EDITORIAL

Decontamination of Oral or Digestive Tract for Patients in the Intensive Care Unit

Christina M. J. E. Vandenbroucke-Grauls, MD, PhD; Jos W. M. van der Meer, MD, PhD

The study by Wittekamp and colleagues[1] in this issue of *JAMA* evaluating strategies for decontamination of mechanically ventilated patients in the intensive care unit (ICU) fills an important gap in the evidence regarding these practices. Since the first use of selective decontamination of the digestive tract (SDD) in critically ill patients in the 1980s, the effectiveness of this approach to prevent ICU-acquired infections and reduce ICU-related mortality has been a continuous source of debate. In addition, the use of SDD or selective oropharyngeal decontamination (SOD) entails the continuous use of antibiotics among patients who do not have bacterial infections, thereby raising concerns about the possible development of antibiotic resistance.

Related article

The principle behind SDD is that by reducing the numbers of potentially pathogenic bacteria in the gut, many ICU-acquired infections can be prevented. Initial trials showed a reduction in infections but failed to demonstrate an effect on mortality. Many years and many more trials were needed before a beneficial effect on mortality was demonstrated in 2 trials conducted in the Netherlands in 2003 and 2009.[2-6] Since the publication of the study in 2009, the use of SDD or SOD (this variant includes only oral decontamination) has been included in ICU guidelines and antimicrobial use guidelines in the Netherlands,[7] and nearly 60% of Dutch ICUs now routinely use 1 of the 2 regimens.[7-9]

Outside the Netherlands, SDD and SOD have never been broadly implemented in Europe: these regimens are used in approximately 10% of European ICUs.[9] In the United States, a recent survey among infection preventionists in a random sample of 571 nonfederal hospitals suggested that approximately 80% of ICUs in the United States use antiseptic mouthwash (not specified) and 25% use topical and/or systemic antibiotics for SDD or SOD.[10] Reasons for the lower use of decontamination strategies outside the Netherlands are uncertainties about effectiveness in reducing mortality and about safety with respect to the development of antimicrobial resistance. These concerns are especially relevant to countries with higher antibiotic resistance rates than the Netherlands, the country with the lowest resistance rates of Europe, as SDD and SOD might have different effects in different resistance environments.[9,11]

The trial by Wittekamp et al[1] was undertaken to address these concerns. The authors compared a modified version of SDD (with oral nonabsorbable antimicrobial agents, but without a 4-day course of intravenous third-generation cephalosporins), SOD, and a regimen of oral washing with chlorhexidine (CHX mouthwash). The rate of ICU-acquired bloodstream infections with multidrug resistant gram- negative bacteria (MDRGNB) was the primary end point and mortality was the secondary end point. The trial involved 8665 patients in 13 ICUs in 6 different countries. After a baseline period, the 3 regimens were applied during consecutive time periods of 6 months in random order per ICU.

The authors found that ICU-acquired bloodstream infection with MDRGNB occurred in 2.1%, 1.8%, 1.5%, and 1.2% of included patients during the baseline, CHX, SOD, and SDD periods, respectively, with absolute risk reductions of 0.3% (95% CI, −0.6% to 1.1%) for CHX, 0.6% (95% CI, −0.2% to 1.4%) for SOD, and 0.8% (95% CI, 0.1% to 1.6%) for SDD compared with baseline rates. Adjusted hazard ratios were 1.13 (95% CI, 0.68-1.88), 0.89 (95% CI, 0.55-1.45), and 0.70 (95% CI, 0.43-1.14) during CHX, SOD, and SDD vs baseline, respectively. Crude mortality risks on day 28 were 31.9% during baseline and 32.9%, 32.4%, and 34.1% during the CHX, SOD, and SDD periods, respectively. Adjusted odds ratios for 28-day mortality were 1.07 (95% CI, 0.86-1.32), 1.05 (95% CI, 0.85-1.29), and 1.03 (95% CI, 0.80-1.32) for CHX, SOD, and SDD vs baseline, respectively. In addition, there was no significant difference in the unit-wide prevalence of carriage of antibiotic-resistant bacteria between the intervention periods compared with baseline prevalence.

Based on these findings, the authors concluded that "Among patients receiving mechanical ventilation in ICUs with moderate to high antibiotic resistance prevalence, use of CHX mouthwash, SOD, or SDD was not associated with reductions in ICU-acquired bloodstream infections caused by multidrug-resistant gram-negative bacteria compared with standard care."[1] However, several important factors need to be carefully considered in the interpretation of these findings.

Wittekamp et al[1] conducted a complicated study that involved ICUs in several different European countries. The ethical issues must have been numerous and challenging, and the logistics of the study must have been arduous. It is therefore somewhat unfortunate that the authors used an historical baseline period to compare the outcomes associated with the different regimens. Trials with historical control groups have become less common because of

the possible bias and uncertainty about differences in care practices and patient populations between baseline and study periods. Such studies tend to favor the experimental treatment; even so, the decontamination regimens failed to show a positive association with reductions in bloodstream infections or mortality. One possibility is that in this trial, SDD failed because the 4-day course of intravenous third-generation cephalosporins that is always used with SDD in the Netherlands was omitted, but, as stated by the authors, SOD also failed, which worked in the Netherlands, but never includes prophylaxis with intravenous cephalosporins. The authors also performed a secondary analysis excluding all bloodstream infections with third-generation cephalosporin-sensitive bacteria that did occur in the SDD treatment period. This analysis did not show any benefit of SDD compared with the baseline period.

The question remains why SDD and SOD seem to have positive effects on infections and mortality in Dutch ICUs and not in ICUs in other European countries. Wittekamp et al[1] propose that the high rates of resistance to third-generation cephalosporins, rates that are approximately 3 times greater than those that are observed in Dutch ICUs (25% vs 6%),[1,12] and the higher frequency of infections with other highly resistant microorganisms preclude a positive effect of SDD and SOD. On the other hand, resistance rates to aminoglycosides and colistin (the drugs used for digestive or oral decontamination) are reported as being the same in European ICUs as in the Netherlands.[13] The answer to this question therefore remains elusive.

Another aim of the study was to determine whether the use of SDD, SOD, or CHX affected resistance rates or use of systemic antibiotics. Resistance rates were determined by monthly prevalence measurements of resistant bacteria found in surveillance cultures of rectal and respiratory specimens of all patients in the ICU, that is, not only of patients receiving SDD, SOD, or CHX, but also of all other patients present in the unit at that moment. It is not easy to interpret the results presented (in Table 5 in the article) because these are the mean of monthly prevalence measurements (eg, 6 measurements) in 13 ICUs. Because these numbers are aggregated over 6-month periods, it is not possible to determine whether there was any trend in resistance rates.

Detection of changes in antibiotic resistance between regimens and over time is subject to several problems. First and most important is the time scale. A 6-month period is probably too short to observe changes. A definitive study should last at least several years before providing a more accurate answer.[14] Also, changes in resistance might only be detected after discontinuation of SDD once the patients leave the ICU, eg, in the hospital where the ICU is located, or in patients' digestive tract weeks after being discharged. Second, respiratory specimens from patients receiving SDD or SOD, and rectal specimens from patients receiving SDD, are impregnated with antibiotics. Because the doses used in this study were high, it is probable that this dosage inhibited growth of bacteria, even of those with moderate or no clinically meaningful susceptibility to these antibiotics. Therefore, negative culture results do not guarantee that no clinically resistant bacteria are present. Third, colistin resistance, which was also assessed in this study, is difficult to detect.[15] In the present study, colistin resistance was monitored by an automated system (see eTable 10 in the supplementary material) that has been shown to have a high rate of failure in the detection of colistin resistance.[16]

The study by Wittekamp et al[1] contributes important data to the decades-long debate about the use of decontamination strategies to prevent bloodstream infections and mortality in critically ill patients. It shows no benefits in situations with higher antibiotic resistance patterns that unfortunately still prevail in most ICUs around the world.

ARTICLE INFORMATION

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REFERENCES

1. Wittekamp BH, Plantinga NL, Cooper BS, et al. Decontamination strategies and bloodstream infections with antibiotic-resistant microorganisms in ventilated patients: a randomized clinical trial [published online October 22, 2018]. *JAMA*. doi:10.1001/jama.2018.13765

2. Vandenbroucke-Grauls CM, Vandenbroucke JP. Effect of selective decontamination of the digestive tract on respiratory tract infections and mortality in the intensive care unit. *Lancet*. 1991;338(8771):859-862. doi:10.1016/0140-6736(91)91510-2

3. Selective Decontamination of the Digestive Tract Trialists' Collaborative Group. Meta-analysis of randomised controlled trials of selective decontamination of the digestive tract: Selective Decontamination of the Digestive Tract Trialists' Collaborative Group. *BMJ*. 1993;307(6903):525-532. doi:10.1136/bmj.307.6903.525

4. van Nieuwenhoven CA, Buskens E, van Tiel FH, Bonten MJ. Relationship between methodological trial quality and the effects of selective digestive decontamination on pneumonia and mortality in critically ill patients. *JAMA*. 2001;286(3):335-340. doi:10.1001/jama.286.3.335

5. 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. doi:10.1016/S0140-6736(03)14409-1

6. 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. doi:10.1056/NEJMoa0800394

7. Nederlandse Vereniging voor Intensive Care (Dutch Society for Intensive Care). SWAB Richtlijn: selectieve decontaminatie bij patienten op de intensive care (2014). https://nvic.nl/richtlijnen/swab-richtlijn-selectieve-decontaminatie-bij-patienten-op-de-intensive-care-2014 Accessed September 10, 2018.

8. Dutch Working Party on Antibiotic Policy. Guidelines. https://www.swab.nl/guidelines Accessed September 10, 2018.

9. Reis Miranda D, Citerio G, Perner A, et al. Use of selective digestive tract decontamination in

European intensive cares: the ifs and whys. *Minerva Anestesiol*. 2015;81(7):734-742.

10. Krein SL, Greene MT, Apisarnthanarak A, et al. Infection prevention practices in Japan, Thailand, and the United States: results from national surveys. *Clin Infect Dis*. 2017;64(suppl_2):S105-S111. doi:10.1093/cid/cix073

11. Duncan EM, Cuthbertson BH, Prior ME, et al; SuDDICU International Study Group. The views of health care professionals about selective decontamination of the digestive tract: an international, theoretically informed interview study. *J Crit Care*. 2014;29(4):634-640. doi:10.1016/j.jcrc.2014.03.013

12. Oostdijk EAN, Kesecioglu J, Schultz MJ, et al. Notice of retraction and replacement: Oostdijk et al. effects of decontamination of the oropharynx and intestinal tract on antibiotic resistance in ICUs: a randomized clinical trial. JAMA. 2014;312(14):1429-1437. *JAMA*. 2017;317(15):1583-1584. doi:10.1001/jama.2017.1282

13. Surveillance of Antimicrobial Resistance in Europe. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2016. https://ecdc.europa.eu/sites/portal/files/documents/AMR-surveillance-Europe-2016.pdf. Accessed September 26, 2018.

14. 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. doi:10.1016/S1473-3099(12)70322-5

15. European Committee on Antimicrobial Susceptibility Testing. EUCAST warnings concerning antimicrobial susceptibility testing products or procedures. http://www.eucast.org/ast_of_bacteria/warnings/#c13111 Accessed September 10, 2018.

16. Jayol A, Nordmann P, Lehours P, Poirel L, Dubois V. Comparison of methods for detection of plasmid-mediated and chromosomally encoded colistin resistance in Enterobacteriaceae. *Clin Microbiol Infect*. 2018;24(2):175-179. doi:10.1016/j.cmi.2017.06.002

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Decontamination Strategies and Bloodstream Infections With Antibiotic-Resistant Microorganisms in Ventilated Patients
A Randomized Clinical Trial

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IMPORTANCE The effects of chlorhexidine (CHX) mouthwash, selective oropharyngeal decontamination (SOD), and selective digestive tract decontamination (SDD) on patient outcomes in ICUs with moderate to high levels of antibiotic resistance are unknown.

OBJECTIVE To determine associations between CHX 2%, SOD, and SDD and the occurrence of ICU-acquired bloodstream infections with multidrug-resistant gram-negative bacteria (MDRGNB) and 28-day mortality in ICUs with moderate to high levels of antibiotic resistance.

DESIGN, SETTING, AND PARTICIPANTS Randomized trial conducted from December 1, 2013, to May 31, 2017, in 13 European ICUs where at least 5% of bloodstream infections are caused by extended-spectrum β-lactamase–producing Enterobacteriaceae. Patients with anticipated mechanical ventilation of more than 24 hours were eligible. The final date of follow-up was September 20, 2017.

INTERVENTIONS Standard care was daily CHX 2% body washings and a hand hygiene improvement program. Following a baseline period from 6 to 14 months, each ICU was assigned in random order to 3 separate 6-month intervention periods with either CHX 2% mouthwash, SOD (mouthpaste with colistin, tobramycin, and nystatin), or SDD (the same mouthpaste and gastrointestinal suspension with the same antibiotics), all applied 4 times daily.

MAIN OUTCOMES AND MEASURES The occurrence of ICU-acquired bloodstream infection with MDRGNB (primary outcome) and 28-day mortality (secondary outcome) during each intervention period compared with the baseline period.

RESULTS A total of 8665 patients (median age, 64.1 years; 5561 men [64.2%]) were included in the study (2251, 2108, 2224, and 2082 in the baseline, CHX, SOD, and SDD periods, respectively). ICU-acquired bloodstream infection with MDRGNB occurred among 144 patients (154 episodes) in 2.1%, 1.8%, 1.5%, and 1.2% of included patients during the baseline, CHX, SOD, and SDD periods, respectively. Absolute risk reductions were 0.3% (95% CI, −0.6% to 1.1%), 0.6% (95% CI, −0.2% to 1.4%), and 0.8% (95% CI, 0.1% to 1.6%) for CHX, SOD, and SDD, respectively, compared with baseline. Adjusted hazard ratios were 1.13 (95% CI, 0.68-1.88), 0.89 (95% CI, 0.55-1.45), and 0.70 (95% CI, 0.43-1.14) during the CHX, SOD, and SDD periods, respectively, vs baseline. Crude mortality risks on day 28 were 31.9%, 32.9%, 32.4%, and 34.1% during the baseline, CHX, SOD, and SDD periods, respectively. Adjusted odds ratios for 28-day mortality were 1.07 (95% CI, 0.86-1.32), 1.05 (95% CI, 0.85-1.29), and 1.03 (95% CI, 0.80-1.32) for CHX, SOD, and SDD, respectively, vs baseline.

CONCLUSIONS AND RELEVANCE Among patients receiving mechanical ventilation in ICUs with moderate to high antibiotic resistance prevalence, use of CHX mouthwash, SOD, or SDD was not associated with reductions in ICU-acquired bloodstream infections caused by MDRGNB compared with standard care.

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Visual Abstract

Editorial

Supplemental content

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Care of patients in intensive care units (ICUs) is frequently complicated by infections, which are associated with increased morbidity, mortality, and health care costs.[1,2] Selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) consist of topical antimicrobial agents targeting aerobic gram-negative pathogens, *Staphylococcus aureus*, and yeasts in the gastrointestinal tract (SDD) and oropharynx (SDD/SOD), and they aim to prevent infections. In ICUs with low levels of antibiotic resistance, SDD and SOD have been associated with improved patient outcomes,[3,4] with SDD being more efficacious than SOD.[5,6] Currently, SDD and SOD are routinely used in ICUs in the Netherlands, but their use has not been widely adopted in other countries,[7] mainly because of limited efficacy data in settings with higher levels of antibiotic resistance and concern about emergence of antibiotic resistance, although the latter is not supported by meta-analyses.[8] In contrast, chlorhexidine (CHX) mouthwash is widely used in ICU patients and its use has been associated with a lower incidence of ventilator-associated pneumonia,[9,10] with CHX 2% being more efficacious than lower concentrations.[9] Yet, in meta-analyses, CHX mouthwash was associated with higher mortality in ICU patients.[11,12] SDD and SOD have never been compared head to head with CHX mouthwash in ICU patients.

Given the equipoise on the effectiveness and ecological safety of these decontamination strategies in ICUs with moderate to high levels of antibiotic resistance, a randomized trial was conducted in 6 European countries to quantify the association between CHX mouthwash, SOD, and SDD and ICU-acquired bloodstream infections (BSIs) with multidrug-resistant gram-negative bacteria (MDRGNB), patient mortality, and unitwide prevalence of antibiotic resistance.

Key Points

Question Is use of chlorhexidine 2% mouthwash, selective oropharyngeal decontamination (SOD), or selective digestive tract decontamination (SDD) associated with reduced risk of bloodstream infections due to multidrug-resistant gram-negative bacteria among ventilated patients in intensive care units (ICUs) with moderate to high prevalence of antibiotic resistance?

Findings In this randomized trial of 8665 patients, the use of chlorhexidine 1% mouthwash, SOD, or SDD was not associated with significant differences in ICU-acquired bloodstream infections with multidrug-resistant gram-negative bacteria (adjusted hazard ratios, 1.13, 0.89, and 0.70, respectively), compared with a baseline period of chlorhexidine body washing and a hand hygiene improvement program.

Meaning Among ventilated patients in ICUs with moderate to high prevalence of antibiotic resistance, use of chlorhexidine 1% mouthwash, SOD, or SDD was not associated with a significant difference in bloodstream infections with multidrug-resistant gram-negative bacteria compared with standard care.

Methods

Study Design

A nonblinded multicenter trial with cluster randomization and crossover of interventions was conducted in 13 ICUs from Belgium, Spain, Portugal, Italy, Slovenia, and the United Kingdom between December 1, 2013, and May 31, 2017. The full trial protocol and statistical analysis plans are in Supplement 1. The characteristics of the participating centers are in eTable 1 in Supplement 2. Institutional review board approval for data collection was obtained prior to study start, and, where required, national regulatory authorities approved the study protocol prior to randomization of interventions. All hospitals obtained a waiver for individual patient informed consent because interventions aimed to achieve ward-level ecologic effects (and patient-based randomization might lead to contamination of effects) and interventions were considered to have minimal risks of harm.

Only ICUs with an extended-spectrum β-lactamase prevalence of at least 5% among Enterobacteriacea-causing BSI were eligible (study protocol in Supplement 1). ICUs with endemic levels of carbapenem-resistant Enterobacteriaceae, multidrug-resistant *Pseudomonas* or *Acinetobacter* species or with vancomycin-resistant enterococci (all defined as >10% of ICU-acquired bacteremia with that species) were excluded from participation.

All hospitals started with a baseline period of at least 6 months, which included daily CHX-digluconate 2% body washing (CHX-BW) for all ICU patients until ICU discharge and implementation of the World Health Organization hand hygiene program, including weekly observations.[13] CHX mouthwash (0.12% or 0.20%) was allowed as part of standard care if this was part of regular care before the study. Universal CHX-BW and monitoring of hand hygiene continued throughout the 3 following intervention periods. After the baseline period, the 3 study interventions (CHX mouthwash, SOD, and SDD) were implemented in a sequential computer-generated randomized order in each participating center. Randomization of the order of interventions aimed to reduce effects of changes in time in antibiotic resistance or clinical practice that might affect study outcomes. All study periods were intended to last 6 months and were separated by a 1-month washout/in period.

Patients

Patients with an expected duration of invasive mechanical ventilation of at least 24 hours were eligible. Exclusion criteria included age younger than 18 years, pregnancy, and allergy to any study intervention component. Eligible patients admitted during the first 2 weeks of the washout/in period received the new intervention but were not part of the study population; patients admitted during the second 2 weeks received the new intervention and were analyzed as such.

Interventions

CHX 2% mouthwash, SOD, and SDD were manufactured by the pharmacy of the University Medical Center Utrecht, the Netherlands. CHX 2% mouthwash was replaced by CHX 1% oral gel in March 2015 after the reporting of oral mucosal adverse effects in 29 of 295 patients (9.8%) treated in 2

hospitals.[14] The oropharyngeal paste used during SOD and SDD contained 0.19 million units of colistin sulfate, 10 mg of tobramycin sulfate, and 0.1 million units of nystatin per dosage (0.5 g) and the gastrointestinal suspension contained 1.9 million units of colistin sulfate, 80 mg of tobramycin sulfate, and 2.0 million units of nystatin per dosage (10 mL through nasogastric tube). Although the SDD regimen, where used routinely (eg, the Netherlands),[3-5] usually includes a 4-day course of intravenous cephalosporin, prophylactic use of these antibiotics was not considered appropriate in settings with a moderate to high prevalence of antibiotic resistance, and was therefore not part of the study protocol. CHX mouthwash, SOD, and SDD were initiated after study inclusion and applied 4 times daily after regular oral care until mechanical ventilation was stopped. Adherence to decontamination strategies was monitored with monthly adherence measurements and recording of interruptions in individual patients.

Rectum and respiratory surveillance samples (endotracheal aspirate, when possible, or throat swabs) were obtained twice weekly from study patients, and once monthly from all patients present in the unit on that day for point prevalence surveys. Microbiology methods are described in eAppendix 1 in Supplement 2. A safety committee consisting of 3 independent experts reviewed the results of monthly point prevalence samples at 3-month intervals, but not clinical outcomes. The committee members were blinded to the interventions applied and could recommend interruption of the study in a participating ICU if an increase in antibiotic resistance was apparent.

Outcomes

The primary outcome was the incidence of ICU-acquired BSI with MDRGNB in study patients during use of CHX, SOD, or SDD compared with standard care. Secondary outcomes were ICU-acquired BSI with highly resistant microorganism (HRMO), defined as MDRGNB or methicillin-resistant *S aureus* or vancomycin-resistant enterococci; mortality at day 28 from ICU admission, at ICU discharge, and at hospital discharge (all prespecified); and ICU-acquired BSI with any pathogen (post hoc). Other secondary outcomes are subject to future analyses and not reported in this article: cross-transmission rates of MDRGNB, the occurrence of ICU-acquired rectum and respiratory tract MDRGNB colonization, and associations between colonization and BSI. Ward-level exploratory outcomes included the unitwide prevalence of HRMO measured by monthly point prevalence surveys of the rectum and respiratory tract of all patients in the ICU to monitor ecologic safety, and the unitwide use of systemic antibiotics (descriptive analyses), expressed as defined daily doses per patient day. As a post hoc exploratory analysis, carriage rates with antibiotic-resistant GNB in the rectum and respiratory tract were determined based on the results of surveillance cultures plated on extended-spectrum β-lactamase selective media and obtained twice weekly from study patients.

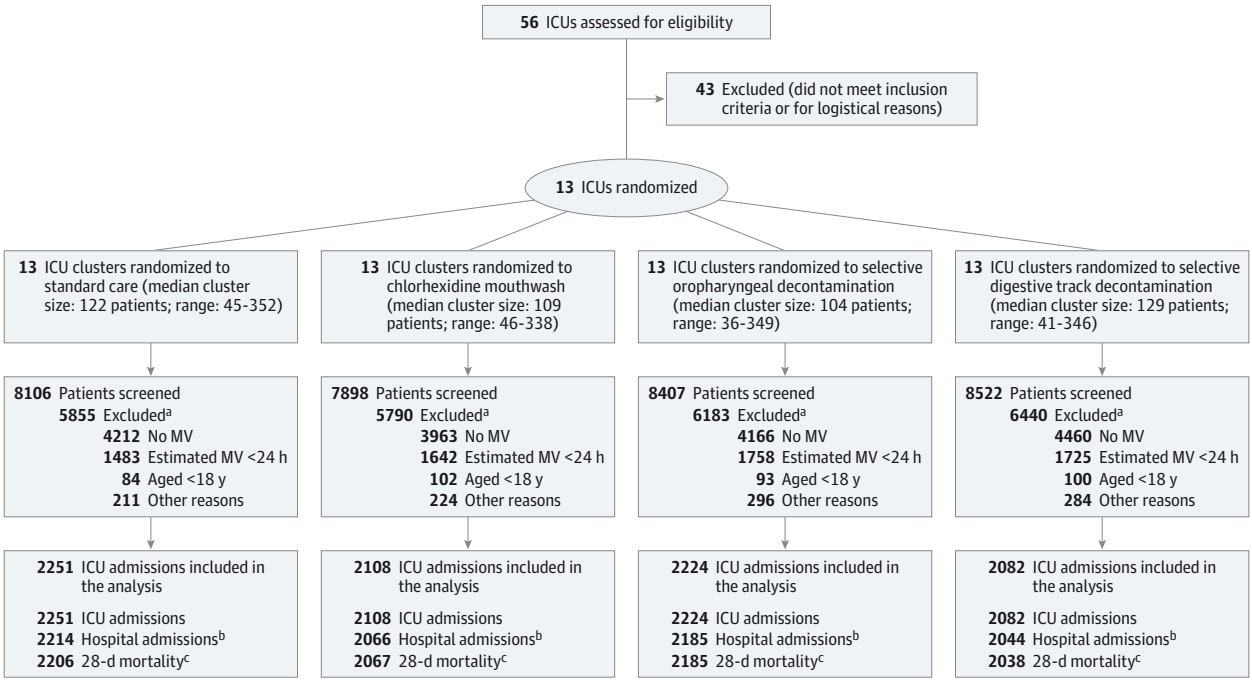
ICU-acquired BSI was defined as bacteremia or candidemia diagnosed from day 2 of ICU stay onwards, with the initial day of ICU admission being designated as day 0. Only the first episode per patient was used in the analyses. Microorganisms excluded from the definition of BSI are listed in eTable 2 in Supplement 2. Definitions of MDRGNB and HRMO are listed in eTable 3 in Supplement 2 and mainly include Enterobacteriaceae resistant to third-generation cephalosporins and GNB resistant to carbapenems, colistin, or 3 or more antibiotics.[15]

Sample Size and Statistical Analyses

To determine the effects of CHX, SOD, and SDD as if these were implemented in ICUs in addition to standard care, each intervention was compared with standard care (baseline period) for all outcomes. Study funding was obtained from a grant call that specifically asked for evaluation of interventions in ICUs that could reduce the incidence of ICU-acquired BSI with MDRGNB. We, therefore, used this as the primary outcome, but based the sample size calculation on 28-day mortality, considered to be a more clinically relevant outcome. A 10% (relative) reduction in 28-day mortality and a 50% relative reduction in the incidence of ICU-acquired MDRGNB BSI were considered clinically relevant.[4] To demonstrate a 10% relative difference in 28-day mortality for each intervention compared with baseline, 10 800 patients were required (using a baseline 28-day mortality of 27.5%; $\alpha = .05$; 80% power), including a margin of 600 patients per study arm to include cluster effects and differences in baseline characteristics. However, an error in the calculation of variance between study groups was discovered after study completion, which had led to lower patient numbers than required for the power of 80%. Details of the sample size calculation are in eAppendix 2 in Supplement 2.

Three cohorts were created for the analyses of clinical outcomes: unique ICU admissions for ICU mortality and ICU-acquired BSI (with MDRGNB, HRMO, and any pathogen), unique hospital admissions for hospital mortality, and unique ICU admissions with no prior ICU admission within 30 days for 28-day mortality (**Figure**). All analyses were performed on cases without missing covariates or outcomes. To adjust for differences in patient characteristics between study periods, propensity scores were calculated using generalized boosted methods,[16] and inverse probability weighting was used to balance the distribution of the confounders center, age, sex, Charlson Comorbidity Index score,[17] disease severity, admission type (medical or surgical), antibiotic use on ICU admission, and location before ICU admission (same hospital, other hospital or long-term care facility, or home). Because ICUs used different disease severity scoring systems, separate propensity score models were made for ICUs using either Acute Physiology and Chronic Health Evaluation (APACHE) II or Simplified Acute Physiology Score (SAPS II) scores, and the derivative weights used in the final models. ICU-acquired BSI and ICU and hospital mortality were analyzed with Cox-proportional hazard analyses stratified for center, with discharge and death as competing events where applicable. The Schoenefeld Goodness of Fit test was used to test the proportionality assumption and there was no evidence to reject the proportional hazard assumption at 5% significance level.

Figure. Flowchart and Cohorts for Analyses



Abbreviations: ICU, intensive care unit; MV, mechanical ventilation.

[a] Some patients had multiple reasons for exclusion.

[b] The cohort for hospital mortality included 8509 unique hospital admissions, 37 with missing hospital mortality status.

[c] The cohort for 28-day mortality included 8496 unique ICU admissions with no prior ICU admission within 30 days, 56 with missing 28-day mortality status.

For the analysis of 28-day mortality, a mixed-effects logistic regression model was used with a fixed effect for center and a random effect for the 52 center-period combinations (4 period orders [A-B-C-D] × 13 ICUs). All models were adjusted for the confounders and mean hand hygiene compliance per study period per center. A sensitivity analysis was performed on the mortality outcomes excluding patients who stayed fewer than 3 days in the ICU because they might have been overrepresented in the baseline period. Based on the study findings, an additional post hoc sensitivity analysis was performed to explore potential consequences of not including prophylaxis with third-generation cephalosporins in the SDD regimen and of stopping SDD at the end of mechanical ventilation (rather than at ICU discharge), as had been performed in previous Dutch studies.[3-5] In this analysis, all SDD-treated patients with ICU-acquired BSI caused by a pathogen susceptible to third-generation cephalosporins during the first 4 days and/or with ICU-acquired BSI with any pathogen after the end of mechanical ventilation were considered alive for all mortality outcomes, thereby maximizing the potentially missed effects of both changes to previous protocols. As a third post hoc sensitivity analysis, head-to-head comparisons between the randomized intervention groups were performed for all patient-level outcomes.

The unitwide prevalence of HRMO carriage based on point prevalence surveys was analyzed separately for rectum and respiratory tract, with binomial models (log link) for each outcome; these specific models included correction for underlying time trends per ICU and estimated a mean time trend per study period (as an exploratory analysis). Because the potential for type I error due to multiple comparisons was not addressed, secondary analyses were considered exploratory.

A 2-sided significance level of .05 was used for all analyses. SPSS (IBM, version 21) and R software, version 3.3.2 (R Project for Statistical Computing) were used for data preparation and statistical analyses, respectively.

Results

Between December 1, 2013, and May 31, 2017, 32 933 ICU admissions were screened, of which 8665 were included, yielding 8509 unique hospital admissions and 8496 inclusions for 28-day mortality (Figure; see eTable 4 in Supplement 2 for baseline characteristics of screened patients). The median durations of study periods were 6 months (range, 6-14.5) for baseline and 6 (range, 4.6-6), 6 (range, 5-8.5), and 6 (range 5-7) months for the CHX, SOD, and SDD periods, respectively (**Table 1**). Proportions of BSI caused by HRMO and Enterobacteriaceae resistant to third-generation cephalosporins, both among all BSI episodes, were 25.5% and 15.1%, respectively. Per study period, 26.7% to 29.7% of screened patients were eligible and 91% to 94% of these patients were enrolled. Of the 8665 included patients, 5561 were male

Table 1. Baseline Characteristics of the Study Population

Characteristic	No. (%) Baseline (n = 2251)	CHX (n = 2108)	SOD (n = 2224)	SDD (n = 2082)
Patient Characteristics				
Age, mean (SD), y	62.0 (15.6)	61.4 (15.7)	61.6 (15.7)	62.8 (15.5)
Sex				
Male	1420 (63.1)	1358 (64.4)	1439 (64.7)	1344 (64.6)
Female	831 (36.9)	750 (35.6)	785 (35.3)	738 (35.4)
APACHE II scores for 5 hospitals, mean (SD)[a]	20.3 (8.6)	19.8 (8.2)	20.5 (9.3)	21.8 (8.7)
SAPS II scores for 8 hospitals, mean (SD)[b]	53.0 (18.0)	54.8 (17.9)	54.4 (17.5)	55.0 (18.0)
Type of ICU admission				
Medical	1464 (65.3)	1323 (63.0)	1442 (64.9)	1385 (66.6)
Trauma with surgery	138 (6.2)	142 (6.8)	156 (7.0)	115 (5.5)
Trauma, no surgery	113 (5.0)	88 (4.2)	104 (4.7)	88 (4.2)
Surgical, scheduled	198 (8.8)	173 (8.2)	173 (7.8)	178 (8.6)
Surgical, unscheduled	328 (14.6)	374 (17.8)	346 (15.6)	314 (15.1)
Surgical, unspecified	10 (0.4)	8 (0.4)	3 (0.1)	2 (0.1)
Location before ICU admission				
Same hospital	1020 (45.3)	1032 (49.0)	1025 (46.1)	1035 (49.7)
Another hospital or long term care facility	400 (17.8)	312 (14.8)	316 (14.2)	301 (14.5)
Home (directly or via emergency department)	831 (36.9)	764 (36.2)	883 (39.7)	746 (35.8)
Antibiotic at the time of ICU admission	943 (41.9)	832 (39.5)	992 (44.6)	744 (35.8)
Sites of organ failure				
Respiratory illness	1023 (45.5)	990 (47.0)	998 (44.9)	985 (47.3)
Cardiovascular illness	828 (36.8)	811 (38.5)	835 (37.5)	792 (38.0)
Neurologic illness	686 (30.5)	674 (32.0)	615 (27.7)	603 (29.0)
Other illness (renal, hepatic, metabolic, hematologic, and/or other)	633 (28.1)	617 (29.3)	742 (33.4)	676 (32.5)
Charlson Comorbidity Index score, mean (SD)[c]	2.15 (2.42)	2.38 (2.49)	2.35 (2.42)	2.42 (2.56)
0	738 (32.8)	631 (29.9)	653 (29.4)	626 (30.1)
1-2	759 (33.7)	674 (32.0)	718 (32.3)	654 (31.4)
3-4	399 (17.7)	398 (18.9)	461 (20.7)	410 (19.7)
>4	355 (15.8)	405 (19.2)	392 (17.6)	392 (18.8)
ICU Characteristics (Type, No. of beds)[d]	**Order of Study Arms per ICU (Duration, mo) [No. of Study Patients][e]**			
ICU 1 (mixed, 36 beds)	A (6) [212]	B (5.6) [214][f]	C (6) [245]	D (6) [229]
ICU 9 (mixed, 42 beds)	A (6) [333]	B (6) [338]	C (5) [309][h]	D (6) [317]
ICU 2 (mixed, 24 beds)	A (6) [77]	B (4.6) [59][f]	D (6) [101]	C (6) [80]
ICU 11 (mixed, 8 beds)	A (9) [63][g]	B (6) [50]	D (6) [70]	C (5) [54][k]
ICU 5 (mixed, 30 beds)	A (6) [169]	C (6) [277]	B (8.5) [349][g]	D (6) [248]
ICU 12 (mixed, 22 beds)	A (8) [352][i]	C (6) [272]	B (6) [248]	D (6) [237]
ICU 4 (mixed, 42 beds)	A (6) [266]	C (6) [285]	D (6) [334]	B (7) [346][g]
ICU 7 (mixed, 10 beds)	A (14.5) [297][i]	C (6) [109]	D (6) [104]	B (6) [129]
ICU 8 (mixed, 15 beds)	A (6) [85]	D (6) [92]	B (6) [85]	C (6) [75]
ICU 3 (medical, 12 beds)	A (6) [45]	D (6) [46]	B (6) [36]	C (6) [41]
ICU 10 (medical, 24 beds)	A (8) [113][j]	D (6) [85]	C (6) [85]	B (6) [92]
ICU 6 (mixed, 12 beds)	A (6) [122]	D (6) [177]	C (3.5 + 2.5) [155][h]	B (6) [144]
ICU 13 (mixed, 9 beds)	A (7) [117][i]	D (6) [104]	C (6) [103]	B (6) [90]

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CHX, chlorhexidine mouthwash; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SDD, selective digestive tract decontamination; SOD, selective oropharyngeal decontamination.

[a] The APACHE II disease severity score ranges from 0 to 71, with higher scores indicating increased severity and an increased probability of in-hospital death. A patient with an APACHE II score of 20 would have an estimated probability of in-hospital death ranging from 6.3% to 71%, depending on the reason for ICU admission and the need for emergency surgery.[18]

[b] The SAPS II disease severity score ranges from 0 to 163, with higher scores indicating increased severity and an increased probability of in-hospital death. A patient with a SAPS II score of 52 would have an estimated probability of in-hospital death of 50%.[19]

[c] The Charlson Comorbidity Index ranges from ranges from 0 to 37, with higher scores associated with a higher probability of 1-year mortality.[17]

[d] ICUs are numbered in in order of study start date (eTable 1 in Supplement 2).

[e] A, B, C, and D represent the first, second, third, and fourth study periods, respectively.

[f] Suspension of CHX 2% intervention period due to oromucosal adverse effects.

[g] Prolongation of study period, pending approval for the amendment for the switch from CHX 2% mouthwash to CHX 1% oral gel.

[h] Interruption of SOD period due to increase in antibiotic-resistant bacteria.

[i] Prolongation of baseline period, pending approval from the regulatory agencies for the introduction of study interventions.

[j] Prolongation of baseline period for local logistic reasons.

[k] Shortened study period for logistical reasons.

(64.2%) and their median age was 64.1 years (range, 18-98). Patient characteristics differing between baseline and intervention periods included the mean APACHE II and SAPS II scores and the proportion of patients receiving antibiotics at ICU admission (Table 1; eTable 5 in Supplement 2).

Among study patients, the mean proportions receiving decontamination according to protocol, determined by monthly compliance measurements, were 92.5%, 92.4%, and 94.2% during the CHX, SOD, and SDD periods, respectively (eTable 6 in Supplement 2). There were 23 ICU admissions with missing covariates and 1, 37, and 56 patients with a missing ICU, hospital, and 28-day mortality status, respectively. Average hand hygiene compliance was 64.1% during the baseline period and ranged from 72.2% to 72.5% during the intervention periods (eTable 7 in Supplement 2). Five ICUs used CHX 0.12% and 6 used 0.20% mouthwash as part of standard care. The intracluster correlation coefficient was 0.001.

Deviations From Study Protocol

The study was temporarily interrupted in 2 centers. In one center, an increased prevalence of colistin-resistant *Klebsiella pneumoniae* was identified by the safety committee, which led to the identification of a clonal outbreak after SOD had been used for 3.5 months. After a 7-month period of outbreak containment, SOD was reintroduced. In another center, the hospital infection control committee interrupted the study after SOD had been used for 5 months, pending evaluations of an increased prevalence of carbapenem-resistant Enterobacteriaceae. Further investigation revealed that the outbreak was polyclonal and occurring in multiple hospital wards simultaneously. After an interruption of 7 months, the next randomized study phase (being SDD) was introduced after institutional review board approval. During both interruptions, SOD was not applied and patients included in the intervals were not included in the analyses.

Adverse Events

CHX 2% mouthwash was replaced by CHX 1% oral gel after adverse events, mainly consisting of oromucosal lesions, recorded in a total of 29 (9.8%) of 295 patients treated with CHX 2% in the 2 centers that first implemented CHX 2%.[14] No serious adverse events were reported during the use of CHX 1%, SOD, and SDD.

ICU-Acquired BSIs

ICU-acquired BSI with MDRGNB (primary outcome) occurred in 144 patients (154 episodes), most frequently with *K pneumoniae* (n = 56), *Enterobacter cloacae* (n = 20), *Pseudomonas aeruginosa* (n = 17), and *Escherichia coli* (n = 15) (**Table 2**). These occurred in 2.1%, 1.8%, 1.5%, and 1.2% of the patients included in the baseline, CHX, SOD, and SDD periods, respectively. Absolute risk reductions were 0.3% (95% CI, −0.6% to 1.1%), 0.6% (95% CI, −0.2% to 1.4%), and 0.8% (95% CI, 0.1% to 1.6%) for CHX, SOD, and SDD, respectively, compared with the baseline period. Corresponding adjusted hazard ratios (aHRs) of ICU-acquired MDRGNB BSI, compared with baseline, were 1.13 (95% CI, 0.68 to 1.88), 0.89 (95% CI, 0.55 to 1.45), and 0.70 (95% CI, 0.43 - 1.14) during the CHX, SOD, and SDD periods, respectively (**Table 3**). Incidences per center can be found in eTable 8 in Supplement 2.

ICU-acquired BSI with HRMO occurred in 169 patients (182 episodes) (Table 2). Risks for ICU-acquired BSI with HRMO were 2.4%, 2.1%, 1.7%, and 1.6% during the baseline, CHX, SOD, and SDD periods, respectively. Absolute risk reductions were 0.3% (95% CI, −0.6% to 1.2%), 0.6% (95% CI, −0.2% to 1.5%), and 0.7% (95% CI, −0.1% to 1.6%) for CHX, SOD, and SDD, compared with baseline, respectively. Corresponding aHRs of HRMO BSI during study interventions, compared with baseline, were 1.07 (95% CI, 0.58 to 1.99), 0.83 (95% CI, 0.46 to 1.51), and 0.77 (0.38 to 1.52) during CHX, SOD, and SDD, respectively (Table 3).

Mortality

The risk rates for mortality on day 28 were 31.9%, 32.9%, 32.4%, and 34.1% during the baseline, CHX, SOD, and SDD periods, respectively. Absolute risk reductions were −1.1% (95% CI, −3.9% to 1.8%), −0.5% (95% CI, −3.3% to 2.3%), −2.2% (95% CI, −5.0% to 0.7%) for CHX, SOD, and SDD, respectively, compared with baseline. Corresponding adjusted odds ratios for 28-day mortality were 1.07 (95% CI, 0.86 to 1.32), 1.05 (95% CI, 0.85 to 1.29), and 1.03 (95% CI, 0.80 to 1.32) during CHX, SOD, and SDD, respectively (Table 3). The risk rates for ICU mortality were 30.7%, 31.5%, 30.8%, and 31.0% during the baseline, CHX, SOD, and SDD periods, respectively. Absolute risk reductions were −0.8% (95% CI, −3.6% to 1.9%), −0.1% (95% CI, −2.8% to 2.6%), and −0.3% (95% CI, −3.0% to 2.5%) for CHX, SOD, and SDD, respectively, compared with baseline. Corresponding aHRs were 1.03 (95% CI, 0.92 to 1.16), 1.00 (95% CI, 0.89 to 1.14), and 0.95 (95% CI, 0.81 to 1.11) during the CHX, SOD, and SDD periods, respectively. The risk rates for hospital mortality were 38.0%, 38.1%, 38.7%, and 40.3% during the baseline, CHX, SOD, and SDD periods, respectively. Absolute risk reductions were 0.0% (95% CI, −2.9% to 2.9%), −0.7% (95% CI, −3.5% to 2.2%), and −2.2% (95% CI, −5.2% to 0.7%) for CHX, SOD, and SDD, respectively, compared with baseline. Corresponding adjusted odds ratios were 0.97 (95% CI, 0.85-1.11), 1.00 (95% CI, 0.87-1.14), and 0.96 (95% CI, 0.82-1.12) during the CHX, SOD, and SDD periods, respectively.

Antibiotic Use and Resistance

The unitwide consumption of systemic antibiotics was 1.1, 1.0, 1.0, and 1.1 defined daily doses per patient day during the baseline, CHX, SOD, and SDD periods, respectively (eTable 9 in Supplement 2).

In total, 5536 respiratory and 5441 rectal samples were obtained from 5706 survey participants during 329-point prevalence surveys (**Table 4**; eTable 10 in Supplement 2). Completeness of susceptibility testing was greater than 95% (eTable 11 in Supplement 2). Based on the point prevalence surveys, the overall prevalence of carriage with MDRGNB ranged from 17.1% to 25.3% in rectum samples and of carriage with MDRGNB from 10.2% to 15.2% in respiratory tract samples, without statistically significant differences between study groups (**Table 5**). The prevalence of colistin resistance did not increase during the intervention periods (Table 5; eTables 10 and 12 in Supplement 2).

Table 2. ICU-Acquired Bloodstream Infections per Study Group

Study Group	Baseline (n = 2251)		CHX (n = 2108)		SOD (n = 2224)		SDD (n = 2082)	
	No. of Episodes	Proportion of BSI Episodes, %	No. of Episodes	Proportion of BSI Episodes,%	No. of Episodes	Proportion of BSI Episodes,%	No. of Episodes	Proportion of BSI Episodes,%
Primary Outcome: ICU-Acquired BSIs With Multidrug-Resistant Gram-Negative Bacteria (MDRGNB)[a,b]								
BSI with MDRGNB, No. of episodes, (No. of patients)	52 (47)		41 (38)		34 (33)		27 (26)	
Enterobacteriaceae	39	75.0	29	70.7	26	76.5	24	88.9
Resistant to third-generation cephalosporins	35		25		24		24	
Resistant to colistin	2		2		5		5	
Glucose nonfermenting gram-negative bacteria	9	17.3	10	24.4	5	14.7	3	11.1
Pseudomonas species	4		9		3		2	
Other glucose nonfermenting gram-negative bacteria[c]	4	7.7	2	4.9	3	8.8	0	0.0
Secondary Outcomes: ICU-Acquired BSIs With Highly Resistant Microorganisms (HRMOs)[a,d]								
BSI with HRMO, No. of episodes (No. of patients)	58 (53)		49 (44)[e]		40 (38)[e]		35 (34)	
MDRGNB, No. of episodes (No. of patients)	52 (47)	89.7	41 (38)	83.7	34 (33)	85.0	27 (26)	77.1
Highly resistant Gram-positive bacteria, No. of episodes (No. of patients)	6 (6)	10.3	8 (8)	16.3	6 (6)	15.0	8 (8)	22.9
Vancomycin-resistant enterococci	3		4		3		0	
Methicillin-resistant *Staphylococcus aureus*	3		4		3		8	
ICU-Acquired BSIs With Any Pathogen[a,f]								
BSI with any pathogen, No. of episodes (No. of patients)	199 (154)		201 (156)		172 (140)		141 (123)	
Enterobacteriaceae	99	49.7	90	44.8	77	44.8	51	36.2
Intrinsic colistin resistant	30		13		14		10	
Glucose nonfermenting gram-negative bacteria	31	15.6	19	9.5	20	11.6	15	10.6
Pseudomonas species	21		16		15		9	
Gram-positive bacteria	43	21.6	61	30.3	47	27.3	50	35.5
Enterococcus faecium/faecalis	27		32		34		32	
Staphylococcus aureus	13		25		12		17	
Yeasts	15	7.5	22	10.9	23	13.4	18	12.8
Other[g]	11	5.5	9	4.5	5	2.9	7	5.0

Abbreviations: BSI, bloodstream infection; CHX, chlorhexidine mouthwash; ICU, intensive care unit; SDD, selective digestive tract decontamination; SOD, selective oropharyngeal decontamination.

[a] BSI defined as first occurrence of unique species on day 2 of ICU stay onwards, with the initial day of ICU admission being designated as day 0. ICU-acquired BSIs with any pathogen was a post hoc outcome.

[b] In brief, MDRGNB include Enterobacteriaceae resistant to third-generation cephalosporins, gram-negative bacteria resistant to carbapenems, colistin, or 3 or more antibiotics from separate classes (complete definition in eTable 3 in Supplement 2).

[c] *Stenotrophomonas* spp, *Burkholderia* spp, and *Achromobacter* spp.

[d] HRMOs include MDRGNB, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococci (complete definition in eTable 3 in Supplement 2).

[e] Two patients in the CHX period and 1 patient in the SOD period had a BSI both with MDRGNB and gram-positive HRMO.

[f] Excluding coagulase-negative *Staphylococcus*, *Micrococcus*, and *Clostridium* species and nonpneumococcal Streptococci (eTable 2 in Supplement 2), also including HRMO.

[g] These included BSI with *Bacteroides* spp (18), *Parabacteroides* spp (2), *Haemophilus influenzae* (3), and *Streptococcus pneumoniae* (9).

Table 3. Associations Between Interventions and ICU-Acquired BSI and Patient Mortality

	Crude Analyses				Adjusted Analyses, Adjusted Hazard Ratio (95% CI)[a]		
	Baseline (n = 2251)	CHX (n = 2108)	SOD (n = 2224)	SDD (n = 2082)	CHX vs Baseline	SOD vs Baseline	SDD vs Baseline
Primary Outcome							
Patients with ICU-acquired BSI with MDRGNB							
Incidence, No. (%)	47 (2.1)	38 (1.8)	33 (1.5)	26 (1.2)			
Absolute risk reduction vs baseline, % (95% CI)		0.3 (−0.6 to 1.1)	0.6 (−0.2 to 1.4)	0.8 (0.1 to 1.6)			
Rate (per 1000 patient days at risk)	1.62	1.34	1.14	0.94	1.13 (0.68 to 1.88)	0.89 (0.55 to 1.45)	0.70 (0.43 to 1.14)
Secondary Outcomes							
Patients with ICU-acquired BSI with HRMO[b]							
Incidence, No. (%)	53 (2.4)	44 (2.1)	38 (1.7)	34 (1.6)			
Absolute risk reduction vs baseline, % (95% CI)		0.3 (−0.6 to 1.2)	0.6 (−0.2 to 1.5)	0.7 (−0.1 to 1.6)			
Rate (per 1000 patient days at risk)	1.84	1.56	1.32	1.24	1.07 (0.58 to 1.99)	0.83 (0.46 to 1.51)	0.77 (0.38 to 1.52)
Patients with ICU-acquired BSI (any pathogen)							
Incidence, No. (%)	154 (6.8)	156 (7.4)	140 (6.3)	123 (5.9)			
Absolute risk reduction vs baseline, % (95% CI)		−0.6 (−2.1 to 1.0)	0.5 (−0.9 to 2.0)	0.9 (−0.5 to 2.4)			
Rate (per 1000 patient days at risk)	5.69	5.95	5.12	4.67	1.08 (0.85 to 1.39)	0.94 (0.76 to 1.17)	0.79 (0.60 to 1.05)
Mortality in ICU[c]							
Incidence, no./No. (%)	691/2251 (30.7)	664/2107 (31.5)	685/2224 (30.8)	645/2082 (31.0)			
Absolute risk reduction vs baseline, % (95% CI)		−0.8 (−3.6 to 1.9)	−0.1 (−2.8 to 2.6)	−0.3 (−3.0 to 2.5)	1.03 (0.92 to 1.16)	1.00 (0.89 to 1.14)	0.95 (0.81 to 1.11)
Mortality in hospital[d]							
Incidence, no./No. (%)	839/2206 (38.0)	782/2055 (38.1)	845/2184 (38.7)	816/2027 (40.3)			
Absolute risk reduction vs baseline, % (95% CI)		0.0 (−2.9 to 2.9)	−0.7 (−3.5 to 2.2)	−2.2 (−5.2 to 0.7)	0.97 (0.85 to 1.11)	1.00 (0.87 to 1.14)	0.96 (0.82 to 1.12)
Mortality at 28 d from ICU admission[e]							
Incidence, no./No. (%)	701/2198 (31.9)	675/2049 (32.9)	703/2171 (32.4)	689/2022 (34.1)			
Absolute risk reduction vs baseline, % (95% CI)		−1.1 (−3.9 to 1.8)	−0.5 (−3.3 to 2.3)	−2.2 (−5.0 to 0.7)	1.07 (0.86 to 1.32)[f]	1.05 (0.85 to 1.29)[f]	1.03 (0.80 to 1.32)[f]
Other outcomes, median (IQR), d							
ICU	10 (5 to 18)	10 (6 to 19)	10 (6 to 18)	11 (6 to 18)			
In hospital	23 (11 to 45)	24 (12 to 45)	23 (12 to 43)	24 (12 to 44)			
On mechanical ventilation in ICU	6 (3 to 13)	7 (4 to 13)	6 (3 to 12)	7 (3 to 12)			

Abbreviations: BSI, bloodstream infection; CHX, chlorhexidine mouthwash; HRMO, highly resistant microorganism; ICU, intensive care unit; IQR, interquartile range; MDRGNB, multidrug-resistant gram-negative bacteria; SDD, selective digestive tract decontamination; SOD, selective oropharyngeal decontamination.

[a] All models accounted for clustering using a fixed effect on ICU and a random effect on study period (13 ICUs × 4 study periods) and were adjusted for age, sex, Charlson Comorbidity Index score, APACHE II or SAPS II score, admission type, antibiotic use on ICU admission, location before ICU admission (in both propensity score and final models), and mean hand hygiene compliance per study period (only in final models).

[b] Includes MDRGNB and highly resistant gram-positive microorganisms (methicillin-resistant *S aureus* and vancomycin-resistant *E faecium/E faecalis*), according to definitions in eTable 3 in Supplement 2.

[c] One missing outcome.

[d] The cohort included 8509 unique hospital admissions, of which 37 were missing hospital mortality status.

[e] The cohort for 28-day mortality included 8496 unique ICU admissions with no prior ICU admission within 30 days, of which 56 were missing 28-day mortality status.

[f] Adjusted odds ratio (95% CI).

Sensitivity Analyses

Post hoc sensitivity analyses in which BSIs were assumed to have been prevented by third-generation cephalosporins and SDD treatment until the end of ICU stay yielded similar results for SDD (eTable 13 in Supplement 2). Sensitivity analyses excluding patients who stayed in an ICU fewer than 3 days led to similar results for all mortality outcomes (eTable 13 in Supplement 2).

Table 4. Descriptive Statistics of Point Prevalence Surveys for Unitwide Carriage of Antibiotic-Resistant Microorganisms in the Rectum and Respiratory Tract

Descriptive Statistics Point Prevalence Surveys	Baseline	CHX	SOD	SDD
Proportion of patients in the unit screened, %	93.1	94.3	92.2	92.3
No. of patients sampled	1456	1424	1469	1407
Included in study population, % of patients sampled	63.0	61.7	60.7	59.8
No. of rectal samples (% of patients sampled)	1392 (95.6)	1370 (96.2)	1419 (96.6)	1355 (96.3)
No. of respiratory samples (% of patients sampled)	1381 (94.8)	1333 (93.6)	1408 (95.8)	1319 (93.7)

Abbreviations: CHX, chlorhexidine mouthwash; SDD, selective digestive tract decontamination; SOD, selective oropharyngeal decontamination.

Table 5. Prevalence of Unitwide Carriage of Antibiotic-Resistant Microorganisms in the Rectum and Respiratory Tract (Exploratory Outcome)

	Baseline	CHX		SOD		SDD	
	Prevalence, %	Prevalence, %	aRR (95% CI)[a]	Prevalence, %	aRR (95% CI)[a]	Prevalence, %	aRR (95% CI)[a]
Rectum							
HRMO enterobacteriaceae	16.1	21.7	1.07 (0.99-1.16)	19.7	1.04 (0.96-1.13)	13.9	1.05 (0.95-1.16)
Third-generation cephalosporin resistance	15.8	21.5	1.07 (0.99-1.16)	19.2	1.04 (0.96-1.13)	13.7	1.07 (0.97-1.18)
Carbapenem resistance	3.2	3.1	0.68 (0.54-0.86)	2.9	0.85 (0.71-1.03)	2.6	0.80 (0.64-1.01)
Resistance to ≥3 antibiotics (or classes)	10.8	15.5	1.07 (0.97-1.19)	14.2	1.06 (0.96-1.17)	10.0	1.10 (0.97-1.24)
Colistin resistance[b]	0.5	1.6	0.81 (0.54-1.21)	1.8	0.97 (0.65-1.45)	1.3	0.96 (0.60-1.54)
HRMO glucose nonfermenting GNB	3.2	3.2	0.77 (0.62-0.95)	3.3	0.93 (0.76-1.14)	2.3	0.81 (0.63-1.04)
MDRGNB, regardless of antibiotic susceptibility	1.0	1.5	0.80 (0.50-1.27)	1.1	0.80 (0.49-1.30)	1.6	1.01 (0.64-1.58)
Any MDRGNB (aggregate)	19.3	25.3	1.03 (0.96-1.11)	23.0	1.03 (0.96-1.11)	17.1	1.04 (0.96-1.14)
VRE	2.2	1.5	0.96 (0.74-1.24)	1.8	0.94 (0.73-1.21)	4.2	1.03 (0.84-1.27)
Respiratory Tract							
HRMO Enterobacteriaceae	6.6	7.6	0.94 (0.81-1.09)	4.2	0.93 (0.80-1.09)	4.7	0.94 (0.78-1.13)
Third-generation cephalosporin resistance	6.4	7.4	0.95 (0.82-1.10)	4.2	0.93 (0.80-1.09)	4.5	0.94 (0.78-1.13)
Carbapenem resistance	1.4	1.1	0.71 (0.47-1.07)	0.9	0.68 (0.48-0.94)	0.5	0.59 (0.37-0.97)
Resistance to ≥3 antibiotics (or classes)	4.0	5.2	1.02 (0.84-1.23)	3.3	0.92 (0.76-1.12)	3.5	1.04 (0.83-1.31)
Colistin resistance[b]	0.1	0.8	0.57 (0.29-1.14)	0.9	0.66 (0.36-1.21)	0.3	0.61 (0.30-1.22)
HRMO glucose nonfermenting GNB	3.4	2.9	0.80 (0.64-1.00)	3.8	0.84 (0.70-1.00)	2.7	0.75 (0.58-0.96)
MDRGNB, regardless of antibiotic susceptibility	3.8	5.2	1.16 (0.94-1.44)	3.2	0.97 (0.77-1.22)	3.6	1.04 (0.83-1.31)
Any MDRGNB (aggregate)	12.9	15.2	0.98 (0.88-1.08)	10.3	0.93 (0.84-1.04)	10.2	0.94 (0.83-1.06)
MRSA	1.7	1.1	0.95 (0.66-1.36)	1.3	0.77 (0.59-1.00)	1.7	0.73 (0.54-0.97)

Abbreviations: aRR, adjusted relative risk; CHX, chlorhexidine mouthwash; GNB, gram-negative bacteria; HRMO, highly resistant microorganism; MDRGNB, multidrug-resistant gram-negative bacteria (eTable 3 in Supplement 2); MRSA, methicillin-resistant *S aureus*; SDD, selective digestive tract decontamination; SOD, selective oropharyngeal decontamination; VRE, vancomycin-resistant *E faecium/E faecalis*.

[a] aRR per month, all models were corrected for underlying time trends per center.

[b] Excluding Enterobacteriaceae with intrinsic colistin resistance (*Proteus* spp, *Morganella* spp, *Serratia* spp, *Providencia* spp, and *Hafnia alvei*).

Post Hoc Outcomes

Overall, 573 patients had 713 episodes of ICU-acquired BSI with any pathogen, most frequently caused by Enterococcus spp (n = 125), Klebsiella spp (n = 121), Candida spp (n = 69), *S aureus* (n = 67), and *Pseudomonas* spp (n = 61) (Table 2). These occurred in 6.8%, 7.4%, 6.3%, and 5.9% during the baseline, CHX, SOD, and SDD periods, respectively. Absolute risk reductions were −0.6% (95% CI, −2.1% to 1.0%), 0.5% (95% CI, −0.9% to 2.0%), and 0.9% (95% CI, −0.5% to 2.4%) for CHX, SOD, and SDD, respectively, compared with baseline. As compared with baseline, the aHRs were 1.08 (95% CI, 0.85 to 1.39), 0.94 (95% CI, 0.76 to 1.17), and 0.79 (95% CI, 0.60 to 1.05) for CHX, SOD and SDD, respectively (Table 3). SDD was associated with lower risk of ICU-acquired MDRGNB BSI compared with CHX (aHR, 0.62; 95% CI, 0.39 - 0.98) (eTable 14 in Supplement 2). There were

no statistically significant differences in any of the mortality outcomes in the post hoc head-to-head comparisons between interventions (eTable 14 in Supplement 2). There were no statistically significant associations between interventions and competing end points in any of these analyses (eTable 15 in Supplement 2).

In an exploratory analysis based on the results of surveillance cultures plated on extended-spectrum β-lactamase selective media and obtained twice weekly from study patients, carriage rates with antibiotic-resistant GNB in the rectum during SDD and in the respiratory tract during SDD/SOD appeared to remain stable, in comparison with other study groups where there appeared to be a gradual increase in colonization during ICU stay (eFigure in Supplement 2). On day 14 of ICU stay, the proportion of rectal cultures growing GNB from selective media was 14.8% during SDD and 28.3% during the baseline period.

Discussion

In this cluster randomized multicenter study in 13 European ICUs, decontamination strategies with either antibiotics (SDD or SOD) or CHX mouthwash were not associated with reductions in ICU-acquired BSI with MDRGNB, nor mortality, in ventilated ICU patients when compared with standard care, which included universal daily BWs with CHX during ICU stay and a hand hygiene program. Furthermore, the unitwide prevalence of carriage with antibiotic-resistant bacteria did not change during the interventions, which is consistent with results obtained in all large SDD trials of the last 20 years.[8]

The strengths of this study include participation of ICUs in 6 European countries, with resistance rates that better reflect the average European or American setting than Dutch ICUs, thereby improving external validity and generalizability of findings, as well as the detailed unitwide resistance monitoring with monthly point prevalence studies.

The findings of the current study differ in several aspects from those obtained in similar studies in Dutch centers.[3-5] First, the current study aimed to test decontamination regimens in ICUs with higher prevalence of antibiotic resistance. Indeed, the observed 17.6% unitwide rectal carriage rate of third-generation cephalosporin-resistant Enterobacteriaceae and an overall proportion of 25.5% of ICU-acquired BSIs caused by HRMO are considerably higher than in previous Dutch studies.[3-5] Decontamination strategies using conventional SDD or SOD regimens may be less effective in this context, especially in areas with high prevalence of resistance to aminoglycosides or colistin among GNB. The unitwide prevalence of colonization with gentamicin-resistant GNB was 8.3% in the rectum and 4.5% in the respiratory tract, which is twice as high as in a previous Dutch study performed between 2004 and 2006,[4] but comparable with the more recent Dutch study performed between 2009 and 2013.[5]

Second, SDD did not include a 4-day course of intravenous third-generation cephalosporins, which might have reduced the effects of SDD. During SDD, there were 48 episodes of ICU-acquired BSIs occurring within the first 4 days of inclusion, 17 of which involved pathogens susceptible to third-generation cephalosporins. Absence of cefotaxime during SDD cannot explain the discrepant findings for SOD, which was also associated with a reduction in mortality and ICU-acquired BSI in a previous Dutch study.[4]

Third, interventions were discontinued at the end of mechanical ventilation, instead of at ICU discharge. In a previous Dutch study, SDD and SOD were administered during more than 95% of patients' days,[4,5] whereas in the current study, mechanical ventilation days accounted for 69.2% of ICU days in study patients, reflecting the maximum proportion of time during which patients received study interventions. In fact, during CHX, SOD, and SDD, there were 32, 23, and 33 ICU-acquired BSI episodes that occurred on days without mechanical ventilation. A post hoc sensitivity analysis in which BSIs were assumed to have been prevented by third-generation cephalosporins and SDD treatment until the end of ICU stay yielded similar results for SDD. It is, therefore, unlikely that these protocol variations explain the discrepant findings with regard to SDD efficacy for patient outcome compared with previous studies.

Fourth, standard care in the current study included strategies that may have influenced carriage and transmission of HRMO and were not implemented in previous Dutch studies, such as oral care with antiseptics (CHX mouthwash 0.12% or 0.20%) in 11 of 13 centers, implementation of the World Health Organization hand hygiene program and daily CHX 2% BWs for all patients in the ICU until discharge. Although the effects of these strategies on colonization and infection with GNB cannot be assessed within the current study, they may have reduced the potential of the 3 interventions to offer additional benefits.[20]

Limitations

This study has several limitations. First, its design involves the inherent risk of (selection) bias due to cluster randomization and the fixed start with the baseline period, precluding adjustment for changes in ICU organization, ecology, or unmeasured patient characteristics over time. The study was also designed to compare each intervention with standard care, but not with each other. The head-to-head comparisons of the 3 interventions for primary and secondary outcomes, as reported, were based on a post hoc analysis.

Second, the originally targeted sample size of 10 800 patients was not reached, and accordingly, the study may have been underpowered to detect a clinically relevant difference in the primary outcome. However, post hoc power calculation revealed that this study had 80% power to detect an absolute reduction in hospital mortality of 4.2%, which is within the 2.9% to 5.3% range that was suggested by meta-analyses,[12] and 78.7% power to detect a 50% relative reduction in ICU-acquired BSI caused by MDRGNB. The confidence intervals for the primary outcome, BSI, do leave room for a potential effect of SDD in a larger study. Yet, as most hazard rates for the mortality outcomes were close to or even above 1, a larger study population would probably not

have resulted in a statistically significant association for any of the mortality outcomes. For example, the aHR of 0.96 for hospital mortality during SDD corresponds to a relative risk reduction of 2.25% and an absolute risk reduction of 0.95% compared with baseline (with 38% hospital mortality).

Third, monitoring of carriage with MDRGNB ended at ICU discharge, precluding evaluation of long-term effects of the interventions.

Conclusions

Among patients receiving mechanical ventilation in ICUs with moderate to high antibiotic resistance prevalence, use of CHX 1% mouthwash, SOD, or SDD was not associated with reductions in ICU-acquired bloodstream infections caused by MDRGNB as compared with standard care.

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REFERENCES

1. Vincent JL, Rello J, Marshall J, et al; EPIC II Group of Investigators. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302(21):2323-2329. doi:10.1001/jama.2009.1754

2. Scott RD. The direct medical costs of healthcare-associated infections in US hospitals and the benefits of prevention. Centers for Disease Control and Prevention. https://www.cdc.gov/hai/pdfs/hai/scott_costpaper.pdf. Published March 2009. Accessed January 4, 2017.

3. 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. doi:10.1016/S0140-6736(03)14409-1

4. 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. doi:10.1056/NEJMoa0800394

5. Oostdijk EAN, Kesecioglu J, Schultz MJ, et al. Notice of retraction and replacement: Oostdijk et al. effects of decontamination of the oropharynx and intestinal tract on antibiotic resistance in ICUs: a randomized clinical trial. JAMA. 2014;312(14):1429-1437. *JAMA*. 2017;317(15):1583-1584. doi:10.1001/jama.2017.1282

6. Plantinga NL, de Smet AMGA, Oostdijk EAN, et al. Selective digestive and oropharyngeal decontamination in medical and surgical ICU patients: individual patient data meta-analysis.

[Published online September 6, 2017]. *Clin Microbiol Infect*. 2018;24(5):505-513. doi:10.1016/j.cmi.2017.08.019

7. Duncan EM, Cuthbertson BH, Prior ME, et al; SuDDICU International Study Group. The views of health care professionals about selective decontamination of the digestive tract: an international, theoretically informed interview study. *J Crit Care*. 2014;29(4):634-640. doi:10.1016/j.jcrc.2014.03.013

8. 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. doi:10.1016/S1473-3099(12)70322-5

9. Labeau SO, Van de Vyver K, Brusselaers N, Vogelaers D, Blot SI. Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis. *Lancet Infect Dis*. 2011;11(11):845-854. doi:10.1016/S1473-3099(11)70127-X

10. Hua F, Xie H, Worthington HV, Furness S, Zhang Q, Li C. Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia. *Cochrane Database Syst Rev*. 2016;10(10):CD008367. doi:10.1002/14651858.CD008367.pub3

11. Klompas M, Speck K, Howell MD, Greene LR, Berenholtz SM. Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: systematic review and meta-analysis. *JAMA Intern Med*. 2014;174(5):751-761. doi:10.1001/jamainternmed.2014.359

12. Price R, MacLennan G, Glen J; SuDDICU Collaboration. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. *BMJ*. 2014;348:g2197. doi:10.1136/bmj.g2197

13. World Health Organization. WHO guidelines on hand hygiene in health care: first global patient safety challenge: clean care is safer care. http://apps.who.int/iris/bitstream/10665/44102/1/9789241597906_eng.pdf. Published 2009. Accessed January 4, 2017.

14. Plantinga NL, Wittekamp BHJ, Leleu K, et al. Oral mucosal adverse events with chlorhexidine 2% mouthwash in ICU. *Intensive Care Med*. 2016;42(4):620-621. doi:10.1007/s00134-016-4217-7

15. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. 2012;18(3):268-281. doi:10.1111/j.1469-0691.2011.03570.x

16. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med*. 2013;32(19):3388-3414. doi:10.1002/sim.5753

17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8

18. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-829. doi:10.1097/00003246-198510000-00009

19. Le Gall JR, Neumann A, Hemery F, et al. Mortality prediction using SAPS II: an update for French intensive care units. *Crit Care*. 2005;9(6):R645-R652. doi:10.1186/cc3821

20. Derde LPG, Cooper BS, Goossens H, et al; MOSAR WP3 Study Team. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. *Lancet Infect Dis*. 2014;14(1):31-39. doi:10.1016/S1473-3099(13)70295-0