylactic administration of colistin on a daily basis in many patients simultaneously, as in SDD and SOD, must therefore be accompanied by careful monitoring of both aminoglycoside and colistin resistance, and containment strategies should be developed and implemented immediately when cross-transmission of resistant bacteria is demonstrated or highly suspected. The prevalence of methicillin-resistant *S aureus*, vancomycin-resistant enterococci, and carbapenem-resistant gram-negative bacteria is low in Dutch ICUs, and little is known about the efficacy and ecological safety of SDD or SOD in settings with higher prevalence of antibiotic-resistant bacteria. A cluster-randomized study evaluating the effects of several decontamination strategies, including SDD and SOD, in areas with levels of methicillin-resistant *S aureus*, vancomycin-resistant enterococci, and multidrug-resistant gram-negative bacteria higher than those observed in Dutch ICUs is ongoing.[18]

The current study confirms previous observations that intestinal decontamination is important in preventing ICU-acquired bacteremia with gram-negative bacteria, especially Enterobacteriaceae.[3,19] Yet because of the low incidence and minor absolute risk difference between the 2 study groups, the number needed to treat with SDD to prevent 1 episode of ICU-acquired bacteremia (as compared with SOD) was 77 and was 355 for ICU-acquired bacteremia caused by an aminoglycoside-resistant gram-negative bacterium. It is therefore not surprising that the observed reduction in ICU-acquired bacteremia during SDD was not associated with a detectable effect on patient outcome.

The current study has several limitations. There was no control group of ICUs not applying SDD or SOD, because this was considered unethical in the Netherlands after previous studies demonstrated improved patient survival attributable to SDD and SOD.[2,3] In addition, 5 ICUs used ceftriaxone instead of cefotaxime for systemic prophylaxis during SDD, but both agents have a similar spectrum of activity, and the variation reflects clinical practice. In the present analysis we did not quantify systemic antibiotic use. Previously, De Smet et al quantified the total number of defined daily doses during SDD and SOD and in a standard-care control group, showing a nonsignificant reduction in total antibiotic use of 11.9% during SDD and 10.1% during SOD, compared with standard care; this reduction was most pronounced for quinolones and carbapenems.[3]

Strengths of the study include its size and design, allowing evaluation of the unit-wide effects of both interventions. Cluster randomized trials are susceptible to inclusion bias, and in this study the decision to initiate SDD and SOD in individual patients was made by physicians. We aimed to minimize the potential of bias by including all patients who received SDD or SOD and all patients with an ICU length of stay of at least 48 hours who did not receive SDD or SOD, which accounted for 18% of the study population. Naturally, these proportions differed between ICUs because of differences in ICU level and patient case-mix. Baseline characteristics were comparable for both study groups, with the exception of the mean APACHE IV score, which was higher during SOD. It is unlikely that this resulted from inclusion bias, which was supported by the fact that adjustment of results with all covariates related to a patient's prognosis did not change the results of crude analyses.

Because the most important clinical outcomes, ie, survival and length of stay in the ICU and hospital, were comparable for SOD and SDD, and because SDD is more costly, the cost-benefit ratio of SOD is more beneficial, as has been suggested.[20] Substantial increases in the costs of amphotericin B increased the daily costs considerably, especially for SDD. Nystatin could be a less expensive alternative, if demonstrated equally effective in preventing yeast colonization.

Conclusions

Unit-wide application of SDD and SOD was associated with low levels of antibiotic resistance and no differences in mortality and length of stay. Compared with SOD, SDD was associated with lower rectal carriage of antibiotic-resistant gram-negative bacteria and ICU-acquired bacteremia but a more pronounced gradual increase in aminoglycoside-resistant gram-negative bacteria.

ARTICLE INFORMATION

†Deceased

Published Online: October 1, 2014. doi:10.1001/jama.2014.7247.

Author Affiliations: Department of Medical Microbiology, University Medical Center Utrecht, Utrecht (Oostdijk, Bonten); Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht (Oostdijk, Kesecioglu); Department of Intensive Care, Academic Medical Center, University of Amsterdam, Amsterdam (Schultz); Department of Medical Microbiology, Academic Medical Center, University of Amsterdam, Amsterdam (Visser); Department of Intensive Care Medicine, Leiden University Medical Center, Leiden (de Jonge, van Essen); Department of Medical Microbiology, Leiden University Medical Center, Leiden (Bernards); Department of Intensive Care, HagaZiekenhuis, The Hague (Purmer, Koeman); Department of Medical Microbiology, HagaZiekenhuis, The Hague (Brimicombe); Department of Intensive Care, Maastricht University Medical Centre+, Maastricht (Bergmans); Department of Medical Microbiology, Maastricht University Medical Centre+, Maastricht (van Tiel); Department of Intensive Care, Rijnstate Hospital, Arnhem (Bosch); Laboratory for Medical Microbiology and Immunology, Rijnstate Hospital, Arnhem (Mascini, van Griethuysen); Department of Intensive Care Medicine, Catharina Hospital, Eindhoven (Bindels); Laboratory for Medical Microbiology, Laboratories for Pathology and Medical Microbiology, Catharina Hospital, Eindhoven (Jansz); Department of Intensive Care, Deventer Hospital, Deventer (van Steveninck); Department of Medical Microbiology, Deventer Hospital, Deventer (van der Zwet); Department of Intensive Care, Diakonessenhuis Utrecht, Utrecht (Fijen); Department of Medical Microbiology, Diakonessenhuis Utrecht, Utrecht (Thijsen); Department of Intensive Care, BovenIJ Hospital, Amsterdam (de Jong); Department of Medical Microbiology, Zaans Medical Center, Zaandam (Oudbier); Department of Intensive Care, Groene Hart Hospital, Gouda (Raben); Department of Medical Microbiology, Groene Hart Hospital, Gouda (van der Vorm); Department of Medical Microbiology, Rijnland Hospital, Leiderdorp (Rothbarth); Department of Intensive Care, Flevo Hospital, Almere (Rijkeboer); Department of Medical Microbiology, Flevo Hospital, Almere (Gruteke); Department of Intensive Care, Sint Lucas Andreas Hospital, Amsterdam (Hart-Sweet); Department of Medical Microbiology, Sint Lucas Andreas Hospital, Amsterdam (Peerbooms); Department of Intensive Care, Antonius Hospital,

Sneek (Winsser); Izore, Centre for Infectious Diseases Friesland, Leeuwarden (van Elsacker-Niele, Brandenburg); Nij Smellinghe Hospital, Drachten (Demmendaal); Department of Critical Care, University of Groningen, University Medical Center Groningen, Groningen (de Smet); Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands (Bonten).

Author Contributions: Dr Oostdijk had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Oostdijk, Kesecioglu, Schultz, Purmer, Bosch, van Griethuysen, Bindels, Fijen, Thijsen, Hart-Sweet, de Smet, Bonten.
Acquisition, analysis, or interpretation of data: Oostdijk, Kesecioglu, Visser, E. de Jong, van Essen, Bernards, Purmer, Brimicombe, Bergmans, van Tiel, Mascini, van Griethuysen, Bindels, Jansz, van Steveninck, van der Zwet, Fijen, R. de Jong, Oudbier, Raben, van der Vorm, Koeman, Rothbarth, Rijkeboer, Gruteke, Peerbooms, Winsser, van Elsacker-Niele, Demmendaal, Brandenburg, Bonten.
Drafting of the manuscript: Oostdijk, Kesecioglu, Bergmans, van Steveninck, Demmendaal, Bonten.
Critical revision of the manuscript for important intellectual content: Kesecioglu, Schultz, Visser, E. de Jong, van Essen, Bernards, Purmer, Brimicombe, Bergmans, van Tiel, Bosch, Mascini, van Griethuysen, Bindels, Jansz, van der Zwet, Fijen, Thijsen, R. de Jong, Oudbier, Raben, van der Vorm, Koeman, Rothbarth, Rijkeboer, Gruteke, Hart-Sweet, Peerbooms, Winsser, van Elsacker-Niele, Brandenburg, de Smet, Bonten.
Statistical analysis: Oostdijk, Bonten.
Obtained funding: E. de Jong, Bonten.
Administrative, technical, or material support: Kesecioglu, Schultz, Visser, van Essen, Bernards, Purmer, Brimicombe, Bergmans, Bosch, van Griethuysen, Jansz, van Steveninck, van der Zwet, R. de Jong, Oudbier, van der Vorm, Koeman, Rijkeboer, Winsser, van Elsacker-Niele, Demmendaal, de Smet, Bonten.
Study supervision: Kesecioglu, Fijen, Thijsen, Bonten.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Kesecioglu reported receiving personal fees from Becton Dickinson. No other authors reported disclosures.

Funding/Support: Dr Bonten was supported by the Netherlands Organization for Scientific Research (NWO-VICI 918.76.611).

Role of the Funder/Sponsor: The Netherlands Organization for Scientific Research had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Additional Contributions: We would like to thank all the nursing and medical staff and laboratory technicians of the participating hospitals and Fieke Kloosterman (Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, the Netherlands) for quality surveys. Ms Kloosterman received no compensation for her contributions.

REFERENCES

1. Bergmans DC, Bonten MJ, Gaillard CA, et al. Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study. *Am J Respir Crit Care Med*. 2001;164(3):382-388.

2. de Jonge E, Schultz MJ, Spanjaard L, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet*. 2003;362(9389):1011-1016.

3. de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med*. 2009; 360(1):20-31.

4. Daneman N, Sarwar S, Fowler RA, Cuthbertson BH; SuDDICU Canadian Study Group. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13 (4):328-341.

5. Al Naiemi N, Heddema ER, Bart A, et al. Emergence of multidrug-resistant Gram-negative bacteria during selective decontamination of the digestive tract on an intensive care unit. *J Antimicrob Chemother*. 2006;58(4):853-856.

6. Halaby T, Al Naiemi N, Kluytmans J, van der Palen J, Vandenbroucke-Grauls CM. Emergence of colistin resistance in Enterobacteriaceae after the introduction of selective digestive tract decontamination in an intensive care unit. *Antimicrob Agents Chemother*. 2013;57(7):3224-3229.

7. Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. *Clin Trials*. 2008;5(3):225-239.

8. Campbell MK, Piaggio G, Elbourne DR, Altman DG; CONSORT Group. Consort 2010 statement: extension to cluster randomised trials. *BMJ*. 2012; 345:e5661.

9. Schulz KF, Grimes DA. Sample size calculations in randomised trials: mandatory and mystical. *Lancet*. 2005;365(9467):1348-1353.

10. Kluytmans-Vandenbergh MF, Kluytmans JA, Voss A. Dutch guideline for preventing nosocomial transmission of highly resistant microorganisms (HRMO). *Infection*. 2005;33(5-6):309-313.

11. Heininger A, Meyer E, Schwab F, Marschal M, Unertl K, Krueger WA. Effects of long-term routine use of selective digestive decontamination on antimicrobial resistance. *Intensive Care Med*. 2006; 32(10):1569-1576.

12. Leone M, Albanese J, Antonini F, Nguyen-Michel A, Martin C. Long-term (6-year) effect of selective digestive decontamination on antimicrobial resistance in intensive care, multiple-trauma patients. *Crit Care Med*. 2003;31 (8):2090-2095.

13. Houben AJ, Oostdijk EA, van der Voort PH, Monen JC, Bonten MJ, van der Bij AK; ISIS-AR Study Group. Selective decontamination of the oropharynx and the digestive tract, and antimicrobial resistance: a 4 year ecological study in 38 intensive care units in the Netherlands. *J Antimicrob Chemother*. 2014;69(3):797-804.

14. Jernberg C, Löfmark S, Edlund C, Jansson JK. Long-term impacts of antibiotic exposure on the human intestinal microbiota. *Microbiology*. 2010; 156(pt 11):3216-3223.

15. Sommer MO, Dantas G, Church GM. Functional characterization of the antibiotic resistance reservoir in the human microflora. *Science*. 2009; 325(5944):1128-1131.

16. Buelow E, Gonzalez TB, Versluis D, et al. Effects of selective digestive decontamination (SDD) on the gut resistome. *J Antimicrob Chemother*. 2014; 69(8):2215-2223.

17. Oostdijk EA, Smits L, de Smet AM, Leverstein-van Hall MA, Kesecioglu J, Bonten MJ. Colistin resistance in gram-negative bacteria during prophylactic topical colistin use in intensive care units. *Intensive Care Med*. 2013;39(4):653-660.

18. R-GNOSIS (Resistance in Gram-Negative Organisms: Studying Intervention Strategies) website. http://www.r-gnosis.eu/. Accessed July 29, 2014.

19. Oostdijk EA, de Smet AM, Kesecioglu J, Bonten MJ; Dutch SOD-SDD Trialists Group. The role of intestinal colonization with gram-negative bacteria as a source for intensive care unit-acquired bacteremia. *Crit Care Med*. 2011;39(5):961-966.

20. Oostdijk EA, de Wit GA, Bakker M, de Smet AM, Bonten MJ; Dutch SOD-SDD Trialists Group. Selective decontamination of the digestive tract and selective oropharyngeal decontamination in intensive care unit patients: a cost-effectiveness analysis. *BMJ Open*. 2013;3(3):e002529.