SELECTIVE DECONTAMINATION OF THE OROPHARYNX AND THE DIGESTIVE TRACT IN ICU PATIENTS

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Selective decontamination of the oropharynx and the digestive tract in ICU patients

Selectieve decontaminatie van de oropharynx en de tractus digestivus bij intensive care patiënten

(met een samenvatting in het Nederlands)

Proefschrift

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Chapter 1 | General introduction

Intensive Care Unit (ICU)-acquired infections are frequent and important complications of the treatment of critically ill patients, and their occurrence has been associated with increased morbidity, mortality and health care costs.[1] Among all types of ICU-acquired infections, infections of the respiratory tract, most notably Ventilator-Associated Pneumonia (VAP), are most prevalent. Almost all episodes of VAP are preceded by bacterial colonization of the oropharynx.[2-4] Reductions in the incidence of VAP have been achieved by prophylactic topical application of non-absorbable antibiotics in the oropharyngeal cavity (Selective Oropharyngeal Decontamination (SOD))[5,6] and by the same approach in combination with application of non-absorbable antibiotics in the stomach and a short course of systemic antibiotics (Selective Decontamination of the Digestive tract (SDD)).[7,8]

The concept of colonization resistance, one of the underlying fundamentals of SDD was developed by van der Waay.[9] SDD in its full form was applied for the first time to ICU-patients by Stoutenbeek and coworkers.[10] SDD aims to prevent secondary colonization with Gram-negative bacteria, *S. aureus* and yeasts through application of non-absorbable antimicrobial agents in the oropharynx and gastrointestinal tract, pre-emptive treatment of possible infections with commensal respiratory tract bacteria through systemic administration of cephalosporins during the first four days in ICU, and maintaining the anaerobic intestinal flora through selectively using antibiotics (both topically and systemically) without anti-anaerobic activity. Despite beneficial effects of SDD on infection rates, most individual studies were underpowered to demonstrate statistically significant effects on patient survival. Only in meta-analyses and some single center randomized studies SDD was associated with improved patient survival. Yet, methods, designs and generalizibility of these studies have been criticized because of a lack of cross-over in a study performed in two ICUs [7, 11] because outcome results were only different after exclusion of patients[8] or in subgroup analysis[12] or because only burn wound patients were studied.[13]

SOD (application of topical antibiotics in the oropharynx only) has been proposed as an alternative to SDD for the prevention of VAP[5,6], as beneficial effects of SOD on VAP prevention appeared comparable to those found in SDD studies.[11,14] Yet, a head-to-head comparison of both strategies has never been performed.

Because of the afore-mentioned methodological issues and fear for increased selection of antibiotic resistant pathogens, the routine use of SDD and SOD has remained controversial, and was not recommended in international guidelines.

The primary aim of this thesis was to quantify the effects of both SDD and SOD trial on patient outcome and antibiotic resistance in Dutch ICUs. To that extent we designed a pragmatic cluster-randomized multi-center study with cross-over design to compare both strategies mutually and to standard care.

In chapter 2, as an introduction, the latest published scientific evidence on SDD and SOD, as of 2006 and 2007 has been reviewed.

Chapter 3 contains the objectives, methods and the main results of the cluster-randomized multi-center study with cross-over design on SDD and SOD.

The effects of SDD and SOD on respiratory tract colonization and on ICU-acquired bacteremia cases caused by highly resistant microorganisms are described in more detail in chapter 4.

It has been hypothesized that patients that received SDD during ICU-stay might have higher nosocomial infection rates after ICU-discharge. This hypothesis was investigated in two tertiary care hospitals, in which incidence rates of hospital acquired infections were determined during the first 14 days after ICU-discharge after for patients that received either SDD, SOD or standard care. The results are described in chapter 5.

The results of, one of many, meta-analysis suggested that SDD was more effective in surgical than in non-surgical patients.[15] This hypothesis was evaluated in chapter 6, in which the differential effects of SDD and SOD in surgical and non-surgical patients are described.

During the multi-center study, surveillance cultures from respiratory and intestinal tract were obtained on one specific day (third Tuesday of each month) from all patients present in the ICU, regardless whether they received SDD or SOD. These 18 point-prevalence studies in 13 ICUs allowed a detailed analysis on the effects of SDD and SOD on the bacterial ecology in an ICU-ward. These analyses and results are described and discussed in chapter 7.

In chapter 8 we describe the results of questionnaires that monitored the expectations on the effects of SDD, among ICU nurses and physicians, during the execution of the SDD-SOD trial. In addition, perceived workload and patient friendliness of SDD and SOD, as compared to standard care, were determined.

Since colistin is one of the antibiotics used in SDD and SOD, and since bacterial susceptibility testing for colistin in microbiology labs was not standard procedure at the start of our study, seven methods of colistin susceptibility testing were compared, using clinical isolates of the SDD-SOD trial, in chapter 9.

An example of a serious adverse event related to SDD, which was caused by accumulation of the oral paste, is described in chapter 10.

The results of all studies are summarized and discussed in chapter 11, together with some general directions and suggestions for clinical guidelines and future research.

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Chapter 2 | Selective decontamination of the digestive tract

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ABSTRACT

Purpose of review

The aim of this article is to review relevant studies on the topic of selective decontamination of the digestive tract published in 2006 and 2007.

Recent findings

The only recently published randomized controlled selective decontamination of the digestive tract study failed to demonstrate a benefit of selective decontamination on survival among trauma patients. In fact, two new meta-analyses of selective decontamination of the digestive tract studies were presented: one demonstrated reduced incidences of Gram-negative bacteraemia; in the other no reduction in fungaemia was found. Although selective decontamination of the digestive tract has been associated with increased selection of methicillin-resistant *Staphylococcus aureus* (MRSA), transmission of MRSA was controlled in a Spanish unit when using selective decontamination in combination with topical vancomycin. Several randomized studies and one meta-analysis suggest that oropharyngeal decontamination with antiseptics is also highly effective in preventing respiratory tract infection in critically ill patients.

Summary

The evidence that selective decontamination of the digestive tract improves patient outcome in mixed ICU patients is still based upon meta-analysis and two single centre studies in MRSA-naïve settings. Larger and preferably multicentre studies are needed to confirm these observations. Further remaining questions are whether oropharyngeal decontamination alone is as effective as the full selective decontamination of the digestive tract regimen and whether selective decontamination could be applied successfully in settings with high levels of antibiotic resistance.

INTRODUCTION

Selective decontamination of the digestive tract (SDD) is an infection prevention measure, introduced for ICU patients in 1983 by Stoutenbeek and co-workers[1]. SDD combines the use of nonabsorbable antibiotics (usually tobramycin, colistin and amphotericin B) applied in the oropharynx, stomach and intestines in combination with a short course (usually 4 days) of systemic antibiotic therapy with a second generation cephalosporin (most frequently cefotaxime). The underlying philosophy is that the topical antibiotics eradicate and prevent colonization with potentially pathogenic microorganisms, such as *Staphylococcus aureus, Pseudomonas aeruginosa* and Enterobacteriaceae. The short course of systemic antibiotic therapy aims to preemptively treat infections with commensal respiratory tract flora, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, which are incubating at the time of ICU admission. Despite multiple studies, with multiple variations of the original SDD scheme in different patient populations, SDD has not become a widely used infection prevention tool. Objections against its use have always been insufficient evidence of (cost) efficacy and the potential danger for selection of antibiotic resistance. In this review we will address the most recent (mainly published in 2006 and 2007) findings on SDD and other forms of topical antimicrobial prophylaxis in ICU patients.

CLINICAL TRIALS

The only randomized controlled SDD study published in the last 2 years was a multicenter study of 401 multiple trauma patients, executed between 1991 and 1994 in Europe, Australia and New Zealand.[2] Because of the generally low prevalence of co-morbidity among trauma patients, this population has been considered to benefit optimally from SDD. The primary endpoint of this multicenter study was mortality from infection or from multiple organ failure during treatment on the ICU or up to 2 weeks after discharge from the ICU. Overall mortality rates were 20.9% with SDD and 22.0% in controls. The authors concluded that the study was underpowered to detect a mortality benefit of SDD.[2] Yet, if the observed absolute outcome difference (1.1%) between the two study groups is the true difference, 11.000 patients would have been needed to sufficiently power the study.

META-ANALYSIS

Up till 2005, 11 meta-analyses of randomized controlled trials of SDD had been published. The 12th, published in January 2007, included 8065 critically ill patients and confirmed the findings of previous analyses that SDD (including the systemic component) was associated with a lower odds ratio for overall mortality (OR 0.80; 95% CI 0.69–0.94).[3] Furthermore, SDD was associated with reduced incidences of bloodstream infections (OR 0.73; 95% CI 0.59–0.90), especially Gram-negative bloodstream infections (OR 0.39; 95% CI 0.24–0.63). Notwithstanding the usefulness of meta-analyses for

hypothesis generation, repeated meta-analyses with huge overlap of included studies, repeatedly reporting the same outcome, should not be considered as cumulating evidence. Instead, the results should be used to design randomized trials to confirm these observations. So far, SDD was associated with improved patient outcome in only three prospective randomized studies[4–6], of which one was performed in burn patients.[6] The positive results of these well designed studies have led to at least one initiative to evaluate SDD, and also selective oropharyngeal decontamination (SOD), in a large cluster-randomized cross- over study with patient outcome as primary endpoint (M. Bonten, personal communication).

In another meta-analysis the effect of amphotericin B or nystatin as part of SDD on the incidence of reported fungal infections and fungaemia was determined.[7] In all, 42 randomized trials were included (6075 patients), all comparing SDD with amphotericin B or nystatin as part of the topical components to nontreated controls. The incidence of fungal infections was reduced (OR 0.30; 95% CI 0.17–0.53), but no significant effect was observed for the incidence of fungaemia (OR 0.89; 95% CI 0.16–4.95). Of note, in 28 trials (3608 patients, of which 1898 received SDD) with relevant data, 18 patients developed fungaemia (six receiving SDD). The aggregated odds ratio was based on two studies only, as all other studies had odds ratio with either zero or infinite value. The authors conclude that these findings justify the inclusion of an antifungal component in SDD[7]. Since fungal infections (except fungaemia), however, are difficult to distinguish from fungal colonization [which is supported by the finding that fungal carriage was equally reduced (OR 0.32; 95% CI 0.19–0.53) as fungal infections], it is uncertain whether the reduced fungal infection rate is associated with any change in patient outcome. The incidence of the only unequivocal infection, that is fungaemia, was extremely low (0.3 and 0.7% in patients with and without SDD) and it seems unlikely that this difference (OR 0.89) will influence patient outcome.

SPECIFIC PATIENT POPULATIONS

After the first application of SDD in trauma patients in the ICU, the concept has also been evaluated in other patient populations, such as those with acute pancreatitis. Sawa and co-workers[8] retrospectively analysed the association between and SDD and outcome of severe acute pancreatitis in a cohort of 90 patients, treated in their institute between 1991 and 2004. Seventy patients had received SDD, of whom 38 also had received early enteral nutrition via a jejunal tube. These patients were compared to 20 patients that had received neither SDD nor early enteral nutrition. Although not statistically significant, patients not receiving SDD or early enteral nutrition appeared more severely ill, as they had higher APACHE II and Ranson scores on admission. SDD treatment was associated with (nonsignificant) reductions in incidence of organ dysfunction during hospitalization (from 70 to 59%) and mortality (from 40 to 21%). Unfortunately, the study from Sawa et al. suffers from several methodological flaws, such as its retrospective

nature, low patient numbers and possible differences in baseline risk between the different groups. To the best of our knowledge, SDD had been previously evaluated in this specific patient population only once. About 15 years ago Luiten and co-workers randomized 102 patients with severe acute pancreatitis to SDD or standard care.[9] SDD treated patients had, after adjustment for Imrie score and Balthazar grade, a lower mortality rate (22 as compared to 35%), presumably as a result of reductions in Gram-negative pancreatic infections. The results from this randomized trial by Luiten et al. remain the best evidence so far, and antimicrobial prophylaxis for patients with necrotic acute pancreatitis still is considered an issue for which no recommendations can be made.[10]

In another approach only the oropharyngeal component of SDD (SOD), without intestinal decontamination or systemic prophylaxis, was evaluated in a randomized placebo-controlled double-blind design, in 203 patients with acute stroke.[11] In this study SOD was associated with lower respiratory tract colonization rates with Gram-negative bacteria and a lower incidence of pneumonia, but mortality rates remained unchanged.

ANTIBIOTIC RESISTANCE

Selection of multiresistant pathogens nonsusceptible to the antibiotics used in SDD or induction (and then selection) of pathogens previously susceptible to SDD antibiotics is a potential adverse effect of SDD.[12,13] In a German ICU, prevalence rates of antibiotic resistant pathogens during 5-year use of SDD were compared to prevalence rates in reference ICUs not using SDD.[14] MRSA prevalence (2.76 to 2.58 isolates per 1000 patient-days) remained stable in the ICU using SDD and was below the average in the reference units (4.26 isolates per 1000 patient-days). Similarly, aminoglycoside and β-lactam-resistant Gram-negative rods did not increase during SDD. Of note though, in the SDD unit all patients were screened for MRSA carriage twice weekly and colonized patients were treated with rigorous isolation measures in one-bed rooms. As this was not common practice in the reference ICUs, the effects of SDD without such measures remain uncertain. The use of SDD was associated with a sharp increase of vancomyin-resistant enterococci (VRE) isolates, which resulted from a hospital-wide outbreak with these pathogens. In another report, SDD was associated with a small outbreak (four patients) of plasmid-mediated extendedspectrum β-lactamase (ESBL) genes.[15]

The two studies in which a significantly improved patient outcome was demonstrated[4,5] were executed in almost total absence of MRSA and VRE. Previously, the use of SDD in a setting with MRSA endemicity, in Austria, had led to a large increase of MRSA prevalence.[16] Cerda and co-workers[17] evaluated MRSA dynamics in a Spanish intensive care burn unit during a nine-year period. The first 5 years (1995–2000) were followed by a 4-year period in which all patients received SDD in combination with four times daily 4% vancomycin gel into the nose, 4% vancomycin paste into the

oropharynx and 500 mg vancomcyin solution via the nasogastric tube. The number of patients admitted with MRSA carriage was 6.2% in period one and 2.7% in the second period. Taking this reduction in introduction of MRSA into account, incidence densities of acquired colonization with MRSA were reduced by about 75% in the second period. These data suggest that, indeed, addition of topical vancomycin to SDD not only prevents emergence of MRSA, but also controls its spread to a large extent. The findings could have been confounded by changes (or changed compliance) in infection control measures. Moreover, the before–after design and the use of statistical tests neglecting the effects of patient dependency may have led to false statistical outcomes.[18] Patient dependency (implying that the likelihood of transmission depends on the number of other patients being colonized) is characteristic for cross-transmission, and statistical tests such as χ^2 and Student *t*-test consider all observations to be independent. Applying these tests to datasets in which observations are not independent, such as those obtained in before–after studies, may falsely yield *P*-values below 0.05 in up to 40% of analyses, even when there is no change in the dynamics between both periods compared.[18] Shardell et al.[19] reviewed analysis of interrupted time series. Nevertheless, if future studies in MRSA-naive settings confirm the benefits of SDD on patient outcome, the data from Cerda and co-workers are promising that SDD could also be effective in settings with MRSA endemicity.

ADVERSE EFFECTS OF SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT

Topical application of antibiotics in Orabase is generally considered safe. Smit and co-workers[20], however, described three patients with total obstruction of the esophagus (n=2) and jejunum due to accumulation of orally applied paste.

OROPHARYNGEAL DECONTAMINATION

The results of several studies had already suggested that decontamination of the oropharyngeal cavity with topical antibiotics, without enteral decontamination and without systemic prophylaxis during the first days of intubation, was associated with reductions in the incidence of ventilator-associated pneumonia (VAP) comparable to the effects observed in SDD studies.[21,22] This concept was pursued in an international double-blind placebo-controlled trial using iseganan HCl for oral decontamination.[23] Iseganan HCl is a synthetic protegrin analog that possesses a broad spectrum of activity in-vitro against aerobic and anaerobic Gram-positive and Gram-negative bacteria and yeasts, with a low propensity for inducing resistance.[24] Yet, in-vivo iseganan HCl had little effect on the total numbers of Gram-negative microorganisms and *S. aureus* in oral specimens, and it appeared ineffective in improving outcome or reducing the incidence of VAP in mechanically ventilated patients.[23]

Three randomized studies evaluated the effects of oropharyngeal decontamination with chloorhexidine on the incidence of VAP.[25,26,27] Two placebo-controlled double-blind multicenter studies, one in The Netherlands and one in France, included mixed populations of mechanically ventilated patients.[25,27] In the Dutch study, an oropharyngeal paste with either 2% chlorhexidine or 2% chlorhexidine with 2% colistin, applied four times daily to the buccal cavity, reduced the daily risk of developing VAP to 55 and 65% of the placebo rates, respectively.[25] In the French study, in which medication (0.2% of chloorhexidine in a gel) was applied to the gingiva and dental plaque only, no differences in the incidence of VAP were observed.[27] Segers and co-workers[26] evaluated the effects of oral and nasal decontamination with 0.12% chlorhexidine gluconate in cardiosurgical patients, and witnessed a significant reduction in the overall incidence of nosocomial infections from 26.2% to 19.8%. Finally, all studies evaluating some form of oropharyngeal decontamination were meta-analyzed.[28] The aggregated effects of four studies using antibiotics (including the study on iseganan[23], but not the study from Pugin[22]) revealed a nonsignificant effect on the incidence of VAP (OR 0.69; 95% CI 0.41–1.18). The aggregated effects of seven studies on chlorhexidine oropharyngeal decontamination revealed an odds ratio of 0.56 (95% CI 0.39–0.81) for the development of VAP. The odds ratios for the effects of both intervention types on overall mortality were 0.94(95% CI 0.73–1.11) for antibiotics and 0.96(95% CI 0.69–1.33) for antiseptics.[28] It is tempting to speculate that oropharyngeal decontamination with antibiotics, or even with antiseptics such as chlorhexidine, would be equally effective in reducing the incidence of VAP and improving patient outcome. Large studies with a head-to-head comparison of these interventions are, therefore, needed.

CONCLUSION

The evidence that SDD improves patient outcome in mixed ICU-patients is still based upon meta-analysis and two single center studies in MRSA-naïve settings. Larger and preferably multicenter studies are needed to confirm these observations. Further remaining questions are whether oropharyngeal decontamination alone is as effective as the full SDD regimen and whether SDD could be applied successfully in settings with high levels of antibiotic resistance.

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Chapter 3 | Decontamination of the Digestive Tract and Oropharynx in ICU Patients

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ABSTRACT

Background

Selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) are infection-prevention measures used in the treatment of some patients in intensive care, but reported effects on patient outcome are conflicting.

Methods

We evaluated the effectiveness of SDD and SOD in a crossover study using cluster randomization in 13 intensive care units (ICUs), all in the Netherlands. Patients with an expected duration of intubation of more than 48 hours or an expected ICU stay of more than 72 hours were eligible. In each ICU, three regimens (SDD, SOD, and standard care) were applied in random order over the course of 6 months. Mortality at day 28 was the primary end point. SDD consisted of 4 days of intravenous cefotaxime and topical application of tobramycin, colistin, and amphotericin B in the oropharynx and stomach. SOD consisted of oropharyngeal application only of the same antibiotics. Monthly point-prevalence studies were performed to analyze antibiotic resistance.

Results

A total of 5939 patients were enrolled in the study, with 1990 assigned to standard care, 1904 to SOD, and 2045 to SDD; crude mortality in the groups at day 28 was 27.5%, 26.6%, and 26.9%, respectively. In a random-effects logistic-regression model with age, sex, Acute Physiology and Chronic Health Evaluation (APACHE II) score, intubation status, and medical specialty used as covariates, odds ratios for death at day 28 in the SOD and SDD groups, as compared with the standard-care group, were 0.86 (95% confidence interval [CI], 0.74 to 0.99) and 0.83 (95% CI, 0.72 to 0.97), respectively.

Conclusions

In an ICU population in which the mortality rate associated with standard care was 27.5% at day 28, the rate was reduced by an estimated 3.5 percentage points with SDD and by 2.9 percentage points with SOD. (Controlled Clinical Trials number, ISRCTN35176830.)

INTRODUCTION

Infections acquired in the intensive care unit (ICU) are important complications of the treatment of critically ill patients, increasing morbidity, mortality, and health care costs.[1] Reductions in the incidence of respiratory tract infections have been achieved with the use of prophylactic antibiotic regimens, such as selective decontamination of the digestive tract (SDD)[2,3] and selective oropharyngeal decontamination (SOD).[4,5]

The SDD approach[6,7] consists of prevention of secondary colonization with gram-negative bacteria, *Staphylococcus aureus*, and yeasts through application of nonabsorbable antimicrobial agents in the oropharynx and gastrointestinal tract, preemptive treatment of possible infections with commensal respiratory tract bacteria through systemic administration of cephalosporins during the patient's first 4 days in the ICU, and maintenance of anaerobic intestinal flora through selective use of antibiotics (administered both topically and systemically) without antianaerobic activity.[7] Despite the beneficial effects of SDD on infection rates, most studies have lacked sufficient statistical power to detect effects on survival. In meta-analyses and in three single-center, randomized studies, the use of SDD, including a short course of systemic antibiotics, was associated with improved survival.[2,3,8-10]

SOD (application of topical antibiotics in the oropharynx only) has been postulated as an alternative to SDD for the prevention of ventilator-associated pneumonia.[4,5] Although several studies have identified the pivotal role of oropharyngeal colonization in the pathogenesis of ventilator-associated pneumonia[11,12] and the efficacy of SOD in preventing ventilator-associated pneumonia appears to be similar to the efficacy of SDD,[13,14] a head-to-head comparison of the two strategies is needed. Because of methodologic issues,[15,16] such as single-center study designs with limited generalizability, and concern about increased selection of antibiotic-resistant pathogens,[17,18] the routine use of SDD and SOD has remained controversial and has not been recommended in international guidelines.[19,20]

METHODS

Study Design

We performed a controlled, crossover study using cluster randomization in 13 ICUs between May 2004 and July 2006. The participating ICUs differed in size and teaching status, reflecting all levels of intensive care in the Netherlands. (More information on the ICUs can be found in the Supplementary Appendix) Since the interventions included ecologic changes in the ICU, an individualized, randomized design would have allowed the treatment of a patient in one study group to influence the treatment of a patient in another group. Therefore, cluster randomization was used, and all three study regimens (SDD, SOD, and standard care) were administered to all eligible patients over the course of 6 months, with the order of regimens randomly assigned. A cross-over design was used to control for unit-specific characteristics. Randomization

was performed by a clinical pharmacist who was not involved in patient care in any of the participating units and who was unaware of the identity of each ICU. The order in which the regimens were assigned was randomly generated by computer software (Design, version 2.0, a Systat Module), with allocation to the wards in consecutive order of study start. Study periods were preceded by washout and wash-in periods (for more information see the Supplementary Appendix). The antibiotics used were purchased by the hospitals. All authors vouch for the completeness and accuracy of the data presented.

Patients admitted to the ICU with an expected duration of mechanical ventilation of more than 48 hours or an anticipated ICU stay of more than 72 hours were eligible. Eligibility was assessed by physicians responsible for patient care in each unit. Pregnant patients and patients with documented or presumed allergy to any component of the antimicrobial study regimens were excluded.

The study protocol was approved by the institutional review board at each participating hospital. After reviewing the protocol, the boards waived the requirement for informed consent. Permission to use patient-specific medical data for analysis was obtained from patients or their representatives.

Inclusion rates were determined for each ICU and each study period. Research nurses visited each center regularly (at least twice per study period) and evaluated up to 50 consecutively admitted patients per visit (starting from a randomly chosen date) for eligibility and study inclusion.

The SDD regimen, which consisted of 4 days of intravenous cefotaxime and topical application of tobramycin, colistin, and amphotericin B in the oropharynx and stomach, was identical to the regimen used by de Jonge et al.[2] (for more information see the Supplementary Appendix). The use of antibiotics with antianaerobic activity, such as amoxicillin, penicillin, amoxicillin-clavulanic acid, and carbapenems, was discouraged during the SDD period. Surveillance cultures of endotracheal aspirates and oropharyngeal and rectal swabs were obtained on admission and twice weekly thereafter.

SOD consisted of oropharyngeal application of the same paste used for SDD, with surveillance cultures of endotracheal aspirates and oropharyngeal swabs obtained on admission and twice weekly thereafter; there were no restrictions on physicians' choices of systemic antibiotic therapy. During the period of standard care, no surveillance cultures were obtained from patients, and there were no restrictions on physicians' choices of systemic antibiotic therapy.

Antibiotic resistance was monitored with the use of point-prevalence studies on the third Tuesday of each month. On these days, rectal swabs and endotracheal aspirates or throat swabs for surveillance cultures were obtained from all ICU patients, whether or not they were included in the study. The prevalence of specific pathogen-resistance combinations was determined. (Details on the processing of surveillance cultures during SDD and SOD and on the monthly point-prevalence studies are available in the Supplementary Appendix.)

Approaches to infection control (other than the regimens being studied) did not change during the period of the study in any of the ICUs. (Oropharyngeal care is described in the Supplementary Appendix.)

Statistical Analysis

The original analysis plan, which specified in-hospital death as the primary end point, did not take into account analysis of cluster effects and failed to specify how to address imbalances in baseline characteristics between study groups. However, the study design did not preclude post-randomization selection bias.[21] It was subsequently recognized that such an analysis plan failed to conform to the Consolidated Standards for the Reporting of Trials (CONSORT) guidelines for reporting cluster-randomization trials.[22] Failure to account for cluster effects (e.g., with the use of a random-effects model) would have increased the chance of reporting spuriously significant findings, and in the event of selection bias, failure to adjust for baseline characteristics could have led to bias in either direction.[21,23] When confronted with these problems, we consulted a panel of experts in the field of clinical epidemiology and data analysis with no prior involvement in the study and no knowledge of outcome data. The panel unanimously recommended a revised analysis plan that overcame these problems. This plan specified mortality at day 28 as the primary end point (because it was thought that knowledge of the intervention being applied at any given time could have influenced discharge policies, compromising the reliability of hospital discharge as an end point) and the use of a random-effects logistic-regression model to adjust for all available covariates (the score on the Acute Physiology and Chronic Health Evaluation [APACHE II], intubation status, medical specialty [classified as surgical or other], age, and sex).

This plan was adopted, with no further revisions, and day 28 mortality data were subsequently collected through hospital and government systems (these data had not been available when the analysis plan was formulated). In-hospital mortality, prevalence of antibiotic resistance, and duration of mechanical ventilation, ICU stay, and hospital stay for surviving patients were secondary end points. (Details on the power calculation and statistical analysis of secondary end points are available in the Supplementary Appendix.)

RESULTS

Characteristics of the patients

From May 2004 through July 2006, a total of 5939 patients were enrolled in 13 participating centers: 1990 received standard care, 1904 received SOD, and 2045 received SDD. Permission for use of patient-specific medical data could not be obtained for 12 patients (11 in the SDD group and 1 in the standard-care group), who were excluded from all analyses except those for unadjusted mortality; 44 patients were discharged alive from the hospital but were lost to follow-up at day 28. Overall, 48 patients crossed over to a

Table 1. Baseline characteristics of the patients*

Variable	SDD (N = 2045)	SOD (N =1904)	Standard Care (N = 1990)	P value SDD vs. Standard Care	P value SOD vs. Standard Care	P value SDD vs. SOD
Age – yr †	62.4 ± 15.9	61.4 ± 16.3	61.4 ± 16.2	0.04	0.88	0.05
Male sex – no. (%)	1244 (61.2)	1213 (63.7)	1220 (61.3)	0.90	0.13	0.09
Mean APACHE II score	19.6 ± 7.8	19.5 ± 8.2	18.6 ± 7.9	0.00	0.001	0.63
APACHE II ≥ 20 – no. (%)	969 (47.4)	897 (47.1)	837 (42.1)	0.001	0.002	0.87
Mechanical ventilation –no.(%)	1890 (92.9)	1793 (94.2)	1753 (88.1)	0.000	0.000	0.12
Reason for admission type– no. (%)				0.03	0.03	0.95
- Surgical	923 (45.4)	866 (45.5)	973 (48.9)			
- Medical	1111 (54.6)	1038 (54.5)	1016 (51.1)			
Specialism – no. (%)						
- Surgery	605 (29.7)	551 (28.9)	609 (30.6)	0.56	0.26	0.60
- Cardiothoracic surgery	353 (17.4)	284 (14.9)	321 (16.1)	0.31	0.31	0.04
- Neurosurgery	105 (5.2)	140 (7.4)	145 (7.3)	0.006	0.95	0.005
- Neurology	124 (6.1)	144 (7.6)	128 (6.4)	0.70	0.19	0.08
- Internal medicine	382 (18.8)	371 (19.5)	393 (19.8)	0.45	0.84	0.60
- Cardiology	159 (7.8)	147 (7.7)	129 (6.5)	0.11	0.13	0.95
- Pulmonology	152 (7.5)	138 (7.2)	127 (6.4)	0.19	0.31	0.81
- Other	153 (7.5)	126 (6.6)	137 (6.9)	0.47	0.75	0.29
- Unknown	1 (0)	3 (0.2)	0 (0)	1.00	0.12	0.36
Previous or preexistent condition – no. (%)						
- Cardiovascular disease	1031 (50.7)	899 (47.2)	976 (49.1)	0.31	0.25	0.03
- Pulmonary disease	530 (26.1)	448 (23.5)	489 (24.6)	0.29	0.45	0.07
- Diabetes mellitus	281 (13.8)	274 (14.4)	302 (15.2)	0.23	0.50	0.61
- Chronic renal insufficiency	155 (7.6)	135 (7.1)	119 (6.0)	0.05	0.17	0.54
- Malignant solid tumor	220 (10.8)	193 (10.1)	196 (9.9)	0.33	0.79	0.50
- Metastasized cancer	71 (3.5)	56 (2.9)	64 (3.2)	0.66	0.64	0.37
- Haematologic cancer	56 (2.8)	51 (2.7)	48 (2.4)	0.55	0.61	0.92
- Immunodepression or AIDS	60 (2.9)	47 (2.5)	47 (2.4)	0.28	0.84	0.38
- Alcohol or drugabuse	112 (5.5)	120 (6.3)	111 (5.6)	0.95	0.34	0.31
Place from which patient was admitted to ICU – no. (%)						
- Emergency room	509 (25.0)	475 (24.9)	465(23.4)	0.23	0.26	0.97
- Other ICU	135 (6.6)	121 (6.4)	116 (5.8)	0.30	0.50	0.75
- Hospital ward	961 (47.2)	915 (48.1)	943 (47.4)	0.80	0.80	1.00
- Other	440 (21.5)	393 (20.5)	466 (23.4)	0.11	0.21	0.77

* Plus-minus values are means ± SD. Permission for use of patient-specific data could not be obtained for 11 patients in the selective digestive tract decontamination (SDD) group and 1 patient in the standard-care group. AIDS denotes acquired immunodeficiency syndrome, APACHE Acute Physiology and Chronic Health Evaluation, and SOD selective oropharyngeal decontamination.

† Values for age are based on age at the time of hospital admission.

subsequent study period. The total number of patients included in the study per center ranged from 119 in a 4-bed ICU in a nonteaching hospital to 1013 patients in a 43-bed ICU in a university hospital. (Details on patient enrollment per center are available in the Supplementary Appendix.)

Eligibility was determined for a total of 6565 ICU admissions (with 300 to 1518 patients screened for eligibility per center). The average proportion of ICU patients eligible for study inclusion per center was 29.5% and ranged from 16.3 to 51.8%. Patients who were not eligible for the study had short ICU stays, in most cases after elective surgery. Of all eligible patients, 89.2% were included. Inclusion rates ranged from 51.8 to 100% per center. The mean inclusion rates for the SDD, SOD, and standard-care periods were 89.1%, 86.9%, and 91.6%, respectively ($P = 0.03$ for standard care vs. SOD, $P>0.05$ for the other comparisons), and rates for the first, second, and third periods were 88.5%, 86.6%, and 92.8%, respectively ($P = 0.02$ for the first period vs. the third period, $P>0.05$ for the other comparisons).

There were differences in baseline characteristics between patients in the standard-care group and those in the SOD and SDD groups (Table 1). Patients who received standard care had slightly lower APACHE II scores, were less likely to be receiving mechanical ventilation, and were more likely to have been admitted for surgical reasons. The proportions of patients who received antibiotics before admission to the ICU were similar in all three study groups. In the SOD and SDD groups, medication was administered according to protocol on 95.7% and 97.5% of all patientdays, respectively. Noncompliance, which was most frequent at the end of the ICU stay, was most often due to the patient's decision to decline medication.

Primary and secondary clinical end points

Crude mortality at day 28 for patients in the standard-care, SOD, and SDD groups was 27.5%, 26.6%, and 26.9%, respectively. In a random-effects logistic-regression model adjusted for age, sex, APACHE II score, intubation status, medical specialty, study site, and study period, odds ratios for death during the first 28 days for the SOD and SDD groups, as compared with the standard-care group, were 0.86 (95% confidence interval [CI], 0.74 to 0.99; $P = 0.045$) and 0.83 (95% CI, 0.72 to 0.97; $P = 0.02$), respectively (Table 2). When covariates were added to the model one at a time in order of statistical significance, it was evident that those with significant imbalances had the largest effect on the odds ratio (for more information see the Supplementary Appendix). The intracluster correlation coefficient was 0.010. With a baseline rate of death during the first 28 days of 27.5%, absolute and relative reductions in mortality at day 28 were 3.5% and 13%, respectively, for the SDD group and 2.9% and 11%, respectively, for the SOD group, corresponding with the needed-to-treat numbers of 29 and 34 to prevent one casualty at day 28 for SDD and SOD, respectively. There was a tendency for SDD and SOD to be associated with reductions in durations of mechanical ventilation, ICU stay,

Table 2. Primary and Secondary End Points*

End Point	Study Group			Unadjusted Odds Ratio or Hazard Ratio (95% CI)†			Adjusted Odds Ratio or Hazard Ratio (95% CI)†		
	Standard Care (N=1990)	SDD (N=2045)	SOD (N=1904)	Standard Care	SDD	SOD	Standard Care	SDD	SOD
Death – no. (%)									
During the first 28 days	544 (27.5%)	546 (26.9%)	502 (26.6%)	1.00	0.94 (0.82-1.08)	0.95 (0.82-1.10)	1.00	0.83 (0.72-0.97)	0.86 (0.74-0.99)
In the ICU	443 (22.3%)	440 (21.5%)	416 (21.8%)	1.00	0.91 (0.79-1.06)	0.97 (0.83-1.13)	1.00	0.81 (0.69-0.94)	0.87 (0.74-1.02)
In the hospital	632 (31.8%)	665 (32.6%)	584 (30.7%)	1.00	0.99 (0.86-1.13)	0.94 (0.82-1.08)	1.00	0.88 (0.76-1.01)	0.85 (0.74-0.98)
Time to outcome for survivors at day 28 – days									
Cessation of mechancial ventilation				1.00	1.06 (0.96-1.18)	1.01 (0.89-1.15)	1.00	1.10 (0.99-1.22)	1.03 (0.90-1.17)
Median	8	7	8						
Interquartile range	3-17	4-15	4-15						
Discharge from ICU				1.00	1.02 (0.92-1.12)	1.00 (0.89-1.11)	1.00	1.09 (0.99-1.21)	1.06 (0.94-1.19)
Median	9	9	9						
Interquartile range	6-19	6-18	6-17						
Discharge from hospital				1.00	1.04 (0.91-1.19)	1.05 (0.91-1.22)	1.00	1.13 (1.01-1.25)	1.13 (0.96-1.32)
Median	29	28	28						
Interquartile range	16-48	16-45	16-47						

* Ratios for death are odds ratios, and ratios for time to outcome are hazard ratios. All adjusted and duration outcomes exclude the 12 patients who declined to provide permission to use data, and all outcomes for death at 28 days exclude an additional 44 patients for whom data were unavailable. In-hospital mortality data were unavailable for three patients (two in the selective digestive decontamination [SDD] and one in the standard-care group). Other mortality outcomes include all patients assigned to a study regimen. Data on the duration of the hospital stay and the duration of mechanical ventilation were unavailable for three patients (two in the selective oropharyngeal decontamination [SOD] and one in the SDD group) and eight patients (five in the SOD group and three in the standard-care group), respectively.
† Odds ratios were calculated with the use of random-effects logistic-regression models to account for ICU-level clustering. All models for adjusted outcomes included the Acute Physiology and Chronic Health Evaluation (APACHE II) score (≥ 20 vs. <20, age (>65 years vs. ≤ 65 years), intubation status during ICU stay, reason for admission to ICU (surgical vs. medical) and sex. The odds ratios for the outcome of death during the first 28 day were 2.56 (95% CI, 2.26 to 2.92) for APACHE II score of 20 or more, 1.87 (95% CI, 1.65 to 2.12) for an age greater than 65 years, 1.67 (95% CI, 1.29 to 2.15) for mechanical ventilation during the ICU stay, 0.61 (95%CI, 0.53 to 0.69) for surgical admission, and 1.09 (95% CI, 0.96 to1.24) for male sex. Corresponding estimates for death in the ICU and in-hospital death were broadly similar. Hazard ratios were calculated from a Cox regression model with censoring at day 28 and with adjustment for ICU-level clustering (hazard ratios >1.00 indicate a tendency toward a shorter duration of mechanical ventilation and a shorter ICU or hospital stay). Models for adjusted outcomes included the same covariates as those in the logistic-regression models except for the duration of hospital stay, which was stratified according to surgical status because of a departure from the proportional-hazards assumption. Infinite durations were used for patients who died.

and hospital stay (Table 2). There was no evidence of an association of temporal trends, autocorrelation, or period-level effects with primary or secondary end points.

Microbiologic findings

Among patients receiving SDD or SOD as compared with those receiving standard care, crude incidences of ICU-acquired bacteremia were significantly reduced for *S. aureus*, glucose-nonfermenting gram-negative rods (mainly *Pseudomonas aeruginosa*), and Enterobacteriaceae (Table 3). Patients receiving SDD had a lower incidence of ICU-acquired bacteremia with Enterobacteriaceae than did those receiving SOD. The incidence of ICU-acquired candidemia tended to be lower in the SDD group than in either the SOD group or the standard-care group, although the difference was not significant. No significant differences among the three study groups were observed for infection with *Streptococcus pneumoniae* or Enterococcus species. *Clostridium difficile* toxin was detected in 15 patients (0.8%) in the standard-care group, 5 patients (0.3%) in the SOD group, and 9 patients (0.4%) in the SDD group.

The estimated completeness of surveillance cultures per center was, on average, 87% (range, 70 to 97) for respiratory tract samples and 87% (range, 62 to 100) for rectal samples. The rate of isolation of gram-negative bacteria from rectal swabs among patients receiving SDD was reduced from 56% at day 3 to 25% at day 8 and 15% at day 14 (Fig. 1). The rate of culture positivity for gram-negative bacteria in oropharyngeal swabs from patients receiving SDD ranged from 18% at day 2 to 4% at day 8. Among patients treated with SOD, culture positivity ranged from 20% at day 2 to 7% at day 8 (Fig. 1).

In all, 2596 patients were included in the monthly point-prevalence surveillance studies for respiratory tract colonization (894 in the SDD group, 811 in the SOD group, and 891 in the standard-care group), and 2963 patients were included in the analysis of rectal colonization (988 in the SDD group, 947 in the SOD group, and 1028 in the

Table 3. Cumulative Incidence of ICU-acquired bacteremia and candidaemia*

Type of infection	Study group			Crude Odds Ratio (95%CI)		
	Standard Care N=1990	SOD N= 1904	SDD N=2045	SDD vs. Standard Care	SOD vs. Standard Care	SDD vs. SOD
	no. (%)					
Staphylococcus aureus	22 (1.1)	9 (0.5)	9 (0.4)	0.40 (0.18-0.86)	0.43 (0.20-0.93)	0.93 (0.37-2.40)
Streptococcus pneumoniae	3 (0.2)	1 (0.1)	1 (0.0)	0.32 (0.03-3.12)	0.35 (0.04-3.35)	0.93 (0.06-14.90)
GNF-GNR†	36 (1.8)	17 (0.9)	16 (0.8)	0.43 (0.24-0.77)	0.49 (0.27-0.87)	0.88 (0.44-1.74)
Enterobacteriaceae	87 (4.4)	59 (3.1)	18 (0.9)	0.19 (0.12-0.32)	0.70 (0.50-0.98)	0.28 (0.16-0.47)
Enterococcus species	55 (2.8)	49 (2.6)	48 (2.3)	0.85 (0.57-1.25)	0.93 (0.63-1.37)	0.91 (0.61-1.36)
Candida species	16 (0.8)	14 (0.7)	8 (0.4)	0.49 (0.21-1.11)	0.91 (0.45-1.85)	0.53 (0.23-1.24)
Patients with at least one episode of bacteremia or candidaemia – no. (%)	186 (9.0)	124 (6.5)	88 (4.3)	0.44 (0.34-0.57)	0.68 (0.53-0.86)	0.65 (0.49-0.85)

* SDD denotes selective digestive tract decontamination, and SOD selective oropharyngeal decontamination.

† Glucose-nonfermenting gram-negative rods (GNF-GNR) are characteristic of *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*,and acinetobacter species

Table 4. Detection of antibiotic-resistant gram-negative bacteria in rectal and respiratory tract samples during point-prevalence surveys*

Organism	Resistant to Aminoglycosides†			Resistant to Ciprofloxacin			Resistant to Ceftazidime			Multi-resistant A‡			Multi-resistant B§		
	Standard Care	SOD	SDD	Standard Care	SOD	SDD	Standard Care	SOD	SDD	Standard Care	SOD	SDD	Standard Care	SOD	SDD
	percentage of patients														
Rectal samples															
Escherichia coli	4.5¶	4.9¶	1.8	4.9¶	4.5	2.9	3.3¶	2.3	1.3	2.2¶	2.3¶	0.5	1.4	1.0	0.5
Klebsiella pneumoniae	2.6¶	1.4	1.0	3.0#¶	1.4	0.7	2.2¶	1.1	0.4	0.6	1.0	0.6	1.9¶#	0.3	0.3
Enterobacter cloacae	1.7¶	1.8¶	0.6	1.3	1.6	0.5	4.7¶	4.2¶	1.7	1.0	1.1	0.5	0.6	1.0	0.2
Pseudomonas aeruginosa	1.2	1.0	0.7	1.6	1.6	0.7	2.6¶	1.8¶	0.7	1.3¶	0.8	0.4	0.4	0.3	0.4
Respiratory tract samples															
E. coli	1.3¶	0.5	0	1.0¶	0.2	0.4	1.0¶	0.5	0	0.4	0.1	0	0.4	0.2	0
K. pneumoniae	2.0¶#	0.5	0.2	2.4¶#	0.4	0.2	1.9¶#	0.6	0.2	0.1	0.2	0.1	2.0	0.2	0.1
E. cloacae	1.5¶	0.5	0.4	1.1#	0.2	0.4	3.8¶#	0.6	1.2	0.6	0.2	0	0.6	0.1	0.3
P. aeruginosa	2.6¶	1.8	1.0	3.7#	1.8	0.9	3.5¶#	1.1	0.4	2.2	1.2	0.4	0.8	0.1	0.1

* The total number of rectal samples and the mean (+ SD) number of patients from whom they were obtained during the six point-prevalence surveys were as follows for the three study groups: standard care,1028 samples from 171+13 patients; selective oropharyngeal decontamination (SOD), 947 samples from158+11 patients; and selective digestive decontamination SDD, 988 samples from 165+8 patients. The total number of respiratory samples and the mean number of patients were as follows: standard care, 891 samples from 149+3 patients; SOD, 811 samples from 135+12 patients; and SDD, 894 samples from 149+7 patients.

† The aminoglycosides were gentamicin and tobramycin.

‡ These bacteria are resistant to the aminoglycosides gentamicin and tobramycin and to ciprofloxacin or ceftazidime

§ These bacteria are resistant to the aminoglycosides gentamicin and tobramycin and to ciprofloxacin and ceftazidime

¶ $P<0.05$ as compared to SDD

\# $P<0.05$ as compared to SOD

standard-care group). Estimated completeness of culture surveillance per center was, on average, 87% (range, 67 to 98) for rectal samples and 82% (range, 69 to 95) for respiratory tract samples. The data from six point-prevalence measurements per study period were analyzed together. For all pathogen-antibiotic combinations, the rate of nonsusceptibility was less than 5% (Table 4). For multidrug resistance, the rate of nonsusceptibility was less than 2.5% for two antibiotics and less than or equal to 2% for three antibiotics. The proportion of patients with gram-negative bacteria in rectal swabs that were not susceptible to the marker antibiotics was lower with SDD than with standard care or SOD (Table 4). The proportions of patients with nonsusceptible bacteria in respiratory tract samples were similar in the SDD and SOD groups and were lower than the proportion in the standard-care group. There were no patients with methicillin-resistant *S. aureus*; eight patients had vancomycin-resistant enterococci in rectal swabs: six in the standard-care group (0.6%) and two in the SOD group (0.2%).

Antibiotic use

The median number of defined daily doses of systemic antibiotic agents (including antifungal agents) per patient-day did not differ significantly among the SDD, SOD, and standard-care periods: 0.72 (interquartile range, 0.44 to 1.33), 0.84 (interquartile range, 0.25 to 1.58), and 0.84 (interquartile range, 0.29 to 1.55), respectively. During treatment with SDD as compared with standard care, the use of antimicrobial agents

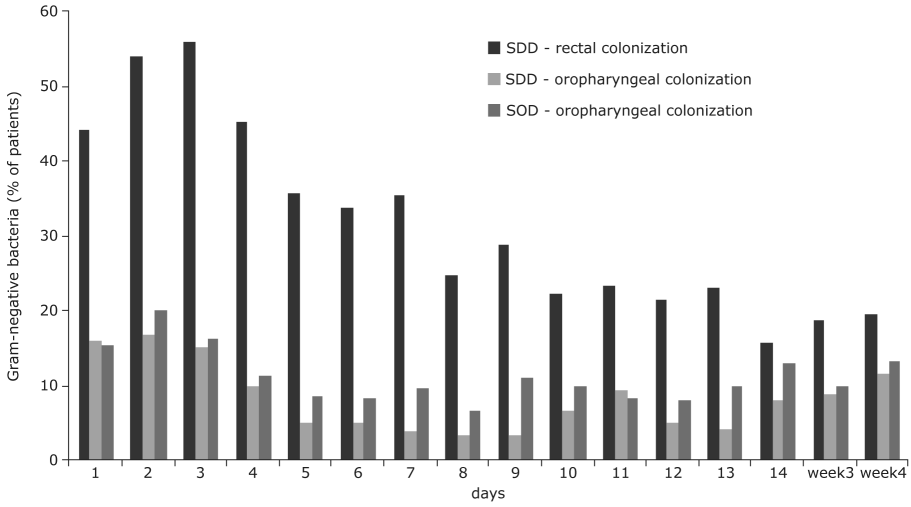

Figure 1. Rectal and oropharyngeal colonization with Gram-negative bacteria in patients receiving SDD and SOD

with antianaerobic activity was reduced by 27.8% for broad-spectrum penicillins, 45.7% for carbapenems, and 11.6% for lincosamides (Table 5). Furthermore, quinolone use (mainly ciprofloxacin) was reduced by 31.4%. In contrast, systemic use of cephalosporins increased by 86.6%. There were less pronounced differences in antibiotic use between the SOD group and the standard-care group (Table 5). Total defined daily doses were 11.9% and 10.1% lower with SDD and SOD, respectively, than with standard care.

Adverse events

In one patient receiving SDD, esophageal obstruction developed as a result of clotted oropharyngeal medication, which was removed through endoscopy.[24]

Table 5. Antibiotic use*

	SDD		SOD		Standard Care
	No. of Defined Daily Doses	Percent Change (vs. Standard Care)	No. of Defined Daily Doses	Percent Change (vs. Standard Care)	No. of Defined Daily Doses
Penicillins	9,767	-27.8	12,805	-5.3	13,523
Carbapenems	724	-45.7	995	-25.4	1,334
Cefalosporins	8,473	+86.6	3,935	-13,3	4,541
Quinolones	2,637	-31.4	3,291	-14.4	3,846
Lincosamides	473	-11.6	553	+3.4	535
Other antibiotics	7,589	-23.4	8,720	-12.0	9,909
All systemic antibiotics	29,663	-11.9	30,299	-10.1	33,688

* SDD denotes selective digestive tract decontamination, and SOD selective oropharyngeal decontamination.

DISCUSSION

These data show an absolute reduction in mortality of 3.5 and 2.9 percentage points (corresponding to relative reductions of 13% and 11%) at day 28 with SDD and SOD, respectively, among patients admitted to Dutch ICUs. Patients were treated with topical components at a cost per day of $1 for SOD and $12 for SDD, without evidence of the emergence of antibiotic-resistant pathogens or increased rates of detection of *C. difficile* toxin (at least during the relatively short period of study). This benefit was discernible only after adjustment for covariates. The overall study period was not long enough to evaluate the effect of the prophylactic regimens on microbial flora.

The strengths of the study include its pragmatic, multicenter, crossover design and the monitoring of inclusion rates. Overall, an estimated 89% of eligible patients were included. Cluster randomization was needed to avoid the possibility that one study regimen would influence the outcome of another regimen. A consequence of this study

design is the absence of concealment of randomization. Although randomized treatment assignments for study periods were concealed, the actual inclusion of patients was not randomized, and the physicians responsible for patient inclusion were aware of the assigned intervention. Blinding of physicians (or having a third person, who was unaware of the assigned interventions, overseeing inclusion) was deemed impossible. To minimize the risk of selection bias due to differences in patient inclusion among study centers and during different study periods, inclusion rates were monitored frequently for any instances of selective inclusion. Nevertheless, despite the use of objective inclusion criteria and the provision of continual feedback on inclusion rates to the participating centers, baseline differences were present between the standard-care group and both intervention groups, with patients in the intervention groups tending to be older, more likely to be intubated, and less likely to be surgical patients and tending to have a higher baseline APACHE II score. These differences were not consistent with chance, and they account for the differences between the crude and adjusted outcomes (Table 2).

The microbiologic aims of treatment with SDD or SOD were achieved in this study. During the SDD periods, all patients received intravenous prophylaxis with cefotaxime, and the desired microbiologic effects on carriage of gram-negative bacteria in the respiratory and intestinal tracts were achieved. Rates of eradication of gram-negative bacteria in the intestines and oropharynx were slightly higher than those reported by Stoutenbeek et al.[7] and others.[25,26] During the SDD and SOD study periods, prevalence rates for antibiotic-resistant gram-negative bacteria were lower than they were during the standard-care periods. These results are consistent with the finding, reported by de Jonge et al.[2] and others,[27,28] that in settings with low levels of circulating antibiotic-resistant organisms, SDD is not associated with increased selection or induction of antibiotic resistance in the short term. However, in settings with high levels of endemic, multidrug-resistant gram-negative bacteria[17,29] or methicillin-resistant *S. aureus*,[18] SDD was associated with increased selection of such pathogens.

A limitation of our study is that the original analysis plan was not appropriate for the study design. Although analyses similar to that originally proposed have been widely used to assess data from cluster-randomization trials, they increase the chance of incorrect inferences. Conclusions based on such analyses cannot be considered reliable.[21,22] Faced with the choice between performing an analysis known to be inappropriate and creating a new analysis plan, we decided that the latter was preferable. Very similar conclusions about the interventions would have been reached had the primary outcome been in-hospital mortality, as originally planned (with SDD very slightly less effective than SOD), after adjustment for baseline imbalances (Table 2). Evidence for the effectiveness of the interventions is supported by the significant reductions in the incidence of ICU-acquired bacteremia for important nosocomial pathogens in both intervention groups. Of note, the multiple comparisons of standard care with SDD and SOD increase the likelihood of type I errors.

Our finding that SDD and SOD have similar effects on survival raises questions about the relevance of systemic therapy with cefotaxime during the first 4 days of gastric and intestinal decontamination. Considering the importance of antibiotic resistance in ICUs, the SOD regimen seems preferable to the SDD regimen because it does not include widespread systemic prophylaxis with cephalosporins and involves a lower volume of topical antibiotics, thus minimizing the risk of selection for and development of antibiotic resistance in the long term. Furthermore, oropharyngeal decontamination with antiseptic agents, such as chlorhexidine, might be an alternative in environments with high levels of antibiotic resistance.[13,30,31]

We thank the nursing and medical staff of the participating ICUs, the hospital pharmacists and medical microbiologists at the participating hospitals, the hospital pharmacists of ZNB of Leeuwarden for preparation of study medications, research nurses Fieke Kloosterman and Ilja te Paske for quality surveys, and Diederick Grobbee, Arno Hoes, Ale Algra, Martin Bootsma, and Jan Vandenbroucke for analytical advice. The study is dedicated to Hilly de Vries-Hospers, M.D., Ph.D., medical microbiologist at the UMC Groningen, who died in 2005.

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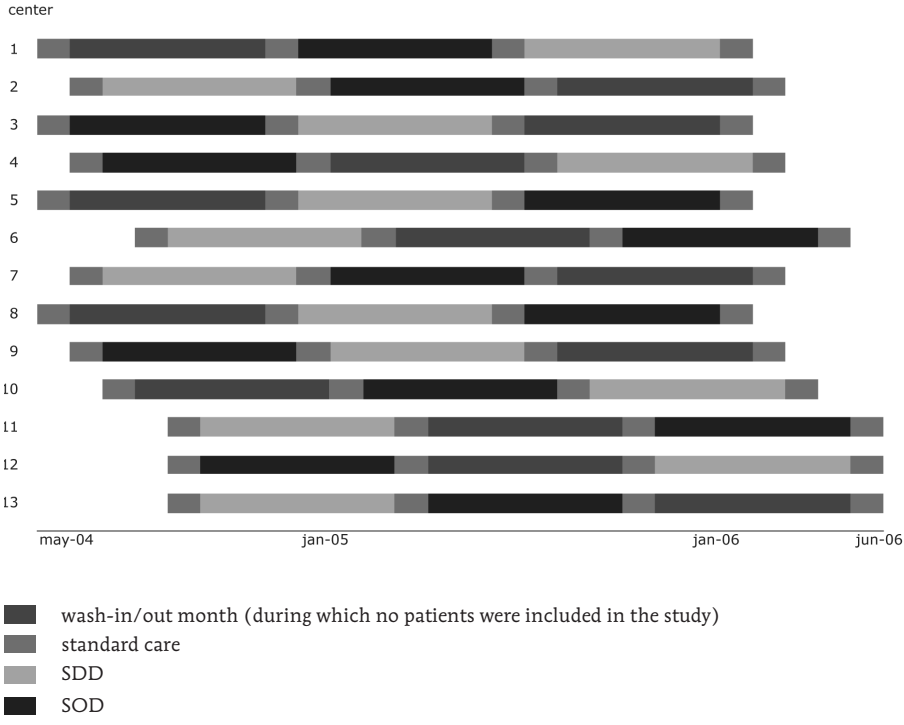
Supplementary appendix

METHODS

The first study period was preceded by a one month wash-in period. In this month, newly admitted patients were already treated according to the center-specific allocation treatment for the first period, but actual inclusion started after this wash-in period. Successive study periods were separated by one month wash-out/wash-in periods. In the first two weeks patients included during the previous study period remained to be treated according to that period, but newly admitted patients already received the treatment of the forthcoming period. After two weeks, patients still receiving treatment according to the previous period were switched to treatment of the forthcoming period. Actual inclusion for the new period only started at the first day of the new period (figure study scheme)

Study scheme in each of the 13 participating centers



SDD regimen

The SDD regimen was identical to that used by de Jonge et al[2], and consisted of oropharyngeal application (every 6 h) of a paste containing polymyxin E, tobramycin and amphotericin B each in a 2% concentration and administration (every 6 h) of a 10 ml suspension containing 100 mg polymyxin E, 80 mg tobramycin and 500 mg amphotericin B via the nasogastric tube. Topical antibiotics were applied until ICU-discharge. The costs of these topical antibiotics was $12 per day. In addition, cefotaxime (1000 mg, every 6 h) was administered intravenously during the first four days of study. Cefotaxime was replaced by ciprofloxacin (twice daily 400 mg) in case of documented cephalosporin allergy. Patients with a clinical suspicion or documented infection when admitted to ICU were treated according to standard clinical practice. In these patients cefotaxime was not added to carbapenems, fluoroquinolones, ceftazidime or piperacillin/tazobactam. Cefotaxime was replaced by ciprofloxacin (twice daily 400 mg) in case of documented cefalosporin allergy.

Protocol modifications for patients with tracheostomy, jejunostomy or colostomy, as well as for those with persistent respiratory tract colonization with yeasts or Gram negative bacteria. In patients with tracheostomy the paste was applied around the tracheostomy. In patients with a duodenal tube or jejunostomy, 5 ml of the suspension was given via the gastric tube and the remaining 5 ml via the duodenal tube or jejunostomy. Patients with colostoma or ileostoma received SDD-suppositories (containing 100 mg polymyxin E, 40 mg tobramycin and 500 mg amphotericin B) twice daily in the distal part of the gut. Surveillance cultures of endotracheal aspirates, oropharyngeal and rectal swabs were performed on admission and twice weekly. Based on these surveillance cultures, several adaptations of the SDD regimen were possible: (a) application of oropharyngeal paste was increased to 8 times daily, if the first surveillance culture of the throat yielded yeasts, until two surveillance cultures were negative; (b) 5 ml (5 mg) amphotericin B was nebulized 4 times daily if a sputum surveillance culture (not admission culture) yielded yeasts, until two sputum cultures became negative; (c) 5 ml (80 mg) polymyxin E was nebulized 4 times daily if a sputum surveillance culture (not admission culture) yielded Gram negative bacteria, until two sputum cultures were negative.

SOD regimen

Protocol modifications for patients with tracheostomy and persistent respiratory tract colonization with yeasts. In patients with tracheostomy the paste was applied around the tracheostomy. Surveillance cultures of endotracheal aspirates and oropharyngeal swabs were performed on admission and twice weekly. Based on these surveillance cultures, adaptation of the SOD regimen was possible: application of oropharyngeal paste was increased to 8 times daily, if the first surveillance culture of the throat yielded yeasts, until two surveillance cultures were negative. The costs of these topical antibiotics were $1 per day.

Microbiology

Surveillance cultures of throat, rectum and sputum were inoculated on McConkey-agar (with and without tobramycin or cefotaxime), blood agar plate, Sabouraud agar plate and a Chocolat agar plate. Surveillance cultures were not obtained from patients during the control period. Microbiological cultures obtained for clinical reasons were processed according to current clinical practice.

Surveillance cultures obtained during the 1-day point prevalence studies were inoculated on selective media: McConkey-agar plates with cefotaxime (8 mg/L) or ciprofloxacin (2mg/L) or polymyxin E (50 IU/ml) or tobramycin 8 mg/L. Cultures were analyzed qualitatively for the presence of Gram-negative bacteria and minimum inhibitory concentrations (MIC) were determined for all Gram negative bacteria growing on the selective media. We analyzed the proportions of pathogens not susceptible to either gentamicin or tobramycin (breakpoint for non-susceptibility 4 mg/L), ciprofloxacin (breakpoint for non-susceptibility 2 mg/L) and ceftazidime (breakpoint for non-susceptibility 16 mg/L) (Clinical and Laboratory Standards Institution. Performance standards for antimicrobial susceptibility testing. Fifteenth information supplement (M100-S15). Wayne, PA, USA: CLSI. 2005).

Microbiological cultures, and fecal samples submitted for Clostridium *difficile* toxin determination, obtained for clinical reasons were processed according to current clinical practice. Occurrence of ICU-acquired bacteremia (i.e., documented >48 hours after ICU-admission) was analyzed for *S. aureus*, Glucose Non-Fermenting Gram-negative Rods (GNF-GNR) (i.e., *Pseudomonas aeruginosa, Stenothrophomonas maltophilia* and Acinetobacter spp), Enterobacteriaceae, *S. pneumoniae* and *Enterococcus spp*.

Oropharyngeal care

Oropharyngeal care consisted of oral washings with sterile water (3-4 times daily). In case of a visually contaminated oropharyngeal cavity, this was cleaned with a swab moistened in 1.5% hydrogen peroxide. Teeth were brushed twice daily. Chlorhexidine was not used for oral care.

Endpoints and statistical analysis

With an estimated ICU-mortality rate of 20% for eligible patients in the participating ICUs and considering a 20% relative reduction of ICU-mortality to be clinically relevant, it was calculated that 1,150 patients would need to be included in each study arm in the absence of any intracluster correlation (β= 0.8 and α= 0.05). No estimates of the intra-cluster correlation coefficient were available, but assuming an intra-cluster coefficient of 0.05 would have increased the required sample size to 1,840 per study arm.

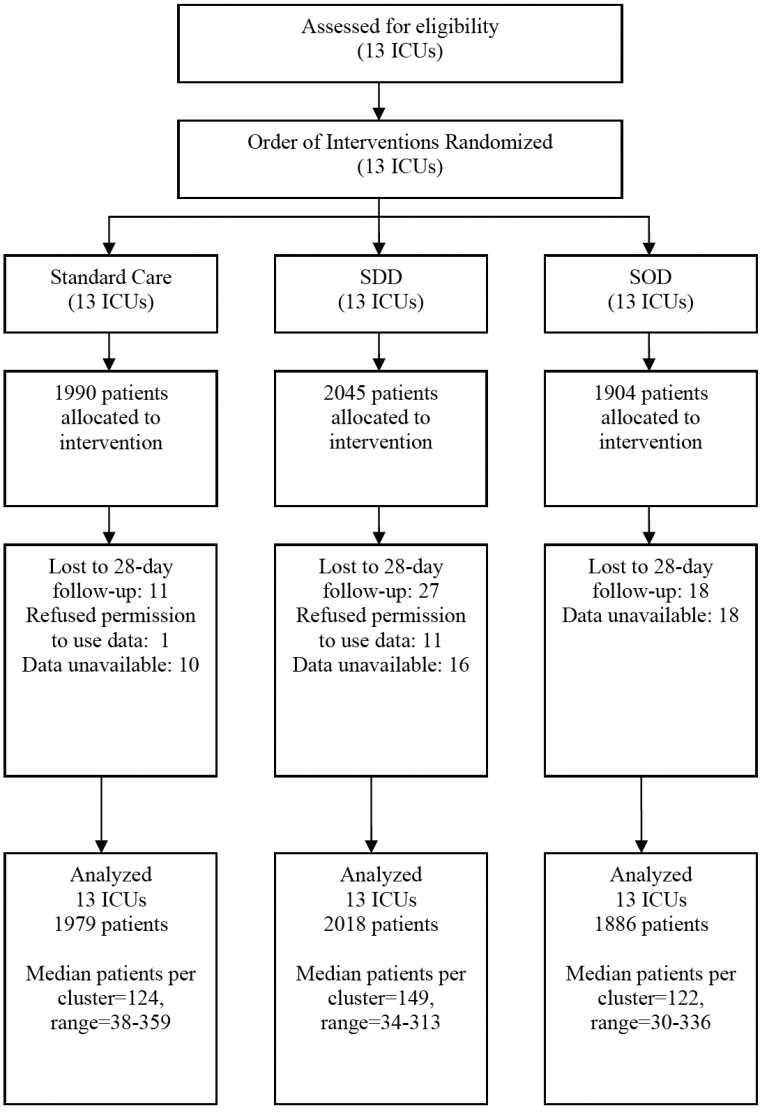
Time to cessation of ventilation, ICU-discharge and hospital-discharge were analysed using Cox regression models, with all observations censored at day 28. Since deaths will lead to informative censoring and act in the opposite direction to any positive effect of the interventions on these outcomes, patients who died were considered to have infinite times to cessation of ventilation or discharge. Analysis of mortality and time-to-event data was performed using STATA 8.0 (STATA Corporation, College Station, Texas). All other statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS,Chicago, Illinois) version 12.0.2.

Results

Patients with cross-over to subsequent study period:

- standard care to SOD: 18
- standard care to SDD: 5
- SOD to standard care: 13
- SOD to SDD: 4
- SDD to standard care: 6
- SDD to SOD: 2

Flowchart


Assessed for eligibility
(13 ICUs)
Order of Interventions Randomized
(13 ICUs)
Standard Care
(13 ICUs)
SDD
(13 ICUs)
SOD
(13 ICUs)
1990 patients
allocated to
intervention
2045 patients
allocated to
intervention
1904 patients
allocated to
intervention
Lost to 28-day
follow-up: 11
Refused permission
to use data: 1
Data unavailable: 10
Lost to 28-day
follow-up: 27
Refused permission
to use data: 11
Data unavailable: 16
Lost to 28-day
follow-up: 18
Data unavailable: 18
Analyzed
13 ICUs
1979 patients
Median patients per
cluster=124,
range=38-359
Analyzed
13 ICUs
2018 patients
Median patients per
cluster=149,
range=34-313
Analyzed
13 ICUs
1886 patients
Median patients per
cluster=122,
range=30-336

Characteristics of the participating ICUs					
Center	Hospital-type	ICU-beds	Number of included patients	Inclusion Rate † (%)	Study order‡
1	university	26	626	92	SC-SOD-SDD
2	teaching	31	681	84	SDD-SOD-SC
3	non-teaching	4	119	71	SOD-SDD-SC
4	teaching	10	200	52	SOD-SC-SDD
5	teaching	10	340	94	SC-SDD-SOD
6	teaching	8	197	90	SDD-SC-SOD
7	teaching	6	147	87	SDD-SOD-SC
8	teaching	12	369	74	SC-SDD-SOD
9	teaching	22	410	57	SOD-SDD-SC
10	university	43	1,013	89	SC-SOD-SDD
11	university	31	777	98	SDD-SC-SOD
12	university	19	646	99	SOD-SC-SDD
13	teaching	23	414	100	SDD-SOD-SC
Totals		197	5,939		

† The number of included patients divided by the number of eligible patients represents the inclusion rate

‡ Standard Care (SC), Selective Oropharyngeal Decontamination (SOD) and Selective Decontamination of the Digestive tract (SDD)

Mortality rates (%) on day 28 in patients with APACHE II-score < or ≥ 20 per participating center and per studygroup						
	APACHE II < 20			APACHE II ≥ 20		
	Studygroup			Studygroup		
Center	Standard Care	SOD	SDD	Standard Care	SOD	SDD
	No. of patients (%)					
1	94 (17.0)	75 (12.0)	76 (6.6)	126 (41.3)	128 (32.8)	127 (31.5)
2	219 (16.9)	150 (20.7)	137 (19.0)	51 (43.1)	52 (40.4)	72 (37.5)
3	36 (13.9)	22 (13.6)	23 (26.1)	18 (38.9)	8 (62.5)	12 (16.7)
4	22 (13.6)	29 (31.0)	39 (17.9)	16 (31.3)	35 (51.4)	59 (44.1)
5	74 (23.0)	57 (26.3)	76 (22.4)	32 (56.3)	61 (32.8)	40 (45.0)
6	13 (23.0)	5 (0.0)	15 (6.7)	54 (31.5)	65 (29.2)	45 (26.7)
7	21 (19.0)	22 (22.7)	20 (15.0)	26 (38.5)	26 (53.8)	32 (56.3)
8	41 (14.6)	49 (18.4)	39 (12.8)	84 (36.9)	74 (32.4)	82 (40.2)
9	60 (25)	45 (24.4)	82 (20.7)	51 (43.1)	57 (54.4)	115 (41.7)
10	248 (16.9)	242 (13.2)	221 (17.2)	112 (37.5)	97 (41.2)	93 (30.1)
11	128 (13.3)	125 (16.8)	162 (12.3)	119 (32.8)	137 (28.5)	106 (34.9)
12	119 (12.6)	108 (14.8)	110 (13.6)	90 (47.8)	106 (31.1)	113 (43.4)
13	78 (29.5)	78 (25.6)	76 (26.3)	58 (56.9)	51 (29.4)	73 (38.4)

Stepwise random effects logistic regression model accounting for ICU-level clustering.

	SDD	SOD	APACHE>=20	AGE>65	POST-OP / SURGICAL	VENTILATED	MALE	z-score of added covariate
1	0.939 (0.816, 1.081) P=0.384	0.950 (0.823, 1.096) P=0.481	-	-	-	-	-	-
2	0.884 (0.753, 1.037) P=0.131	0.900 (0.770, 1.052) P=0.186	3.022 (2.642, 3.456)	-	-	-	-	16.14
3	0.861 (0.744, 0.996) P=0.044	0.891 (0.768, 1.033) P=0.125	2.820 (2.491, 3.193)	1.770 (1.565, 2.001)	-	-	-	9.09
4	0.851 (0.734, 0.986) P=0.031	0.884 (0.762, 1.026) P=0.104	2.618 (2.304, 2.975)	1.868 (1.648, 2.118)	0.624 (0.550, 0.709)	-	-	-7.22
5	0.835 (0.720, 0.968) P=0.017	0.859 (0.740, 0.998) P=0.047	2.563 (2.255, 2.914)	1.869 (1.649, 2.119)	0.608 (0.535, 0.691)	1.679 (1.302, 2.165)	-	3.99
6	0.835 (0.720, 0.968) P=0.016	0.858 (0.739, 0.996) P=0.045	2.565 (2.256, 2.916)	1.870 (1.650, 2.120)	0.607 (0.534, 0.690)	1.670 (1.295, 2.154)	1.093 (0.964, 1.238)	1.39

Odds ratios (95% CIs) from random effects logistic regression models accounting for ICU-level clustering (using the xtlogit command in STATA)

Chapter 4 | Effects of Selective Digestive and Selective Oropharyngeal Decontamination on bacteremia and respiratory tract colonization with Highly Resistant Microorganisms

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In preparation

ABSTRACT

Background

Selective Digestive tract Decontamination (SDD) and Selective Oropharyngeal Decontamination (SOD) were associated with improved day-28 survival in intensive care patients, but the effects on infections and respiratory tract colonization with Highly-Resistant Microorganisms (HRMO) are unknown.

Methods

SDD, SOD and standard care (SC), during periods of six months each, were evaluated in an open clustered group-randomized cross-over study in 13 ICUs, with the order of interventions randomized per center. SOD consisted of four times daily topical application of tobramycin, colistin and amphotericin B in the oropharynx. SDD consisted of SOD and topical application of the same antibiotics in the stomach and four days of intravenous cefotaxime. Cultures of respiratory tract were obtained twice weekly during SDD and SOD, and on clinical indication only during SC. HRMO were defined according to Dutch guidelines. All blood and respiratory tract culture results were evaluated.

Results

5,927 patients were available for analysis: 1,989 (SC), 1,904 (SOD) and 2,034 (SDD). Compared to SC, odds ratios (OR) for ICU-acquired bacteremia were 0.48 (95%CI 0.38-0.60) during SDD and 0.66 (95%CI 0.53-0.82) during SOD. The OR for ICU-acquired bacteremia caused by HRMO during SDD was 0.41 (95%CI 0.18-0.94) as compared to SC, which corresponds to a rate reduction of 59%, an absolute risk reduction (ARR) of 0.6% and a number needed to treat (NNT) of 170. As compared to SOD, the OR for SDD was 0.37 (95%CI 0.16-0.85), which corresponds to a rate reduction of 63%, an ARR of 0.7% and a NNT of 145. ICU-acquired respiratory colonization of Gram-negative bacteria was highest among patients receiving SC. ORs for acquiring HRMO colonization, as compared to SC, were 0.58 (0.43-0.78) and 0.65 (0.49-0.87) for SDD and SOD respectively, corresponding to 38% and 32% rate reductions, 5.5% and 4.6% ARR and with NNT of 18 and 22, respectively. Acquired colonization with cefotaxime-resistant or colistin-resistant pathogens was lowest during SDD.

Conclusions

As compared to SC, ICU-acquired bacteremia and respiratory tract colonization with HRMO were 48% and 59% lower during SDD and acquired respiratory tract colonization with HRMO was 38% lower during SOD.

INTRODUCTION

Infections acquired in Intensive Care Units (ICU) have been associated with higher morbidity and mortality rates and increased health care costs.[1] Reductions in respiratory tract infection rates have been achieved by prophylactic antibiotic regimens, such as Selective Decontamination of the Digestive tract (SDD)[2,3] and Selective Oropharyngeal Decontamination (SOD).[4,5] Yet, prophylactic use of antibiotics may enhance selection of antibiotic resistant pathogens, which is considered the major drawback of these interventions. The concept of SDD consists of prevention of ICU-acquired colonization with Gram-negative bacteria, *S. aureus* and yeasts through application of non-absorbable antimicrobial agents in the oropharynx and gastrointestinal tract, pre-emptive treatment of possible infections with commensal respiratory tract bacteria through systemic administration of cefalosporins during the first four days in ICU, and maintaining the anaerobic intestinal flora through selectively using antibiotics (both topically and systemically) without anti-anaerobic activity.[6,7] SOD consists of oropharyngeal decontamination only, without any specific recommendations on antibiotic use.

We previously reported on the clinical outcomes of a multicenter study in which SOD and SDD, compared to standard care, were both associated with improved day 28 survival and lower incidences of ICU-acquired bacteremia with the most important pathogens.[8] The objective of the present analyses was to quantify the effects of both interventions on respiratory tract colonization and on ICU-acquired bacteremia caused by highly resistant microorganisms (HRMOs).

METHODS

A pragmatic open clustered group-randomized controlled cross-over study was performed in 13 ICUs between May 2004 and July 2006. The participating ICUs differed in size and teaching status, covering all levels of intensive care in the Netherlands. Since the interventions included ecological changes in the ICU, an individualized, randomized design would have led to interference between treated and untreated patients. Therefore, cluster randomization was required and all three study regimens (SDD, SOD and standard care (SC)) were applied to all eligible patients during six months with the order of regimens randomly assigned. Patients admitted to the ICU with an expected duration of mechanical ventilation >48 or an anticipated ICU stay >72 hours were eligible, which was assessed by physicians responsible for patient care in each unit.[8]

The SDD regimen consisted of four days of intravenous cefotaxime and topical application of tobramycin, colistin and amphotericin B in the oropharynx and stomach. The use of 'colonization resistance impairing antibiotics', such as amoxicillin, penicillin, amoxicillin-clavulanic acid and carbapenems was discouraged during the SDD period. Surveillance cultures of endotracheal aspirates and oropharyngeal and rectal swabs were performed on admission and subsequently twice weekly.

SOD consisted of oropharyngeal application of the same paste as used for SDD, with surveillance cultures of endotracheal aspirates and oropharyngeal swabs performed on admission and twice weekly and without restrictions in physicians' choices of systemic antibiotic therapy.

During the standard care period participating ICU's were free to follow their own guidelines and surveillance cultures were not performed in all ICU's. Also there were no restrictions in the choice of systemic antibiotic therapy.

All microbiological culture results from blood and endotracheal aspirate samples obtained from patients included in the study were used for the current analysis. Bacterial growth in respiratory tract samples is labeled as colonization throughout this manuscript. In patients with multiple sputum cultures performed on a single day, the results were interpreted as being one culture. Bacterial growth in sputum samples obtained on the day of admission or any of the two following days were considered 'colonization on admission'. Bacterial growth in samples obtained after this period (from the third day on), and with documented absence in cultures before day three, was considered 'ICU-acquired'.

Blood cultures were obtained on clinical indication, as judged by the responsible physicians, in all three study periods. In patients with several blood cultures on a single day, results were pooled and considered as the results of a single blood culture. Bacterial growth in blood cultures obtained on the day of admission or on any of the two following days were considered as bacteremia on admission. Growth on day three or later was defined as an ICU-acquired bacteremia.

Definition of Highly Resistant Micoorganisms

HRMO were defined according to the national guideline (Table 1).[9] Three main groups of HRMO are distinguished: Enterobacteriaceae, Gram-negative non-fermenters and Gram-positive bacteria. During the study period determination of Extended Spectrum β-Lactamase (ESBL) was not standardized and different methods were used in the participating laboratories. Therefore, resistance to any of the third generation cephalosporins, such as cefotaxime, ceftazidime and ceftriaxon was used as proxy for presence of ESBL in *Escherichia coli* and Klebsiella spp.

Data analysis

Statistical analysis was performed with SPSS for Windows 15.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was defined as a *P* value of less than 0,05. Crude odds ratios were calculated, as were percentages in reduction, absolute risk reduction and number needed to treat. A time to first event analysis was performed using a Kaplan Meier survival analysis with a follow up until 40 days or discharge from the ICU if this was before 40 days. The differences between groups were tested using the logrank test. Patients who had a HRMO isolated after day two in the ICU, with the same species of

Table 1. Definitions of Highly Resistant Microorganisms

Enterobacteriaceae	ESBL*	quinolones	aminoglycosides	carbapenems	cotrimoxazole	
E.coli	A	B	B	A		
Klebsiella spp	A	B	B	A		
Other	A	B	B	A	B	
GNF-GNR	ceftazidime	quinolones	aminoglycosides	carbapenems	cotrimoxazole	piperacilline
Acinetobacter spp	B	B	B	A		
Stenotrophomonas spp					A	
Other (including *Pseudomonas aeruginosa*)	C	C	C	C		C
Gram-positive bacteria	penicillins	glycopeptides	oxacillin	meticillin		
Streptococcus pneumoniae	A	A				
Enterococcus faecium	B	B				
Staphylococcus aureus			A	A		

ESBL extended spectrum β-lactamase

A resistance against an antibacterial agent from one of the indicated groups of this category is sufficient to define the microorganism as highly resistant

B resistance against antibacterial agents from at least two of the indicated groups of this category is required to define the microorganism as highly resistant

C resistance against antibacterial agents from at least three of the indicated groups of this category is required to define the microorganism as highly resistant

* During the study period determination of ESBL was not standardized and multiple different methods were used in the participating laboratories. Therefore, resistance to any of the third generation cephalosporins, such as cefotaxime, ceftazidime and ceftriaxon was used as proxy for presence of ESBL in *Escherichia coli* and Klebsiella spp

HRMO also isolated during the first two days of stay in the ICU were not considered as an event for ICU-acquired HRMO. The same rule was applied for cefotaxime and tobramycin resistant Gram-negative rods.

RESULTS

A total of 5,939 patients were included and data from 5,927 patients were available for analysis: 1,989 patients received SC during 26,908 patientdays, 1,904 received SOD during 25,006 patientdays and 2,034 received SDD during 27,068 patientdays (Table 2).

Bacteremia and candidemia

Blood cultures were obtained from 3,421 patients with frequencies of 0.11, 0.13 and 0.11 blood cultures per patientday during SC, SOD and SDD, respectively (Table 3). During the first two days of ICU-admission bacteremia occurred in 305 patients; 128 (6.4%) during SC, 83 (4.4%) during SOD and 94 (4.6%) during SDD. In 12 patients (0.2%) bacteremia on admission was caused by HRMO (6, 3 and 3 during SC, SOD and SDD, respectively).

In all, 5,463 patients (92%) had an ICU-stay of ≥ 3 days: 1,837, 1,758 and 1,868 in SC, SOD and SDD, respectively. Compared to SC, odds ratios (OR) for developing ICU-acquired bacteremia were lower during SDD (OR 0.48 (95%CI 0.38-0.60)) and SOD (OR 0.66 (95%CI 0.53-0.82)). For ICU-acquired bacteremia SDD was, as compared to SC, associated with a 48% rate reduction, a 6.3% absolute risk reduction (ARR) and a number needed to treat (NNT) of 26. Both SDD and SOD were associated with reductions in ICU-acquired bacteremia caused by Glucose Non-Fermenting Gram-negative Rods,

Table 2. Patient populations and microbiological sampling

	Study groups		
	Standard Care N=1,989	**SOD N= 1,904**	**SDD N=2,034**
No. of patientdays	26,908	25,006	27,068
No. of patients with LOS ≥ 3 days (%)	1,837 (92)	1,758 (92)	1,868 (92)
Blood cultures			
No. of patients with one or more blood cultures (%)	1,125 (56.6)	1,194 (62.7)	1,102 (54.2)
No. of days with one ore more blood culture(s)	2,988	3,180	2,887
No. of blood culture days/patientdays	0.11	0.13	0.11
Sputum cultures			
No. of patients with one or more sputum cultures during first 2 days in ICU (%)	688 (34.6)	1,044 (54.8)	1,025 (50.4)
No. of sputum culture days during the first two days in ICU (No. of patientdays)	762 (5,919)	1,184 (5,653)	1,125 (6,053)
No. of sputum culture days/patientdays during first two days in ICU	0.13	0.20	0.19
No. of sputum culture days after day two in ICU (No. of patient days)	4,422 (20,989)	5,651 (19,353)	6,260 (21,015)
No. of sputum culture days/patientdays after day 2 in ICU	0.21	0.29	0.30

Table 3. Incidences of ICU-acquired bacteremia and candidemia

	Study groups			Crude Odds Ratio (95%CI)		
	SC N=1837	SOD N=1758	SDD N=1868	SDD vs SC	SOD vs SC	SDD vs SOD
All microorganisms, excluding CNS#	239 (13.0)	158 (9.0)	124 (6.6)	0.48 (0.38-0.60)	0.66 (0.53-0.82)	0.72 (0.56-0.92)
GNF-GNR¶	38 (2.1)	19 (1.1)	21 (1.1)	0.54 (0.31-0.92)	0.52 (0.30-0.90)	NS
Enterobacteriaceae	91 (5.0)	69 (3.9)	23 (1.2)	0.24 (0.16-0.39)	0.78 (0.57-1.08)	0.30 (0.19-0.49)
Enterococcus spp	61 (3.3)	52 (3.0)	51 (2.7)	NS	NS	NS
Candida spp and other yeasts†	18 (1.0)	20 (1.1)	6 (0.3)	0.33 (0.13-0.82)	NS	0.28 (0.11-0.70)
Staphylococcus aureus	29 (1.6)	9 (0.5)	8 (0.4)	0.27 (0.12-0.59)	0.32 (0.15-0.68)	NS
Anaerobic microorganisms	16 (0.9)	14 (0.8)	13 (0.7)	NS	NS	NS
Other gram positive microorganisms	31 (1.7)	24 (1.4)	18 (1)	NS	NS	NS
No. of HRMO episodes	19	20	8	0.41 (0.18-0.94)	1.10 (0.59-2.07)	0.37 (0.16-0.85)
- Acinetobacter spp	2	-	1			
- *Enterobacter cloacae*	5	8	-			
- *Escherichia coli*	6	6	2			
- Klebsiella spp	3	3	3			
- *Pseudomonas aeruginosa*	2	-	1			
- *Stenothrophomonas maltophilia*	1	-	-			
- *Serratia marcescens*	-	2	-			
- Hafnia spp	-	1	-			
- *MRSA**	-	-	1			

NS not significant
\# CNS coagulase negative staphylococci
¶ Glucose Non-Fermenting Gram-negative Rods; Pseudomonas aeruginosa, Stenotrophomonas maltophilia and Acinetobacter species
* MRSA: meticillin resistant Staphylococcus aureus (one patient in SDD group at day 24)
† One Saccharomyces cerevisiae in the Standard Care group

Enterobacteriaceae and *Staphylococcus aureus* (Table 3). SDD, but not SOD, was also associated with a lower incidence of ICU-acquired candidemia (OR 0.33 (95% CI 0.13-0.82)).

When compared to SOD, SDD treated patients had lower ORs of developing ICU-acquired bacteremia (0.72, 95%CI 0.56-0.92)) and candidemia (OR 0.28; 95%CI 0.11-0.70). These odds ratios correspond to a 26% rate reduction, a 2.4% ARR and a NNT of 43 for bacteremia and a rate reduction of 72%, an ARR of 0.8% and a NNT of 127 for candidemia. The difference in bacteremia rates between SOD and SDD patients mainly resulted from lower incidences of infections caused by Enterobacteriaceae (OR 0.30; 95%CI 0.19-0.49) (Table 3).

There were 47 episodes of ICU-acquired bacteremia caused by HRMO: 8 during SDD and 19 and 20 during SC and SOD, respectively. Odds ratios for developing ICU-acquired bacteremia caused by HRMO during SDD were 0.41 (95%CI 0.18-0.94) as compared to SC, which corresponds to a rate reduction of 59%, an ARR of 0.6% and a NNT of 170. As compared to SOD the odds ratio for SDD was 0.37 (95%CI 0.16-0.85), which corresponds to a rate reduction of 63%, an ARR of 0.7% and a NNT of 145 (Table 3).

Respiratory tract colonization

In all, 19,404 microbiological cultures from endotracheal aspirates were performed. When divided between the time periods of analysis, frequencies of microbiological cultures from endotracheal aspirates were lowest during SC (0.13 and 0.21 per patientday during the first three days in ICU and from day three on in ICU, respectively). These frequencies were 0.2 and 0.19 per patientday for SOD and SDD for the first three days in ICU and 0.29 and 0.30, respectively, for the periods from day three on (Table 2). Culture frequency, therefore, was 30% lower during SC.

On admission, endotracheal aspirate cultures were obtained from 688 (34.6%), 1044 (54.8%) and 1025 (50.4%) patients during SC, SOD and SDD, respectively. GNF-GNR were found in 9.3%, 7.7%, and 6.3% of SC, SOD and SDD patients with cultures obtained, respectively. Proportions were (during SC, SOD and SDD) 19.9%, 15.9% and 15.6% for Enterobacteriaceae; 29.5%, 33.3% and 34.9% for Candida spp. (or other yeasts). The prevalence of HRMO at the time of ICU-admission was low, ranging from 2.4% during SDD and 3.9% during SOD, and was not statistically significant between study groups.

Cultures of endotracheal aspirates had been obtained from 2,595 of 5,463 patients with an ICU-stay of ≥ 3 days: 881 (49%) of 1,837 during SC, 886 (50%) of 1,758 during SOD and 828 (44%) of 1,868 during SDD.

After day three in the ICU, acquisition of colonization of all groups of Gram-negative bacteria was highest among patients receiving SC. Acquisition rates of Acinetobacter species and *Stenotrophomonas maltophilia* (gathered as one group) and of other GNF-GNR (predominantly *Pseudomonas aeruginosa*) were comparable among patients

Table 4. ICU-acquired respiratory tract colonization

	No. of patients with LOS ≥ 3 days and with sputum culture			Crude Odds Ratio (95%CI)		
	SC N=881	SOD N=886	SDD N=828	SDD vs SC	SOD vs SC	SDD vs SOD
Acinetobacter spp and *Stenotrophomonas maltophilia*	123 (14.0)	92 (10.4)	92 (11.1)	0.77 (0.57-1.03)	0.71 (0.53-0.95)	1.08 0.79-1.46
Other GNF-GNR ¶	215 (24.4)	149 (16.8)	167 (20.2)	0.78 (0.62-0.98)	0.63 (0.50-0.79)	1.25 (0.98-1.60)
Escherichia coli and Klebsiella spp	300 (34.1)	185 (20.9)	63 (7.6)	0.16 (0.12-0.21)	0.51 (0.41-0.63)	0.31 (0.23-0.42)
Other Enterobacteriaceae	323 (36.7)	230 (26.0)	130 (15.7)	0.30 (0.26-0.41)	0.61 (0.49-0.74)	0.53 (0.42-0.68)
Other gram negative microorganisms†	133 (15.1)	60 (6.8)	14 (1.7)	0.10 (0.06-0.17)	0.41 (0.30-0.56)	0.24 (0.13-0.43)
Enterococcus spp #	37 (4.2)	32 (3.6)	93 (11.2)	2.89 (1.95-4.29)	0.85 (0.53-1.39)	3.38 (2.23-5.11)
Candida spp and other yeasts	393 (44.6)	476 (52.7)	465 (56.2)	1.59 (1.31-1.93)	1.44 (1.20-1.74)	1.10 0.91-1.33
Aspergillus spp and other fungi	28 (3.2)	43 (4.9)	47 (5.7)	1.83 (1.14-2.96)	1.55 (0.96-2.52)	1.18 (0.77-1.80)
Staphylococcus aureus	174 (19.8)	111 (12.5)	95 (11.5)	0.53 (0.40-0.69)	0.58 (0.45-0.75)	0.90 (0.68-1.21
Streptococcus pneumoniae	15 (1.7)	18 (2.0)	5 (0.6)	0.35 (0.13-0.97)	1.20 (0.60-2.39)	0.29 (0.11-0.79)
Acquired HRMO	128 (14.5)	88 (10.0)	74 (8.9)	0.58 (0.43-0.78)	0.65 (0.49-0.87)	0.89 (0.64-1.23)
- Acinetobacter spp	14	3	7			
- *Stenothrophomonas maltophilia*	8	6	7			
- *Pseudomonas aeruginosa*	29	9	10			
- Other GNF-GNR	3	5	20			
- Enterobacter spp	18	19	9			
- *Escherichia coli*	23	9	4			
- Klebsiella spp	22	21	9			
- Citrobacter spp	4	3	0			
- Morganella spp	1	0	1			
- Proteus spp	2	0	2			
- *Serratia marcescens*	3	9	3			
- *Streptococcus pneumoniae*	1	2	0			
- *Staphylococcus aureus*	0	2	2			

NS not significant

¶ GNF-GNR: Glucose Non-Fermenting Gram-negative Rods such as Acinetobacter spp

‡ 2 patients in SOD and 2 patients in SDD group acquired meticillin resistant *Staphylococcus aureus*

no vancomycin resistant Enterococci

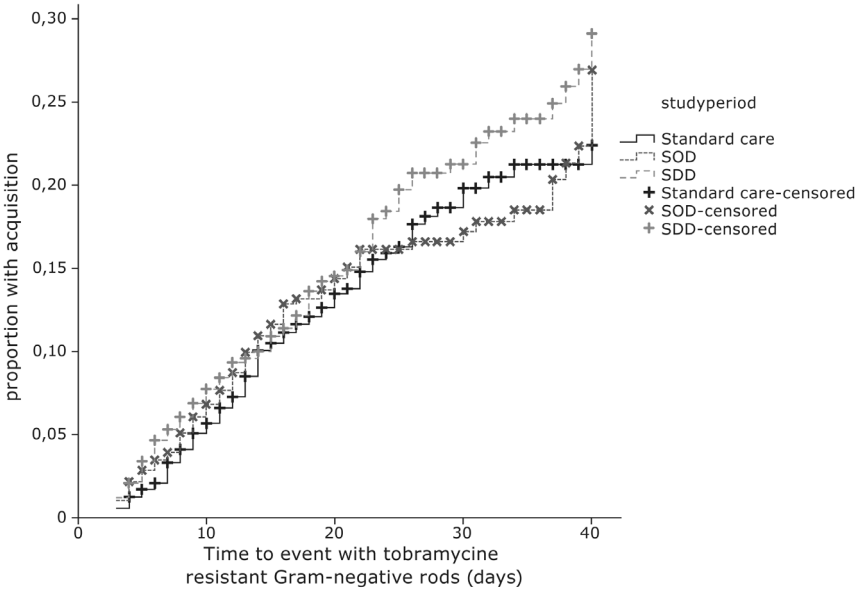
† Haemophilus spp, Neisseria spp and Pasteurella spp

receiving SDD or SOD. Yet, acquired colonization with Enterobacteriaceae was markedly lower among patients receiving SDD, as compared to SOD (Table 4).

Among Gram-positive bacteria acquired colonization with enterococci occurred most frequently in patients receiving SDD; ORs being 2.89 (1.95-4.29) and 3.38 (2.23-5.11) when compared to SC and SOD, respectively. Acquired carriage with yeasts and fungi occurred more frequently in patients receiving SDD and SOD than SC (Table 4).

After day three in ICU, acquired colonization with HRMO was documented in 290 patients. Acquisition with HRMO occurred most frequently during SC (14.5%) and less frequently during SDD (8.9%) and SOD (10.0%). The crude ORs for acquiring colonization with HRMO, as compared to SC, were 0.58 (0.45-0.78) and 0.65 (0.49-0.87) for SDD and SOD respectively. As compared to SC, SDD and SOD were associated with 38% and 32% rate reductions, 5.5% and 4.6% ARR and with a NNT of 18 and 22, respectively. Gram-negative bacteria accounted for 98% of all HRMO. Four patients acquired respiratory tract colonization with meticillin resistant Staphylococcus aureus (MRSA). This occurred in two centers, for two patients receiving SOD and two receiving SDD. None of the patients acquired Vancomycin Resistant Enterococci (VRE) (Table 4).

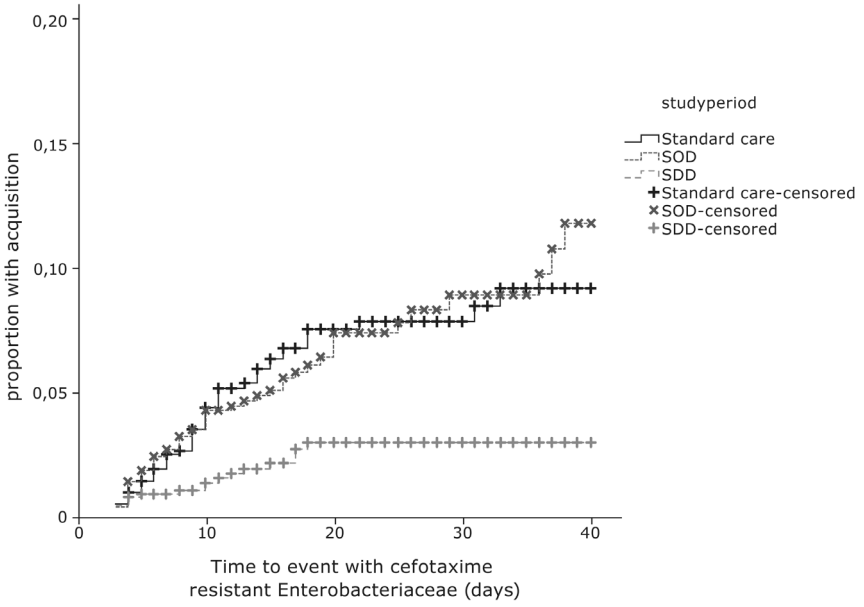
Figure 1. TTE Tobramycin resistant Gram-negative rods;
P-values SDD vs SC 0.142; SOD vs SC 0.497; SDD vs SOD 0.423



Tobramycin and colistin were used as topical antibiotics in all patients during SOD (only in oropharyngeal paste) and SDD (in oropharyngeal paste and enteral suspension). Cefotaxime was administered intravenously during the first four days in all patients receiving SDD. Gram-negative bacteria resistant to either of these antibiotics were rarely found during the first two days of ICU-admission. In all, 13 (1.9%), 42 (4.0%) and 30 (2.9%) patients were colonized with a Gram-negative bacterium resistant to tobramycin on ICU-admission, during SC, SOD and SDD respectively. Presence of cefotaxime resistance was only analyzed for Enterobacteriaceae, and prevalence rates on admission were 1.3%, 1.9% and 2.9% during SC, SOD and SDD, respectively.

ICU-acquired colonization with Gram-negative bacteria resistant to tobramycin occurred with equal frequency and at equal times during all three study periods (Figure 1). Although acquisition with tobramycin-resistant Enterobacteriaceae was lowest during SDD, this was compensated by higher acquisition rates of tobramycin-resistant non-fermenting Gram-negative rods (Table 5). Acquired colonization with cefotaxime-resistant Enterobacteriaceae occurred less frequent and later during SDD (Figure 2). SDD was associated with a 62% reduction in acquisition rate of cefotaxime-resistant Enterobacteriaceae, corresponding to an ARR of 4% and a NNT of 26.

Figure 2. TTE cefotaxime resistant *Enterobacteriaceae*,
P-values: SDD vs SC 0.000; SOD vs SC 0.952; SDD vs SOD 0.000



The incidence of ICU-acquired respiratory tract colonization with Gram-negative bacteria intrinsically resistant to colistine (i.e. Proteus species and Serratia species) was lowest during SDD (6.6%) with ORs for SDD of 0.41 (95%CI 0.29-0.57) and 0.49 (95%CI 0.5-0.69) compared to SC and SOD, respectively. These ORs correspond to rate reductions of 55% and 48%, ARR of 8% and 6% and NNT of 12 and 17 for SDD as compared to SC and SOD, respectively.

The consequences of the lower culture frequency during SC, were further investigated by comparing ORs for acquired colonization with Enterobacteriaceae, non-fermenters and Candida species for the units with comparable culture frequencies in all three study periods and those with lower culture frequencies during SC. The average

Table 5. ICU-acquired respiratory tract colonization with tobramycin, colistin and/or cefotaxime resistant Gram-negative bacteria

	No. of patients with LOS ≥ 3 days and with sputum culture			**Crude Odds Ratio (95%CI)**		
	SC N=881	SOD N=886	SDD N=828	SDD vs SC	SOD vs SC	SDD vs SOD
Tobramycin resistance:						
- *Escherichia coli* and Klebsiella spp	31 (3.5)	19 (2.1)	9 (1.1)	0.30 (0.14-0.64)	0.60 (0.34-1.07)	0.50 (0.23-1.11)
- Other Enterobacteriaceae	25 (2.8)	41 (4.6)	15 (1.8)	NS	1.66 (1.00-2.76)	0.38 (0.21-0.69)
- Acinetobacter spp and *Stenotrophomonas maltophilia*	40 (4.5)	45 (5.1)	49 (5.9)	NS	NS	NS
- Other GNF-GNR¶	18 (2.0)	20 (2.3)	49 (5.9)	3.02 (1.74-5.2)	2.72 (1.60-4.60)	NS
- Any Gram-negative rods	104 (11.8)	112 (12.6)	115 (13.9)	1.21 (0.91-1.60)	1.08 (0.81-1.44)	1.11 (0.84-1.47)
Cefotaxime resistance:						
- *Escherichia coli* and Klebsiella spp	13 (1.5)	12 (1.4)	2 (0.2)	0.16 (0.04-0.72)	NS	0.18 (0.04-0.79)
- Other Enterobacteriaceae	44 (5.0)	42 (4.7)	18 (2.2)	0.42 (0.24-0.74)	NS	0.45 (0.25-0.78)
- With any Enterobacteriaceae	56 (6.4)	56 (6.3)	20 (2.4)	0.36 (0.22-0.61)	0.99 (0.68-1.46)	0.37 (0.22-0.62)
Colistine resistance:						
- Proteus spp and Serratia spp	130 (14.8)	112 (12.6)	55 (6.6)	0.41 (0.29-0.57)	0.84 (0.64-1.10)	0.49 (0.35-0.69)

¶ GNF-GNR: Glucose Non-Fermenting Gram-negative Rods such as Pseudomonas aeruginosa

culture frequencies in these subgroups were 0.30, 0.31 and 0.32 and 0.18, 0.30, 0.30 respiratory tract cultures per day during SC, SOD and SDD, respectively. The ORs for acquisition of Enterobacteriaceae, though, were comparable, being 0.19 (0.12-0.30) and 0.17 (0.12-0.24) for SDD versus SC; 0.52 (0.36-0.75) and 0.64 (0.50-0.82) for SOD versus SC; and 0.36 (0.22-0.60) and 0.26 (0.18-0.39) for SDD versus SOD, for the centers without and with lower culture frequencies during SC respectively. Odds ratios were also comparable for the other groups of pathogens (data not shown).

DISCUSSION

In ICU settings with low levels of antibiotic-resistance, the use of SDD during a period of six months was, as compared to Standard Care, associated with 48% and 59% reductions in ICU-acquired bacteremia and respiratory tract colonization rates caused by Highly Resistant Microorganisms (HRMO). SOD was, as compared to SC, associated with a 38% reduction in acquired respiratory tract colonization rates caused by HRMO, but not with statistically significant reductions in HRMO bacteremia rates. Acquired respiratory tract colonization with enterococci and Candida species were higher in patients receiving SDD or SOD. The daily usage of topical tobramycin and colistine was not associated with higher acquisition rates of Gram-negative bacteria resistant to these antibiotics. The four-day intravenous administration of cefotaxime as part of SDD was associated with a 62% reduction in the acquisition rate of cefotaxime-resistant Enterobacteriaceae in the respiratory tract, as compared to both SC and SOD.

Our study is the largest prospective evaluation of topical antimicrobial prophylaxis in ICU patients. In 13 Dutch ICUs a cluster-randomized study design was used and local investigators were responsible for inclusion of eligible patients. As the need for informed consent was waived, an estimated overall inclusion rate of 89% was achieved. Nevertheless, there were slight differences in the baseline characteristics between the study groups.[8] Patients in the SDD and SOD groups had higher APACHE II scores, were older, more often mechanically ventilated and more likely to be admitted to the ICU for non-surgical reasons compared to the patients in the standard care group. All these differences suggest that patients receiving SDD or SOD were more severely ill than those receiving standard care. The reductions in day-28 mortality were only apparent after adjustment for these baseline differences. In the current analysis of microbiological outcomes no adjustments were made for these baseline differences. As a result, reported differences between standard care and both intervention periods should, therefore, be considered as conservative estimates.

Another imbalance between the standard care population and both intervention groups is the culture frequency of respiratory tract samples. Respiratory tract samples were obtained twice weekly during SDD and SOD, as part of study protocol, but this was not protocolized during standard care. As a result, culture frequency was 30% lower during standard care, which might have introduced a negative detection bias for ICU-

acquired colonization. It is also possible that endotracheal cultures were more frequently performed in the more severely ill patients during standard care, which could have introduced a positive selection bias. However, when comparing ICUs with similar frequencies of obtaining respiratory tract samples during all three periods to those in which sampling occurred less frequently during SC, odds ratios for acquisition of pathogens were similar. This suggests that the effect of this potential detection bias was limited.

Importantly, there were no significant differences in baseline characteristics and in culture frequencies between patients receiving SDD and SOD. Our data, therefore, allow determination of the effects of enteral decontamination in combination with intravenous administration of cefotaxime during the first four days in ICU on acquisition of respiratory tract colonization. The latter combination was associated with a marked reduction in acquired respiratory tract colonization with Enterobacteriaceae, but not with that of non-fermenting Gram-negative rods, such as Acinetobacter species, *S. maltophilia* and *P. aeruginosa*. As most of the non-fermenters are intrinsically resistant to cefotaxime, it appears that intestinal colonization is a relevant source for Enterobacteriaceae, but not for non-fermenters.

As reported previously, the clinical outcomes, as measured by day-28 mortality, were comparable between patients receiving SDD and SOD[8], and a preference for either of both regimens was, therefore, difficult to make. In the present study we have documented large (and highly significant) relative reductions in bacteremia and acquired colonization rates between both interventions. The clinical significance of these findings can best be expressed in numbers needed to treat (NNT). In fact, 37, 127 and 170 patients should be treated with SDD, as compared to SOD, in order to prevent one episode of bacteremia caused by Enterobacteriaceae, Candida species or HRMO, respectively. The attributable effects of such episodes on survival and length of stay will determine whether these figures justify a preference of SDD over SOD. In our study, with 1904 and 2034 patients receiving SOD and SDD, respectively, these differences in bacteremia rates did not yield significant differences in outcome.[8]

The NNT to prevent one episode of acquired colonization with cefotaxime-resistant Enterobacteriacea or with Enterobacteriaceae intrinsically resistant to colistine were 26 and 17, respectively. Yet, this beneficial effect on the acquisition with cefotaxime-resistant Enterobacteriaceae, is, at least partly, balanced by higher acquisition rates with non-fermenters that are intrinsically resistant to this antibiotic. In all, acquisition rates of acquired respiratory tract colonization with HRMO did not differ significantly between both regimens.

Enhanced selection of antibiotic resistant microorganisms has been considered an important threat of SDD and SOD.[10] The results of our study suggest the opposite. SDD was associated with a 48% reduced HRMO bacteremia rate, and both interventions yielded reductions in acquired respiratory tract colonization with HRMO of 32% for

SOD and 38% for SDD. Moreover, as compared to standard care, SOD was not associated with higher rates of acquired colonization with Gram-negative bacteria resistant to tobramycin or colistin and SDD was even associated with reduced acquisition rates with bacteria resistant to cefotaxime and colistin. These findings confirm the results from another single-center study in the Netherlands, in which SDD was also associated with lower proportions of patients colonized with resistant pathogens in the respiratory tract.[3]

The benefits of prophylactic antibiotic use should always be balanced against the inevitable risks of selection of antibiotic resistant bacteria. As such, the widespread usage of topical antimicrobial prophylaxis in ICU-patients has been subjected to debate for years. The beneficial effects of SDD and SOD on patient outcome, together with the favourable results on infections and colonization with antibiotic-resistant pathogens obtained in our study, justify the widespread use of these interventions in settings with low levels of antibiotic resistance. Yet, the long-term consequences on resistance development should be monitored. Our results also warrant further studies in settings with higher baseline resistance levels.

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Chapter 5 | Decontamination of the Digestive Tract and Oropharynx: Hospital Acquired Infections after Discharge from the Intensive Care Unit

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ABSTRACT

Objective

To determine the incidence rates of hospital acquired infections (HAI) during the first 14 days after ICU discharge after treatment during ICU-stay with Selective Decontamination of the Digestive tract (SDD), Selective Oropharyngeal Decontamination (SOD) or standard care (SC).

Design

Prospective observational study.

Setting

ICUs in two tertiary care hospitals.

Patients

Patients discharged from the ICU to the ward.

Interventions

None.

Measurements and results

Post-ICU incidences of HAI per 1000 days at risk were 11.2, 12.9 and 8.3 for patients that had received SDD (n=296), SOD (n=286) or SC (n=289) respectively in ICU, yielding relative risks, as compared to SC, of 1.49 (CI_{95} 0.9-2.47) for SOD and 1.44 (CI_{95} 0.87-2.39) for SDD. Incidences of surgical site infections (per 100 surgical procedures) were 4 after SC and 11.8 and 8 after SOD and SDD (p=0.04). Among patients that succumbed in the hospital after ICU-stay (n=58) eight (14%) had developed HAI after ICU discharge; 3 of 21 after SDD, 3 of 15 after SOD and 2 of 22 after SC.

Conclusions

Incidences of HAI in general wards tended to be higher in patients that had received either SDD or SOD during ICU-stay, but it seems unlikely that these infections have an effect on hospital mortality rates.

INTRODUCTION

Prophylactic antibiotic regimens, such as Selective Decontamination of the Digestive tract (SDD) and Selective Oropharyngeal Decontamination (SOD) reduce the incidence of respiratory tract infections (RTI) in Intensive Care Unit (ICU) patients and improve survival.[1-6] The concept of SDD, developed in the 1980's[7,8] consists of prevention of secondary colonization with Gram-negative bacteria, *S. aureus*, and yeasts through application of non-absorbable antimicrobial agents in the oropharynx and gastrointestinal tract. Further it consists of pre-emptive treatment of possible infections due to commensal respiratory tract bacteria through systemic administration of cephalosporins during the first four days in ICU and maintaining the anaerobic intestinal flora through the use of antibiotics (both topically and systemically) not active against anaerobic bacteria.[8] In meta-analyses, three single center randomized studies and a recent multicenter trial, SDD was associated with improved patient survival.[1,4,6,9-11] SOD (application of topical antibiotics in the oropharynx only) might be an alternative to SDD, as they are both effective in reducing day 28 mortality in a recent multi-center study.[6]

SDD (and to lesser extent SOD) aim to extensively modulate the microbial ecology of patients. It is unknown how discontinuation of these interventions at ICU discharge changes the patients' microbial ecology and whether this influences their immediate risk of infections. The current study was motivated by the findings from de Jonge et al.[4] In their SDD study the observed relative risk reduction (RRR) in ICU mortality of 35% reduced to 22% at hospital discharge. This reduction in survival benefit after ICU discharge might have been related to an increased incidence of hospital acquired infection (HAI) in those patients that had received SDD in ICU. Nested within a multicenter SDD-SOD trial we prospectively monitored the occurrence of HAI during the first 14 days after ICU discharge in all patients transferred to regular wards in two university hospitals.

PATIENTS AND METHODS

Setting

The study was conducted in two tertiary care hospitals: the University Medical Center Utrecht and the Leiden University Medical Center. Nested within a multi-center SDD-SOD trial[6] the occurrence of HAI during the first 14 days after ICU discharge was prospectively monitored in all patients transferred to regular wards.

Study design, data collection and definitions

In ICU, patients with an expected stay ≥ 72 h, or with an expected duration of mechanical ventilation ≥ 48 h, had received either SDD, SOD or standard care (SC), which rotated in 6-month periods, as described previously.[6]

Data were collected from patient records for a maximum of 14 days post-ICU. The following data were recorded for each patient: gender, age, length of stay at the ICU,

mechanical ventilation and APACHE II score at the ICU. At the wards medical records were prospectively reviewed twice weekly by an Infection Control Professional for HAI according to the Centers for Disease Control and Prevention (CDC) definitions.[12,13]

In the surveillance period the following HAIs (and day of diagnosis) were registered in both hospitals: surgical site infections (SSI), bloodstream infections (BSI), and RTI. In one of the hospitals oropharyngeal infections were also registered. Infection control policies (other than the subject of the study) did not change during the period of the study in either hospital.

Data analysis

The incidence of HAI was expressed per 1,000 days at risk, i.e. days until first HAI, day of discharge or end of observation period. The proportion of patients with HAI was expressed as the total number of patients with HAI per 100 patients surveyed post-ICU, with 95%-confidence interval (CI_{95}). The total number of SSIs was expressed per 100 patients with surgical procedures. Statistical analysis was performed with SPSS for Windows 12.0.1 (SPSS, Inc., Chicago, IL, USA). Differences in continuous variables between groups were determined by Student's *t*-test. Differences in proportions of HAI (with CI_{95}) in the successive study periods were determined. Statistical significance was defined as a *p*-value of less than 0.05.

RESULTS

Patients

Between May 2004 and July 2006, 871 patients were included; 289 after SC, 286 after SOD and 296 SDD (figure 1). Reasons for patients being lost to follow-up (n=122) mainly included their transfer to other hospitals after ICU discharge. Although fewer patients in the SC group had received mechanical ventilation in ICU (84% versus 96% and 94% in SOD and SDD, respectively), other characteristics (such as age, sex, Apache II-score on ICU admission and surgical or non-surgical reasons for admission) were comparable for all three groups (Table 1).

End points

The numbers of patients with HAI were 23, 34 and 34 from the SC, SOD and SDD groups, respectively, yielding incidences per 1,000 days at risk of 8.3, 12.9 and 11.2 for SC, SOD and SDD, respectively (Table 2). As compared to SC, the relative risks for developing HAI in the first 14 days after ICU discharge were 1.49 (CI_{95} 0.9-2.47) after SOD and 1.44 (CI_{95} 0.87-2.39) after SDD. Oropharyngeal infections, only registered in one hospital, occurred in one patient after SC and in four patients after SOD.

Most infections were RTI, with similar incidences and similar time until diagnosis in all three study groups (Table 2). Adjustment for the difference in number of mechanically ventilated patients in ICU did not change these observations. Incidences

Figure 1 Flowchart

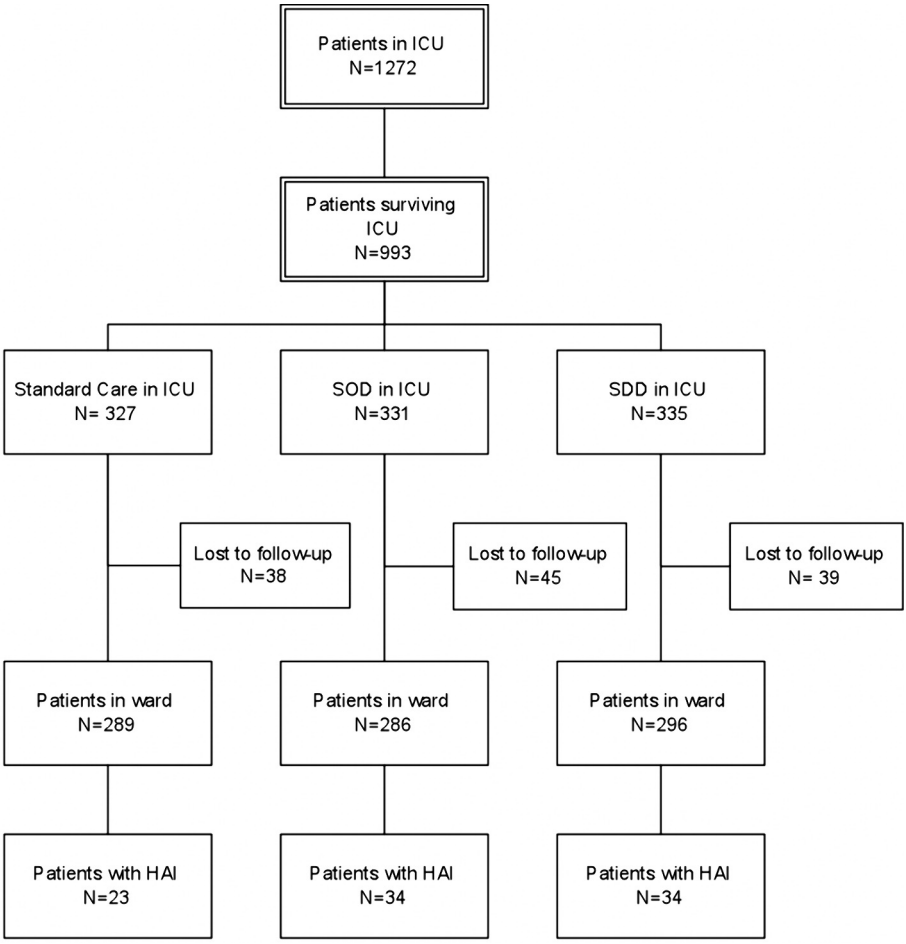

Table 1. Patients characteristics

	Standard Care	SOD	SDD
No. of patients	289	286	296
Sex (male/female)	187/102	181/105	180/116
Age			
Mean (median)	56.7 (59)	57.9 (61)	57.0 (60)
SD	18	17,1	17,5
Range	16-93	12-87	16-87
APACHE II at ICU admission			
Mean (median)	18.9 (18)	19.8 (19)	20.1 (19)
SD	7.85	7.86	7.98
Range	4-48	4-45	0-45
LOS in ICU			
Mean (median)	13.6 (8)	12.6 (8)	14.2 (9)
SD	15	11,8	15,1
Range	1-141	1-93	1-121
Mechanical ventilation in ICU			
Yes (%)	243 (84)*	274 (96)*	279 (94)*
No	46	12	17
Specialty			
Cardiology	9	15	10
Cardiothoracic surgery	13	27	16
Surgery	109	94	117
Medical	61	54	61
Pulmonology	8	8	7
Neurosurgery	38	49	43
Neurology	28	26	23
Other	23	13	19
No. of surgical patients	126	127	137

LOS length of stay

* Standard Care vs. SOD and SDD significantly different ($p = 0.000$), no difference between SOD and SDD.

of BSI were also similar between the three groups, but the duration until infection tended to be longer in the post-intervention groups (means of 4.8 for SC and 7.7 days for SOD and SDD combined, p=0.17 when comparing SC to SDD and SOD combined). Incidences of SSI, expressed per 100 surgical procedures were 4 after SC, as compared to 11.8 after SOD and 8 after SDD (p= 0.04 when comparing SC to SDD and SOD combined). Among the 26 patients with SSI in both post-intervention groups, 18 were diagnosed with superficial infections (15 patients not cultured or with a negative culture) and in 7 patients *Staphylococcus aureus* was documented as the cause of SSI.

Hospital mortality at discharge was 7.6% (22 patients) in the SC group, 5.2% (15 patients) in the SOD group and 7.1% (21 patients) in the SDD group. Hospital mortality among patients that developed HAI was 8.7% (n=2), 8.8% (n=3) and 8.8% (n=3).

DISCUSSION

Incidences of HAI in general wards tended to be higher in patients that had received either SDD or SOD during ICU-stay, but it seems unlikely that these infections have an important effect on hospital mortality rates. Of note, the observed differences in relative risks only approached statistical significance.

To the best of our knowledge this is the first study that has quantified timing and incidences of infections in general wards after ICU discharge related to antimicrobial infection prevention measures in the ICU. Strengths include the prospective monitoring of infections performed by a limited number (n=3) of trained and experienced infection control professionals. The open study design in the ICU was an unavoidable limitation of the present analysis. By using objective, and internationally accepted, criteria we aimed to minimize information bias. The fact that the study was performed in only two tertiary care centers, may reduce the generalizability of our findings.

The observed tendency towards a higher infection rate after an antibiotic intervention in ICU might be related to differences in patient risk factors or to changes in the colonization status between the intervention groups and the patients that received standard care. Indeed, at the time of ICU admission, a higher proportion of patients in the standard group did not receive mechanical ventilation. Yet, there were no significant differences in age, APACHE II score at the time of ICU admission or the lengths of stay in ICU or on mechanical ventilation, or in distribution of medical specialties. We therefore assume that the risk profile at the time of ICU discharge was similar for the three patient populations.

Both SDD and SOD aim to modulate the colonization status of patients, which resulted in lower colonization rates with Gram negative bacteria in the respiratory and intestinal tract[6]. After discontinuation of the prophylactic regimens, though, patients may acquire colonization with typical hospital pathogens or suppressed colonization with such bacteria may reemerge. If these phenomena are relevant, and whether they are responsible for our observations, remains to be determined.

Table 2. Infections, time until diagnosis and mortality

	Standard Care N=289	SOD N=286	SDD N=296
Number of patients with HAI	23	34	34
Number of HAI	26	39	37
Incidence of HAI/1000 days at risk	8.3	12.9	11.2
RR Standard Care versus intervention	-	1.49	1.44
CI_{95}	-	0.9-2.47	0.87-2.39
Proportion of patients (%)with HAI	8	12	11
CI_{95}	5-12	8-16	8-16
Specialty of patients with HAI			
- Cardiology	1	2	-
- Cardiothoracic surgery	-	2	-
- Surgery	12	14	19
- Medical	2	7	4
- Pulmonology	-	-	-
- Neurosurgery	3	3	6
- Neurology	2	4	3
- Other	3	2	2
Mortality: N of patients (%)	22 (7.6)	15 (5.2)	21 (7.1)
Mortality of patients with HAI: N of patients (%)	2(8,7)	3 (8,8)	3 (8,8)
Mean LOS in surveillance on ward (days)	10.1	10.0	11.0
Median; range	13;1-14	14; 1-14	14;1-14
No of RTI	16	18	18
Mean time until diagnosis (days)	4.6	5.0	4.7
Median; range	4.5; 1-9	4.5; 1-13	3.5;1-12
No of BSI	5	5	8
Mean time until diagnosis (days)	4.8	5.6	9.0
Median; range	4.0; 1-8	5; 2-12	10; 1-12
No of SSI	5	15	11
Incidence/100 surgical procedures	4.0	11.8	8.0

Differences in times until diagnosis are not significant between the three groups or between the standard Care group versus SOD and SDD combined.
HAI: hospital acquired infections, RR: Relative Risk, LOS: length of stay, RTI: respiratory tract infection, BSI: blood stream infection, SSI: surgical site infection
The proportion of patients with HAI in the Standard Care period versus SOD and SDD combined (RR 1.47, CI_{95} 0.935-2.305) is not significantly different

Our study was motivated by the observation of a tendency towards higher mortality rates after ICU discharge among patients that had received SDD in a previous study.[4] In the current study, 58 patients (7%) succumbed in the hospital after ICU discharge, and eight (14%) of these patients had been diagnosed with a HAI in the first 14 days after ICU discharge. Overall mortality rates were comparable between the three study groups and the numbers of patients that died after developing a HAI was two in the standard care period and three in both the SDD and SOD period. Considering the low rates of infection, the overall low mortality rates after ICU discharge and the low prevalence of infections among those that succumbed after ICU discharge, we reject the hypothesis that an increased infection rate after ICU discharge affects the clinical outcome of patients that have received SDD or SOD in ICU in spite of a tendency of more infections, especially superficial SSIs, in these patients after ICU discharge.

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Chapter 6 | Effects of Decontamination of the Digestive Tract and Oropharynx in Surgical and Non-Surgical Patients: A Subgroup Analysis.

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submitted

ABSTRACT

Objectives

Selective Digestive Decontamination (SDD) and Selective Oropharyngeal Decontamination (SOD) are effective in improving day 28 survival in ICU patients. In this study possible differential effects in surgical and non-surgical patients are investigated

Design and interventions

A post-hoc subgroup analysis was undertaken using the data of a cluster randomized multicenter trial comparing SDD (n=2034) and SOD (n=1904) to standard care (n=1989) to quantify effects of SDD and SOD among surgical and non-surgical patients.

Patients

The subgroup analyses compromised a total of 2762 surgical patients and 3165 non-surgical patients.

Measurements

The primary study outcome was mortality at day 28. Duration of mechanical ventilation, duration of ICU- and, hospital length of stay and bacteremia rates were secondary outcomes.

Results

Compared to standard care, adjusted odds ratios (ORs) for 28 day mortality were comparable in SDD-treated surgical and non-surgical patients (0.86 (0.69-1.09) and 0.85 (0.70-1.03)), respectively, but durations of mechanical ventilation, ICU-stay and hospital stay were significantly reduced in surgical patients only. In contrast, SOD did not influence 28 day mortality 0.97 (0.77-1.22) among surgical patients, whereas in non-surgical patients adjusted OR was 0.77 (0.63-0.94), which equals a relative mortality reduction of 16.6%, and absolute mortality reduction of 5.5% with a number needed to treat of 18. In patients receiving SOD, incidences of ICU-acquired bacteremia were comparable for surgical and non-surgical patients.

Conclusion

In this subgroup analysis SDD was equally effective in reducing 28 day mortality in surgical and non-surgical patients, whereas SOD was only effective in non-surgical patients. These effects were not explained by differences in ICU-acquired bacteremia rates.

INTRODUCTION

Nosocomial infections frequently occur in critically ill patients, complicating treatment during their stay in the intensive care unit (ICU). Selective decontamination of the digestive tract (SDD) is a frequently studied method aimed to prevent these infections. SDD consists of an oral paste containing non-absorbable antibiotics (e.g. polymyxin E, tobramycin and amphotericin B) which is applied in the oral cavity, application of a suspension with the same antibiotics in the gastrointestinal tract and a short course of systemic antibiotics. Selective Oropharyngeal Decontamination (SOD), in which the same topical antibiotics are applied in the oropharynx only, is considered as an alternative, especially for preventing ventilator-associated pneumonia (VAP).

Multiple trials have evaluated the effects of SDD and SOD, with beneficial effects on infection rates being demonstrated in many studies[1], while improved survival rates are documented in three studies for SDD[2-4] and in one for SOD.[2] In the largest and most recent study both SDD and SOD were associated with a significant relative reduction of day 28 mortality, of 13% and 11% respectively, as compared to standard care in a mixed ICU population of 5939 patients.[2]

The question remains if this overall effect is different in certain subgroups of patients. Results from a meta-analysis[5] suggest that surgical ICU patients might benefit more from SDD than medical ICU patients. It is also unknown whether surgical and non-surgical patients benefit differently from SDD or SOD. The present post hoc analysis of our recent multicenter trial[2] was conducted to determine the effects of SDD and SOD in surgical and non-surgical ICU patients.

MATERIALS AND METHODS

Study Design

This study uses the data of our large open-label clustered group-randomized controlled cross-over study of the effect of SDD and SOD on mortality at day 28 in 13 ICUs in the Netherlands, that was recently published.[2] In short, 5939 patients with an expected duration of intubation >48 hours and/or an expected ICU stay >72 hours were enrolled. In each of the 13 participating ICUs, the three regimens (SDD, SOD and standard care) were applied during 6 months in random order. SOD-treated patients received oropharyngeal application (every 6 h) of a paste containing polymyxin E, tobramycin and amphotericin B each in a 2% concentration. In SDD-treated patients, administration (every 6 h) of a 10 ml suspension containing 100 mg polymyxin E, 80 mg tobramycin and 500 mg amphotericin B via the nasogastric tube was added and cefotaxime (1000mg, every 6 h) was administered intravenously during the first four days of the study. Topical antibiotics were applied until ICU-discharge. The surgical or non-surgical status of a patient was determined by the attending ICU physician at admission. Patients were defined as surgical patients when they were admitted post-operatively and/or due to surgical conditions.

Outcomes

The primary study outcome was mortality at day 28. Duration of mechanical ventilation, duration of ICU- and hospital length of stay and bacteremia rates were secondary outcomes.

Statistical analysis

The statistical analysis was performed using SPSS (SPSS, Inc., Chicago, IL.). Our analysis focused solely on the possible interaction between surgical status and SDD or SOD, no other subgroup analyses were conducted.

The existence of an interaction between surgical status (i.e. surgical patient yes/no) and SDD or SOD on the outcome mortality at day 28 was formally evaluated using logistic regression analyses incorporating terms for SDD or SOD, surgical status and the interaction between SDD or SOD and surgical status. Because of baseline differences between patients receiving SDD or SOD and standard care[2], we adjusted for all available covariates (APACHE >20, Age >65, mechanical ventilation and gender). A Cox proportional-hazards analysis was conducted to evaluate the interaction between surgical status and SDD or SOD regarding time to cessation of ventilation, ICU discharge and hospital discharge. Patients who died were considered to have infinite times to cessation of ventilation and discharge, since deaths will lead to informative censoring and act in the opposite direction to any positive effect of the interventions on these outcomes.[2] To quantify the effect of SDD and SOD among surgical and non-surgical patients regarding the different endpoints, separate analyses for all endpoints were performed. ICU clustering effects were not taken into account since significant cluster effects were not found in earlier analyses.[2]

RESULTS

In total 5.939 patients were included in the trial; data about the surgical status of 12 patients were missing and these were excluded from our subgroup analysis. There were 2762 surgical patients; 973 received standard care, 866 received SOD and 923 SDD. Of the 3165 non-surgical patients; 1016 received standard care, 1038 received SOD and 1111 received SDD. All 616 patients (19.5%), of which the admitting specialism was surgery, cardiothoracic surgery or neurosurgery (Table 1), were admitted for non-surgical conditions without prior surgery and thus were regarded as non-surgical patients. Overall, patients in the SOD and SDD treatment groups were slightly older, had higher APACHE II scores and were more frequently ventilated compared to patients treated in the control period (Table 1). There were no significant differences in baseline characteristics between patients receiving SDD and SOD.

Table 1. Baseline characteristics of the surgical and non-surgical patients

	Surgical			Non-Surgical		
Variable	SDD N=923	SOD N=866	Standard Care N=973	SDD N=1111	SOD N=1038	Standard Care N=1016
Age	64.0±15.3*	63.4±16.0	62.6±16.0	61.1±16.2	59.8±16.4	60.2±16.3
Male sex (%)	588 (63.7)	560 (64.7)	617 (63.4)	655 (59.0)	653 (62.9)	603 (59.4)
Mean APACHE II score	17.7±6.9*	17.6±7.6	17.1±7.3	21.2±8.2*	21.1±8.4*	20.1±8.1
Mechanical ventilation	885 (95.9)*	835 (96.4)*	899 (92.4)	1005 (90.5)*	958 (92.3)*	854 (84.1)
Previous or pre-existent disorders						
Cardiovascular	550 (59.6)*	474 (54.7)	526 (54.1)	481 (43.3)	425 (40.9)	450 (44.3)
Pulmonary	214 (23.2)	149 (17.2)*	221 (22.7)	316 (28.4)	299 (28.8)	268 (26.4)
Diabetes Mellitus	129 (14.0)	138 (15.9)	142 (14.6)	152 (13.7)	136 (13.1)	160 (15.7)
Acute renal failure	28 (3.0)	25 (2.9)	29 (3.0)	44 (4.0)	46 (4.4)	50 (4.9)
Chronic renal failure	73 (7.9)*	66 (7.6)*	52 (5.3)	82 (7.4)	69 (6.6)	67 (6.6)
Malignancy solid organ	139 (15.1)	116 (13.4)	116 (11.9)	81 (7.3)	77 (7.4)	80 (7.9)
Metastasized malignancy	33 (3.6)	25 (2.9)	35 (3.6)	38 (3.4)	31 (3.0)	29 (2.9)
Haematological malignancy	9 (1.0)	6 (0.7)	10 (1.0)	47 (4.2)	45 (4.3)	38 (3.7)
Immunodepression/AIDS	8 (0.9)	11 (1.3)	15 (1.5)	52 (4.7)	36 (3.5)	32 (3.1)
Alcohol and/or drug abuse	35 (3.8)	33 (3.8)	42 (4.3)	77 (6.9)	87 (8.4)	69 (6.8)
Specialism						
Surgery	470 (50.9)	440 (50.8)	489 (50.3)	135 (12.2)	111 (10.7)	120 (11.8)
Cardiothoracic surgery	319 (34.6)	255 (29.4)	293 (30.1)	34 (3.1)	29 (2.8)	28 (2.8)
Neurosurgery	59 (6.4)	80 (9.2)	92 (9.5)	46 (4.1)	60 (5.8)	53 (5.2)
Neurology	5 (0.5)	10 (1.2)	13 (1.3)	119 (10.7)	134 (12.9)	115 (11.3)
Medical	10 (1.1)	26 (3.0)	21 (2.2)	372 (33.5)	345 (33.2)	372 (36.6)
Cardiology	8 (0.9)	8 (0.9)	10 (1.0)	151 (13.6)	139 (13.4)	119 (11.7)
Pulmonology	6 (0.7)	5 (0.6)	5 (0.5)	146 (13.1)	133 (12.8)	122 (12.0)
Other	46 (5.0)	41 (4.7)	50 (5.1)	107 (9.6)	85 (8.2)	87 (8.6)
Patient admitted to ICU from						
Emergency room	130 (14.1)	134 (15.9)	140 (14.4)	379 (34.1)	341 (32.9)	325 (32.0)
Other ICU in the Netherlands	44 (4.7)	36 (4.2)	44 (4.5)	91 (8.2)	85 (8.2)	72 (7.1)
Nursing ward	521 (56.1)	482 (55.7)	519 (53.3)	440 (39.6)	433 (41.7)	424 (41.7)
Other	228 (24.7)	214 (24.7)	270 (27.7)	201 (18.1)	179 (17.2)	195 (19.2)

*P<0.05 as compared to standard care (calculated using the Mann Whitney U test (continuous variables) or chi square test (dichotomous variables))

Table 2. Primary and Secondary Endpoints

				Unadjusted Odds Ratio or Hazard Ratio (CI_{95})			Adjusted Odds Ratio or Hazard Ratio (CI_{95})		
	Standard Care	SDD	SOD	Standard care	SDD	SOD	Standard care	SDD	SOD
Surgical patients									
Allocated patients	N= 973	N= 923	N= 866						
Mortality at day 28 no. (%)	209 (21.6)	191 (20.8)	194 (22.6)	1	0.96 (0.77-1.19)	1.06 (0.85-1.32)	1	0.86 (0.69-1.09)*	0.97 (0.77-1.22)*
Time to outcome for Survivors at day 28 (days)									
Cessation of mechanical ventilation: median (IQR)	7 (13)†	6 (9)†	8 (11)†	1	1.13 (1.02-1.27)#	1.01 (0.90-1.13)#	1	1.15 (1.03-1.28)#	1.00 (0.90-1.12)#
Duration of ICU stay	9 (13)†	9 (9)†	9 (12)†	1	1.10 (0.99-1.23)#	0.99 (0.89-1.11)#	1	1.15 (1.03-1.28)#	1.04 (0.93-1.17)#
Duration of hospital stay	29 (33)†	26 (29)†	29.5 (30)†	1	1.12 (0.97-1.29)#	1.01 (0.88-1.18)#	1	1.17 (1.01-1.35)#	1.08 (0.93-1.25)#
Non-surgical patients									
Allocated patients	N=1016	N=1111	N=1038						
Mortality at day 28 no. (%)	335 (33.2)	349(31.7)	308 (30.0)	1	0.94 (0.78-1.12)	0.86 (0.72-1.04)	1	0.85 (0.70-1.03)*	0.77 (0.63-0.94)*
Time to outcome for Survivors at day 28 (days)									
Cessation of mechanical ventilation: median (IQR)	8 (14)†	8 (14)†	8 (10)†	1	1.03 (0.91-1.16)#	1.07 (0.95-1.21)#	1	1.04 (0.92-1.17)#	1.07 (0.95-1.21)#
Duration of ICU stay	10 (12)†	10 (14)†	10 (11)†	1	0.97 (0.87-1.09)#	1.03 (0.92-1.16)#	1	1.04 (0.93-1.16)#	1.11 (0.99-1.25)#
Duration of hospital stay	29 (32)†	29(30)†	27 (31)†	1	1.01 (0.87-1.17)#	1.11 (0.96-1.28)#	1	1.08 (0.93-1.25)#	1.18 (1.02-1.37)#

Surgical patients: The 28 day mortality outcomes exclude 16 patients (i.e. 4 standard care, 6 SOD and 6 SDD patients) for whom the data were unavailable. Data on the duration of mechanical ventilation was unavailable for 1 patient in the standard care group.

Non-surgical patients: The 28 day mortality outcomes exclude 28 patients for whom the data were unavailable (6 standard care, 12 SOD, 10 SDD). Data on duration of the hospital stay and duration of mechanical ventilation were unavailable for three patients (two in the SOD and one in the SDD group) and for seven patients (two in the standard care group and five in the SOD group)

* adjusted for APACHE II>20, Age >65, Mechanical Ventilation, Gender

† Median (interquartile range) in days for survivors at day 28

Hazard ratios from Cox regression model with censoring at day 28 (hazard ratios larger than one indicate a tendency for shorter durations of ventilation, ICU/ hospital stay). Models for adjusted outcomes included the same covariates as in the logistic regression. Infinite durations were used for patients who died.

Primary outcome

Surgical patients

The crude mortality rates at day 28 were 21.6%, 20.8% and 22.6% for the surgical patients in the standard care, SDD and SOD group, respectively. After adjustment for baseline differences in age, APACHE II scores, proportion being ventilated and gender, ORs were 0.86 (CI_{95} 0.69-1.09) for SDD and 0.97 (CI_{95} 0.77-1.22) for SOD (table 2). There was no significant interaction between surgical status and SDD or SOD regarding mortality at day 28. The adjusted OR for day 28 mortality for SDD versus SOD for surgical patients was 0.90 (CI_{95} 0.70-1.11).

Non-surgical patients

Among the non-surgical patients crude mortality rates at day 28 were 33.2%, 31.7% and 30.0% for the standard care, SDD and SOD groups, respectively, with adjusted ORs of 0.85 (CI_{95} 0.70-1.03) for SDD and 0.77 (CI_{95} 0.63-0.94) for SOD (table 2). Of note, the adjusted ORs for SDD were almost similar among surgical and non-surgical patients (0.86 and 0.85, respectively), but differed extensively between surgical and non-surgical patients receiving SOD (0.97 and 0.77, respectively). The OR of 0.77 for day 28 mortality in non-surgical patients receiving SOD (as compared to patients receiving standard care with a mortality rate at day 28 of 33.0%) equals a relative mortality reduction of 16.6%, an absolute mortality reduction of 5.5% with a number needed to treat of 18. The adjusted OR for day 28 mortality for SDD versus SOD for non-surgical patients was 1.09 (CI_{95} 0.9-1.3).

Secondary outcomes

The duration of mechanical ventilation, ICU and hospital length of stay were, after adjustment for covariates, significantly reduced in surgical patients receiving SDD with Hazard Ratio's of 1.15(CI_{95} 1.03-1.28), 1.15(CI_{95} 1.03-1.28) and 1.17(CI_{95} 1.01-1.35) (table 2). SOD had no apparent effects on any of the secondary endpoints in surgical patients. In non-surgical patients, though, SOD was associated with a significant reduction in hospital stay (HR 1.18 (CI_{95} 1.02-1.37), p value=0.027). In the non-surgical subpopulation SDD was not associated with significant reductions on any secondary outcome.

ICU-acquired bacteremias

Intestinal decontamination and systemic treatment with cefotaxime are the differences between SDD and SOD. We hypothesized that intestinal decontamination might offer additional benefits in surgical patients, as compared to non-surgical patients, which would underscore the observed difference in efficacy between both strategies in surgical patients. Crude incidences of ICU-acquired bacteremias were lower for patients receiving SDD or SOD as compared to standard care (table 3), with the largest differences for

Table 3.Incidences of ICU acquired bacteremia

	Surgical			Non-Surgical		
microorganism	Standard Care N= 973	SOD N= 866	SDD N= 923	Standard Care N= 1016	SOD N= 1038	SDD N= 1016
	No (%)					
Staph. Aureus	11 (1.1)	5 (0.6)	3 (0.3)	11 (1.0)	4 (0.4)	6 (0.6)
Strept. Pneumoniae	1 (0.1)	1 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.1)
GNF-GNR#	17 (1.7)	6 (0.7)	10 (1.1)	19 (1.9)	11 (1.1)	6 (0.6)
Enterobacteriaceae	51 (5.2)	25 (2.9)*	10 (1.1)*†	36 (3.5)	34 (3.3)	8 (0.8)*†
Enterococcus spp	24 (2.5)	23 (2.7)	24 (2.6)	31 (3.1)	26 (2.5)	24 (2.4)
Pts with at least one episode of bacteremia	86 (8.8)	50 (5.8)*	39 (4.2)*	84 (8.3)	60 (5.8)*	41 (4.0)*†

* Significant reductions ($p<0.05$) SOD and SDD vs standard care.

† Significant differences ($p<0.05$) between SOD and SDD within the same population.

GNF-GNR Glucose Non-Fermenting Gram-negative Rods; *Pseudomonas aeruginosa, Stenotrophomonas maltophilia* and Acinetobacter species.

Enterobacteriaceae. However, among patients receiving either SDD or SOD there were no significant differences in incidences of ICU-acquired bacteremias between surgical and non-surgical patients.

DISCUSSION

In this subgroup analysis of our cluster randomized cross-over study with 5939 patients we demonstrated different efficacies of SDD and SOD in surgical and non-surgical patients. The largest effect of both interventions was observed in non-surgical patients receiving SOD. In this subgroup, the adjusted odds ratio for day 28 mortality was 0.77 (CI_{95} 0.63-0.94), which equals a relative mortality reduction of 16.6%, an absolute mortality reduction of 5.5% with a number needed to treat of 18. In contrast, SOD appeared less effective in surgical patients (adjusted OR 0.97). As compared to patients receiving standard care, the beneficial effects of SDD on day 28 mortality were comparable for surgical and non-surgical patients (adjusted odds ratios 0.86 and 0.85, respectively), but with significant reductions in duration of mechanical ventilation, ICU-stay and hospital stay among surgical patients.

These findings suggest that surgical patients benefit from the addition of the enteric and/or systemic component to the SDD regimen. A higher efficacy of SDD, compared to SOD, among surgical patients has been suggested before upon the results of a meta-analysis (5). In that analysis results of studies evaluating SDD or SOD in populations with at least 75% surgical or trauma patients were pooled and compared to the pooled results of studies with lower proportions of surgical patients. Mortality was significantly lower in the eleven studies evaluating SDD or SOD in a predominant

surgical population (pooled OR 0.70; CI_{95} 0.52-0.93), compared to ten trials with predominantly medical patients. Within these studies, survival benefit was largest in the studies using both topical and systemic antibiotic prophylaxis (pooled OR 0.60; CI_{95} 0.41-0.88), as compared to those using topical prophylaxis alone (pooled OR 0.86; CI_{95} 0.51-1.45). Our analysis represents the first head-to-head comparison of SDD and SOD in surgical and non-surgical patients. Strengths of our study are that the definition of subgroups is more specific than in the previous meta-analysis, that treatments were uniform in the different study groups (as compared to multiple different protocols in the meta-analysis) and that it was possible to adjust for confounders.

Nevertheless, our analyses do not provide an explanation for a different efficacy of SDD and SOD in surgical patients. Prior to the analysis, we hypothesized that the addition of systemic prophylaxis with cefotaxime and enteric decontamination, to oral decontamination alone, would reduce the incidence of Gram-negative infections, from which surgical patients might benefit more than non-surgical patients. Indeed, incidences of Gram-negative bacteremias were lower among patients receiving SDD compared to those that received SOD or standard care. However, a similar reduction in surgical and non-surgical patients was observed, indicating that this mechanism of action is unlikely to explain the observed difference between both patient groups. Since the effects of SDD on day 28 mortality are also similar in both subgroups, it appears unlikely that Gram-negative bacteremia differently affects outcome in these two populations. Furthermore, there were no differences in day 28 mortality between SDD and SOD patients that had developed Gram-negative bacteremia (OR 0.88 (CI_{95} 0.36-2.16).

Subgroup analyses are generally not considered as providing definite evidence for several reasons, including spurious associations that may arise because of data dredging, multiple testing and chance findings. In our view, however, these issues do not play a role of major importance in our analyses. First, this subgroup analysis was performed because of a hypothesis that was already known and described before. A single subgroup (surgical status yes/no) was tested, so no data dredging was performed to identify smaller subgroups of possible patient populations with increased benefit. Second, this subgroup analysis was not performed because of absence of beneficial effects in the trial (the situation in which subgroup analyses are most commonly conducted).

CONCLUSION

This subgroup analysis suggests that SDD has similar effects in surgical and non-surgical patients, whereas non-surgical patients had a markedly higher benefit from SOD than surgical patients. In non-surgical patients SOD was associated with statistically significant relative mortality reduction of 16.6%, an absolute mortality reduction of 5.5% with a number needed to treat of 18. Our results indicate that an appropriate patient selection may be important to derive maximum benefit from antibiotic prophylaxis in ICU patients.

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Chapter 7 | Ecological effects of Selective Decontamination on resistant Gram-negative bacterial colonization

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ABSTRACT

Rationale

Selective Digestive tract Decontamination (SDD) and Selective Oropharyngeal Decontamination (SOD) eradicate Gram-negative bacteria (GNB) from the intestinal en respiratory tract in intensive care unit (ICU) patients, but its effect on antibiotic resistance remains controversial.

Objectives

We quantified the effects of SDD and SOD on bacterial ecology in 13 ICUs that participated in a study, in which SDD, SOD or standard care (SC) was used during consecutive periods of 6 months.

Methods

Point prevalence surveys of rectal and respiratory samples were performed once monthly in all patients in ICU (receiving or not receiving SOD/SDD). Effects of SDD on rectal and of SDD/SOD on respiratory tract carriage with GNB were determined by comparing results from consecutive point prevalence surveys during intervention (6 months for SDD and 12 months for SDD/SOD) to consecutive point prevalence data in the pre- and post-intervention periods.

Measurement and Main Results

During SDD average proportions of patients with intestinal colonization with GNB resistant to either ceftazidime, tobramycin and ciprofloxacin were 5%, 7% and 7%, and increased to 15%, 13% and 13% post-intervention ($p<0.05$). During SDD/SOD resistance levels in the respiratory tract were ≤ 6% for all three antibiotics, but increased gradually (for ceftazidime; $p<0.05$ for trend) during intervention and to levels ≥ 10% for all three antibiotics post-intervention ($p<0.05$).

Conclusion

SOD and SDD have marked effects on the bacterial ecology in an ICU with rising ceftazidime resistance prevalence rates in the respiratory tract during intervention and a considerable rebound effect of ceftazidime resistance in the intestinal tract after discontinuation of SDD.

INTRODUCTION

Selective decontamination of the digestive tract (SDD) and Selective Oropharyngeal Decontamination (SOD) are powerful infection prophylaxis regimens for patients in intensive care units (ICU). First introduced in 1984[1], both interventions have been associated with reduced incidences of Ventilator Associated Pneumonia (VAP)[2-4] and improved patient survival.[5,6]

Both SDD and SOD consist of non-absorbable antimicrobial agents with activity against yeasts, *Staphylococcus aureus* and aerobic Gram-negative bacteria, including Enterobacteriaceae and *Pseudomonas aeruginosa*. SOD is applied in the oropharynx only, while in SDD antibiotics are, in addition to oropharyngeal application, also administered to the gastrointestinal tract combined with systemic prophylaxis with a third generation cephalosporin during the first four days. This systemic prophylaxis aims to treat infections caused by commensal respiratory tract flora, such as *Streptococcus pneumonia* and *Haemophilus influenza* already incubating at the time of ICU admission.[7] The aim of the intestinal component is to selectively eradicate potentially pathogenic micro-organisms, while sparing the anaerobic flora. The latter presumably protects against colonization and overgrowth with potential pathogens, the so-called concept of 'colonization resistance'.[8]

The effects of SDD on antibiotic resistance have been the subject of intense controversy. In theory, SDD may select micro-organisms already intrinsically resistant to the regimen, such as Gram-positive bacteria, or those with acquired resistance for the antibiotics used.[7,9,10] Up till now, SDD and SOD have not been associated with increased resistance in settings with low endemicity of antibiotic resistance. Actually, in such settings SDD and SOD were associated with lower incidences of carriage and infections with antibiotic resistant Gram-negative bacteria[5,6,11-13] However, emergence of plasmid mediated extended spectrum β-lactamase (ESBL)[14] and other pathogens, such as meticillin resistant *staphylococcus aureus* (MRSA)[15,16], have been reported as well.

The question to what extent and in what time SDD and SOD affect the bacterial ecology in an ICU ward remains unanswered. Most trials performed so far focussed on antibiotic resistance rates in individual patients. Yet, since SDD, or SOD, is usually administered to patients with an expected ICU-stay of at least two days only, there will always remain ICU patients not receiving SDD or SOD. In a Dutch multi-center SDD-SOD study such patients accounted, on average, for about 70% of all admitted patients, representing about 20% of all patient days in ICU.[5] In that study, surveillance cultures (rectal and oropharyngeal swabs) were obtained once monthly in all patients (including short-stay patients) present in the ICU, during SDD, SOD and standard care, to determine point-prevalence rates of antibiotic resistant Gram-negative bacteria.[5] In the current study, we determined the ecological effects of SDD and SOD.

METHODS

Patients and design

Microbiological data were used from monthly point prevalence surveys performed as part of an open clustered group-randomized cross over study in 13 Intensive Care Units (ICU) in the Netherlands between May 2004 and July 2006 comparing SDD and SOD to standard care.[5] Two six-month intervention periods (SDD and SOD) and one standard care period of six months were conducted in each ICU, with the study order of regimens randomly assigned. Between each period a one month wash-in/wash out period was carried out, during which the new treatment (either SDD or SOD) was implemented, but patient data were not used for analysis.

The study interventions, SDD and SOD, were described previously.[5] In short, both consisted of the non-absorbable anti-microbial agents tobramycin, polymyxin E and amphotericin B. During the use of SDD a 2% mixture of these antibiotics was applied on the buccal mucosa and a suspension (respective doses 80 mg, 100 mg and 500 mg) was administered in the gastrointestinal tract four times a day via a nasogastric tube. Furthermore, for the first four days after ICU admission 1000 mg cefotaxime was administered intravenously four times daily. SOD consisted only of the oropharyngeal application of the 2% mixture of these antibiotics.

An expanded microbiological methods description can be found in the supplementary appendix.

Data analysis

Since the order of study regimens was randomized in each ICU, there were six possible study orders (table 1A). For the analysis of the effects of SDD on rectal colonization, the results of the six point prevalence studies during the SDD period were compared to the consecutive point prevalence results in the periods before and after the SDD period (table 1B). In this analysis, SOD and standard care were gathered, since SOD was found to have no effect on rectal colonization.[5] This is in accordance with previous findings.[2] Data from monthly point prevalence cultures from different centers were pooled according to study period and specific time point. Similarly, for the analysis of respiratory tract colonization SDD and SOD were gathered, as both intended similar effects on respiratory tract colonization (Table 1C).

In this way the results for rectal colonization from the six consecutive point-prevalence surveys during SDD in 13 units were compared to the results from eight periods (four SOD and four standard care) in the six months before SDD and four periods (two SOD and two standard care) in the period between twelve and six months before SDD. Similarly, SDD was compared to equal periods following SDD as shown in table 1B. For respiratory tract colonization 12 consecutive point prevalence results (for SDD and SOD, interrupted by one month wash-in/wash-out) were compared to six and seven

A

	1	2	3
A	Standard care	SOD	SDD
B	Standard care	SDD	SOD
C	SOD	Standard care	SDD
D	SOD	SDD	Standard care
E	SDD	Standard care	SOD
F	SDD	SOD	Standard care

B

	1	2	3	4	5
	Pre-intervention period		Intervention period	Post- intervention period	
A	Standard care (2)	SOD (2)	SDD (2)		
B		Standard care (2)	SDD (2)	SOD (2)	
C	SOD (2)	Standard care (2)	SDD (2)		
D		SOD (2)	SDD (2)	Standard care (2)	
E			SDD (2)	Standard care (2)	SOD (2)
F			SDD (3)	SOD (3)	Standard care (3)
NC	444	624	988	549	358

C

	1	2	3	4	
	Pre-interven-tion period	Intervention period		Post-interven-tion period	
A	Standard care (2)	SOD (2)	SDD (2)		
B	Standard care (2)	SDD (2)	SOD (2)		
C	SOD (2) Standard care (2)	SDD (2)			
D		SOD (2)	SDD (2)	Standard care (2)	
E			SDD (2)	Standard care (2)	SOD (2)
F		SDD (3)	SOD (3)	Standard care (3)	
NC	431	688	724	461	

Table 1 (A) Original study scheme with six possible study order of regimes (A-F). (B) Modification of original study scheme to determine changes over time in rectal colonization. (C) Modification of original study scheme to determine changes over time in respiratory colonization.
NC: number of cultures taken during that particular period ; (n) number of centers per period.
Original sequence is preserved. Each study period lasted six months. Between each period a one month wash-in/wash out period was carried out, during which the new treatment (either SDD or SOD) was implemented, but patient data were not used for analysis (darkest grey).

periods of standard care preceding and following the SDD/SOD periods, respectively. In this analysis, four SOD periods were not used, as standard care followed SOD but preceded SDD (Table 1C). Data obtained during wash in-wash out periods were not used.

Statistical analysis

Proportions of patients colonized with Gram-negative bacteria for every time point were calculated by determining the numerator and denominator of the prevalence. 95% Confidence intervals for the proportions were derived from the standard error of proportion. Differences in proportions between subsequent periods were analyzed with Poisson regression analysis. Non-segmented Poisson regression was performed to

Table 2.

	Average prevalence per period (*mean (95% CI)*)			**Change in prevalence during period (β-*coefficient (P-value)*)**		
	Pre	**Per**	**Post**	**Pre**	**Per**	**Post**
Rectal samples						
Ceftazidime	6% (4.7%-7.5%)	5% (3.9%-6.7%	15% * (12.4%-17.0%)	-0.07 (0.038)	-0.05 (NS)	-0.04 (NS)
Tobramycin	9% * (7.7%-11.2%)	7% (5.5%-8.7%)	13% * (10.4%-14.7%)	0.00 (NS)	-0.05 (NS)	-0.04 (NS)
Ciprofloxacin	12% * (9.7%-13.5%)	7% (5.1%-8.2%)	13% * (10.8%-15.2%)	-0.01 (NS)	0.03 (NS)	-0.03 (NS)
Respiratory samples						
Ceftazidime	10% * (7.6%-13.3%)	4% (2.6%-4.6%)	10% * (7.4%-13.0%)	0.00 (NS)	0.09 (0.039)	0.07 (NS)
Tobramycin	10% * (6.9%-12.5%)	6% (4.5%-6.9%)	12% * (8.8%-14.6%)	0.17 (NS)	0.04 (NS)	-0.04 (NS)
Ciprofloxacin	14% * (10.4%-17.0%)	5% (3.5%-5.7%)	12% * (9.0%-14.9%)	0.05 (NS)	0.02 (NS)	-0.02 (NS)

Table 2: Proportions of patients colonized with antibiotic resistant Gram-negative bacteria during monthly point prevalence surveys per period and monthly changes during the specific periods (adjusted for changes between centers).
Pre: pre-intervention period; Per: intervention period; Post: post-intervention period.
NS: not significant. β-coefficient is considered significant if P-value is below 0.05.
* = $p < 0.05$ as compared to the intervention period. Adjusted for changes between centers.

quantify changes in time trend within the periods.[17] Poisson regression is preferred over more common statistical methods, such as linear regression, because counts are not normally distributed. We adjusted for differences between centers as unit-level observations, in contrast to individual-level observations, could lead to within unit correlation.[18] An alpha value of $P < 0.05$ was set to define statistical significance. Data were analyzed using SPSS version 12.0 (SPSS, Chicago, IL. USA) and R version 2.9.0.

RESULTS

Microbiology

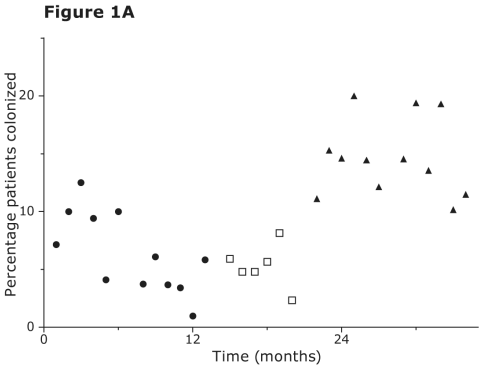
During the monthly point prevalence surveillance studies a total of 2963 rectal and 2304 respiratory tract samples were obtained and processed for specific antimicrobial susceptibility testing. The mean (SD) number of patients sampled at each time point was 99 (38) (median, 89; range, 55 – 165) for rectal samples and 96 (24) (median, 91; range, 64 – 134) for respiratory tract samples. Adherence to obtaining cultures was estimated to be 87% for rectal swabs (ranging from 67% to 98% per center) and 82% for respiratory samples (ranging from 69% to 95% per center).

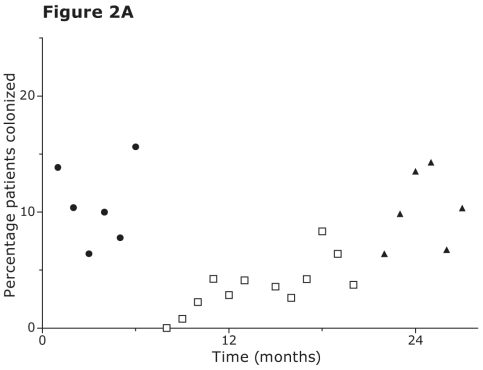
For rectal swabs, growth of any pathogen on the selective media was highest during standard care (44,5 +1,5%; range 42% - 51%) and 6,1% lower during SOD (38.3 +1,6%; range 37% - 50%) and 19.6% lower during SDD (24,9 +1,4%; range 22% - 33%). In the respiratory tract, growth was lower during both SDD (17.7 +1,3%; range 15% - 27%) and SOD (22,1 +1,5%; range 13% - 26%), as compared to standard care (42.5 +1,7%; range 32% - 48%). Because of the small differences between SOD and standard care for rectal swabs and between SDD and SOD for respiratory samples, these groups were analyzed simultaneously (for separate analysis see Table E1 in the supplementary appendix).

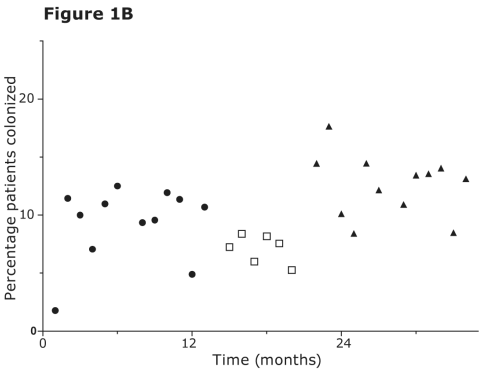
Table 3.

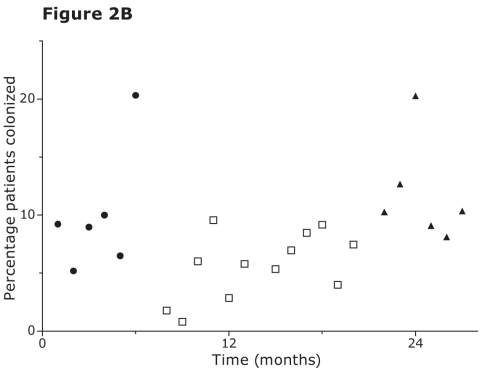
	Rectal tract			Respiratory tract		
	CFT	CIP	TOB	CFT	CIP	TOB
Total	263	244	228	131	113	108
E. coli	69 (26,2%)	122 (50,0%)	110 (48,2%)	13 (9,9%)	15 (13,3%)	16 (14,8%)
Klebsiella pneumoniae	38 (14,4%)	51 (20,9%)	50 (21,9%)	24 (18,3%)	26 (23,0%)	24 (22,2%)
Pseudomonas spp	51 (19,4%)	38 (15,6%)	28 (12,3%)	44 (33,6%)	56 (49,6%)	47 (43,5%)
Enterobacter cloacae	105 (39,9%)	33 (13,5%)	40 (17,5%)	50 (38,2%)	16 (14,2%)	21 (19,4%)

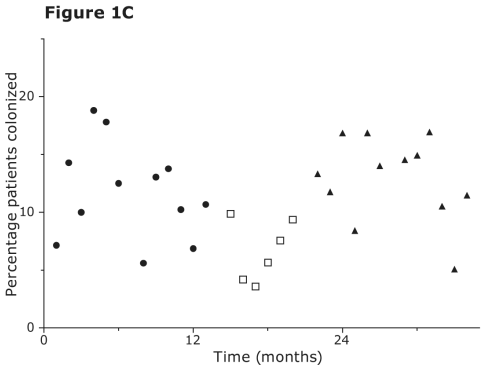
Table 3: Number and percentages of antibiotic resistant Gram-negative isolates and species obtained from rectal en respiratory tract samples during point prevalence surveys. CFT: ceftazidime, CIP: ciprofloxacin, TOB: tobramycin











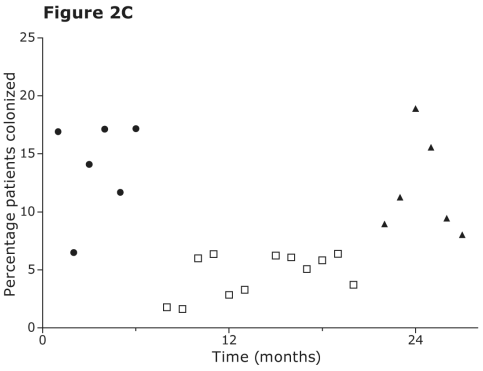


Figure 1: Percentage of patients colonized with Gram- negative rods before, during and after the use of SDD during monthly point prevalence surveillance studies of (1) rectal samples and (2) respiratory samples. (●) pre intervention period; (□) intervention period; (▲) post intervention period for three types of antibiotic agents (A) ceftazidime; (B) tobramycin; (C) ciprofloxacin.

Rectal colonization

Average prevalence rates of colonization with ceftazidime-resistant bacteria were 6% (95% CI, 4.7% - 7.5%) in the pre-SDD period, 5% (95% CI, 3.9%-6.7%) during the SDD, and 15% (95% CI, 12.4%-17.0%) in the period after SDD (table 2). Before SDD there was a decline in the prevalence rates of ceftazidime-resistance (β-coefficient = -0.07; p = 0.038), with stable resistance levels during the entire period of SDD (figure 1), followed by an increase from 2.3% in the last month of SDD to 11.1% in the first month after SDD ($p<0.05$). Resistance levels remained stable in the subsequent twelve months.

Average rates of ciprofloxacin resistance were 12% (95% CI, 9.7%-13.5%) in the pre-SDD periods, which decreased to 7% (95% CI, 5.1%-8.2%) during SDD, and then increased to 13% (95% CI, 10.8%-15.2%) after discontinuation of SDD. Differences between the subsequent periods were statistically significant. Similar trends were observed for tobramycin resistance; the average resistance prevalence was 9% (95% CI, 7.7%-11.2%) before, 7% (95% CI, 5.5%-8.7%) during and 13% (95% CI, 10.4%-14.7%) after SDD.

In all 263, 244 and 228 Gram-negative micro-organisms were isolated from rectal samples with resistance for ceftazidime, ciprofloxacin and tobramycin, respectively (table 3). Among those being resistant to ceftazidime 39,9% (n=105) were *Enterobacter cloacae*. Strains resistant to ciprofloxacin and tobramycin most frequently were *Escherichia coli*: 122 (50,0%) for ciprofloxacin and 110 (48,2%) for tobramycin.

Respiratory tract colonization

The prevalence rates of antibiotic-resistant bacteria in respiratory tract samples decreased significantly after introduction of SDD or SOD (Figure 1). Before intervention, average prevalence rates of resistance were 10%, 10% and 14% for ceftazidime, tobramycin and ciprofloxacin, respectively, which dropped to levels below 7% for all antibiotics ($p<0.05$) after introduction of either SDD or SOD. This immediate drop was followed by a gradual increase during SDD/SOD (for ceftazidime resistance; $p<0.05$ for time trend). There was a slight but statistically significant increase in prevalence of resistance for all three antibiotics after the intervention period. As mentioned, in streamlining the three studies periods we excluded four SOD periods. We, therefore, also repeated our analysis with the inclusion of these four periods, while now excluding the four SDD periods. The interpretation did not change, although the gradual increase in ceftazidime during SDD/SOD fell short of statistical significance.

In all 131, 113 and 108 Gram-negative micro-organisms were isolated from respiratory samples with resistance for ceftazidime, ciprofloxacin and tobramycin, respectively (table 3). Among those being resistant to ceftazidime 38.2% consisted of *E. cloacae* (n=50) and 33,6% of *Pseudomonas aeruginosa* (n=44). Strains resistant to ciprofloxacin and tobramycin most frequently were *P. aeruginosa*: more specific 49,6% (n=56) for ciprofloxacin and 43,5% (n=47) for tobramycin.

Proportions of ciprofloxacin resistant Gram-negative bacteria (both from rectal swabs and respiratory samples) with co-resistance for both ciprofloxacin and ceftazidime were 30,2%, 22,2% and 35,0% during standard care, SOD and SDD, respectively (p = 0,08). Co-resistance for both ciprofloxacin and tobramycin was documented in 37,4%, 44,4%, and 35,0% of the isolates during standard care, SOD and SDD, respectively (p = 0,26).

DISCUSSION

This longitudinal study demonstrates that SOD and SDD both have marked effects on the bacterial ecology in an ICU. The ecological effects were most obvious in the respiratory tract, with large reductions in resistance prevalence rates of Gram-negative bacteria after the start of SDD or SOD, a trend towards increasing rates during the interventions, followed by a rapid return to pre-intervention resistance levels after the interventions. In the intestinal tract, the reduction in resistance prevalence was less pronounced during SDD as compared to respiratory tract colonization, but with a considerable rebound effect of ceftazidime resistance after SDD, with significantly increased prevalence rates as compared to prevalence rates during the intervention and even before intervention. Ceftazidime resistant isolates in rectal samples mainly included *E. cloacae* whereas tobramycin and ciprofloxacin resistant isolates predominantly included *E. coli*. Of note, all samples were also analyzed for vancomycin-resistant enterococci (VRE) and (MRSA). MRSA was not detected in any sample and VRE was isolated from eight rectal swabs, none during SDD (data not shown).

To the best of our knowledge this is the first study to determine the ecological effects of SDD and SOD on a ward-level in a longitudinal and multi-center study design. Furthermore, based upon the determined adherence to study protocol, the microbiological screening results can be considered to represent 'whole-ward ecology' as completeness of sampling was estimated to be 82% for the respiratory and 87% of the rectal cultures. Previous studies focussed on the effects of SDD and SOD in individual patients.[2,6,15,19,20]

To guarantee uniform data collection in 13 microbiology laboratories, a pragmatic and relatively simple study design was needed. We have, therefore, used three antibiotic-containing media as a first selection to detect antibiotic-resistant aerobic Gram-negative micro-organisms, followed by susceptibility testing using automated susceptibility testing systems. The selection of marker antibiotics was based on resistance profiles of Gram-negative bacteria in Dutch ICUs and the antibiotics used in SDD and SOD.

Intestinal carriage with antibiotic resistant bacteria markedly increased after discontinuation of SDD. This association was most obvious for ceftazidime resistance. During SDD intravenous cephalosporin use increased with 87%.[5] We hypothesize that the increase in cephalosporin use selected for cephalosporin resistant isolates, which were suppressed by enterally administered antibiotics without complete eradication, and

their growth emerged after discontinuation of these topical antibiotics then facilitates emergence of such strains. Indeed, SDD has been associated with emergence of intestinal carriage with multidrug-resistant Gram-negative bacteria before[14] and prior use of third-generation cephalosporins has been stated as a major risk factor for subsequent cephalosporin resistance.[21] The increase of ciprofloxacin resistance, however, cannot be explained by this scenario, as ciprofloxacin was not part of SDD and its systemic use was 31% lower during SDD.[5] Yet, antibiotic resistance is frequently present for multiple classes of antibiotics.[22] However in the present study the proportions of ciprofloxacin resistant Gram-negative pathogens not susceptible to both ciprofloxacin and either ceftazidime or tobramycin were comparable in all three periods. Unfortunately, it was not feasible to investigate the genetic mechanisms of resistance in this study.

There was a tendency towards a reduction in rectal colonization during the pre-intervention period, which might reflect a so-called 'Hawthorne-effect'. This implies that nurses and physician's behavior might have been affected by the fact that a trial was executed.[23,24] As part of the study, specific attention was paid to hygiene measurements, which might have reduced the occurrence of cross transmission.

During SDD and SOD, proportions of patients carrying resistant Gram-negative bacteria in the respiratory tract gradually increased, again most prominently for ceftazidime and tobramycin resistance. Opposite to the effects of SDD on intestinal resistance rates, the trend line increased until the last point prevalence survey, suggesting that its maximum level had not been reached after twelve months.

There are several limitations of this study that must be addressed. The adherence to study protocol (i.e., the completeness of cultures obtained) and inclusion rates were based on estimates determined during regular controls in the units by our research nurses. Therefore, exact proportions of patients receiving either SDD or SOD at each specific time point and the exact proportion of cultures obtained were not available. In addition, cultures were processed anonymously, and it was therefore not possible to link carriage to received medications.

Furthermore, in our statistical analysis we assumed that prevalence points were independent from each other. The duration of ICU-stay at the time of sampling is unknown due to the anonimyzed nature of sample taking. However, the average duration of ICU-stay for patients included in the trial (with an expected ICU-stay >48 hours) was nine days during all periods (inter-quartile range: standard care 3-17; SOD 4-15; SDD 4-15) and the average proportion of patients with a length of ICU-stay of more than 30 days was 9% during all periods (standard care 8.7%; SOD 8.9%; SDD 8.6%)[5], which implies that almost all patients were included only once in a point prevalence study. Yet, the clear differences in prevalence rates between and uniformity within study periods, suggests at least some data-dependency.[25] We have calculated average prevalence for each time point and for whole periods (i.e., multiple time points) as numerator and denominator of the prevalence and performed Poisson regression ana-

lysis to control for within unit correlation. Although we would have preferred to perform a time series analysis to adjust for any (auto)correlation over time, the number of point prevalence surveys per time period was insufficient to achieve an acceptable level of variability[26] as well as the number of time points to estimate complex correlation structures.[18]

In the current cluster-randomized cross-over study SDD and SOD were associated with an 13% and 11% mortality reduction at day 28, which provides strong evidence for a beneficial effect of both regimens in ICU settings with low endemic levels of antibiotic resistance. This ecological analysis provides detailed insights in the ecological changes induced by both regimens. SDD and SOD are both associated with a gradual increase in antibiotic resistance in the respiratory tract, which is magnified after discontinuation of both regimens. Therefore, emergence of antibiotic resistance remains a major concern associated with these infection control measures. Future studies should compare the long-term effects of both regimens on antibiotic regimens, in order to determine the most 'cost-beneficial' infection control measure from an ecological perspective for ICU patients.

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Supplementary appendix

MICROBIOLOGIC METHODS

Colonization of the respiratory and rectal tract was monitored by monthly point prevalence cultures of rectal swabs and respiratory samples (endotracheal aspirate or a throat swab). Samples were collected each third Tuesday of the month, in all centers, from all patients present in the ICU, whether or not included in the study. Adherence to obtaining cultures was determined through regular visits of research nurses (at least twice per study period) as described previously.[5] Selective media were used to detect Gram-negative micro-organisms. Cultures from respiratory and rectal samples were inoculated to three types of McConkey-agar plates: supplemented with 8 mg/L cefotaxime, 2 mg/L ciprofloxacin, 50 IU/mL polymyxin E or 8 mg/L tobramycin. Cultures were grown over night at 37°C and analyzed for the presence of Gram-negative bacteria, which were further determined using standard microbiological techniques. Minimum inhibitory concentrations (MIC) were measured for all Gram-negative isolates obtained from overnight cultures by the use of automated susceptibility testing systems; Vitek-2 (BioMérieux S.A. Marcy-l'Etoile, France) or Phoenix (Becton Dickinson and Co, Sparks, MD, USA). Testing was performed according to the manufacturers' guidelines and all required quality control tests were included.

Proportions of marker pathogens (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae* and *Pseudomonas aeruginosa*) not susceptible to either gentamicin or tobramycin (breakpoint for non-susceptibility 4 mg/L), ciprofloxacin (breakpoint for non-susceptibility 2 mg/L) and ceftazidime (breakpoint for non-susceptibility 16 mg/L) were determined. Resistance to ceftazidime was used as a proxy for ESBL production, as standard procedures for detecting ESBL-production had not been implemented during the period of study. Susceptibility testing was performed in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines.

A patient colonized with multiple species with conferred resistance to the same marker antibiotic, was registered as one patient colonized with a micro-organism resistant to that particular antibiotic.

Table E1.						
	Average prevalence (mean (95% CI))					
	Ceftazidime		**Tobramycine**		**Ciprofloxacine**	
Rectal tract	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
SOD and SC n = 1068 n = 907	6.1% (4.7%-7.5%)	14.7% (12.4-17.0%)	9.5% (7.7%-11.2%)	12.6% (10.4-14.7%)	11.6% (9.7%-13.5%)	13.0% (10.8-15.2%)
SOD n = 545 n = 402	4.0% (2.4%-5.7%)	15.9% (12.3-19.5%)	8.1% (5.8%-10.4%)	14.9% (11.4-18.4%)	9.2% (6.8%-11.6%)	15.2% (11.7-18.7%)
SC n = 523 n = 505	8.2% (5.9%-10.6%)	13.7% (10.7-16.7%)	10.9% (8.2 - 13.6%)	10.7% (8.0%-13.4%)	14.1% (11.2-17.1%)	11.3% (8.5%-14.0%)
Respiratory tract	**Intervention**		**Intervention**		**Intervention**	
SDD and SOD N = 1412	3.6% (2.6%-4.6%)		5.7% (4.5%-6.9%)		4.6% (3.5%-5.7%)	
SDD N = 894	3.7% (2.5%-4.9%)		6.0% (4.5%-7.6%)		4.8% (3.4%-6.2%)	
SOD N = 518	3.5% (1.9%-5.1%)		5.0% (3.1%-6.9%)		4.2% (2.5%-6.0%)	

Table E1: Proportions of patients colonized with antibiotic resistant Gram-negative bacteria in the respiratory and rectal tract; data analyzed together and separately.
For rectal tract colonization; the analysis of the pre-intervention and post-intervention period consisted of gathered data from the SOD and standard care period and data from SOD and standard care analyzed separately. The pre-intervention and post-intervention period contain results of 13 consecutive monthly point prevalence surveys.
For respiratory tract colonization; the analysis of the intervention period consisted of data from gathered data from the SDD and SOD period and data from SDD and SOD analyzed separately. The intervention period contains results of 13 consecutive monthly point prevalence surveys.

Chapter 8 | Physicians' and nurses' opinions on Selective Decontamination of the Digestive tract and Selective Oropharyngeal Decontamination

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submitted

ABSTRACT

Objective

To determine expectations of the effects of Selective Decontamination of the Digestive tract (SDD) by Intensive Care Unit (ICU) nurses and physicians, and of perceived workload and patient friendliness of SDD and Selective Oropharyngeal Decontamination (SOD) as compared to Standard Care (SC).

Design and interventions

A qualitative design was used, as part of a group-randomized, controlled, cross-over multi-center study in which during three 6-month periods, either SDD, SOD or SC was used (order randomized per center).

Setting

Thirteen ICUs participated in the trial between 2004 and 2006.

Subjects

Nurses and physicians from participating ICUs.

Measurements and main results

At the end of each study period, questionnaires were sent out. In all, 1024 (71%) questionnaires were returned by nurses and 253 (82%) by physicians. Expectations that SDD improved patient survival increased from 30% and 32% after the first two study periods to 40% at the end of the study (p=0.008), with comparable trends among nurses and physicians. Nurses considered SDD to impose a higher workload (median 5.0, on a scale from 1 (low) to 10 (high)) than SOD (median 4.0) and SC (median 2.0) and both SDD and SOD to be less patient friendly than SC (median 4.0, 4.0 and 6.0 respectively). According to physicians, SDD had a higher workload (median 5.5) than SOD (5.0), which in turn was higher than SC (2.5). Furthermore, physicians graded patient friendliness of SC (median 8.0) higher than that of SDD and SOD (both median 5.0).

Conclusion

The perceived effectiveness of SDD increased as the trial proceeded, both among physicians and nurses. As compared to SC, both SOD and SDD were considered to increase workload and to reduce patient friendliness.

INTRODUCTION

Respiratory tract infections are a serious threat for patients in Intensive Care Units (ICUs).[1] The incidence of these infections can be reduced by use of prophylactic antibiotic regimens, such as Selective Decontamination of the Digestive tract (SDD)[2,3] and Selective Oropharyngeal Decontamination (SOD).[4-6] The concept of SDD consists of prevention of secondary colonization with Gram-negative bacteria, *Staphylococcus aureus* and yeasts through application of non-absorbable antimicrobial agents in the oropharynx and gastrointestinal tract, pre-emptive treatment of possible infections with commensal respiratory tract bacteria through systemic administration of cephalosporins during the first four days in the ICU, and maintaining the anaerobic intestinal flora by a policy favouring antibiotics (both topically and systemically) without anti-anaerobic activity.[7] In SOD only topical antibiotics in the oropharynx are applied and no changes in systemic antimicrobial therapy are pursued.

The use of SDD and SOD has been the subject of intense controversy, due to methodological issues and concern about increased selection of antibiotic-resistant pathogens.[2-4,6-12] From May 2004 to July 2006, a large group-randomized, controlled cross-over multi-center trial was performed in 13 ICUs in the Netherlands in which the effects of SDD and SOD were compared to Standard Care (SC).[13] SDD and SOD were both effective and associated with a 13% and 11% relative reduction in day 28 mortality.[13]

The trial consisted of three six-month study periods in which either SDD, SOD or standard care was used for all patients in the unit with the order of intervention randomized per centre. Because of the existing controversies about SDD and SOD use, we aimed to assess expectations on the effects of SDD and experiences with application of SDD medication.

MATERIALS AND METHODS

Study protocol

Thirteen ICUs participated in the study, differing in size and teaching status and covering all levels of ICUs in the Netherlands. The study protocol included (1) oral hygiene only during SC, (2) oral hygiene plus application of an oral paste during SOD and (3) oral hygiene, application of an oral paste and administration of a suspension through the nasogastric tube and systemic antibiotics for 4 days during SDD (Table 1). In addition, respiratory samples for microbiological cultures were obtained on admission and twice weekly during SDD and SOD, and rectal swabs were obtained on admission and twice weekly during SDD.

A qualitative design was used to determine expectations concerning SDD, experience with SDD, and compliance to the study protocol. The latter was defined as the self-reported level at which nurses performed oral care according to the study protocol. In the last week of each six month study phase, all nurses and physicians working during a single day (including night, day and evening shifts) received the questionnaire, which

could be filled in anonymously (Figure 1). In the second and third questionnaire (at the end of these study periods) it was also asked whether the nurse or physician had filled in a previous questionnaire. In the third questionnaire nurses and physicians additionally were asked to grade workload and patient friendliness for SDD, SOD and SC. Of note, nurses and physicians were not aware of the outcome results of the SDD-SOD trial at the time of the questionnaires.

Questionnaire development

A literature search in PubMed and Cumulative Index to Nursing and Allied Health Literature (CINAHL) in August 2004 did not reveal questionnaires on similar topics that could be used. Therefore, a qualitative study was performed to identify items, i.e. problems encountered when executing the study protocol. The questionnaires were developed upon observations of oral care and semi-structured interviews with 7 nurses from four different hospitals at the start of the trial: 4 in a SDD-period, 1 in a SOD and 2 in a SC period. The observations revealed that nurses did not comply entirely with the oral hygiene protocol. During subsequent interviews the interviewer (IJ) pursued and clarified information on problems encountered during oral care and solutions to resolve reasons for non-compliance. Interviews were audio taped and transcribed verbatim. Transcripts were read and nurses' views regarding problems met during oral care were identified and coded (by IJ and AS). Codes were continuously compared within and between transcripts. Agreement was reached between the researchers as to the major themes to be used in the questionnaires and closed-answer questionnaires within 4 themes were developed:

- problems encountered during oral hygiene
- non-compliance with the protocol
- duration of oral care
- expectations of SDD efficacy

Table 1. Study protocol

Study Period	Oral hygiene	Oral paste†	Suspension¥†	Cefotaxim*
SDD	+	+	+	+
SOD	+	+		
SC	+			

SDD Selective Decontamination of the Digestive tract, SOD Selective Oropharyngeal Decontamination,
SC Standard Care
\+ applied 4 times daily
† Oral paste consists of Polymyxin, Tobramycin, Amphotericin B and is applied in the oropharynx
¥† Suspension consists of Polymyxin, Tobramycin, Amphotericin B and is applied in the gastrointestinal tract through a feeding tube
* Cefotaxim applied intravenous during first 4 days

To maximize response, we designed a short questionnaire. For nurses it contained 4 (SC-period) to 6 (SDD and SOD-period) mostly closed questions, with a possibility to add comments (See Appendix 1). The nurses' questionnaire was pre-tested on 3 nurses, which resulted in a few linguistic changes only.

The questionnaires for physicians consisted of 4 closed and 1 open question in all study periods (see Appendix 2), addressing perceived clinical efficacy of SDD. Physicians were also asked to estimate ICU mortality rates in their standard care and SDD population, which were used to calculate the Presumed Relative Reduction in Mortality (PRRM), being the estimated mortality in SDD divided by the estimated mortality in standard care.

Analysis

Data were analyzed using SPSS15.0 (SPSS Inc, Chicago IL). Changes in opinion over time were analyzed by using χ^2 tests. Differences in time to perform oral hygiene and differences in mean grades were analyzed by using Kruskal-Wallis tests.

RESULTS

In all, 1450 questionnaires were sent out to nurses, of which 1024 were returned (71%): 372 after period 1, 339 after period 2 and 313 after period 3. Of 307 questionnaires sent out to physicians, 253 (82%) were returned: 85 after period 1, 89 after period 2 and 79 after period 3 (Table 2). About a quarter (27% nurses, 24% physicians) completed the questionnaires two or three times.

Expectations on SDD efficacy

The expected effect of SDD on patient outcome, as asked after every study period, increased during the study (p=.004) (Table 2). The proportion of physicians that expected SDD to have no effects on clinical outcomes decreased from 14% after the first two

Figure 1. Number of hospitals with specific orders of interventions and timing of questionnaires

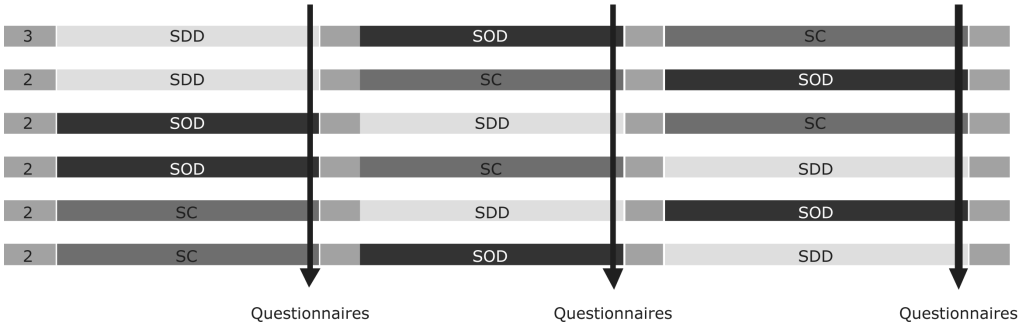

Table 2. Response and expectations of the effect of SDD by nurses and physicians per study period

	Nurses			
	1st	2nd	3rd	p-value†
Response – no. (%)	372 (74)	339 (73)	313 (65)	
Prior experience SDD - %	53	74	87	
Effect SDD – no. (%)				
No effect	101 (33)	80 (26)	63 (22)	.017
Decrease pneumonia	135 (43)	151 (49)	165 (58)	.002
Increase resistance	68 (22)	68 (22)	48 (17)	.209
Decrease resistance	24 (8)	21 (7)	25 (9)	.672
Increase survival*	81 (26)	83 (27)	97 (34)	.062
Other	21 (7)	35 (11)	25 (9)	.129
	Physicians			
	1st	2nd	3rd	p-value†
Response – no. (%)	85 (89)	89 (82)	79 (77)	
Prior experience SDD - %	68	85	90	
Effect SDD – no. (%)				
No effect	12 (14)	12 (14)	3 (4)	.065
Decrease pneumonia	64 (75)	71 (80)	65 (84)	.354
Increase resistance	14 (17)	19 (21)	21 (27)	.247
Decrease resistance	11 (13)	13 (15)	14 (18)	.640
Increase survival*	36 (42)	45 (51)	47 (61)	.059
Other	9 (11)	11 (12)	13 (17)	.478
Median PRRM (IQR)	3.0 (0-25)	12.9 (0-25)	16.7 (0-28.5)	.113
	Total			
	1st	2nd	3rd	p-value†
Effect SDD – no. (%)				
No effect	113 (29)	92 (23)	66 (18)	.004
Decrease pneumonia	199 (50)	222 (56)	230 (68)	.001
Increase resistance	82 (21)	87 (22)	69 (19)	.624
Decrease resistance	35 (9)	34 (9)	39 (11)	.524
Increase survival*	117 (30)	128 (32)	144 (40)	.008
Other	30 (8)	46 (12)	38 (11)	.145

SDD Selective Decontamination of the Digestive tract, PRRM Presumed Relative Reduction in Mortality, IQR Inter Quartile Range

* Increase survival physicians based upon calculation PRRM

† significance based upon x^2 (effect) or Kruskal-Wallis test (median PRRM)

periods to 4% at the end of study (p=.065). For nurses, these proportions were 33%, 26% and 22%, for periods 1 to 3 respectively (p=.017). The most frequently reported expected effect of SDD was a reduction in the incidence of VAP, and these proportions increased during the study (p=.001). Regarding improved ICU survival, overall expectations increased from 30% to 32% and 40% from period 1 to 3, respectively (p=.008). Both nurses (p=.045) and physicians (p=.059) had increasing confidence in a positive effect of SDD on patient survival. This corroborated the median calculated PRRM, as reported by physicians, which increased from 3.0% (as many physicians reported PRRM to be 0%) after period 1 to 16.7% at the end of the study.

The proportion of physicians that expected SDD to affect antibiotic resistance in their unit did not change significantly. An increase in resistance was expected by 17% after period 1 and 27% at the end of study (p=.247), and a decrease in resistance was expected by 13% and 18% (p=.640) at these time points.

Table 3. Free-text responses by nurses and physicians on additional effect of SDD per study period – no.

	Nurses			Physicians		
	1st period	2nd period	3rd period	1st period	2nd period	3rd period
No idea	41	26	15	1	-	-
Better oral hygiene	13	15	11	-	-	-
Increase colonization Enterococci/other bacteriae	1	1	1	4	1	1
Decrease other infections (besides VAP)	2	9	4	3	3	4
Other infection pattern	-	-	-	-	1	1
More frequent growth of yeasts	2	6	5	2	-	1
Less frequent growth of yeasts	-	1	1	-	-	-
Decrease length of stay	1	3	2	1	3	5
Increase length of stay	-	-	-	-	1	-
Better bacterial monitoring/ antibiotics regimen	-	2	-	1	1	1
Increase diarrhea/change intestinal flora	-	2	1	-	-	-
Decrease Multi Organ Failure	1	-	-	-	-	-
Decrease complications	-	-	-	-	1	-
Increase complications(wrong application)	-	-	-	-	-	1
Decrease morbidity	-	-	-	-	-	1
Decrease mechanical ventilation	-	-	-	-	1	1

There was no association between expectations of SDD effects and earlier experience with SDD χ^2 analysis, p= 0.742 and p= 0.975 for physicians and nurses respectively, data not shown). After the third study period, there was no correlation between expected effect (by questionnaires) and observed effect (in the trial) per hospital of SDD on day 28 survival (R^2 = .06), nor between observed effect and PRRM (R^2 = .08).

As additional effects of SDD, nurses mentioned better oral care, more frequent growth of yeasts and a decrease in other infections (such as infections of the oral mucosa) (Table 3). Physicians mostly added a decrease in other infections (beside VAP), like urinary tract infections, a decrease in length of ICU stay and better bacterial monitoring due to culturing (Table 3).

Self-reported compliance to protocol

Problems during oral care, as reported by nurses, occurred frequently. It was reported that especially non-sedated patients experienced oral care as annoying (56%), disliked the flavor of oral paste (46%) and/or suspension (22%), refused to cooperate during oral care (36%) or were nauseous (13%) (Table 4). Despite these problems, the self reported adherence to the study protocol was 70%. Of nurses who did not comply, 8% (7% in SDD, 8% in SOD) reported to have discontinued application and 6% (8% in SDD, 5% in SOD) reported to have modified the study protocol, through using suspension instead of oral paste for oral care. Most modifications of the study protocol were made in non-intubated, non-sedated patients who refused the oral paste. The expected effect of SDD was not associated with being fully adherent to the study protocol (p=0.833).

Time needed for oral care

The estimated median time needed to perform oral care according to the protocol (which included applying oral paste every six hours during the SDD and SOD period) was 3.0 (IQR 0-5) minutes for both standard care and SOD and 5.0 (IQR 2-5) minutes for SDD (p<0.001) (Table 4). Per center, the estimated median additional times needed for oral care during SDD differed from 1.7 to 7.3 minutes. In six out of 13 centers, SDD was considered more time consuming than SOD and SC. Furthermore, in five centers nurses experienced SOD to be less time consuming than SC.

Grades for perceived workload and patient friendliness

At the end of the study both nurses and physicians were asked to grade workload, patient friendliness and effectiveness on a scale of 1 (low) to 10 (high), and this yielded considerable differences between interventions (Table 5).

Both physicians and nurses graded the estimated workload lowest for SC. There were no significant differences between grading by nurses and physicians. Free text from nurses revealed that removing rests of oral paste from the oral cavity (before applying new paste) and increased diarrhea contributed to a higher workload during SDD.

SDD and SOD were considered significantly less patient friendly than SC, both by nurses and physicians. More nurses gave lowest scores for patient friendliness in SDD as compared to SOD (27 and 15 nurses, respectively), while patient friendliness in SOD was more often graded sufficient to excellent (grade 6 or higher) as compared to SDD (37 times in SDD, 63 in SOD). There were differences in grades for patient friendliness given by nurses and physicians for SDD ($p<0.001$) and SOD period ($p<0.05$). In free text, nurses often mentioned the taste and color of the oral paste as patient unfriendly, especially in non-ventilated and non-sedated patients. Furthermore, the suspension of SDD was considered unfriendly, especially when the nasogastric tube was removed and the patient was asked to swallow the suspension.

Table 4. Application of study protocol by nurses per intervention period

	SDD	SOD	SC	p-value
Extra time in min – median (IQR)	5.0 (2-5)	3.0 (0-5)	3.0 (0-5)	.000
Problems - %	79	74		
- Patient disliked taste of oral paste - %	48	44		.336
- Patient disliked suspension - %	22	–		
- Patient was nauseous - %	17	9		.003
- Patient did not cooperate with oral care - %	54	58		.318
	37	34		.377
Change in application Orabase - %	31	29		.305
- once not given - %	14	12		
- given at another time - %	2	4		
- discontinued - %	7	8		
- other - %	8	5		

SDD Selective Decontamination of the Digestive tract, SOD Selective Oropharyngeal Decontamination, SC Standard Care, IQR Inter Quartile Range

Table 5. Median grades (inter quartile ranges) for the three study periods given by nurses and physicians

	SDD		SOD		SC		p-value
	n	median (IQR)	n	median (IQR)	n	median (IQR)	
Nurses							
Workload	223	5.0 (4-7)	222	4.0 (3-6)	209	2.0 (1-4)	.000
Pt friendliness	223	4.0 (2-5)	223	4.0 (3-6)	199	7.0 (3-9)	.000
Physicians							
Workload	32	5.5 (3.25-7)	30	5.0 (3-6)	30	2.5 (2-4)	.000
Pt friendliness	32	5.0 (4-6.75)	30	5.0 (4-6)	27	8.0 (6-9)	.001

n number of responses; SDD Selective Decontamination of the Digestive tract, SOD Selective Oropharyngeal Decontamination, SC Standard Care
IQR inter quartile range; p-value calculated with Kruskal-Wallis tests

DISCUSSION

The results of our study reveal that expectations on the positive effects of SDD, especially on pneumonia and patient survival, increased during the study, both among physicians and nurses, independent of study order and without knowledge of trial results. In contrast to perceived effectiveness, experiences with application of SDD medication were less positive. As compared to SC, SDD was considered to have a higher workload and to be less patient friendly.

The average predicted relative reduction in mortality was highly variable after the first six months of the study, with many physicians reporting that they did not expect SDD to improve survival. The median expected benefit increased during the conduct of the trial, up to a percentage close to the 13% relative risk reduction in day 28 mortality that was actually found.[13]

An important objection against the widespread use of SDD or SOD has been the possibility of an increase of antibiotic resistance. This was an important reason for physicians in the UK for not using SDD.[14] Our survey revealed non-conclusive results on the physicians' expectations on the effects of SDD on antibiotic resistance. During the study increasing proportions of physicians expected that SDD would be associated with either an increase or a decrease of antibiotic resistance. Yet, the actual observed effects revealed that carriage levels with antibiotic-resistant pathogens in the intestines and the respiratory tract reduced during SDD and SOD.[13]

Nurses associated SOD with a lower increase of their workload than SDD. The (statistically significant) difference in duration of oral care in the SDD and SOD period, though, is remarkable, as the oral care protocol did not differ in both interventions. Yet nurses from 5 of the 13 participating centers considered SOD to be less time consuming than SDD and standard care. Previous studies have reported nurses' perception of oral care practices as being difficult and unpleasant to perform.[15,16] In this study, though oral hygiene was the same in SDD and SOD, the perception differed.

Thirty percent of the nurses reported a protocol violation in the application of oropharyngeal decontamination. According to the protocol, oropharyngeal decontamination should be applied four times daily. In case of reported non-adherence, nurses mostly mentioned that they failed to administer the oropharyngeal paste only once. Non-adherence appeared to be associated with the sedation level and ventilation status of a patient: discontinued application of the oropharyngeal paste occurred predominantly in non-ventilated and non-sedated, alert patients. Based on notifications on the patient record forms, we estimated that oropharyngeal decontamination had not been administered in 2.5% and 4.3% of all patient days during SDD and SOD, respectively[13]. It is unlikely that these incidental failures to apply medication affected the effectiveness of the interventions.

There are several limitations to our study. First, it was not possible to fully validate the questionnaires. No (multi-item) factor analysis was performed on the items of the questionnaire, since per topic only one question was included. On the other hand, to enhance validity, we used triangulation: a combination of, in our study, two methods (observations and subsequent interviews) to develop consistent and comprehensive questionnaires about problems and expectations.[17,18] Furthermore, the questionnaire for nurses was pretested, and questions that were not clear were adjusted.

The type of questionnaire design we used allowed respondents to select from a predefined list of options. In doing so, results can be analyzed more easily and objectively, but there is a risk to miss information not listed. On the other hand, we used free-text sections, which were used extensively by the respondents to mention other reasons for non-compliance or problems, beside the predefined categories. The free-text was also analyzed.

A second limitation is the variability in respondents. Different nurses and physicians filled in the first, second and third questionnaire, and changes in expectations might be influenced by the different respondents. However, because of the high response rate in all participating hospitals during each of the study periods, this appears not likely. In addition, restricting the analysis to professionals who filled in the questionnaire twice or even three times revealed similar conclusions (data not shown).

Strengths of our study include the high response rates for both nurses and physicians and the fact that this is, up till now, the only prospective evaluation of perceived opinions related to SDD and SOD.

CONCLUSIONS

The results of our study reveal that expectations on the positive effects of SDD, especially on pneumonia and patient survival, increased during the conduct of the study, both among physicians and nurses, independent of intervention order and without knowledge of trial results. Ultimately, the perceived effects on patient survival were close to the actual observed effects. In contrast to perceived effectiveness, experiences with application of SDD medication were less positive. As compared to SC, SDD was considered to have a higher workload and to be less patient friendly.

Among multiple different interventions aiming to reduce the incidence of VAP in ICU patients, SDD and SOD are the only two associated with demonstrated improvements in patient outcome. Yet, widespread and correct implementation of these interventions will critically depend on the acceptance by health care workers that need to perform these procedures.

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APPENDIX: NURSES' QUESTIONNAIRE

1 *(Question in 2nd and 3rd study period)* Did you complete this questionnaire previously after a prior study period?
❑ Yes ❑ No

2 Did you previously (before this trial) apply SDD?
❑ no
❑ yes, what was your experience with SDD at that time?
  ❑ good, because _____
  ❑ neutral, because _____
  ❑ not good, because _____

3 *(Question in SDD and SOD period)* Keep in mind the last patient you cared for and who was included in the SDD/SOD-trial. Was the following applicable for this patient:

-	patient disliked the flavour of the oral paste (Orabase)	yes / no
-	patient disliked suspension	yes / no
-	patient was nauseous	yes / no
-	patient experienced oral care as annoying	yes / no
-	patient did not cooperate with oral care	yes / no

4 (Question in SDD and SOD period) When at least one of the questions in 3 is answered with "yes": was this a reason to change application of oral paste (Orabase) or suspension?
❑ not applicable (all questions in 3 answered with "no")
❑ no, oral paste and suspension are applied according to protocol
❑ yes, application has changed, namely:
  ❑ oral paste / suspension was not applied once
  ❑ oral paste / suspension was applied at another moment
  ❑ other, namely _____

5 How many minutes do you need **extra** at a time to perform oral care due to the SDD/SOD-trial?
❑ no time extra
❑ about _____ minutes extra per time

6 What do you expect of the effectiveness of SDD?
❑ no effect
❑ indeed effect, namely (more answers possible)
- ❑ decrease in pneumonia
- ❑ increase in resistance
- ❑ decrease in resistance
- ❑ increase of survival of patients
- ❑ other, namely _____

7 *(Question in 3rd study period)* Did you participate in all three study periods of the SDD/SOD-trial?
❑ no, not applicable
❑ if yes, can you give a grade for each of the study periods for the following aspects?

	SDD-period	SOD-period	control-period
Workload (1=low, 10=high workload)			
Patient friendliness (1=poor, 10=excellent)			
Effectiveness (1=poor, 10=excellent)			

8 Do you have other information you like to add concerning the SDD/SOD-trial?
_____
_____
_____

APPENDIX: PHYSICIANS' QUESTIONNAIRE

1 *(Question in 2nd and 3rd study period)* Did you complete this questionnaire previously after a prior study period?
❑ Yes ❑ No

2 What is your profession in ICU?
❑ intensivist
❑ specialist not intensivist
❑ Resident
❑ Intern

3 Have you previously worked with SDD?
❑ yes, during this trial
❑ yes, in this unit before the trial
❑ yes, elsewhere
❑ no, no prior experience with SDD

4 How do you estimate current ICU mortality of the included patient group?
About _____ %

How do you estimate ICU mortality in this patient group after application of SDD?
About _____ %

5 What do you expect of the effectiveness of SDD?
❑ no effect
❑ indeed effect, namely (more answers possible)
  ❑ decrease in pneumonia
  ❑ increase in resistance
  ❑ decrease in resistance
  ❑ other, namely _____

6 Where do you base your expectation of effectiveness and mortality upon (more answers possible):
- ❑ published trials
- ❑ own experience
- ❑ experience of others
- ❑ other, namely _____

7 *(Question added in 3rd study period)* Did you participate in all three study periods of the SDD/SOD-trial?
- ❑ no, not applicable
- ❑ if yes, can you give a grade for each of the study periods for the following aspects?

	SDD-period	SOD-period	SC-period
Workload (1=low, 10=high workload)			
Patient friendliness (1=poor, 10=excellent)			
Effectiveness (1=poor, 10=excellent)			

8 Do you have other information you like to add concerning the SDD/SOD-trial?

_____

_____

_____

Chapter 9 | Comparative evaluation of the VITEK 2, disk diffusion, Etest, broth microdilution, and agar dilution susceptibility testing methods for colistin in clinical isolates, including heteroresistant *E.cloacae* and *A. baumannii* strains

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ABSTRACT

Increasing antibiotic resistance in gram-negative bacteria has recently renewed interest in colistin as a therapeutic option. The increasing use of colistin necessitates the availability of rapid and reliable methods for colistin susceptibility testing. We compared seven methods of colistin susceptibility testing (disk diffusion, agar dilution on Mueller-Hinton [MH] and Isosensitest agar, Etest on MH and Isosensitest agar, broth microdilution and VITEK 2) on 102 clinical isolates collected from patient materials during a selective digestive decontamination or selective oral decontamination trial in an intensive-care unit. Disk diffusion is an unreliable method to measure susceptibility to colistin. High error rates and low levels of reproducibility were observed in the disk diffusion test. The colistin Etest, agar dilution and the VITEK 2 showed a high level of agreement with the broth microdilution reference method. Heteroresistance for colistin was observed in six *Enterobacter cloacae* isolates and in one *Acinetobacter baumannii* isolate. This is the first report of heteroresistance to colistin in *E. cloacae* isolates. Resistance to colistin in these isolates seemed to be induced upon exposure to colistin rather than being caused by stable mutations. Heteroresistant isolates could be detected in the broth microdilution, agar dilution, Etest, or disk diffusion test. The VITEK 2 displayed low sensitivity in the detection of heteroresistant subpopulations of E. cloacae. The VITEK 2 colistin susceptibility test can therefore be considered to be a reliable tool to determine susceptibility to colistin in isolates of genera that are known not to exhibit resistant subpopulations. In isolates of genera known to (occasionally) exhibit heteroresistance, an alternative susceptibility testing method capable of detecting heteroresistance should be used.

INTRODUCTION

The polymyxins are a group of polypeptide antibiotics, that were first isolated in 1947 from a spore-bearing soil bacillus (*Bacillus polymyxa*). Several chemically different polymyxins (A to E) could be isolated from different strains of this bacillus.[19] Only polymyxin B and polymyxin E (colistin) have been used clinically. Systemic use of colistin was restricted, mainly because of reports of serious nephrotoxicity and the emergence of alternative, less toxic antibiotics. Polymyxin B use has continued in the topical treatment of skin, ear and ocular diseases. Increasing antibiotic resistance in gram-negative bacteria has recently renewed the interest in colistin as an intravenous therapeutic option. Colistin is now increasingly being used for life-threatening infections with multidrug-resistant gram-negative bacteria.[6, 7, 13, 14] The increasing use of colistin necessitates the availability of rapid and reliable methods for colistin susceptibility testing.

Disk diffusion is a commonly used method for measuring colistin susceptibility. However, evaluation of in vitro susceptibility testing methods for colistin has shown testing errors with various disk diffusion methods compared to MIC-based methods.[8, 10, 16, 20] Excellent correlations between the Etest and the broth microdilution and agar dilution tests were demonstrated, suggesting that methods based on MICs, rather than disk diffusion methods, should be used to determine the susceptibility to colistin.[4, 8, 9, 16, 21] Automated systems performing rapid identification and antimicrobial susceptibility testing are increasingly being used. A recent validation study by Tan and Ng evaluated the performance of the colistin susceptiblity test contained in the VITEK 2 automated system compared to agar dilution.[22] Based on their data, the VITEK 2 colistin test was considered to be an unreliable method for colistin susceptibility testing.[22]

In susceptibility testing methods using an agar-based medium, the size of the zones of inhibition depend on many variables (e.g., the antimicrobial agent, disk content, and inoculum). One of the most critical variables is the culture medium. From early experiences with the CLSI method, it was clear that different batches of Mueller-Hinton (MH) agar affected the interpretation of susceptibility.[17] Significant differences in medium performance were noted for the aminoglycosides, imipenem and colistin.[1] To circumvent this problem, the British Society for Antimicrobial Chemotherapy (BSAC) published a standardized method of disk susceptibility testing using a medium (Isosensitest agar) with a semidefined composition.[2, 15] However, Isosensitest agar from different manufacturers has also been shown to vary considerably.[1, 11]

In the present study we compared seven methods of colistin/polymyxin B susceptibility testing of clinical isolates from intensive-care units where colistin was routinely administered as part of an ongoing trial using selective decontamination of the gastrointestinal tract.

MATERIALS AND METHODS

Bacterial strains

Gram-negative bacteria were isolated from throat swab, sputum or rectal swab cultures from patients in an intensive-care unit during a selective digestive decontamination (SDD) or selective oral decontamination (SOD) trial. In brief, patients receiving SDD were treated with intravenous cefotaxime during 4 days. Colistin, tobramycin and amphotericin B were applied as a daily suspension via a nastrogastric tube and applied oropharyngeally using an oral paste. Patients receiving SOD were oropharyngeally treated only with the daily oral paste. A total of 80 bacterial isolates were included: *Escherichia coli* (9 isolates), *Enterobacter cloacae* (10 isolates), *Enterobacter aerogenes* (3 isolates), *Enterobacter asburiae* (1 isolate), *Enterobacter amnigenus* (1 isolate), *Klebsiella pneumoniae* (10 isolates), *Klebsiella oxytoca* (4 isolates), *Citrobacter freundii* (10 isolates), *Pseudomonas fluorescens* (3 isolates), *Acinetobacter baumannii* (7 isolates), *Acinetobacter* spp. (2 isolates), *Acinetobacter lwoffii* (1 isolate), *Stenothrophomonas maltophilia* (9 isolates), and *Pseudomonas aeruginosa* (10 isolates). We also tested 22 gram-negative bacterial strains isolated at a later time in the same intensive-care unit from patients not receiving SDD or SOD. These isolates included: *Klebsiella* spp. (10 isolates), *Enterobacter* spp. (9 isolates), and *Citrobacter freundii* (3 isolates). The reference strains *E.coli* ATCC 25922 (colistin MIC, 0.25-1 μg/ml) and *P. aeruginosa* ATCC 27853 (colistin MIC, 0.25-2 μg/ml) were included as quality controls.[8]

Disk diffusion

Disk diffusion testing was performed according to the manufacturer's procedures using both polymyxin B disks (Rosco, Taastrup, Denmark) containing 150 μg polymyxin B and colistin disks (Rosco, Taastrup, Denmark) containing 10 μg colistin. Inocula were prepared by suspending colonies from overnight blood agar plates in sterile saline to a turbidity of a 0.5 McFarland standard. Polymyxin B- or colistin-containing disks were dispensed onto the surface of inoculated agar plates and incubated at 35 C° for 16 to 18 h. We performed the disk diffusion test using both MH agar (Oxoid, Basingstoke, United Kingdom) and Isosensitest agar (Oxoid, Basingstoke, United Kingdom). Interpretation according to the manufacturer's instructions was possible only for the disk diffusion test on MH agar, since zone diameters were available for this medium only. For polymyxin B, the following zone diameters were used for interpretation (Rosco Diagnostica user's guide for Neo-Sensitabs, 2005/2006): Rapidly growing bacteria, ≥ 20 mm, susceptible, 17 to 19 mm, intermediate, ≤ 16 mm, resistant; *Acinetobacter* spp. and *S. maltophilia*, ≥ 22 mm susceptible, ≤ 21 mm, resistant. The following interpretive criteria were used for colistin (Rosco Diagnostica user's guide for Neo-Sensitabs. 2005/2006): rapidly growing bacteria, ≥ 13 mm, susceptible, 11-12 mm, intermediate, ≤ 10 mm, resistant), *Acinetobacter* spp. and *S. maltophilia*, ≥ 13 mm susceptible, 11-12 mm intermediate, ≤ 10 mm resistant.

Broth microdilution

Broth microdilution testing was carried out according to CLSI procedures using cation-adjusted Mueller Hinton broth (BBL-Becton Dickinson, Sparks, MD).[4] Colistin sulfate was obtained from Sigma-Aldrich (St Louis, MO).

Agar dilution

The agar dilution test was performed on MH agar (Oxoid, Basingstoke, United Kingdom) according to the CLSI procedures[4]. Performance on Isosensitest agar (Oxoid, Basingstoke, United Kingdom) was according to the BSAC procedures.[2] Colistin sulfate was obtained from Sigma-Aldrich (St Louis, MO).

Etest

The colistin Etest (AB Biodisk, Solna, Sweden) was performed and interpreted according to the manufacturer's procedures. Both MH agar (Oxoid, Basingstoke, United Kingdom) and Isosensitest agar (Oxoid, Basingstoke, United Kingdom) were used in the testing procedure.

VITEK 2

The VITEK 2 susceptibility card AST-N038 (bioMérieux, Marcy l'Etoile, France) containing a colistin susceptibility test was used according to the manufacturer's instructions. Interpretive breakpoints (MIC ≤ 2 μg/ml, susceptible, and MIC ≥ 4 μg/ml, resistant) were used for the VITEK 2.

RESULTS

All isolates were tested using the above-mentioned methods, and the results were compared to those of broth microdilution, as this was considered the reference method. The colistin MIC measurements for the tested ATCC reference strains were within the published quality control ranges. Table 1 shows the MIC distribution of the tested isolates using the reference broth microdilution test.

In table 2 the results of the various colistin susceptibility testing methods are compared to those of the broth microdilution reference method. Performing the analysis separately for *Enterobacteriaceae* and *Pseudomonas* species did not reveal significant differences. Table 3 shows a comparison between the broth microdilution reference method and the disk diffusion methods for colistin and polymyxin B.

Comparison of agar dilution and broth microdilution

A major difference was found in one *E. cloacae* isolate (MIC of < 0.5 μg/ml on MH agar; MIC > 64 μg/ml on Isosensitest agar). This difference was caused by the presence of a relatively resistant subpopulation consisting of 2 to 10 CFU (depending on the colistin

Table 1. Distribution of MIC ranges of isolates in the reference broth microdilution test

Species	Total no.[a] of isolates	No.[a] of isolates with MIC (µg/ml):									
		<0.5	0.5	1.0	2.0	4.0	8.0	16	32	64	>64
E.coli	9	9									
K. pneumoniae	10	3									7
K.oxytoca	4	4									
C.freundii	10	1						5	4		
P. aeruginosa	10			1	5		4				
P. fluorescens	3	1		1							1
A. baumannii	7	4		1	1						1[b]
Acinetobacter spp.	2	1						1			
A. lwoffii	1	1									
S. maltophilia	9						5	4			
E. cloacae	10	1								3	6[b]
Enterobacter spp.	5	4								1	
Klebsiella spp.[c]	10	10									
Enterobacter spp.[c]	9	9									
C. freundiic	3	3									

[a] Absolute numbers are shown.

[b] Isolates showing heteroresistance. Heteroresistance was observed as either the presence of skipped wells or trailing end points.

[c] Isolates from intensive-care unit patients not receiving SDD/SOD.

Table 2. Percentages of isolates (excluding heteroresistant E. cloacae isolates) tested with various susceptibility testing methods showing a difference in log2 dilutions compared to results of the reference broth microdilution method

Test	% Of isolates showing log2 dilution difference of:								
	>-3	-3	-2	-1	0	1	2	3	>3
Agar dilution MH				4.0	85.4	7.4	3.2		
ISO[a]				18.1	73.4	6.4	2.1		
Etest MH			2.1	15.8	38.9	17.9	20.0	5.3	
Etest ISO	1.0	2.1	1.0	11.6	33.7	18.9	18.9	4.2	6.3
VITEK2			1.1	3.4	71.3	18.4	5.7		

[a] ISO, Isosensitest.

concentration in the agar plate) growing on Isosensitest agar and not on MH agar. Minor differences due to relatively resistant subpopulations were also observed for five *E. cloacae* isolates and one *A. baumannii* isolate. However, these resistant subpopulations were observed growing on both MH and Isosensitest agar plates that contained higher concentrations of colistin. Prior passaging of these resistant colonies on sheep blood agar, followed by repetition of the agar dilution test, yielded an identical result. Directly repeating the agar dilution test with these resistant colonies without prior passaging on sheep blood agar demonstrated a completely resistant phenotype (MIC > 64 μg/ml). Comparison of the results of agar dilution testing to those of the broth microdilution method showed high levels of agreement. Differences were found mainly for the heteroresistant *E. cloacae* isolates. MICs measured for the heteroresistant *A. baumannii* isolate agreed completely.

Table 3. Comparison of disk diffusion testing with the broth microdilution reference method

Species	No. of isolates with reference method MIC (μg/ml)[a] of:		No. of isolates with MH agar disk diffusion result[b] of:					
	≤ 2	≤ 8	Colistin			Polymyxin B		
			S	I	R	S	I	R
E.coli	9		5	4		3	6	
Klebsiella spp.	17	7	10	10	4	13	11	
C.freundii	4	9	5	7	1	11	2	
P. aeruginosa	6	4	10			8	2	
P.fluorescens	2	1	2		1	2	1	
A. baumannii	6	1[c]	2		4 + 1[c]	6		1[c]
Acinetobacter spp.	1	1	1		1	1	1	
A. lwoffii	1		1			1		
S. maltophilia		9	9			5		4
E. cloacae	1	3 + 6[c]	5	1	2 + 2[c]	3		3 + 4[c]
Enterobacter spp.	13	1	11	3		10	4	

[a] For easier comparison, the MICs obtained with the broth microdilution broth reference method have been divided in two categories.

[b] The number of isolates that were sensitive (S), intermediate (I), or resistant (R). Shown are the first measurements with either colistin or polymyxin B.

[c] Heteroresistant isolate.

Comparison of VITEK 2 and broth microdilution

Comparison of the VITEK 2 colistin susceptibility test to the broth microdilution reference test showed a high level of agreement, with the exception of the heteroresistant *E. cloacae* isolates which the VITEK 2 failed to detect. *S. maltophilia* isolates were excluded from the analysis, since the VITEK 2 Advanced Expert System does not interpret the measurements for S. maltophilia.

Comparison of Etest and broth microdilution

Comparing the Etest method to the reference broth microdilution method showed relatively high levels of agreement. The Etest on MH agar failed to detect relatively resistant subpopulations of four *E. cloacae* isolates. The resistant subpopulations of the *E. cloacae* isolates that were missed in the Etest on MH agar were detected in the Etest on Isosensitest agar. Here, 2 to 10 colonies were found to grow within the inhibition zone. The Etest on Isosensitest agar apparently seems to be a more sensitive method to detect resistant subpopulations.

Comparison of disk diffusion and broth microdilution methods

Interpretation of the disk diffusion zone diameters according to the manufacturer's procedures was possible only for measurements on MH agar. The results showed a low level of reproducibility. For polymyxin B, an agreement of only 58% was observed between first and second measurements. On MH agar, resistant colonies growing within the polymyxin B inhibition zone were observed for four *E. cloacae* isolates and one *A. baumannii* isolate. Prior passaging of these resistant colonies on sheep blood agar, followed by repetition of the disk diffusion test, showed an identical result. Directly repeating the disk diffusion test with these resistant colonies, without prior passaging on sheep blood agar demonstrated complete resistance. For five *E. cloacae* isolates and one *A. baumannii* isolate, resistant colonies growing within the polymyxin B inhibition zone were observed on Isosensitest agar, reflecting the tendency of Isosensitest agar to be a better medium to detect heteroresistance.

Testing on MH agar showed resistant colonies within the colistin inhibition zone in two *E. cloacae* isolates and one *A. baumannii* isolate. Resistant colonies growing within the colistin inhibition zone were found for six *E. cloacae* isolates and one *A. baumannii* isolate using disk diffusion testing on Isosensitest agar, again reflecting the tendency of Isosensitest agar to be a better medium for detecting heteroresistance.

To compare the disk diffusion test results with those of the broth microdilution reference test, the MICs obtained with the broth microdilution reference test were divided in two categories (≤ 2 μg/ml and ≥ 8 μg/ml). If MICs of ≤ 2 μg/ml are considered sensitive and MICs of ≥ 8 μg/ml as resistant, low levels of agreement were found (table 2).

DISCUSSION

Infections caused by multi-resistant gram-negative bacteria are increasing worldwide. The increasing resistance to many antibiotics limits a lot of therapeutic options and has led to an increase in the use of intravenous colistin.[6, 7, 13, 14] Therefore, reliable methods to test susceptibility to colistin are needed in order to predict the clinical response adequately. Breakpoints for colistin resistance are available for the BSAC testing procedures (MIC ≤ 4 μg/ml, susceptible, and MIC ≥ 8 μg/ml, resistant). Other interpretive breakpoints exist. The Société Française de Microbiologie provides different breakpoints (MIC ≤ 2 μg/ml susceptible and MIC ≥ 4 μg/ml resistant).[18] The U.S. CLSI provides interpretive breakpoints for *Pseudomonas aeruginosa*[5] and *Acinetobacter* spp. (MIC ≤ 2 μg/ml susceptible and MIC ≥ 4 μg/ml resistant).[4] At present, it is still unclear which breakpoints are most appropriate. The current available breakpoints for colistin are based on colistin sulfate. However, for clinical intravenous applications colistin methanesulphonate is used.

The objective of our study was to evaluate seven methods of colistin susceptibility testing. We considered the broth microdilution method to be the reference method, as was done previously.[3] The CLSI standard testing procedures are firmly established and have been used in many studies. The broth microdilution test was able to detect the heteroresistant isolates. Agar dilution testing using either MH agar or Isosensitest agar was performed. We have also used BSAC testing procedures with semidefined Isosensitest agar, as this has been advocated by some authors.[1, 2] Agar dilution methods using either MH agar or Isosensitest agar showed highly concordant results. We found no significant differences in the performance of either of these test media. Easier detection of resistant subpopulations of *E. cloacae* isolates in our study was an advantage of using the Isosensitest agar. For one *E. cloacae* isolate, the resistant colonies found on Isosensitest agar were not detected using agar dilution testing on MH agar. This reflects the seemingly inherent quality of Isosensitest agar to be more sensitive in the detection of resistant subpopulations.

Polymyxins diffuse poorly in agar, resulting in relatively small zones of inhibition. This complicates the differentiation between susceptible and resistant isolates. Several studies have found disk diffusion to be an unreliable method to measure the susceptibility to colistin.[8, 16, 20] We have also found high error rates, as well as a low level of reproducibility between subsequent measurements for the same isolate. Both polymyxin B- and colistin-containing disks were used in our study. Since there is complete cross-resistance between colistin and polymyxin B, testing either colistin or polymyxin B is not expected to make a difference. Polymyxin B was used in this study, as well, because we routinely test for polymyxin B sensitivity in our laboratory in clinical situations possibly requiring topical application of polymyxin B. Comparison to the reference broth microdilution method was omitted because it was not clear which breakpoints would be appropriate to use.

In previous studies, the Etest showed an excellent agreement with agar dilution[16] and broth microdilution[3] methods. Comparing the colistin Etest method to broth microdilution methods showed concordant results. The Etest on MH agar showed somewhat better results than the Etest on Isosensitest agar. Resistant subpopulations of four *E. cloacae* isolates were missed using MH agar, again reflecting the higher sensitivity of Isosensitest agar to detect resistant subpopulations.

So far, there has been only one report in the literature about the performance of automated systems, such as the VITEK 2, for colistin susceptibility testing.[22] Tan and Ng considered the VITEK 2 colistin susceptibility test to be an unreliable method.[22] In contrast, the VITEK 2 colistin susceptibility test performed well in our study. We found a high level of agreement with the reference broth microdilution method. The main disadvantage of the VITEK 2 is its low sensitivity to detect resistant subpopulations of *E. cloacae* isolates. However, the resistant subpopulation in the *A. baumannii* isolates were detected in the VITEK 2, as well as in the other methods for colistin susceptibility testing. The VITEK 2 colistin susceptibility test can therefore be considered to be a reliable tool to determine susceptibility to colistin in isolates that do not exhibit resistant subpopulations. Although the VITEK 2 is an easy-to-use susceptibility testing method in the setting of a routine diagnostic microbiology laboratory, care should be taken in the interpretation of the results for genera in which heteroresistance has been described. For genera in which occasional heteroresistance has been described, an alternative testing method capable of detecting resistant subpopulations should be used.

Resistant colonies, representing a colistin-resistant subpopulation, were observed for six *E. cloacae* isolates and for one *A. baumannii* isolate. Assaying these resistant colonies directly for colistin susceptibility showed them to be completely resistant. Prior passaging of these resistant colonies on sheep blood agar, followed by retesting, showed an identical result, indicating the resistance to be induced upon exposure to colistin rather than being caused by stable mutations. Heteroresistance to colistin in clinical isolates of *A. baumannii* has been described previously.[12] The authors suggested that monotherapy with colistin for treatment of infections caused by heteroresistant *A. baumannii* may be problematic. The achieved concentrations of colistin in plasma may be substantially lower than those required to eradicate the more resistant subpopulations of *A. baumannii*. Therefore, care is required in the use of colistin as monotherapy in infections with *A. baumannii*. Our study is the first to report on heteroresistance in *E. cloacae* isolates. We propose to extend the suggestion of Li et al. to heteroresistant variants of *E. cloacae* isolates as well. As yet, it is not clear whether these colistin-resistant subpopulations are truly clinically significant or merely represent in vitro artifacts. It remains to be investigated whether colistin-resistant subpopulations exist among other bacteria, as well.

We tested bacterial isolates collected from patient materials during a SDD or SOD trial in an intensive care unit. The results showed relatively high levels of resistance to

colistin. This is probably caused by selection of colistin-resistant bacterial isolates. We have also tested isolates from the same intensive-care unit when no SDD or SOD was applied. In these isolates no colistin resistance was found, indicating a higher level of resistance during the SDD or SOD trial. Whether previous exposure to colistin in the SDD or SOD trial affected the selection of heteroresistant isolates remains to be elucidated.

In conclusion, the disk diffusion method is an unreliable method to measure susceptibility to colistin. The VITEK 2 colistin susceptibility test is a reliable and easy-to-use tool to determine susceptibility to colistin in isolates of genera that are known not to exhibit heteroresistance. In isolates of genera that are known to (occasionally) exhibit heteroresistance, a testing method that is able to detect heteroresistance should be used. The Etest and agar dilution test are also reliable methods to measure colistin susceptibility and have the advantage that they can detect heteroresistant isolates. Heteroresistance was observed in several *E. cloacae* and *A. baumannii* isolates. Isosensitest agar was a better medium to detect heteroresistance than MH agar. Further investigation is needed to determine the clinical significance of these heteroresistant isolates.

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Chapter 10 | Accumulation of oral antibiotics as an adverse effect of selective decontamination of the digestive tract: a series of three cases

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INTRODUCTION

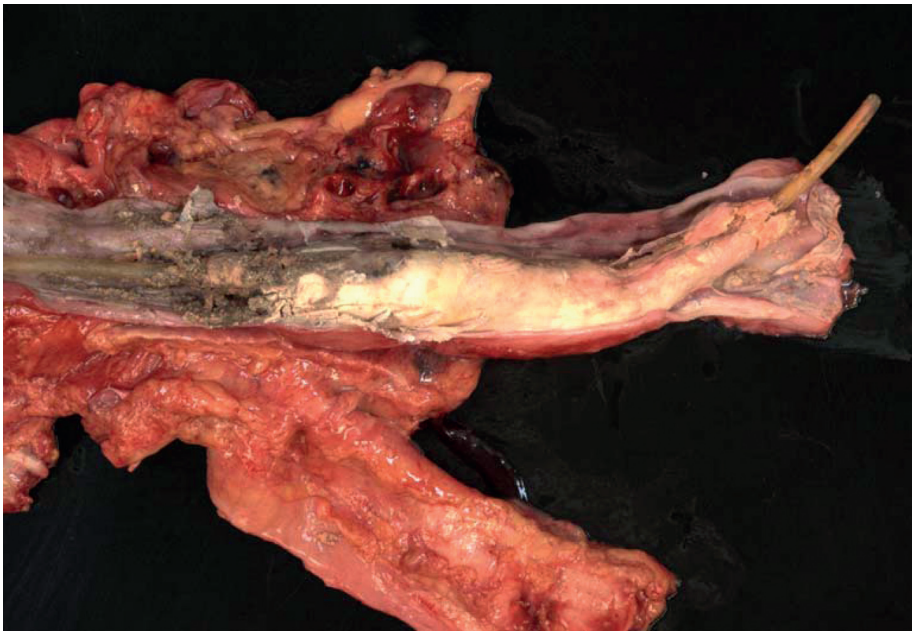
The goal of selective decontamination of the digestive tract (SDD) is to prevent colonization of the digestive tract with potentially pathogenic aerobic bacteria, while leaving the indigenous anaerobic flora largely undisturbed.[1-4] In this paper we report a serious adverse effect of this regimen in intensive care units of three different referral centers.

CASE 1

An 80-year old male patient was admitted to the intensive care unit (ICU) with respiratory insufficiency caused by congestive heart failure accompanying myocardial infarction. SDD and enteral feeding was commenced on arrival on ICU. After 18 days a diagnostic bronchoscopy revealed an incomplete longitudinal tracheal compression. Because of the persistent hemodynamic and respiratory problems, withdrawal of treatment was decided and the patient died shortly after.

Post-mortal examination demonstrated a solid mass completely obstructing the esophagus around an intact gastric tube (Fig. 1). Macroscopically the mass resembled clotted SDD paste, and this was confirmed by identification of tobramycin and amphotericin B by pharmaceutical analysis.

Figure 1. Macroscopic appearance of the mass in case 1



CASE 2

A 70-year old male patient was admitted to the ICU with abdominal sepsis 9 days after a gastrectomy with Roux-Y deviation for carcinoma. After fluid resuscitation and antibiotics combined with SDD, laparotomy was performed. An abcess was drained and a Foley catheter placed in the duodenum for deviation of bile.

Polyethylene glycol (macrogol) was used as a hyperosmotic laxative; enteral feeding was administered from the 2nd day at the ICU.

On day 5 after admission, a relaparotomy was performed because of dislocation of the Foley catheter. Coincidentally an obstructing bezoar was found in the jejunum and extracted.

Pharmaceutical analysis provided identification of amphotericin B and the laxative macrogol.

CASE 3

A 62-year old trauma patient was admitted to the ICU with respiratory insufficiency caused by lung contusion, multiple rib fractures, a cervical vertebra fracture and mild brain injury. After several weeks an attempt to place a nasogastric tube revealed total obstruction of the esophagus. The ENT-physician removed a mass by rigid scope. The mass macroscopically resembled clotted SDD paste. Pharmaceutical analysis was not performed.

DISCUSSION

The classic SDD regimen consists of topical non-absorbed antibiotics (polymyxine B sulphate, amphotericin B and tobramycin) applied to the buccal cavity and through the gastric tube four times a day.[1] Besides the antibiotics the SDD paste consisted of liquid paraffin and Orabase in case 2 and 3 and liquid paraffin and hypromellose in case 1.

Most probably the clotted SDD mass is a result of accumulation of remaining buccally applied SDD paste into the esophagus (cases 1 and 3). The clotted mass in the jejunum (case 2) might be the result of both remained SDD paste and/or SDD suspension. A few recommendations can be made to avoid the problem. Thorough removal of residual SDD paste should prevent accumulation of the paste in the gastrointestinal tract. Also liquid preparations for SDD may reduce the probability of obstructive accumulation.[5]

The limitation of this paper is our inability to assess the incidence of this adverse event. At two of three referral centers SDD is administered to all patients for many years, so the incidence of clinically relevant accumulation is probably very low. Awareness of accumulation of SDD in the digestive tract may lead to prevention or early diagnosis and therapy.

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Chapter 11 | General discussion

BACKGROUND

The intestinal flora is highly diverse and mainly consists of anaerobic bacteria. The intact anaerobic flora is – amongst others – considered an important defence mechanism against acquisitioning of intestinal colonization with (potentially) pathogenic micro-organisms. The digestive tract has – already for long times – been considered an important source of infections in intensive care patients. The commensal flora of the oropharynx consists of hundreds of bacterial species such as enterococci and anaerobic bacteria, which are, mostly for unknown reasons, replaced by Gram-negative bacteria during the first week of treatment in ICU patients. Gastric acidity usually prevents bacterial overgrowth in the stomach. Yet, in ICU-patients reduced acid production due to a high age and underlying diseases, usage of acid-modifying medication (stress ulcer prophylaxis) and intragastric administration of enteral nutrition (with a pH of 6) leads to a gastric environment that favours bacterial growth, especially of Gram-negative bacteria.

Anaerobic bacteria grow well on the mucosa of the gut creating a kind of lining or 'wall paper' on its epithelium.[1] Disruption of this layer by antibiotics that destroy the anaerobic flora may create a port of entry for pathogenic microorganisms.

During the late nineteen-sixties and early nineteen-seventies a Dutch medical microbiologist, professor Van der Waay, and his co-workers developed a concept for infection-prevention based upon this presumed protective effect of an intact intestinal anaerobic flora, which he called 'colonization resistance'. With different combinations of non-absorbable antibiotics he aimed to selectively decontaminate the digestive tract, i.e. to reduce the load of pathogenic aerobic micro-organisms while maintaining the anaerobic flora. This concept was first investigated in mice[2] and later developed into an infection prevention strategy for neutropenic leucemia patients, which the investigators called Selective Decontamination of the Digestive tract (SDD).[3,4]

FROM CONCEPT TO PRACTICE IN THE ICU

Confronted with high infection rates, and accompanying mortality, Stoutenbeek and co-workers considered, in the early nineteen-eighties, critically ill ICU patients also as immunocompromised. After an observational microbiological study among trauma patients during two years they proposed several definitions for colonization and the use of SDD for infection prevention in trauma patients in the ICU.

After a series of observational studies the SDD regimen consisted of application of nonabsorbable antimicrobial agents in the oropharynx and gastrointestinal tract to prevent acquired colonization with Gram-negative bacteria, *Staphylococcus aureus*, and yeasts, in combination with four days of intravenous administration of a second generation cephalosporin to (preemptively) treat incubating respiratory tract infections. Topical and systemic antibiotics were selected based on their antibacterial spectrum and absence of activity on the anaerobic intestinal flora.[5]

EARLIER STUDIES

The first study with SDD in ICU patients was performed by Stoutenbeek et al in 63 trauma patients using an historic control group of 59 trauma patients.[6] This study not only triggered many critical comments and editorials, but also inspired many investigators to perform additional studies in more heterogeneous ICU-patient populations, with different combinations of absorbable and non-absorbable antibiotics, and with or without parenteral antibiotics.[7-10]

Through the following years, a scientific dispute (also with non-scientific arguments) emerged between advocates and opponents of the widespread use of SDD in ICUs. In the Netherlands, it was concluded around the turn of the century, that there was insufficient scientific evidence to recommend SDD as a routine infection control measure in ICU-patients.[11] However, in 2003 a single-center study by de Jonge et al reported highly favourable outcomes in patients receiving SDD, which again fuelled the discussion on several important questions related to 'the case of SDD'.[12,13] Several Letters to the Editor pointed at a number of methodological shortcomings of this study, which led to further heated arguments regarding the clinical benefit of SDD. These discussions led to the design and execution of a multi-center controlled, cross-over study using cluster randomization, of which the results are presented in this thesis.

Ten years after the first experiments with SDD in ICU patients, other researchers proposed that the main effect of SDD, i.e. a reduction in the incidence of ventilator-associated pneumonia (VAP), could be achieved by oropharyngeal decontamination only, without intestinal decontamination and without the routine prophylactic use of systemic antibiotics during the first four days of ventilation.[14,15] Yet, a head-to-head comparison of SDD and SOD had never been performed.

CLINICAL EFFECTS OF SOD AND SDD

In our trial we found that, compared to standard care (SC), both SDD and SOD were associated with a relative reduction of mortality at day 28 with 13% and 11% respectively, corresponding with an absolute reduction of 3.5% and 2.9% (Chapter 3).

Some of the strenghts of this study are its sample size – which was designed to demonstrate statistical significance for a modest but important outcome difference – its multi-center design which allows maximum generalizibility, its pragmatic design to mimic daily clinical practice as much as possible and its cross-over design to account for differences between units. Nevertheless, there are also several limitations. The study was not blinded. Due to the nature of the intervention blinding of physicians was deemed impossible, as knowledge of culture results would immediately have unblinded the study. Because of its unblinded nature, all physicians were aware of the treatment that included patients would receive. As inclusion was based on several criteria, this created the possibility of selection bias. Selective inclusion might have been prevented by designating another person (unaware of the assigned intervention) to be responsible

for inclusion, but this was deemed not feasible. Alternatively, we could have decided to include all patients admitted to the ICU, even those with an anticipated ICU-stay of less than 48 hours. This would have increased the number of inclusions by about 70%. However, since the beneficial effects of antibiotics are only to be expected after three days in ICU and since massive antibiotic exposure may increase selection of antibiotic resistant pathogens, this option was considered unwanted. Finally, we could have performed – in retrospect – an intention to treat analysis of all patients that had been admitted to the participating units. Since this would have represented about 14,000 patients (mostly patients with a short stay in ICU) we considered the additional workload as non-feasible.

To minimize the occurrence of selection bias, inclusion rates were monitored frequently and discussed with local investigators. Yet, despite the use of objective inclusion criteria and the feedback on inclusion rates, in the end, there were baseline differences between the SC and the two intervention groups, but not between the SDD and SOD populations. Patients in the intervention groups (SDD and SOD) were more frequently intubated, were less likely to be surgical patients and had a higher baseline APACHE-score. Further, SDD patients were older compared to SOD and SC patients.

Because of the cluster-randomized study design, and the observed differences in baseline characteristics, the original analysis plan that mainly consisted of hypothesis testing for categorical variables (2 x 3 Chi square test) needed to be extended.

Our first approach was to use Cox regression modelling, with adjustment for baseline characteristics, to determine the differences in hospital mortality between the three groups. With this analysis, there were no significant differences in mortality (ICU-mortality or hospital-mortality) between the three intervention periods. As the duration of follow-up (until death or hospital discharge whichever came first) differs between patients, this was considered the appropriate method. With Cox regression patients that are lost to follow-up will be censored. This is only allowed if the risk to reach the endpoint (i.e. mortality), at the time of censoring, is equal among those that are censored and those that remain in the study. Yet, patients that are discharged alive from the ICU with follow-up of X days have a better prognosis than those that remain in ICU with the same duration of follow-up. This is called informative censoring, which violates the assumptions of Cox regression.

This implied that we had to use a logistic regression model, in which all patients preferably have similar durations of follow-up. Day 28 mortality is frequently used in ICU-studies and was, therefore, chosen as the new primary endpoint. As a result we had to determine the status at day 28 (death or alive) of all (approximately 2,500) patients that had been discharged alive from the hospital before that day. Fortunately, this information can be reliably obtained in the Netherlands. Another advantage of the logistic regression model is that intracluster correlation can be determined, and adjusted for if relevant. Similarity among subjects within pre-existing groups or clusters reduces the variability of responses in a clustered sample, which erodes the power to detect true

differences between study arms. This similarity is expressed by the intracluster correlation coefficient. In our trial, the intracluster correlation coefficient was 0.010, and did, therefore, not affect our analyses.

Although analyses similar to the originally proposed are widely used to assess cluster-randomized studies, they increase the chance of incorrect inferences.[16,17] Cluster-randomized trials offer many advantages, such as allowing unit-wide interventions for which blinding is difficult to achieve, in a pragmatic way that mimics daily practice as much as possible, and for lower costs than generally needed for studies randomizing individual patients. Yet, cluster-randomized trials also call for highly qualified statistical expertise in data analysis.

The question is, how certain can we be that SOD and SDD are associated with an approximate 11-13% reduction in day-28 mortality in all Dutch ICUs? Considering the different levels of ICUs involved in our study, the 89 % inclusion rate of eligible patients and the scrutiny of the statistical analysis, we strongly feel that our findings represent the best estimate currently available on the effects of both interventions. It is unlikely, that a better estimate will be available soon. Therefore, the routine use of SDD or SOD should be recommended for all patients with an expected duration of ICU-stay of at least 2 days, in all ICUs in the Netherlands.

One of the remaining questions is whether SDD and SOD are equally effective in all patient groups. In a subgroup analysis (Chapter 6), we indeed found different effects of SDD and SOD for surgical and non-surgical patients. Compared to SC, SDD was equally effective in reducing 28 day mortality in surgical and non-surgical patients (OR's 0.86 (CI_{95} 0.69-1.09) and 0.85 (CI_{95} 0.70-1.03), respectively), but with significant reductions in duration of mechanical ventilation, ICU-stay and hospital stay among surgical patients. SOD appeared more effective in non-surgical patients (adjusted OR 0.77; CI_{95}: 0.63-0.94) in which a relative mortality reduction of 16.6% and absolute mortality reduction of 5.5% at day 28 was observed. Yet, SOD was not associated with reductions in day-28 mortality in surgical patients and not with significant reductions in duration of mechanical ventilation, ICU- and hospital-stay. These findings suggest that surgical patients benefit from the addition of the enteric and/or systemic component of the SDD regimen. In one meta-analysis a higher efficacy of SDD was observed in surgical patients, compared to SOD.[8] We hypothesized that the addition of systemic prophylaxis with cefotaxime and enteric decontamination, to oral decontamination alone, would reduce the incidence of Gram-negative infections, from which surgical patients might benefit more than non-surgical patients. Indeed, the incidence of Gram-negative bacteremia was lower in patients receiving SDD (compared to those that received SOD or standard care), but this reduction was similar among surgical and non-surgical patients. This indicates that this mechanism cannot explain the observed difference between both patient groups.

It must be stressed that this was a post-hoc subgroup analysis, and there is – yet – no biologically plausible explanation for these remarkable findings. The results should, therefore, be considered as hypothesis generating and further studies are needed to confirm these observations, which – if confirmed – may help to elucidate the mechanisms of protective action of SDD and SOD in specific groups of ICU patients.

MICROBIOLOGICAL EFFECTS OF SOD AND SDD

The microbiological effects of SOD and SDD were analyzed in several ways. The direct effects on colonization of the respiratory and intestinal tract are described in Chapter 4 and the results of the point-prevalence studies in Chapters 3 and 7.

Proportions of SDD-patients with Gram-negative bacteria isolated from rectal swabs decreased from 56% at day 3 to 25% at day 8 and 15% at day 14. Oropharyngeal colonization rates with gram-negative bacteria decreased from 18% at day 2 to 4% at day 8 among SDD-patients, and from 20% at day 2 to 7% at day 8 among SOD-patients. These results were comparable to those reported in other studies.[6,18,19] It can, therefore, be concluded that the microbiological aims of SDD and SOD were achieved.

During the study, surveillance cultures from respiratory and intestinal tract were obtained every third Tuesday of each month from all patients present in the ICU, regardless whether they were included in the study or not. These 18 point-prevalence studies in 13 ICUs allowed a detailed analysis on the effects of SDD and SOD on the bacterial ecology in patients and in an ICU-ward. Effects of SDD (during periods of 6 months) and of SDD/SOD (combined during periods of 12 months) on intestinal and respiratory tract carriage with Gram-negative bacteria were determined by comparing results from consecutive point prevalence surveys during intervention to consecutive point prevalence data in the pre- and post-intervention periods.

During SDD average proportions of patients colonized with ceftazidime, tobramycin or ciprofloxacin resistant Gram-negative bacteria in the intestinal tract were 5%, 7% and 7 %, increasing to 15%, 13% and 13% post-SDD. During SDD/SOD combined, resistance levels in the respiratory tract were ≤ 6% for all three antibiotics, but seemed to increase gradually with a significant increase only for ceftazidime resistance ($p < 0.05$). After discontinuation of SDD/SOD the resistance levels increased to levels of 10% or higher. Obviously, both SDD and SOD have marked ecological effects, most clearly in the respiratory tract. The observed increase of ceftazidime-resistance during SDD/SOD is of concern. Nevertheless, the ecological effects (i.e., lowest resistance levels during interventions) corroborate the effects of SOD and SDD on antibiotic resistance in individual patients (Chapter 4). The gradual increase in resistance during the use of SDD and SOD in the ecological study was not investigated as such in Chapter 4. Yet, we currently witness an emergence of ESBL-producing Gram-negative bacteria in Dutch hospitals, and in ICUs in particular. Our study was executed between 2004 and 2006, which preceded this emergence. Therefore, larger and longer longitudinal studies are

needed to determine the long-term effects of SOD and SDD on antibiotic resistance, with special attention for the changes in antibiotic resistance among Gram-negative bacteria. The observed rebound effect in Chapter 7, could be explained by suppression of antibiotic resistant bacteria present in the gut as long as intestinal decontamination is administered. The resistant flora could become visible (or better said detectable) after patients have been discharged from ICU, and enteral decontamination has been discontinued. One might then propose to continue SDD (or SOD) in these patients after ICU-discharge, in order to reduce the likelihood that such pathogens emerge and be transmitted to other patients. As of now, there is no evidence of such a sequence of events.

On the other hand, if intestinal decontamination effectively suppresses antibiotic resistant pathogens from reaching detection limits of standard microbial culture methods, accumulation of resistance mechanisms might lead to less effective suppression. Therefore, these aspects should be studied in detail, with longer follow-up as in our study.

Additionally all microbiological cultures from blood and endotracheal aspirates were analyzed (Chapters 3 and 4). Crude incidences of ICU-acquired bacteremia were significantly lower during SOD and SDD for *S. aureus*, glucose-nonfermenting gram-negative rods (mainly *Pseudomonas aeruginosa*), and Enterobacteriaceae, as compared to SC. Patients receiving SDD had lower incidences of ICU-acquired bacteremia with Enterobacteriaceae or Highly Resistant Microorganisms (HRMO) than those receiving SOD. The incidence of ICU-acquired candidemia was lower in the SDD group compared to either SOD of SC group. However, incidences of bacteremia caused by HRMO and candidemia were very low, and, therefore, 170 and 127 patients should be treated with SDD, as compared to SOD, in order to prevent one episode. Whether this difference will translate into a difference in clinical outcome between both interventions depends on the overall incidences of candidemia and bacteremia caused by HRMO, the appropriateness of empirical antimicrobial therapy in such patients and the attributable effects of such events on the outcome and length of stay. Higher incidences, with similar rate reductions, will reduce the number needed to treat.

Compared to SOD, SDD was associated with reduced colonization rates with Enterobacteriaceae (including Proteus and Serratia species), other Gram-negative bacteria and *S. aureus*. With regard to resistance to the antibiotics used in SOD and SDD, acquired colonization with tobramycin-resistant Gram-negative bacteria occurred with equal frequency in all three study periods. Colonization with cefotaxime-resistant Enterobacteriaceae occurred later and 62% less frequent during SDD. And colonization with Enterobacteriaceae intrinsically resistant to colistin, also occurred less frequently during SDD. Our findings, therefore, do not support the (widespread) fear that the use of topical antibiotics with or without cefotaxime prophylaxis increases prevalence levels of antibiotic resistance. Further studies are now needed to distinguish the effects of the individual components of SDD. It is still possible that cefotaxime prophylaxis increases

the selection of Gram-negative bacteria resistant to cefotaxime (and other β-lactam antibiotics), but that intestinal decontamination effectively suppresses this effect. This can be studied by comparing patients receiving SOD with and without cefotaxime prophylaxis. And if so, the effects of intestinal decontamination on resistance levels of bacterial colonizing the respiratory tracts of ICU-patients might be even larger, than observed. The latter could be determined by comparing such rates among patients receiving SDD with and without cefotaxime prophylaxis.

In our study, SDD was also associated with lower colonization rates of bacteria intrinsically resistant to colistin, Again, we should bear in mind that the study was executed between 2004 and 2006. Since then colistin is increasingly used as last intravenous treatment option for Gram-negative infections (most notably those caused by Acinetobacter species) resistant to all other antibiotics available. Resistance levels to colistin should, therefore, be carefully monitored in the coming years. The Etest and agar dilution tests are the most reliable methods to determine colistin susceptibility and both have the advantage that they can also detect heteroresistant isolates (Chapter 9).

MRSA AND ENTEROCOCCI

MRSA and VRE are highly prevalent in ICUs in many countries, other than the Netherlands. It is generally considered that SDD (or SOD) is contraindicated in such settings, as these regimens may well increase colonization and infection rates with these bacteria. Yet, few data are available on the effects of SDD or SOD in settings with high levels of MRSA. In an Austrian ICU, the introduction of SDD was followed by increased carriage rates with MRSA.[20] In order to prevent infections with MRSA, some investigators added vancomyin to the SOD or SDD regimen.[14,21] Vancomycin, when applied topically, will not be absorbed and will reach high concentrations in the intestinal tract. In a Spanish burn unit, SDD with topical vancomycin was associated with improved patient outcome and lower colonization rates with MRSA.[21] An inevitable disadvantage of such an approach will be the selection of VRE, in ICUs where both pathogens are prevalent.

Both SDD and SOD were associated with higher rates of acquired respiratory tract colonization, but not with higher bacteremia rates, caused by enterococci. Although commensal bacteria of the intestinal tract, in ICU-patients enterococci will colonize all body sites (especially the skin) and contaminate the inanimate environments. Enterococci have become among the most frequent causes of hospital-acquired infections worldwide, and the proportion of infections caused by ampicillin-resistant enterococci (ARE) has increased substantially in Western countries, including the Netherlands.[22] In the United States, approximately 35% of all ICU-acquired bacteremias caused by enterococci are caused by VRE. The clinical relevance of ARE and VRE-infections still is unclear. Yet, widespread use of topical vancomycin in units with high levels of MRSA will enhance the selective pressure for VRE. This should be carefully balanced against the benefits of SDD or SOD with vancomycin. Of note, ICUs with high levels of MRSA

frequently also have high endemic levels of VRE, at least in the United States. In such settings, addition of chlorhexidine body washings may help in controlling spread and bloodstream infections caused by VRE and MRSA.[23,24]

HOSPITAL ACQUIRED INFECTIONS AFTER TREATMENT WITH SOD AND SDD

It was unknown to what extent discontinuation of SOD and SDD at ICU discharge would affect colonization and infection rates during the remainder of hospitalisation. De Jonge et al observed – in their SDD study – that a relative risk reduction in ICU-mortality of 35% reduced to 22% at hospital discharge.[12] Triggered by these findings we hypothesized that this reduction in survival benefit after ICU discharge might have been related to an increased incidence of hospital-acquired infections (HAI) in patients that had received SDD in the ICU. Nested within our SDD-SOD trial we, therefore, prospectively monitored incidences of HAI during the first 14 days after ICU discharge in all patients transferred to regular wards in two university hospitals (Chapter 5). Most HAI were respiratory tract infections, with similar incidences and similar duration until infections in all three study groups. Incidences of bloodstream infections were also similar between the groups, but time until infection tended to be longer in the post-SOD and post-SDD groups. On the other hand, incidences of surgical site infections (SSI) seemed to increase in the post-intervention groups with incidences of 11.8 per 100 surgical procedures after SOD, 8 per 100 surgical procedures after SDD and 4 per 100 surgical procedures in the post SC-group. The proportion of patients developing post-ICU HAI in the SOD and SDD periods combined tended to be higher than during SC (RR 1.47, CI_{95} 0.935-2.305), though the difference did not reach statistical significance. Considering the low rates of HAI, the overall low mortality rates after ICU-discharge and the low prevalence of infections among those that succumbed after ICU-discharge, the hypothesis that SDD and SOD increase the infection rate and thus affect clinical outcome can be rejected.

OPINIONS AND EXPECTATIONS OF ICU-HEALTH CARE WORKERS ON SOD AND SDD

During the years, medical specialists involved in intensive care medicine, medical microbiology, clinical pharmacy and infectious diseases have held strong opinions about the (lack of) efficacy of SDD or the level of evidence on which these opinions were based. A change of opinion seemed to occur infrequently. We, therefore, investigated whether expectations about SDD among ICU-nurses and ICU-physicians changed during the trial, through regular questionnaires (Chapter 8). Indeed, expectations of the beneficial effects of SDD increased during the study among physicians and nurses, independent of study order or previous experiences with SDD and without knowledge of study results. At the end of the trial 61% of all physicians expected SDD to be associated with a survival benefit and the estimated benefit was a 16.7 % reduction in ICU-mortality.

In the same questionnaires we determined self-reported compliance to study protocol, duration of, and problems encountered during oral hygiene, perceived workload and patient friendliness.

Nurses of 8 of the 13 participating hospitals considered the duration of oral care during SOD as shorter than during SDD (with a statistical difference) while the oral care protocol did not differ between the 2 interventions. Thirty percent of the nurses reported a change in the application of oropharyngeal decontamination, most frequently in non-ventilated and non-sedated, alert patients who expressed unwillingness to receive the oropharyngeal paste. In case of reported non-adherence, nurses reported that they failed to administer the oropharyngeal paste only once. In general SDD was considered to be less patient-friendly and more time-consuming than SC and SOD. It is not surprising that SDD is considered as more time-consuming since eight more applications of medication are needed daily compared to SOD. It is surprising though that, with exactly the same protocol, the oral care in SDD is perceived as more time-consuming compared to SOD and even that in five hospitals nurses considered SOD as less time-consuming than SC.

Nurses play an important role in the implementation of interventions, and their motivation is of equal relevance. Generally nurses will try to protect patients against painful or other uncomfortable actions if they are not necessarily needed. Therefore, the rationale of interventions should be clearly explained through proper education and instruction. Few, if any, studies have addressed the perspectives of nursing practices related to such interventions and many questions, preferably addressed by nursing scientists, are suited for qualitative and quantitative research approaches.

Naturally, SOD and SDD may have adverse effects. Such an example, occurring in three patients, is described in Chapter 10. Three patients suffered from accumulation of the buccally applied oral paste to large clots which caused obstruction in the esophagus or jejunum. One of these patients was included in our study. This complication can be prevented by regular and appropriate oral care.

The study results presented in this thesis provided some answers to long-lasting scientific questions, but also raised new questions that need to be addressed.

1 Can we identify subgroups of ICU-patients that benefit differently from SDD or SOD?
2 What are the effects of SDD and SOD on antibiotic resistance in Dutch ICUs when these regimens are used for longer periods than six months?
3 What is the contribution of each of the SDD components (intravenous cefotaxim, enteral decontamination and the modified antibiotic policy) on the observed differences, compared to SOD, in respiratory tract colonization with antibiotic-susceptible and antibiotic-resistant bacteria?

4 What are the effects of SDD and SOD on colonization and infection rates with antibiotic-resistant bacteria in individual patients after discharge from ICU?
5 What is the effect of SDD and SOD, as compared to standard care, on patient survival in ICUs with higher levels of antibiotic resistant pathogens, such as MRSA, VRE, ESBL-producing Enterobacteriaceae, or Metallo-betalactamase producing Gram-negative bacteria?
6 To what extent adds addition of chlorhexidine body washings to the observed effects of SDD and SOD?
7 Is oropharyngeal decontamination with chlorhexidine equally effective in improving day 28 survival as SOD and SDD?
8 Do the beneficial effects of SDD and SOD on day 28 mortality translate into persistent survival benefits in these patients?
9 What is the price per life year gained with SDD and SOD?

But even before all these questions have been answered, it seems prudent to recommend the use of SDD or SOD for all patients in Dutch ICUs, and other ICU settings with comparable low antibiotic resistance levels, with an expected stay of at least three days or of at least two days when being mechanically ventilated.

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Samenvatting

ACHTERGROND

De darmflora is zeer divers en bestaat voornamelijk uit anaerobe bacteriën. Deze anaerobe bacteriën vormen een van de belangrijke verdedigingsmechanismen tegen kolonisatie van de darm met potentieel pathogene micro-organismen. Het maag-darmkanaal wordt al lange tijd beschouwd als een belangrijke bron voor infecties bij patiënten op de intensive care (IC). Anaerobe bacteriën groeien goed op het slijmvlies van de darm en vormen daar als het ware een bekledende laag. Verstoring van deze laag, bijvoorbeeld door antibiotica die anaerobe bacteriën vernietigen, kan een porte d'entrée vormen voor pathogene micro-organismen.

Eind zestiger en begin zeventiger jaren van de vorige eeuw ontwikkelde een Nederlandse arts-microbioloog, professor van der Waay, met zijn collegae een infectiepreventie concept gebaseerd op deze veronderstelde beschermende werking van een intacte anaerobe bacteriële darmflora, welke hij 'kolonisatie resistentie' noemde. Met verschillende combinaties van niet-resorbeerbare antibiotica streefde hij ernaar de darm selectief te decontamineren, d.w.z. de hoeveelheid pathogene aerobe micro-organismen te verlagen terwijl de anaerobe flora gespaard bleef. Dit concept werd eerst onderzocht in muizen en werd later ontwikkeld tot een infectiepreventie strategie voor immuungecompromitteerde neutropene leukemie patiënten. Deze onderzoekers noemden de methode 'Selectieve Decontaminatie van de tractus Digestivus', kortweg SDD.

VAN CONCEPT NAAR PRAKTIJK OP DE IC

Geconfronteerd met een hoge incidentie van infecties en daarmee geassocieerde sterfte bij patiënten op de IC, beschouwden Stoutenbeek en zijn collegae begin jaren tachtig deze kritisch zieke patiënten ook als immuungecompromitteerd. Op basis van een twee jaar durend observationeel microbiologisch onderzoek bij traumapatiënten werden meerdere definities voor kolonisatie en het gebruik van SDD voor infectiepreventie bij traumapatiënten op de IC opgesteld.

Na een aantal observationele studies bestond het SDD-schema uit de lokale toediening van niet-absorbeerbare antibiotica in de mond-keelholte en het maag-darmkanaal (om verworven kolonisatie met Gram-negatieve bacteriën, *Staphylococcus aureus* en gisten te voorkomen) in combinatie met parenterale toediening gedurende vier dagen van een tweede generatie cefalosporine (om eventuele opkomende luchtweginfecties te behandelen). Lokale en parenterale antibiotica werden geselecteerd op basis van hun antimicrobiële spectrum, en met name het ontbreken van effect op de anaerobe darmflora.

EERDERE STUDIES

De eerste studie met SDD bij IC-patiënten werd uitgevoerd door Stoutenbeek en collegae bij 63 traumapatiënten die werden vergeleken met een historische controlegroep van 59 traumapatiënten. Dit onderzoek leverde niet alleen veel kritisch commentaar op, maar

inspireerde ook veel onderzoekers tot het uitvoeren van nieuwe studies in meer heterogene IC-patiëntenpopulaties met verschillende combinaties van resorbeerbare en niet-resorbeerbare antibiotica, en met of zonder parenterale antibiotica.

In de daaropvolgende jaren ontstond een wetenschappelijke discussie tussen voor- en tegenstanders van een wijdverbreid gebruik van SDD op IC's. In Nederland werd rond de eeuwwisseling geconcludeerd dat er onvoldoende wetenschappelijk bewijs was om SDD als een routine infectiepreventie maatregel toe te passen bij IC-patiënten. In 2003 echter werd een single-center onderzoek van de Jonge en collegae gepubliceerd waarbij zeer gunstige uitkomsten werden gemeld bij patiënten die SDD kregen. Dit wakkerde opnieuw de discussie aan over een aantal belangrijke vragen met betrekking tot SDD. Verschillende commentaren wezen op een aantal methodologische tekortkomingen van deze studie, wat leidde tot verhitte discussies over het klinische voordeel van SDD. Deze discussies hebben geresulteerd in het ontwerp en de uitvoering van een multicenter, gecontroleerd, cross-over onderzoek met clusterrandomisatie, waarvan de resultaten worden gepresenteerd in dit proefschrift.

Tien jaar na de eerste experimenten met SDD bij IC-patiënten, hebben andere onderzoekers voorgesteld dat het belangrijkste effect van SDD, een reductie van de incidentie van beademingsrelateerde pneumonie, ook zou kunnen worden bereikt door selectieve orofaryngeale decontaminatie (SOD) zonder decontaminatie van de darm en zonder het routinematig profylactisch gebruik van parenterale antibiotica tijdens de eerste vier dagen van de beademing. Echter, een directe vergelijking van SDD en SOD was nog niet uitgevoerd.

KLINISCHE EFFECTEN VAN SOD EN SDD

In ons onderzoek vonden we dat, in vergelijking tot standaard zorg (SZ), zowel SDD als SOD waren geassocieerd met een relatieve reductie van de mortaliteit op dag 28 met 13% en 11%, wat overeenkomt met een absolute vermindering van respectievelijk 3,5% en 2,9% (Hoofdstuk 3).

Sterke kanten van dit onderzoek zijn de populatiegrootte – bedoeld om een statistisch significant, bescheiden maar belangrijk, uitkomstverschil aan te tonen – de multicenter opzet die maximale generaliseerbaarheid mogelijk maakt, de pragmatische opzet waarmee de dagelijkse klinische praktijk zoveel mogelijk nagebootst kon worden en het cross-over ontwerp om rekening te houden met verschillen tussen de IC-afdelingen. Aan de andere kant heeft dit onderzoek ook een aantal beperkingen. Het is niet geblindeerd uitgevoerd. Door de aard van de interventies werd het blinderen van artsen onmogelijk geacht, omdat kennis van de resultaten van de afgenomen microbiologische kweken de blindering direct ongedaan zou maken. Als gevolg hiervan waren alle artsen op de hoogte van de behandeling die geïncludeerde patiënten zouden krijgen. Omdat de inclusie van patiënten in het onderzoek was gebaseerd op verschillende criteria ontstond de mogelijkheid van selectiebias. Het selectief includeren van patiënten had voorkomen

kunnen worden door het aanwijzen van een derde persoon (niet op de hoogte van de toegewezen interventie) die verantwoordelijk was voor inclusie, maar dit werd niet haalbaar geacht. Een andere mogelijkheid zou zijn geweest alle op de IC opgenomen patiënten te includeren in de studie, dus ook patiënten met een verwachte IC-opnameduur van minder dan 48 uur. Hiermee zou het aantal inclusies met ongeveer 70% zijn verhoogd. Echter, omdat de gunstige effecten van antibiotica pas te verwachten zijn na drie dagen op de IC en omdat door massale blootstelling aan antibiotica selectie van antibioticaresistente ziekteverwekkers kan toenemen, werd deze optie als ongewenst beschouwd.

Om de kans op selectiebias te minimaliseren werden de inclusiepercentages regelmatig gecontroleerd en besproken met de lokale onderzoekers. Desondanks bleek aan het einde van het onderzoek dat de patiëntkarakteristieken verschilden tussen de controlegroep (SZ) enerzijds en de twee interventie groepen anderzijds, maar niet tussen de SDD en SOD groepen onderling. Patiënten in de SDD en SOD groepen waren vaker beademd, waren minder vaak chirurgische patiënten en hadden een hogere APACHE-score bij opname. Daarnaast waren SDD patiënten ouder dan SOD en SZ patiënten.

Vanwege de toegepaste clusterrandomisatie en de waargenomen verschillen in patientkarakteristieken bij opname werd de oorspronkelijke statistische analyse, die bestond uit het vergelijken van categorische variabelen middels de Chi-kwadraat test, verder uitgebreid.

Onze eerste benadering was het uitvoeren van Cox-regressie, met correctie voor verschillen in patiëntkarakteristieken bij opname, om de verschillen te bepalen tussen de ziekenhuissterfte van de drie groepen. Bij deze analyse werden geen significante verschillen gevonden in sterfte (IC of ziekenhuis) tussen de drie studiegroepen. Omdat de duur van de follow-up (tot overlijden of ontslag uit het ziekenhuis) verschilt tussen patiënten, werd dit aanvankelijk beschouwd als de juiste methode. Echter, met Cox-regressie worden patiënten die worden ontslagen van de IC (loss to follow-up) gecensored. Dit is alleen toegestaan indien het risico op het bereiken van het eindpunt (in dit geval overlijden), op het moment van censoring, gelijk is voor patiënten die worden gecensored en patiënten die in de studie blijven. Echter, patiënten die levend zijn ontslagen van de IC met een follow-up van X dagen hebben een betere prognose dan diegenen die op de IC blijven met dezelfde follow-up duur. Dit betekent dat er sprake is van informatieve censoring en dat niet wordt voldaan aan een van de aannames van de Cox-regressie methode.

Een en ander betekende dat we een logistisch regressie model moesten gebruiken, waarin alle patiënten bij voorkeur een vergelijkbare follow-up duur hebben. Omdat de dag-28 mortaliteit vaak wordt gebruikt in IC-studies, werd deze gekozen als nieuw primair eindpunt. Als gevolg daarvan moest van alle (ongeveer 2500) patiënten die voor dag 28 het ziekenhuis levend verlaten hadden alsnog worden achterhaald of zij op dag 28 wel of niet nog in leven waren. Gelukkig kan deze informatie betrouwbaar

worden verkregen in Nederland. Een ander voordeel van het logistieke regressie model is dat de zgn. intracluster correlatie kan worden bepaald en dat daarvoor zonodig kan worden gecorrigeerd. Vergelijkbaarheid van patiënten binnen al bestaande groepen of clusters vermindert de variabiliteit in de respons in een geclusterde steekproef, wat de kans om echte verschillen tussen de groepen te vinden vermindert. Deze vergelijkbaarheid wordt uitgedrukt in de intracluster correlatiecoëfficiënt. In ons onderzoek was de intracluster correlatiecoëfficiënt 0,010, wat betekent dat intracluster correlatie de analyses niet heeft beïnvloed.

Hoewel analyses die vergelijkbaar zijn met de oorspronkelijk voorgestelde analyse op grote schaal worden gebruikt om cluster-gerandomiseerde studies te beoordelen, verhogen ze de kans op onjuiste conclusies. Cluster-gerandomiseerde onderzoeken bieden veel voordelen, zoals het mogelijk maken van afdelingsbrede interventies waarbij blindering op een pragmatische manier moeilijk is en waarbij de dagelijkse praktijk zoveel mogelijk nagebootst kan worden. Daarnaast gaan ze over het algemeen gepaard met lagere kosten dan studies waarbij individuele patiënten worden gerandomiseerd. Daarentegen vragen cluster-gerandomiseerde onderzoeken wel om hooggekwalificeerde statistische expertise bij de analyse van de gegevens.

De vraag is hoe zeker we kunnen zijn dat SOD en SDD geassocieerd zijn met een reductie van de sterfte van 11 en 13% op dag 28 na opname op een Nederlandse IC? Gezien de verschillende niveaus van IC's die betrokken zijn in onze studie, het feit dat 89% van de voor het onderzoek in aanmerking komende patiënten zijn geïncludeerd en de zorgvuldige statistische analyse, zijn we er van overtuigd dat onze bevindingen de beste momenteel beschikbare schatting is van de effecten van beide interventies. Het is onwaarschijnlijk dat een betere schatting op korte termijn beschikbaar komt. Daarom zou voor alle Nederlandse IC's het routinematig gebruik van SDD of SOD moeten worden aanbevolen voor alle patiënten met een verwachte duur van de IC-opname van tenminste 2 dagen.

Een van de resterende vragen is of SDD en SOD even doeltreffend zijn in alle patiëntengroepen. In een subgroepanalyse (Hoofdstuk 6) vonden we inderdaad verschillende effecten van SDD en SOD voor chirurgische en niet-chirurgische patiënten. Vergeleken met SZ, was SDD even effectief in het verminderen van de dag-28 mortaliteit bij chirurgische en niet-chirurgische patiënten (OR 0,86 (BI_{95}: 0.69-1.09) en 0,85 (BI_{95}: 0.70-1.03), respectievelijk), met een significante vermindering van de beademingsduur en de IC- en ziekenhuis-opnameduur bij chirurgische patiënten. SOD bleek doeltreffender in niet-chirurgische patiënten (OR 0,77; BI_{95}: 0,63 - 0,94) waarbij een relatieve sterftereductie van 16,6% en een absolute sterftereductie van 5,5% op dag 28 werd waargenomen. SOD was echter niet geassocieerd met een reductie in de dag-28 mortaliteit bij chirurgische patiënten of met een significante vermindering van de beademingsduur of de IC- en ziekenhuis-opnameduur. Deze bevindingen suggereren dat chirurgische patiënten profiteren van de toevoeging van de intestinale en/of syste-

mische component van het SDD-regime. In een meta-analyse werd een hogere effectiviteit van SDD waargenomen bij chirurgische patiënten dan van SOD. Wij veronderstelden dat het toevoegen van parenterale profylaxe met cefotaxim en intestinale decontaminatie aan orale decontaminatie alléén de incidentie van Gram-negatieve infecties zou verminderen, waarvan chirurgische patiënten mogelijk meer zouden profiteren dan niet-chirurgische patiënten. Inderdaad was de incidentie van Gram-negatieve bacteriëmie lager voor patiënten met SDD vergeleken met patiënten die SOD of SZ ontvingen. Echter, een verschil tussen chirurgische en niet-chirurgische patiënten werd niet gevonden. Dit betekent dat dit mechanisme niet het waargenomen verschil tussen beide groepen patiënten kan verklaren.

Benadrukt moet worden dat dit een post-hoc subgroepanalyse is, en dat er op dit moment nog geen duidelijke biologische verklaring is voor deze opmerkelijke bevindingen. De resultaten moeten daarom worden beschouwd als hypothese genererend. Er is meer onderzoek nodig om deze bevindingen te bevestigen en, indien bevestigd, de mechanismen van het beschermende effect van SDD en SOD in specifieke groepen van IC-patiënten te verhelderen.

MICROBIOLOGISCHE EFFECTEN VAN SOD EN SDD

De microbiologische effecten van SOD en SDD werden op verschillende manieren geanalyseerd. De directe effecten op de kolonisatie van de luchtwegen en het maag-darmkanaal zijn beschreven in hoofdstuk 4 en de resultaten van de puntprevalentie studies in de hoofdstukken 3 en 7. Het percentage SDD-patiënten waarbij Gram-negatieve bacteriën werden geïsoleerd uit rectumkweken daalde van 56% op dag 3 tot 25% op dag 8 en 15% op dag 14. Kolonisatie van de mondkeelholte met Gram-negatieve bacteriën daalde van 18% op dag 2 tot 4% op dag 8 voor SDD-patiënten, en van 20% op dag 2 tot 7% op dag 8 voor SOD-patiënten. Deze resultaten waren vergelijkbaar met die gerapporteerd in andere studies. Er kan daarom worden geconcludeerd dat de microbiologische doelstellingen (decontaminatie) voor SDD en SOD werden bereikt.

Tijdens de studie werden iedere derde dinsdag van elke maand surveillance kweken afgenomen van de luchtwegen (sputum) en het maag-darmkanaal (rectum) bij alle patiënten die op de IC waren opgenomen, ongeacht of ze waren geïncludeerd in de studie of niet. Deze 18 puntprevalentie studies in 13 IC's hebben een gedetailleerde analyse van de effecten van SDD en SOD op de bacteriële ecologie bij patiënten en binnen een IC mogelijk gemaakt. Effecten van SDD (gedurende periodes van 6 maanden) en van SDD/SOD (gecombineerd gedurende periodes van 12 maanden) op dragerschap met Gram-negatieve bacteriën in het maag-darmkanaal en de luchtwegen werden bepaald door het vergelijken van de resultaten van opeenvolgende puntprevalentie onderzoeken tijdens de interventie en in de pre- en postinterventie periodes.

Tijdens de SDD-periode waren de gemiddelde percentages van patiënten die waren gekoloniseerd met ceftazidime-, tobramycine- of ciprofloxacine-resistente Gram-negatieve bacteriën in het maag-darmkanaal respectievelijk 5%, 7% en 7%, oplopend tot 15%, 13% en 13% in de periode na SDD. Tijdens de gecombineerde SDD/SOD-periode waren de resistentiepercentages in de luchtwegen ≤ 6% voor de drie eerdergenoemde antibiotica, maar leken deze geleidelijk toe te nemen, waarbij een aanzienlijke stijging alleen werd gezien voor de ceftazidime-resistentie (p <0,05). Na het staken van de SDD/SOD namen de resistentiepercentages toe tot 10% of hoger. Het is duidelijk dat zowel SDD als SOD ecologische effecten hebben, vooral in de luchtwegen. De waargenomen toename in ceftazidime-resistentie tijdens SDD/SOD is zorgwekkend. De ecologische effecten (d.w.z. de laagste resistentie niveaus gedurende de interventieperiodes) bevestigen de effecten van de SOD en SDD op antibiotica-resistentie bij individuele patiënten (hoofdstuk 4). De geleidelijke toename in resistentie tijdens het gebruik van SDD en SOD in de ecologische studie is als zodanig niet onderzocht in hoofdstuk 4. Momenteel is er echter wel sprake van een toename van extended spectrum β-lactamase (ESBL)-producerende Gram-negatieve bacteriën in Nederlandse ziekenhuizen, en op IC's in het bijzonder. Onze studie werd uitgevoerd tussen 2004 en 2006, voorafgaand aan deze toename. Daarom zijn grotere en langduriger longitudinale studies nodig om de lange-termijn effecten van SOD en SDD op antibiotica-resistentie, in het bijzonder bij Gram-negatieve bacteriën, te bepalen. Het waargenomen zgn. reboundeffect in hoofdstuk 7 zou kunnen worden verklaard door onderdrukking van antibiotica-resistente bacteriën in de darm zolang intestinale decontaminatie wordt toegediend. Nadat patiënten zijn ontslagen van de IC, en de intestinale decontaminatie is gestaakt, zou de resistente flora dan detecteerbaar worden. Men zou dan ook kunnen overwegen SDD (of SOD) na ontslag van de IC bij deze patiënten te continueren om de kans op uitgroei van dergelijke pathogenen en overdracht naar andere patiënten te beperken. Tot op heden is er geen bewijs voor de beschreven opeenvolging van gebeurtenissen.

Aan de andere kant, wanneer intestinale decontaminatie antibiotica-resistente ziekteverwekkers zodanig onderdrukt dat deze met de standaard kweekmethoden niet gedetecteerd worden kan een accumulatie van resistentie mechanismen vervolgens leiden tot minder effectieve onderdrukking. Het is daarom van belang dat deze aspecten in detail worden bestudeerd met een langere follow-up dan in onze studie.

Daarnaast werden alle microbiologische kweken van bloed en endotracheale aspiraten geanalyseerd (hoofdstukken 3 en 4). De incidentie van IC-verworven bacteriëmie met *S. aureus*, niet-fermenterende Gram-negatieve staven (voornamelijk *Pseudomonas aeruginosa*) en Enterobacteriaceae was significant lager tijdens SOD en SDD dan tijdens SZ. Patiënten met SDD hadden een lagere incidentie van IC-verworven bacteriëmie met Enterobacteriaceae of bijzonder resistente micro-organismen (BRMO) dan patiënten met SOD. De incidentie van IC-verworven candidemie was lager in de SDD-groep dan in de SOD- groep en de SZ groep. Echter, het aantal BRMO-bacteriëmieen en candidemieen

was zeer laag. Respectievelijk 170 en 127 patiënten zouden moeten worden behandeld met SDD om, in vergelijking met behandeling met SOD één geval van bacteriëmie of candidemie te voorkomen. Of dit verschil zich zal vertalen in een verschil in klinische uitkomst tussen beide interventies is afhankelijk van de totale incidentie van candidemie en BRMO-bacteriëmie, de geschiktheid van empirische antimicrobiële therapie bij deze patiënten en de gevolgen van dergelijke gebeurtenissen op de klinische uitkomst en de opnameduur. Hogere incidenties van candidemie en bacteriëmie bij een onveranderd effect van SDD en SOD zal het aantal patiënten wat behandeld moet worden om één ziektegeval te voorkomen verlagen.

Vergeleken met SOD was SDD geassocieerd met een lagere kolonisatiegraad van de luchtwegen met Enterobacteriaceae (waaronder Proteus en Serratia spp), andere Gram-negatieve bacteriën en *S. aureus*. De frequentie van verworven kolonisatie met tobramycine-resistente Gram-negatieve bacteriën was vergelijkbaar voor alle drie de studieperiodes. Kolonisatie met cefotaxim-resistente Enterobacteriaceae ontstond later en 62% minder vaak tijdens SDD. Kolonisatie met Enterobacteriaceae die intrinsiek resistent waren tegen colistine deed zich eveneens minder vaak voor tijdens de SDD periode.

De wijdverbreide angst dat het gebruik van lokale antibiotica, al dan niet gecombineerd met cefotaxim, de prevalentie van antibiotica-resistentie zal verhogen wordt niet door onze bevindingen bevestigd. Verdere studies zijn nodig om de effecten van de afzonderlijke componenten van SDD van elkaar te kunnen onderscheiden. Het is nog steeds mogelijk dat cefotaxim profylaxe de selectie van Gram-negatieve bacteriën die resistent zijn tegen cefotaxim (en andere β-lactam antibiotica) vergroot, maar dat intestinale decontaminatie deze werking effectief onderdrukt. Dit kan worden bestudeerd door het vergelijken van patiënten die SOD krijgen met en zonder profylaxe met cefotaxim. Indien dit het geval is zouden de effecten van intestinale decontaminatie op de resistentieniveaus van bacteriën die de luchtwegen van IC-patiënten koloniseren mogelijk nog groter zijn dan nu waargenomen. Dit laatste zou kunnen worden bepaald door het vergelijken van patiënten met SDD met en zonder cefotaxim profylaxe. In onze studie was SDD ook geassocieerd met een lagere kolonisatiegraad met bacteriën die intrinsiek resistent zijn tegen colistine. Ook hier moeten we rekening houden met het feit dat onze studie werd uitgevoerd tussen 2004 en 2006. Sindsdien wordt colistine in toenemende mate gebruikt als laatste mogelijkheid voor de intraveneuze behandeling van infecties met Gram-negatieve bacteriën (vooral Acinetobacter spp) die resistent zijn tegen alle andere antibiotica. Resistentie tegen colistine moet daarom zorgvuldig worden gecontroleerd in de komende jaren. De E-test en agar dilutie zijn de meest betrouwbare methoden om de gevoeligheid voor colistine te bepalen en beiden hebben het voordeel dat ook heteroresistente isolaten kunnen worden gedetecteerd (hoofdstuk 9).

MRSA EN ENTEROKOKKEN

Anders dan in Nederland, komen meticilline-resistente *Staphylococcus aureus* (MRSA) en vancomycine-resistente enterokokken (VRE) in veel landen zeer frequent voor op IC's. Over het algemeen wordt het gebruik van SDD (of SOD) in deze omgevingen als gecontra-indiceerd beschouwd, omdat deze regimes mogelijk de kans op kolonisatie en infectie met MRSA en VRE verhogen. Er zijn nog weinig gegevens beschikbaar over de effecten van SDD of SOD voor IC's waar MRSA veel voorkomt. Op een Oostenrijkse IC, werd de introductie van SDD gevolgd door een toename in de frequentie van MRSA-dragerschap. Om infecties met MRSA te voorkomen voegden sommige onderzoekers vancomycine toe aan het SOD- of SDD-regime. Oraal toegepaste vancomycine wordt niet geresorbeerd en bereikt hoge concentraties in het maag-darmkanaal. In een Spaanse brandwonden-IC was SDD met vancomycine per os geassocieerd met een verbeterde klinische uitkomst en een lagere MRSA kolonisatiegraad. Een onvermijdelijk nadeel van een dergelijke aanpak is de selectie van VRE op IC's waar beide ziekteverwekkers voorkomen.

Zowel SDD als SOD waren geassocieerd met hogere graad van verworven kolonisatie van de luchtwegen, maar niet met een hogere incidentie van bacteriëmie met enterokokken. Hoewel enterokokken behoren tot de normale flora van het maag-darmkanaal, koloniseren ze bij IC-patiënten relatief gemakkelijk het hele lichaam (vooral de huid) en besmetten ze ook de omgeving. Wereldwijd zijn enterokokken uitgegroeid tot een van de meest voorkomende verwekkers van ziekenhuisinfecties, en het percentage infecties veroorzaakt door ampicilline-resistente enterokokken (ARE) is aanzienlijk gestegen in de westerse landen, waaronder Nederland. In de Verenigde Staten wordt ongeveer 35% van alle IC-verworven enterokokken-bacteriëmieen veroorzaakt door VRE. De klinische relevantie van ARE- en VRE-infecties is nog onduidelijk. Desondanks zal het gebruik van vancomycine per os op IC's met een hoog endemisch niveau van MRSA de selectiedruk voor VRE doen toenemen. Dit moet zorgvuldig worden afgewogen tegen de voordelen van SDD of SOD met vancomycine. Bovendien hebben IC's in de Verenigde Staten vaak niet alleen een hoog endemisch niveau van MRSA, maar ook van VRE. In dergelijke instellingen kan het dagelijks wassen van het lichaam met chloorhexidine helpen bij de preventie van verspreiding van VRE en MRSA en van bacteriëmie met deze verwekkers.

ZIEKENHUISINFECTIES NA BEHANDELING MET SOD EN SDD

Het is onbekend in welke mate het staken van SOD en SDD bij ontslag van de IC de frequentie van kolonisatie en infectie gedurende de rest van de ziekenhuisopname beïnvloedt. De Jonge en mede-auteurs observeerden in hun SDD studie een afname van de relatieve risicoreductie van 35% voor IC-mortaliteit naar 22% voor mortaliteit bij ontslag uit het ziekenhuis. Aangezet door deze bevindingen ontwikkelden wij de hypothese dat deze afname in overlevingswinst na ontslag van de IC veroorzaakt zou kunnen zijn door een toename van ziekenhuisinfecties bij patiënten die SDD had gekregen op de IC.

Binnen onze SDD-SOD studies hebben wij daarom in twee academische ziekenhuizen bij alle patiënten die vanuit de IC werden overgeplaatst naar reguliere verpleegafdelingen een prospectieve registratie van ziekenhuisinfecties uitgevoerd gedurende de eerste 14 dagen na ontslag van de IC (hoofdstuk 5). De meeste ziekenhuisinfecties waren infecties van de luchtwegen, met vergelijkbare incidenties en vergelijkbare tijd tot het ontstaan van de infectie in de drie studiegroepen. De incidentie van bacteriëmie was ook vergelijkbaar tussen de groepen, maar de tijd tot het ontstaan van de infectie was doorgaans langer in de post-SOD en post-SDD groepen. Aan de andere kant leek het aantal gevallen van postoperatieve wondinfecties hoger in de postinterventie groepen met een incidentie van 11,8 per 100 chirurgische procedures na SOD, 8 per 100 chirurgische procedures na SDD en 4 per 100 chirurgische procedures na SZ. Het percentage patiënten dat na ontslag van de IC een ziekenhuisinfectie ontwikkelde was tijdens de gecombineerde SOD en SDD perioden doorgaans hoger dan tijdens SZ periode (RR 1,47; 95% BI 0,935 – 2,305), hoewel het verschil niet statistisch significant was. Gezien de lage incidentie van ziekenhuisinfecties, het algemeen lage sterftecijfer na ontslag van de IC en de lage prevalentie van infecties onder degenen die overleden na ontslag van de IC, kan de hypothese dat infecties vaker voorkomen na staken van SDD en SOD en daardoor het klinische resultaat negatief beïnvloeden worden verworpen.

MENINGEN EN VERWACHTINGEN VAN IC-VERPLEEGKUNDIGEN EN ARTSEN OVER SOD EN SDD

In de loop der jaren hebben diverse medisch specialisten vanuit de intensive care geneeskunde, de medische microbiologie, de klinische farmacie en de infectieziekten uitgesproken meningen geventileerd over de (on)werkzaamheid van SDD of het niveau van bewijs waarop deze meningen waren gebaseerd. Opvallend hierbij was dat een verandering van mening zelden werd gezien. Daarom hebben we door middel van periodieke enquêtes onderzocht of de verwachtingen met betrekking tot SDD onder IC-verpleegkundigen en artsen veranderden tijdens het onderzoek (hoofdstuk 8). Inderdaad stegen de verwachtingen over een gunstig effect van SDD in de loop van het onderzoek onder artsen en verpleegkundigen, onafhankelijk van de studievolgorde, eerdere ervaringen met SDD en zonder kennis van de studieresultaten. Aan het einde van de studie verwachtte 61% van alle artsen dat SDD geassocieerd was met een betere overleving en het geschatte effect was een afname van de IC-sterfte met 16.7%. In dezelfde vragenlijsten onderzochten we de door IC-verpleegkundigen zelfgerapporteerde naleving van het studieprotocol, de duur van, en ondervonden problemen bij de mondverzorging, de ervaren werkdruk en de patiëntvriendelijkheid. Terwijl het mondverzorgingsprotocol bij SDD en SOD niet verschilde, rapporteerden verpleegkundigen van 8 van de 13 deelnemende ziekenhuizen bij SDD een als korter ervaren duur van de mondverzorging dan bij SDD (met een statistisch significant verschil). Dertig procent van de verpleegkundigen maakte melding van een wijziging in de toepassing van orofaryngeale decontaminatie,

meestal bij niet-beademde en niet-gesedeerde alerte patiënten die aangaven de mondpasta niet te willen hebben. In geval van melding van het niet naleven van het protocol, gaven verpleegkundigen aan dat dit slechts eenmalig was gebeurd. In het algemeen werd SDD beschouwd als minder patiëntvriendelijk en meer tijdrovend dan SZ en SOD. Het is niet verwonderlijk dat SDD als meer tijdrovend wordt beschouwd aangezien er dagelijks acht extra medicatiegiften nodig zijn ten opzichte van SOD. Het is wel verrassend dat met een identiek protocol, de mondverzorging bij SDD als meer tijdrovend wordt ervaren dan bij SOD en dat in vijf ziekenhuizen verpleegkundigen de mondverzorging bij SOD zelfs als minder tijdrovend beschouwden dan bij SZ.

Verpleegkundigen spelen een belangrijke rol bij de implementatie van interventies, en hun motivatie is van groot belang. In het algemeen zullen verpleegkundigen proberen patiënten zoveel mogelijk te beschermen tegen niet noodzakelijke, pijnlijke of andere ongerieflijke behandelingen. Het is dan ook van belang dat de ratio van interventies duidelijk wordt uitgelegd door middel van goed onderwijs en instructie. Studies besteden zelden aandacht aan het perspectief van de verpleegkundige praktijk bij dergelijke interventies, terwijl veel vragen geschikt zijn voor een kwalitatieve en kwantitatieve onderzoeksaanpak, bij voorkeur uitgevoerd door verpleegkundige wetenschappers.

Natuurlijk kunnen SOD en SDD nadelige gevolgen hebben. Een voorbeeld hiervan, opgetreden bij drie patiënten, wordt beschreven in hoofdstuk 10. Bij deze patiënten veroorzaakte accumulatie van de mondpasta een obstructie van de slokdarm of het jejunum. Een van deze patiënten nam deel aan onze studie. Deze complicatie kan worden voorkomen door regelmatige en adequate mondverzorging.

De in dit proefschrift gepresenteerde resultaten geven antwoord op een aantal al lang bestaande wetenschappelijke vragen, maar werpen ook nieuwe vragen op die moeten worden onderzocht.

1 Kunnen we subgroepen van IC-patiënten identificeren die op verschillende wijze profiteren van SDD of SOD?
2 Wat zijn de effecten van SDD en SOD op antibiotica-resistentie op Nederlandse IC's wanneer deze interventies langer dan zes maanden worden gebruikt?
3 Wat is de bijdrage van elk van de SDD-componenten (parenterale cefotaxim, intestinale decontaminatie en een anaeroben sparend antibiotica beleid) op de waargenomen verschillen in de kolonisatie van de luchtwegen met antibiotica-gevoelige en antibiotica-resistente bacteriën, in vergelijking tot SOD?
4 Wat zijn de effecten van SDD en SOD op het voorkomen van kolonisatie en infectie met antibiotica-resistente bacteriën bij individuele patiënten na ontslag van de IC?

5 Wat is het effect van SDD en SOD, in vergelijking tot standaardbehandeling, op de overleving van patiënten op IC's met hogere endemische niveaus van antibiotica-resistente ziekteverwekkers, zoals MRSA, VRE, ESBL-producerende Enterobacteriaceae, of metallo-β-lactamase producerende Gram-negatieve bacteriën?
6 In hoeverre voegt toepassing van het dagelijks wassen van het lichaam met chloorhexidine iets toe aan de waargenomen effecten van SDD en SOD?
7 Is orofaryngeale decontaminatie met chloorhexidine even effectief als SDD en SOD in de verbetering van overleving op dag 28 na opname op de IC?
8 Vertalen de gunstige effecten van SDD en SOD op de dag 28-mortaliteit na opname op de IC zich in een voortdurend overlevingsvoordeel bij deze patiënten?
9 Wat zijn de kosten per gewonnen levensjaar voor SDD en SOD?

Maar zelfs voordat al deze vragen zijn beantwoord lijkt het verstandig om het gebruik van SDD of SOD aan te bevelen voor alle patiënten op de Nederlandse IC's, en op andere IC's met een vergelijkbaar laag niveau van antibiotica-resistentie, wanneer de verwachte beademingsduur tenminste twee dagen is of de verwachte opnameduur tenminste drie dagen.

Dankwoord

Terugkijkend op de afgelopen zeven jaar is één ding duidelijk: onderzoek doe je gelukkig niet alleen. Naast dank aan alle IC-patiënten die in de onderzoeksperiodes op de deelnemende intensive care afdelingen opgenomen waren, ben ik aan veel anderen dank verschuldigd: IC-verpleegkundigen, research-verpleegkundigen, afdelings-assistenten, microbiologisch laboranten, secretaresses, adviseurs infectiepreventie, arts-assistenten, intensivisten in opleiding, ziekenhuisapothekers (ook uit Leeuwarden!), medisch microbiologen, intensivisten, mede-onderzoekers/auteurs. Iedereen heeft zich enorm ingezet om dit grote onderzoek te doen slagen, puur op motivatie en zonder geldelijke ondersteuning van buitenaf. Twee mensen kunnen deze afronding niet meer meemaken: Hilly de Vries-Hospers uit Groningen en Annelies Gossink-Franssen uit Leiden. Beiden bijzondere vrouwen die niet snel vergeten zullen worden.

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B.S. Cooper, PhD.: Dear Ben, thank you very, very much for shaking us!

Dr. M.C.J. Bootsma. Beste Martin, "en zo werd hoofdstuk 4 nog veel meer werk dan het verhaal in het parochieblaadje van het dorpje 'Nieuw Engeland'", dat zou de laatste zin van een wat narrig sprookje kunnen zijn. Het was allesbehalve een sprookje maar gelukkig is het mede door jouw vele pogingen en onverstoorbaarheid toch tot een goed einde gekomen.

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"jij moet zeker weer werken mam": helaas schattebollen

"kost het ook nog geld (met ondertoon van ongeloof)?": ja

"En wat levert het dan op?": eh.....

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Curriculum Vitae

Anna Maria Gerarda Andrea (Anne Marie) de Smet was born December 18th, 1959 in Tilburg, The Netherlands. After graduating high school at the 'St. Thomas college' in Venlo in 1978, she started medical studies at the University of Groningen. In 1986 she began working as a trainee at the Nederlands Tijdschrift voor Geneeskunde in Amsterdam. She started her residency in Anesthesiology at the University Hospital Groningen (supervisors: Prof. dr. D. Langrehr, dr. B. Ballast and Prof. dr. P. Hennis) in 1987. Between 1992 and 1993 she followed a fellowship in Intensive Care Medicine at the Onze Lieve Vrouwe Gasthuis in Amsterdam (Supervisor dr. C.P. Stoutenbeek). She became a staff member of the Division of Perioperative care and Emergency medicine of the University Medical Center Utrecht in 1993. Within the Division, she was responsible for the Intensive Care Unit from 1995 until 2005. In 2002, she started the scientific investigation which lead to this thesis. In 2005 she became a staff member in the newly created Intensive Care Center at the University Medical Center Utrecht. She held positions in the board of the 'Staf members' of the University Medical Center Utrecht from 2000 to 2004. Moreover she served as a board member of the Netherlands Society of Intensive Care between 2002 and 2008. From August 2006 on, she combined clinical research in Utrecht with a staff membership in the Intensive Care Unit of the Canisius-Wilhelmina Hospital in Nijmegen. In October 2008 she returned to the Intensive Care of the Onze Lieve Vrouwe Gasthuis in Amsterdam.

Anne Marie de Smet married Marc van den Berg in 1993. Together, they have three children, Noor (1994), Fietje (1996) and Pieter (1998).

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