EDITORIAL

Rational Use of Antibiotics in the ICU
Balancing Stewardship and Clinical Outcomes

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Clinicians working in the intensive care unit (ICU) setting encounter the dilemma of prescribing antibiotics to treat critically ill patients with serious infections while minimizing the emergence and spread of antimicrobial resistance. Delaying the administration of appropriate antibiotic therapy (ie, an antibiotic regimen active against the causative pathogen based on in vitro testing) in the ICU has been associated with an increase in hospital mortality.[1] One of the most important risk factors for delayed appropriate antibiotic therapy in seriously ill infected patients is prior exposure to antibiotics, typically administered within the previous 90 days.[1]

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Prior antibiotic exposure promotes colonization and subsequent infection with antibiotic-resistant pathogens, complicating initial choice of antibiotics, thereby increasing the likelihood that delayed administration of appropriate antibiotic therapy will occur. Moreover, more prolonged durations of exposure to antibiotics seem to be most important in promoting the emergence of antibiotic-resistant pathogens in critically ill patients.[2] Thus, clinicians working in the ICU must balance the needs of the patient they are directly treating with antibiotics with the needs of the other patients in the ICU who could subsequently be exposed to antibiotic-resistant bacteria induced by the currently prescribed antibiotic regimens.

The importance of the global problem of increasing antimicrobial resistance is highlighted by a recent report from the Centers for Disease Control and Prevention indicating that infections attributed to antibiotic-resistant pathogens represent one of the most serious health threats.[3] In this issue of *JAMA*, Oostdijk and colleagues[4] used a cluster randomized crossover trial to study 2 different methods of administering antibiotic prophylaxis in patients requiring ICU care: selective digestive tract decontamination (SDD) (n = 6166 patients) vs selective oropharyngeal decontamination (SOD) (n = 5881 patients). Both regimens consisted of a combination of colistin, tobramycin, and amphotericin B.[4] The SDD regimen also involved 4 days of intravenous antibiotic prophylaxis with a broad-spectrum cephalosporin. Both regimens are considered "selective" in that they aim to suppress overgrowth in the gut by unwanted potentially pathogenic microorganisms. Monthly point-prevalence surveys of respiratory and perianal culture samples were performed and demonstrated that the prevalence of antibiotic-resistant gram-negative bacteria in perianal swabs and ICU-acquired bacteremia were significantly less common with SDD compared with SOD (5.6% vs 11.8%, respectively; $P < .001$). However, there appeared to be significantly greater perianal carriage with aminoglycoside-resistant bacteria over time with the use of SDD (7% per month) than with SOD (4% per month). No differences in hospital mortality or other clinical outcomes were observed.

Several important limitations of this report should be noted. First, this study was performed in the Netherlands, a country having historically low rates of antibiotic resistance compared with other parts of Europe. It is possible that the routine use of SDD or SOD could promote greater emergence of antibiotic resistance in ICUs in which the endemic background rate of colonization with antibiotic-resistant bacteria is greater than that observed in the Netherlands. The authors acknowledge the importance of their observation of increased perianal carriage of aminoglycoside-resistant bacteria during SDD administration, a finding similar to that observed in a previous study conducted by the same group demonstrating emergence of ceftazidime resistance over time with SDD.[5] Of great concern is emergence of resistance to antibiotics, such as colistin, reserved for the treatment of antibiotic-resistant infections. Indeed, colistin resistance in gram-negative bacteria is increasingly reported in many parts of the world, including Europe, and has been associated with SDD use.[6] The description of carbapenem-resistant Enterobacteriaceae acquiring colistin resistance is particularly concerning because these pathogens would potentially be resistant to all available antibiotic classes.[7]

Another limitation is the lack of a control group in which patients received neither SDD nor SOD. The rationale for exclusion of a control group seems to be an earlier study performed by the Netherlands group suggesting a mortality reduction with both SDD and SOD compared with placebo,[8] even though in that study no reduction in crude mortality was observed with SDD and SOD. A post hoc random-effects logistic regression model adjusting for age, sex, severity of illness, intubation status, and medical specialty was required to demonstrate an association of SDD and SOD with mortality. Intuitively, the most important potential limitation of the routine use of SDD and SOD is that these interventions promote greater overall use of antimicrobial agents in the ICU, despite preventing nosocomial infections that could reduce subsequent need for antimicrobial therapy. The association between increasing antibiotic use and emergence of resistance is well established, especially in the ICU setting.[9] The current trial by Oostdijk et al[4] was not designed to assess the effect of SDD or SOD on total antimicrobial exposure in ICU patients. Given the important linkage between antibiotic use and emergence of resistance in the ICU, nonantibiotic pharmacologic and nonpharmacologic

approaches for preventing infection and minimizing emergence of antibiotic resistance would seem to be the most logical approaches to pursue for future study.

A number of novel methods aimed at improving the early identification of pathogens and related antibiotic susceptibilities are on the horizon. Such technological advances offer a strategy that could potentially maximize the administration of appropriate antibiotic therapy while minimizing unnecessary antibiotic exposure. These approaches include the use of molecular methods (eg, polymerase chain reaction electrospray ionization mass spectrometry and MALDI-TOF [matrix-assisted laser desorption/ionization time-of-flight]) as well as advanced automated microscopy techniques that allow the identification of bacterial species, the presence of antibiotic resistance genes, and bacterial killing by specific antibiotics within 4 to 6 hours using direct specimen inoculation.[10,11] Accurate and timely identification of the causative pathogens associated with infection would avoid the need for prolonged empirical antimicrobial therapies, which are often used for critically ill patients to maximize the likelihood of pathogen coverage and potentially limit the duration of antibiotic treatment by identifying quantitative pathogen-related thresholds for the discontinuation of antibiotics. These methods are being developed for commercial use, and it is expected that they could become available for routine use over the next 5 to 7 years.

Recent metagenomic approaches have demonstrated an increase in the number of antibiotic resistance genes, and especially of genes conferring resistance to aminoglycosides, among the gut flora from patients receiving SDD.[12] Investigational methods are emerging that have the potential to prevent nosocomial infections and minimize resistance emergence by maintaining the gut microbiome. Probiotic use in selected ICU populations has been shown to reduce ICU-acquired infections, including ventilator-associated pneumonia and *Clostridium difficile*–associated diarrhea.[13] Novel vaccines, monoclonal antibodies, and host immune-modulating therapies hold promise for future therapies aimed at the prevention and treatment of infections in ICU patients while exerting minimal microbiome effects on the host.[14] Moving forward, in conjunction with the development of novel antibiotics, alternative nonantibiotic strategies for the prevention and treatment of serious infections should be pursued to optimize the balance in favor of both patient outcomes and antimicrobial stewardship.

The investigation by Oostdijk et al represents another important study performed by expert investigators and aimed at determining the optimal use of topical antibiotic prophylaxis for ICU patients with a specific focus on intestinal and oropharyngeal decontamination. Despite a large amount of research in this area, clinicians are still unclear on the optimal use of SDD and SOD. For the time being in the United States, SOD seems to be a more reasonable approach for the prevention of pathogenic bacterial overgrowth in critically ill patients. The use of SDD in the United States should probably be avoided until multicenter studies demonstrate the overall efficacy of SDD in hospitals with more widespread background antibiotic resistance.

ARTICLE INFORMATION

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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

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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.

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Editorial

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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.

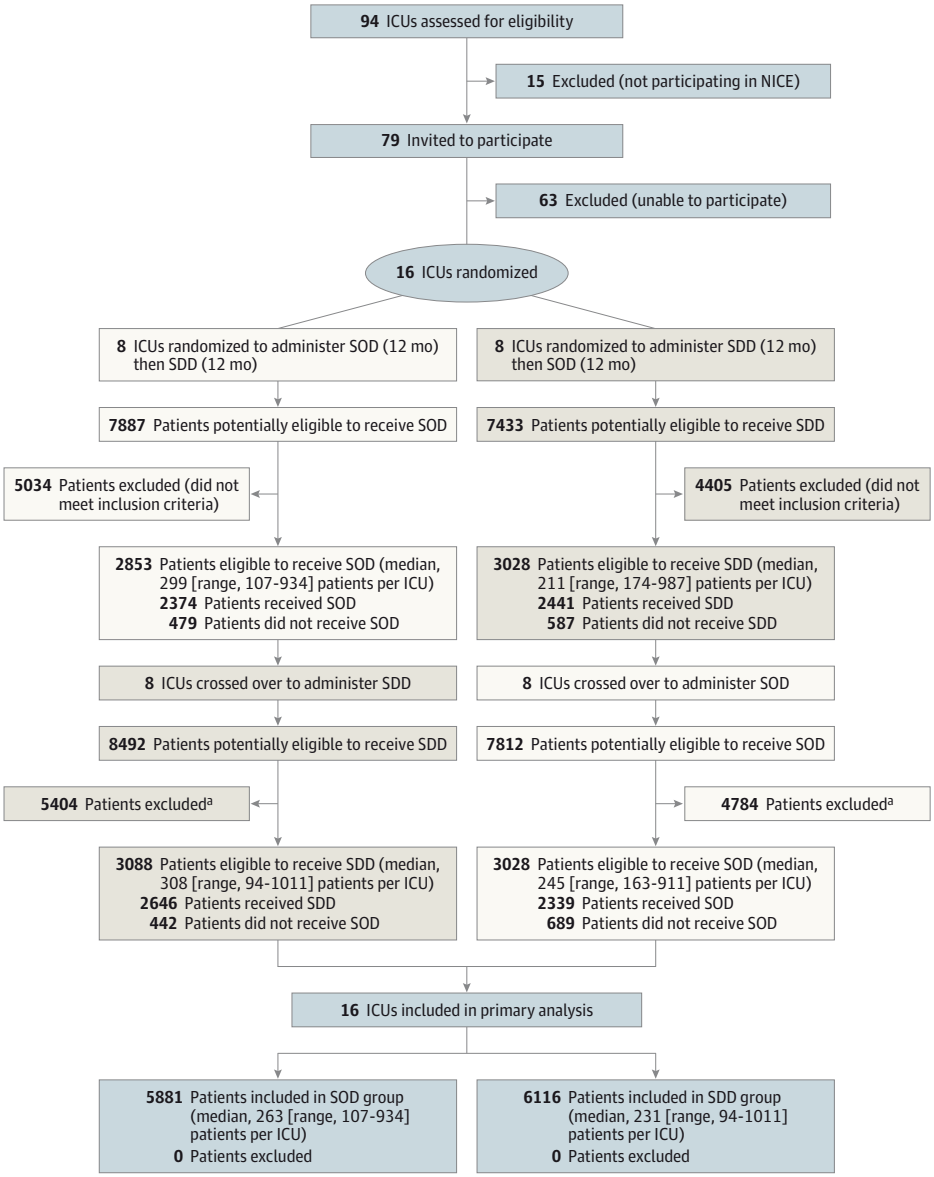
The SDD and SOD regimens have been described[2,3] and consisted of oropharyngeal application (every 6 hours) of a paste containing colistin, tobramycin, and amphotericin B, each in a 2% concentration (in patients receiving SDD and SOD), and administration (every 6 hours) of a 10-mL suspension containing 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			
	SOD (n = 5442)	SDD (n = 5549)	OR, SDD vs SOD (95% CI)	*P* Value
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

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