

The effects of selective
decontamination in Dutch
Intensive Care Units

Evelien Oostdijk

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The effects of selective decontamination in Dutch Intensive Care Units

Effecten van selectieve decontaminatie in Nederlandse Intensive Cares

(met een samenvatting in het Nederlands)

Proefschrift

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PART I

Introduction

Chapter 1

General introduction

Selective decontamination of the digestive tract (SDD) and selective oropharyngeal decontamination (SOD) are powerful infection prophylaxis regimens for patients in intensive care units (ICUs). Both consist of a mouth paste containing tobramycin, colistin and amphotericin B. In addition, SDD consists of an intestinal suspension with the same antibiotics combined with a systemic prophylaxis, usually a third generation cephalosporin. As ICU-infections are often preceded by colonization with so-called potential pathogens, such as *Escherichia coli* and *Pseudomonas aeruginosa*, the topical non-absorbable antibiotics aim to selectively eradicate the potential pathogens while leaving the anaerobic flora undisturbed.(1) The systemic component aims to pre-emptively treat infections caused by commensal respiratory tract flora incubating at the time of ICU-admission. Eligible patients are usually patients with an expected length of ICU-stay of more than 48hours. Topical antibiotics are applied four times daily until ICU-discharge. Part of the SDD and SOD strategy is a surveillance protocol to monitor the effectiveness of the regimens and to detect resistant strains. A sputum- and a throat sample should be obtained on ICU-admission and twice per week during SOD and SDD and in addition during SDD a rectal swab should be collected.

Since the introduction in 1984, more than 45 randomized studies and multiple observational studies in a variety of ICU populations have been performed. Various meta analyses have been published, showing a beneficial effect on patient-outcome without emergence of antibiotic resistance.(2-4) In 2009 a cluster-randomized cross-over study was published comparing SOD and SDD to standard care, i.e. no SDD/SOD, in 13 Dutch ICUs.(5) With regard to their primary endpoint, day-28 mortality, they found that both SDD and SOD performed better as compared to standard care (adjusted OR 0.86 (95%CI 0.74-0.99) and 0.83 (95%CI 0.72-0.97) for SOD and SDD respectively). In addition, less ICU-acquired bacteremias occurred during both SOD and SDD and for SDD also less bacteremias with highly resistant microorganisms were acquired in ICU.

Still, SDD and SOD are highly controversial in ICU-medicine. Fear exists that collateral damage associated with the use of antibiotics will occur and resistance will emerge,(6) although longitudinal studies performed so far did not detect an increase in resistance rates.(7, 8) Another controversial topic is the prophylactic use of colistin as part of SOD and SDD. Resistance to carbapenems is emerging worldwide, leaving colistin as one of the last treatment options for infections with multi-resistant gram-negatives.(9)

Although SDD and SOD are both associated with better patient outcome as compared to no SDD or SOD, it is debatable which regimen should be preferred. Regarding survival, both perform better as compared to standard care, but De Smet et al did not find a significant difference between SDD and SOD.(5) A marked difference is the lower incidence of bacteremias with gram-negative bacteria during SDD as compared to SOD (OR 0.28 (95%CI 0.16-0.47)).(5) Another item are costs; so far it is unknown whether SDD and SOD are cost-effective as no formal cost-effectiveness analysis has been performed.

In this thesis we aimed to provide an overview of various aspects related to Selective Decontamination. The primary aim was to perform a head-to-head comparison of SDD versus SOD in a multicentre cluster-randomized cross over trial with study periods of twelve months to determine trends in antibiotic resistance prevalence.

OUTLINE OF THIS THESIS

In chapter 2 the latest studies involving antibiotic resistance in Europe have been reviewed to determine trends in antibiotic resistance in European ICUs

In chapter 3 we discussed methodological issues associated with studying the effects of SDD and SOD in ICU.

Chapter 4 contains the objectives, methods and main results of the multi-center cluster-randomized cross-over study on SDD and SOD.

To determine whether ecological changes occur during prolonged use of SDD in ICU, we determined trends in time before, during and after the unit-wide implementation of SDD. The results of this study are presented in chapter 5.

As colistin resistance is associated with the prolonged use of colistin, we discuss in chapter 6 the association between the use of SDD and the emergence of colistin resistance.

SDD has been studied most frequently in settings with low endemicity of antibiotic resistance. In chapter 7 we used mathematical modelling to determine how SDD performs in settings with higher baseline resistance rates.

Chapter 8 consists of a four-year observational study in ICUs not using SDD/SOD and ICUs with SDD or SOD use. Trends in antibiotic resistance were determined and discussed.

As cephalosporin resistance is emerging, we compared in chapter 9 the eradication efficacy of SDD of cephalosporin susceptible versus resistant Enterobacteriaceae colonizing the intestinal tract during SDD.

SDD is highly effective in preventing ICU-acquired bacteremias caused by gram-negative bacteria as compared to SOD. Besides the systemic prophylaxis, intestinal decontamination is pursued during SDD and not during SOD. We determined in chapter 10 the role of intestinal gram-negative carriage as a source for ICU-acquired bacteremia.

In chapter 11 one-year survival was determined for SOD, SDD and control group patients.

Chapter 12 contains a formal cost-effectiveness analysis of SDD and SOD versus control.

The results of all chapters are summarized and discussed in chapter 13.

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Chapter 2

Recent trends in antibiotic resistance in European ICUs

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ABSTRACT

Purpose of the review: Antimicrobial resistance is an emerging problem in ICUs worldwide. As numbers of published results from (inter)national surveillance studies rise rapidly, the amount of new information may be overwhelming. Therefore, we reviewed recent trends in antibiotic resistance in ICUs across Europe in the past 18 months.

Recent findings: In this period, infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) appeared to stabilize (and even decrease) in some countries, and infection rates due to Gram-positive bacteria resistant to vancomycin, linezolid or daptomycin have remained low. In contrast, we are witnessing a continent-wide emergence of infections caused by multi-resistant Gram-negative bacteria, especially *Escherichia coli* and *Klebsiella pneumoniae*, with easily exchangeable resistance genes located on plasmids, producing enzymes such as extended spectrum beta-lactamases (ESBL) and carbapenamases. In the absence of new antibiotics, prevention of infections, reducing unnecessary antibiotic use, optimizing adherence to universal hygienic and infection control measures, and improving implementation of diagnostic tests are our only tools to combat this threat.

Summary: As the epidemiology of antibiotic resistance in ICU is rapidly changing towards more frequently occurring epidemics and endemicity of multi- and pan resistant Gram-negative pathogens, better infection control and improved diagnostics will become even more important than before.

INTRODUCTION

Antibiotic resistance is a daunting phenomenon with a growing impact on patient safety, particularly in Intensive Care Units (ICUs).[1] Critically ill patients are prone for colonization and infection with antibiotic resistant bacteria because of frequent exposure to antibiotics, the presence of multiple, often invasive, devices, and the occurrence of so-called immune paralysis often in combination with disrupted skin and mucosal barriers. As critical illness may affect pharmacodynamics and pharmacokinetics of antibiotics, optimal penetration in infected tissues may not always be achieved, hampering successful treatment and promoting antibiotic resistance. This dangerous array of risk factors perpetually drives a vicious circle of increased infection incidence, increasing the need for broad-spectrum antibiotics, reduced antimicrobial efficacy and increased selection of antibiotic resistance.

This review addresses recent developments of the European epidemiology of antibiotic resistance in ICUs, with a focus on methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative bacteria producing extended spectrum beta-lactamases (ESBL) and carbapenemases.

Methicillin-resistant *Staphylococcus aureus*

The prevalence of MRSA infections among *S. aureus* bacteraemia varies widely across European countries, ranging from less than 1% in Scandinavian countries to 50% in the southern European countries.[2] In a prospective cohort study, performed between 2005 and 2008, of almost 120,000 patients in European ICUs (mainly in France, Spain and Austria), *S. aureus* pneumonia and bacteraemia developed in 1.3% and 0.4% of all patients, of which 34% and 38% were caused by MRSA, respectively.[3*] In Italy, *S. aureus* was responsible for 23% of all ICU-acquired infections in 125 Italian ICUs and 39% of ventilator associated pneumonia (VAP)-episodes and 71% of bacteraemia episodes were caused by MRSA.[4]

In most hospitals, MRSA prevalence is higher in ICUs than in general wards, most probably because of the before-mentioned risk factors for MRSA colonization and infection.[5] However, MRSA colonization and infection rates may differ extensively between different types of ICU. For instance, incidence ratios in medical ICUs were markedly lower (incidence rate ratio, 0.42) than in other ICU types in Germany.[6]

As compared to MSSA, episodes of bacteraemia[7] and pneumonia[8] caused by MRSA have been associated with higher health care costs, more frequent ICU admissions[7] and a higher ICU-mortality.[3*, 8] Whether this higher mortality in ICU is truly attributable to methicillin resistance is difficult to disentangle because of the confounding effects of, for instance, co-morbidity. In the largest study in the field, antibiotic resistance appeared not to be associated with increased length of ICU stay.[3*]

Because of these high incidences of MRSA infections various infection control interventions were implemented in many European countries, which were followed by stabilizing and even decreasing incidences of MRSA infections in France and the United Kingdom.[2, 9] In French ICUs the incidence of MRSA infections decreased from 2.95 to 1.23 per 1,000 hospital days (relative change, -58%; P=0.001) between 1996 and 2007.[10] In the UK, a nation-wide implemented prevention program was associated with 57% reduction in MRSA bacteraemia episodes between 2006 and 2008.[11]

Vancomycin is probably still the most widely used antibiotic to treat MRSA infections, although linezolid and daptomycin are also available. Vancomycin resistance in *S. aureus* (VRSA), through acquisition of the *vanA* gene from vancomycin-resistant enterococci (VRE), was first reported in the United States in 2002.[12] Yet, since then only few other VRSA isolates have been reported from the US, but not from Europe.[13] The fear of widespread transfer of the *vanA* gene among *S. aureus*, therefore, has not become reality, possibly due to fitness costs associated with expression of the *vanA* gene.[14]

S. aureus strains with intermediate vancomycin susceptibility (VISA) are far more common. VISA is associated with a thickened cell wall capable of binding and thus reducing the availability of vancomycin. VISA develops mainly in MRSA, by serial mutations after prolonged vancomycin exposure.[15*] In a global study of more than 20,000 *S. aureus* isolates, obtained between 2004 and 2009, 8.9% of European MRSA isolates had a MIC $\geq 2\mu\text{g/mL}$ for vancomycin.[16*] Nevertheless, more than 98% of all MRSA isolates were susceptible to vancomycin (MIC $\leq 2\mu\text{g/mL}$) and VRSA was not encountered. There were three linezolid-resistant *S. aureus* isolates, of which only one originated from Europe. Yet, an outbreak of linezolid-resistant MRSA was recently reported in a Spanish ICU.[17] Here, horizontal transmission of resistance was suspected, as different MRSA clones as well as other staphylococci were carrying the *cfz* gene.[18]

Other multi-resistant Gram-positive micro organisms appear less relevant in European ICUs. In the European Antimicrobial Resistance Surveillance Network the prevalence of VRE among enterococcal bloodstream infections was less than or equal to 5%, or even absent, in 13 of 24 countries that reported at least ten *E. faecium* isolates. Three countries (Greece, Ireland, and the UK) reported more than 25% VRE isolates, and VRE appears to be spreading in Swedish hospitals.[2, 19]

Gram-negative bacteria producing extended spectrum beta-lactamases

Gram-negative bacteria are common pathogens in ICU and are able to transfer resistance genes via plasmids without the necessity to replicate (horizontal transfer), which markedly increases the transmission potential of resistance. These plasmids may contain other genes, including virulence factors.

ESBL confer resistance to penicillins and most cephalosporins, including third generation cephalosporins and as of now, more than 700 different ESBLs have been described. Although third-generation cephalosporin resistance is frequently used as proxy for ESBL-production, such a resistance phenotype can also result from non-ESBL AmpC enzymes, upregulation of efflux pumps, changes in membrane porins and altered penicillin binding proteins.

The prevalence of ESBL-producing bacteria varies considerably in Europe. *E. coli* are most prevalent among infections with ESBL-producing bacteria, with reported prevalences ranging from 1.8% to 19.2% (based on the phenotype of third generation cephalosporin resistance) among bloodstream infections in 28 countries in 2009.[20-23]

Of special interest is the epidemiology of a certain *E. coli* genotype (ST131) which appears to emerge rapidly, both among isolates associated with infections as well as with colonization.[24, 25*] Described initially in 2008 in Europe, Asia and North-America, retrospective analyses of isolates suggest that this genotype infected patients only sporadically in the 20th century. *E. coli* ST131 has been associated with plasmid-borne CTX-M-15-genes and fluoroquinolone-resistance. *K. pneumoniae* is the other major reservoir of ESBL genes in hospitalized patients. Compared to *E. coli*, the prevalence of ESBL-producing *Klebsiella* spp. among bloodstream isolates in different countries varies even more (from 0% to 70%), although this variation also results from huge variations in episodes of bacteraemia included per country (ranging from 17 to 1634). Nosocomial outbreaks frequently occur across Europe, in some cases with specific sources such as contaminated medication and endoscopes.[26-30]

Carbapenemases

Carbapenems are the treatment of choice for infections caused by ESBL-producing bacteria. Yet, Gram-negative bacteria are increasingly capable of producing enzymes able to hydrolyse carbapenems, so-called carbapenemases. It is a diverse group of enzymes that can be distinguished into three classes and various subgroups, of which *K. pneumoniae* carbapenemases (KPC) and the New Delhi metallo-beta-lactamase enzyme (NDM-1) are currently most relevant. KPCs and NDM-1 have been associated with rapid global spread and KPCs have caused several outbreaks in ICUs. Besides the ability to hydrolyse carbapenems, carbapenemase producing Gram-negative bacteria often confer resistance to a variety of other antibiotics, such as aminoglycosides, fluoroquinolones and cephalosporins, limiting treatment options to colistin, fosfomycin and tigecycline,[31] yet even pan-resistant Gram-negatives have been described already.[32**]

Klebsiella pneumoniae carbapenemases (KPCs) were initially described in *K. pneumoniae*, but were later also demonstrated in other species such as *Enterobacter* spp. and *E. coli*. The plasmids carrying KPC genes are extremely mobile allowing transfer to different species within the Enterobacteriaceae family.[33, 34]

The first KPC was isolated in 1996 in the United States.[35] As of 2011, KPCs have been found in at least ten countries in four continents, with notable numbers of outbreaks in Israel and the United States.[36, 37] In Europe carbapenemases appear to be most prevalent in Greece, where carbapenem resistance among *K. pneumoniae* blood isolates in ICU patients increased from 1% in 2001 to 80% in 2010.[38-40] For KPCs the epidemiology is almost completely monoclonal as 96% of 173 *K. pneumoniae* isolates obtained in 21 Greek hospitals belonged to the same pulsetype. [41] Yet, the number of reported outbreaks in other European countries is rapidly cumulating. [42-48] Apparently transfer of patients from endemic settings, such as hospitals in the US, Israel or Greece, facilitated the dissemination of KPC-producing *K. pneumoniae* in Europe.[25*, 48-52] Moreover, since these bacteria can be carried without signs of infection, healthy people that migrate between countries and continents may also contribute to spread. [39, 48, 53]

New Delhi metallo-beta-lactamase enzyme (NDM-1), encoded by the *bla*_{NDM-1} gene, was recently discovered in a patient in Sweden who was transferred after hospitalisation in New Delhi, India.[54] The patient was colonized with both *E. coli* and *K. pneumoniae* carrying plasmids containing the *bla*_{NDM-1} gene. India and other Asian countries are considered the epicentre of this new epidemic, with one Indian study reporting NDM-prevalence of >90% among carbapenem resistant Enterobacteriaceae and a prevalence of >10% of carbapenem resistance among *K. pneumoniae* in some hospitals.[55] In addition, *bla*_{NDM-1} harbouring bacteria were obtained from 51 of 171 seepage water samples and from two of 50 public tap water samples in New Delhi, indicating its ubiquitous presence.[56**] It is assumed that over-the-counter use of antibiotics facilitates NDM-1 selection and spread through faecal-oral transmission through environmental contamination.

The number of reports of infections and carriage with NDM-1 in Europe is rapidly cumulating. [57, 58] Cases are often related to transfer of patients from endemic areas, especially from hospitals in India, Pakistan or the Balkans.[32**, 59-61]

Burden of disease

It is difficult to quantify the burden of disease, expressed as the excess risk of dying or the attributable length of stay (LOS), due to infections caused by these antibiotic resistant bacteria. In two French studies infections caused by ESBL-producing bacteria were not associated with statistically significant increases of LOS or higher mortality in surgical patients.[20, 22] Yet, in a Spanish study of cancer patients infections caused by antibiotic resistant Gram-negative bacteria, mostly ESBL-producing *E. coli*, were associated with higher rates of ICU admission, longer ventilation times and increased mortality. Yet, inadequate empirical antibiotic treatment because of antibiotic resistance was not associated with unfavourable outcomes.[62] Although it is widely believed that antibiotic resistance negatively influences patient outcome, accurately quantifying these effects is - methodologically – challenging because of the plethora of confounders.

Infection control

Disciplined and relentless application of universal infection control measures such as hand hygiene, environmental cleaning and isolation or cohorting of colonized patients are still cornerstones of infection control practices in ICU. In addition, new diagnostic tools, for instance biomarkers such as procalcitonin, may enhance our abilities to implement tailor-made antibiotic treatment durations, reducing the total volume of antibiotic exposure.[63-65, 66**] Furthermore, more rapid identification of antibiotic resistance in microbiology laboratories, for instance with molecular testing or chromogenic media, may enhance our abilities to identify carrier.[67] However such an approach – screening of carriage on admission followed by enhanced control measures for carriers – failed to reduce acquisition rates with MRSA and VRE in American ICUs, possibly because of the long turn-around time between obtaining screening cultures and reporting results.[68] A cluster-randomized trial in 13 European ICUs, evaluating a step-wise approach of increasing hand hygiene adherence in combination with universal chlorhexidine bodywashing, followed by rapid screening on admission with enhanced barrier precautions for carriers has been completed recently, and results are expected in early 2012.[69]

It is generally assumed that antibiotic resistance is associated with the quantity of antibiotic consumption, as confirmed in a large observational study in 53 German ICUs.[21] Yet, the same investigators failed to demonstrate that reducing cephalosporin use during placement of cerebrospinal shunts (from “standard” prophylaxis for 48 hours to three weeks to a single dose of cefuroxime) reduced antibiotic resistance.[70] Likewise, in a study by Nijssen et al.[71] in a Dutch ICU a 35% reduction in the use of beta-lactam antibiotics was not associated with lower acquisition rates of cephalosporin resistant bacteria. Yet, the replacement of beta-lactam antibiotics by fluoroquinolones was associated with markedly higher acquisition rates of fluoroquinolone resistant bacteria.

Scheduled rotation of antibiotics in ICU is another – still controversial – measure to influence antibiotic resistance. In a two-centre Italian trial rotation of cephalosporins, fluoroquinolones, carbapenems and piperacillin-tazobactam during 12 months was associated with a non-significant reduction of the incidence of VAP caused by Gram-negative bacteria, including antibiotic resistant bacteria, without determinable effects on LOS or ICU-mortality.[72] Commendable for its two-centre study design and careful monitoring of all relevant antibiotics, adherence to hand hygiene was not determined. In addition, only clinical samples related diagnosing VAP were used for analyses, which may underestimate the true incidence of acquisition of antibiotic-resistant bacteria. This study adds to the growing body of evidence that temporary modulation of antibiotic policies has an effect on the bacterial ecology in ICUs, but the optimal settings for this approach to reduce resistance remains to be determined.

Finally, another – controversial – approach is the use of topical antibiotics to limit the spread of antibiotic resistance in ICUs. The regimens studied most extensively in this regard are selective decontamination of the digestive tract (SDD) and selective oropharyngeal decontamination (SOD). SDD aims to decolonize the aerobic flora in the oropharynx and gastro-intestinal tract in ICU-patients through application of topical antibiotics in the oropharynx and gut in combination with a 4-day course of cefotaxim. SOD only aims to eradicate potential pathogenic microorganisms from the oropharynx. In a cluster-randomized multi-centre cross-over study in 13 ICUs in the Netherlands SDD and SOD were, as compared to standard care, associated with a statistically significant reduction of day-28 mortality.[73] Moreover, in these ICUs with low levels of antibiotic resistance, SDD was associated with lower rates of ICU-acquired bacteraemia caused by highly-resistant microorganisms (mainly Gram-negatives), as compared to SOD and standard care.[74] Furthermore, effective decontamination of the gut appeared associated with a lower risk of developing ICU-acquired Gram-negative bacteraemia, underscoring the critical role of the gut as a source for bacteraemia in these patients.[75] Both SDD and SOD were associated with lower rates of ICU-acquired respiratory tract colonization with highly-resistant microorganisms.[74] In a longitudinal analysis of the bacterial ecology in these 13 units, it was apparent that prevalences of antibiotic resistant Gram-negatives were lowest during periods in which long-stay patients received topical antibiotics.[76] Yet, ceftazidime resistance in the intestinal flora appeared to increase after a period of SDD and ceftazidime resistance in respiratory samples tended to increase during SDD and SOD.[76] Therefore, controversy remains about the safety of SDD and SOD and its efficacy in high endemicity settings remains to be determined.[77] Interestingly, though, a decolonisation strategy including SDD was successful in for ESBL-eradication in 16 of 18 patients.[78]

Conclusion

Antibiotic resistance is now deferring the treatment of a significant and still growing proportion of infections in ICU patients across Europe. Although incidences of MRSA infections seem to be stabilizing (or decreasing) in some countries, multi-resistant Gram-negative bacteria are now most cumbersome. In the absence of new antibiotics, prevention of infections, reducing unnecessary antibiotic use, optimizing adherence to universal hygienic and infection control measures, and improving implementation of diagnostic tests are our only tools to combat this phenomenal threat.

Key Points:

1. Infections caused by antibiotic-resistant bacteria continue to increase in European ICUs.
2. Although infection rates caused by multi-resistant Gram-positive pathogens seem to stabilize in some countries, infections caused by multi-resistant Gram-negative bacteria – in particular ESBL- and carbapenemase-producing Enterobacteriaceae – are emerging.

3. In the absence of new antibiotics, prevention of infections, reducing unnecessary antibiotic use, optimizing adherence to universal hygienic and infection control measures, and improving implementation of diagnostic tests are our only tools to combat this phenomenal threat.

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Chapter 3

*Selective decontamination in European
intensive care patients*

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Selective Decontamination of the Digestive Tract (SDD) is both one of the most studied and one of the most debated preventive measures for critically ill patients in intensive care units (ICU) (see box). After the first trials in haematology patients in the nineteen-seventies(1, 2), the concept was introduced in ICU-populations in the nineteen-eighties(3), and frequently studied in the following decade(4). Various different regimens were studied, including strictly oropharyngeal decontamination (Selective Oropharyngeal Decontamination (SOD)) (see box). At the turn of the century there were more than 50 randomized, though mostly small and single-center, trials and several meta-analyses. The summarized conclusions from these studies was that SDD was associated with reductions of respiratory tract infections in ICUs with low levels of antibiotic resistance, but that improvement of patient outcome (i.e. better ICU-survival) could be demonstrated in meta-analyses only(5, 6).

Since that time numbers of new SDD-studies declined and this measure was not widely adopted in European ICUs, mainly because the evidence for better patient outcome was considered not convincing, and because of the unknown – possibly detrimental – effects of prophylactic antibiotic use on antibiotic resistance development. The Netherlands became the exception to this rule, due to two studies, both demonstrating survival benefits of patients receiving SDD(7, 8). In both studies, SDD was used as a unit-wide intervention in ICUs with low prevalence of antibiotic resistant bacteria and in both studies SDD was associated with lower, instead of higher, rates of antibiotic resistance. Yet, the absolute day-28 mortality reduction in the largest study was 3.5% (relative reduction was 13%) and only determinable in a random effects logistic regression model with adjustment for baseline differences between study groups(8). Moreover, in the latter study, SDD was equally effective in improving patient outcome as Selective Oropharyngeal Decontamination (SOD).

The beneficial results of SDD and SOD obtained in Dutch ICUs raise the question whether both measures could be equally beneficial in other European countries. Here, we address some methodological issues relevant for future attempts to quantify the effects of SDD or SOD in critically ill patients.

Study design

The two studies in which SDD was associated with improved patient outcome tested SDD as a unit-wide intervention. In one study, SDD was administered to all patients that provided informed consent in one ICU during a 2-year study period (n=466), and results were compared to those of another ICU (in the same hospital) where none of the patients received SDD (n=468)(7). Allocation of patients to either of both wards was randomized if both units had beds available, but this was not further specified. In the other study, SDD was also administered to all patients eligible during a 6-month period in 13 ICUs (n=2,045), and the results were compared to those

obtained in 6-month periods in which all patients received either SOD (n=1,904) or no topical antibiotics (n=1,990)(8). The latter was – at that time - considered standard of care. In this cluster-randomized cross-over study, each of the 13 ICUs used SDD, SOD and standard care during 6-month periods, with the order of interventions randomized per center. Importantly, in the latter study there was no individualized randomization, which bears the risk, intrinsic to any cluster-randomized study, of biased patient inclusion(9). Therefore, baseline characteristics related to patient prognosis must be included in the analysis.

There is an obvious reason to evaluate SDD and SOD as a unit-wide measure. Both measures aim to reduce bacterial carriage in individual patients, which may influence the risk of acquisition of bacterial colonization (followed by infection) of other patients. This patient-dependency might reduce the true effects of interventions when patients with and without SDD (or SOD) are treated in the same unit(10). As a result, failure to demonstrate beneficial outcome results in an individual patient randomized study may not reflect true effects when using these measures in all patients.

Outcome measures

A number of outcomes can be measured when studying infection prevention strategies in the ICU, including infection rates and antibiotic use, length of stay or of mechanical ventilation, and mortality rates in the ICU or at a fixed time-point (eg, 28 days), or ventilator-free days (surviving) at 28 days. Which of these is most appropriate as the primary end-point in decontamination studies? It is widely believed that SDD and SOD exert their effects largely through prevention of respiratory tract infections, such as ventilator-associated pneumonia (VAP). As compared to SOD, the intestinal decontamination part of SDD seems to reduce the occurrence of ICU-acquired bacteremia with Gram-negative bacilli, but it is unlikely that this effect can be determinable in survival differences(11). Diagnosing VAP is difficult and relies for an important part on microbiological culture results from respiratory samples(12). The topical antibiotics applied in the oropharynx, though, aim to eradicate bacterial colonization of the upper respiratory tract, which will inevitably influence culture results. Only samples obtained from the distal parts of the lung that cannot be reached by the topical antibiotics will provide reliable diagnostic samples. Therefore, unambiguous, patients-centered, outcomes, such as survival should be used as end-points when evaluating these interventions. Moreover, since recent studies have convincingly demonstrated that the attributable mortality of VAP is much lower than previously assumed, it is difficult to extrapolate a reduction in VAP incidence to improved patient survival(13-15).

What should be the targeted mortality reduction? The relative reduction in day-28 mortality in the Dutch multicenter study was 13% for SDD and 11% for SOD, corresponding to absolute mortality reductions at day 28 of 3.5% and 2.7%, respectively(8). Based on these estimates, derived in units with low levels of antibiotic resistance, at least 2,000 patients per intervention group are needed to gain sufficient power. However, it would be highly relevant to determine

outcome effects of these interventions on longer time scales, such as day 90 or one year survival, which may well enhance the number of patients needed. Furthermore, it is difficult to anticipate the magnitude of the effect on patient outcome in settings with different bacterial ecology, i.e., with higher prevalence of antibiotic resistant bacteria. If the preventive effects on infection development are similar in such a setting, but attributable mortality of infection is higher because of more infections being caused by antibiotic resistant bacteria, the effects on patient survival could be larger than those obtained in Dutch ICUs. In contrast, if fewer infections are prevented because of antibiotic resistance, it can be expected that effects on survival will be smaller (or even absent).

Antibiotic resistance

The global emergence of antibiotic resistance, especially among Enterobacteriaceae, necessitates enhanced infection control strategies, also in ICUs. In theory, SDD and SOD could have a synergistic effect with basic infection control measures such as hand hygiene and barrier precautions. Reductions of bacterial loads at places frequently contacted by nursing staff (i.e., the respiratory tract region), would reduce the likelihood of cross-transmission. Yet, the evidence on the effects of SDD on antibiotic resistance is highly conflicting. In settings with low levels of antibiotic resistance, such as Dutch ICUs, SDD and SOD were associated with lower rates of antibiotic resistant Gram-negative bacteria(7, 16), and ongoing follow-up studies seem to confirm these findings (M. Bonten, unpublished data).

Less certain are the effects of topical antibiotics in settings with higher levels of resistance. There is – already “old” – evidence that SDD can help to control outbreaks with multi-resistant *Klebsiella* strains(17), and persistently low levels of resistance have been reported from several centers using SDD for prolonged periods of time. In contrast, in some studies the use of SDD was associated with increasing rates of carriage and infections caused by antibiotic-resistant pathogens (mostly gram-positive)(18-21).

Colistin is one of the antibiotics used in SDD and SOD. The recent rise of infections caused by carbapenem-resistant Gram-negative bacteria makes this agent a last-resort antibiotic. It is therefore imperative to determine the effects of topical use of colistin on resistance development in Gram-negative bacteria. Furthermore, it is unknown whether patients recolonize with resistant bacteria when SDD is discontinued. Another aspect related to antibiotic resistance is the total amount of intravenous antibiotic use. According to the “classical” SDD protocol, all patients should receive intravenous antibiotics during the first four days. However, systemic antibiotics are also prescribed to virtually all eligible ICU patients, whether or not they are receiving SOD or no topical prophylaxis at all(8). In the Dutch multi-center study, the total use of intravenous antibiotics (including the SDD component) was around 10% lower during SDD and SOD(8). It is unknown to what extent such a reduction in systemic antibiotic use may influence resistance development.

Other considerations

A formal cost-benefit analysis of SDD does not exist. In the Dutch multi-center study it was estimated that the daily antibiotic costs of SDD and SOD were \$12 and \$1, respectively(8). Yet, especially the price of amphotericin B has markedly risen in recent years. Today, the commercial price of SDD and SOD would be around €200 and €40 per day, respectively. Since the necessity of amphotericin B as a component of SDD has never been determined, it might be worthwhile to investigate SDD with other topical antimycotic agents (e.g., nystatin)(22-25).

Based on the Dutch multi-center study, one could conclude that SOD and SDD are equally effective in improving patient outcome. If confirmed, this implies that the improved outcome essentially results from the effects of the strategy on oropharyngeal bacterial carriage. Chlorhexidine oropharyngeal care has also been associated with a 50% reduction in VAP(26), quite similar to the reported effects of SOD(27), but both interventions have never been compared directly. A recent meta-analysis suggests a dose-response relationship with optimal preventive effects of chlorhexidine oropharyngeal care when using a concentration of 2%(28). If chlorhexidine is indeed equally effective as SDD and SOD, it would overcome all the potential problems with using topical antibiotics for prophylaxis in critically ill patients.

Future studies

Currently, there is only one large randomized clinical trial registered which evaluates the effects of SDD or SOD, again in Dutch ICUs (Table 1). Based on the favourable results obtained in Dutch ICUs, the logical next step seems to investigate SDD and SOD in settings with different bacterial ecology. Yet, when preparing such studies some important lessons can be learned from the former studies. The beneficial effects of the interventions tested in individual studies have only been apparent when applied as unit-wide interventions. It is, therefore, advisable to apply this approach in any further study. Because of the difficulties in objectively diagnosing VAP and the fact that SDD and SOD cannot be applied in a double-blind manner, it is advisable to use an unambiguous primary outcome, such as patient survival. Considering the small absolute reduction in day-28 mortality derived in Dutch ICUs, study groups should include at least 2,000 subjects. Detailed monitoring of antibiotic resistance is imperative, especially for colistin resistance; finally, studies comparing these interventions with 2% chlorhexidine oropharyngeal care are warranted.

Study	Year	Institute	Patients	Design	Primary objective	Intervention	Study Status
Microbiologic Effect of Selective Decontamination of the Digestive Tract With Colistin, Gentamicin and Nystatin	2007	University of Pittsburgh Pennsylvania	40	observational	effect of SDD on vancomycin resistant enterococci colonisation	SDD (colistin, gentamicin, nystatin)	Not started, terminated
Selective Digestive Decontamination in Carriers of Carbapenem-resistant <i>Klebsiella</i> Pneumoniae	2008	Soroka University Medical Center, Israel	<i>unknown</i>	blinded RCT	effect of SDD on carbapenem resistant <i>Klebsiella</i>	SDD (gentamicin and polymyxin E)	Completed
The effects of SDD and SOD on antibiotic resistance in the ICU	2009	University Medical Center Utrecht, Utrecht, The Netherlands	10,000	randomized cross-over multicentre trial	effect of SDD and SDD on antimicrobial resistance	SDD and SOD (amphotericin B, tobramycin, colistin and cefotaxim in SDD)	Running
Resistant gram negative bacteria after cessation of SDD or SOD in ICU patients	2010	Leiden University Medical Center, Leiden, The Netherlands	1200	Prospective observational multi-center trial	Rectal colonization with any resistant aerobic Gram-negative bacteria at any time point within 10 days after ICU discharge.	SDD and SOD (amphotericin B, tobramycin, colistin and cefotaxim in SDD)	Running
R-GNOSIS: Decolonization strategies in Intensive Care	2011	University Medical Center Utrecht, Utrecht, The Netherlands	10,400	randomized cross-over multicentre trial	Effect of SDD, SOD and chlorhexidine mouthwash on gram negative bacteremia rate	SDD and SOD (amphotericin B, tobramycin, colistin and chlorhexidine 2%)	Prior to participant recruitment

Table 1. Registered trials (www.clinicaltrials.gov, M. Bonten, personal communication)

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PART II

Selective decontamination and antibiotic resistance

Chapter 4

*The effects of decontamination of the oropharynx
and intestinal tract on antibiotic resistance in
Dutch Intensive Care Units*

ABSTRACT

Background: Selective Digestive tract Decontamination (SDD) and Selective Oropharyngeal Decontamination (SOD) are prophylactic antibiotic regimens used in Intensive Care Units (ICU) that have been associated with improved patient outcome. We compared the effects of SDD and SOD, applied as unit-wide interventions, on patient outcome and antibiotic resistance.

Methods: We conducted a pragmatic, cluster-randomized cross-over trial comparing 12 months of SOD to 12 months of SDD in 16 Dutch ICUs. Patients with an expected length of ICU-stay >48hours were eligible to receive SDD/SOD. Monthly one-day point prevalence surveys of respiratory and rectal samples were performed to determine trends in carriage with antibiotic resistant gram-negative bacteria (ARGNB). The clinical outcome analysis included all patients that had received ≥ 1 dosage of SDD or SOD or that stayed >48hours in ICU.

Results: In all, 5,881 patients and 6,116 patients were included in the clinical outcome analysis for SOD and SDD, respectively. Based on point-prevalence surveys, rectal carriage with ARGNB was lower during SDD, and during both interventions there was a significant trend towards an increase of aminoglycoside resistant GNB, which was more pronounced for SDD. Day 28-mortality was 25.4% and 24.1% during SOD and SDD respectively (adjusted OR 0.963 (95%CI 0.877-1.057) $p > 0.05$), and there were no statistically significant differences in any other outcome parameters. ICU-acquired bacteremia with Enterobacteriaceae was 58% lower during SDD.

Discussion: Unit-wide application of SDD and SOD was associated with low levels of antibiotic resistance and no differences in clinically relevant outcome. In settings with low levels of ARGNB both measures appear safe, but the observed trend of a gradually increasing prevalence of aminoglycoside resistant GNB warrants careful microbiological monitoring.

BACKGROUND

Intensive care unit (ICU)-acquired infections are important complications of the treatment of critically ill patients, increasing morbidity, mortality and health care costs(1). Reductions in the incidence of ICU-acquired respiratory tract infections have been achieved by prophylactic antibiotic regimens, such as Selective Decontamination of the Digestive tract (SDD) and Selective Oropharyngeal Decontamination (SOD)(2, 3). Both SDD and SOD consist of non-absorbable antibiotics with activity against Gram-negative bacteria, yeasts and *Staphylococcus aureus* that are applied in the oropharynx q.i.d. throughout ICU-stay. SDD also includes application of topical antibiotics in the gastrointestinal tract and of systemic prophylaxis with a third generation cephalosporin during the first four days of ICU-stay.

In the largest study in this field, SDD and SOD were compared, as a unit-wide intervention, to standard care (no SDD or SOD) in a cluster-randomized cross-over study in 13 Dutch ICUs with low levels of antibiotic resistance (4). In this study of 5,939 patients, SDD and SOD were, as compared to standard care, associated with relative reductions of death at day 28 of 13% and 11%, respectively, and SDD and SOD had comparable effectiveness in reducing length of stay in ICU or hospital and systemic antibiotic use. In subsequent analyses of this study, incidences of acquisition of respiratory tract colonization with antibiotic resistant bacteria were significantly reduced during SDD and SOD, and incidences of ICU-acquired bacteremia with antibiotic resistant bacteria were lower during SDD, as compared to SOD (5). On a ward-level, though, SDD was associated with a gradual increase in the prevalence of Gram-negative bacteria resistant to third-generation cephalosporins (6), and SDD and SOD appeared to differently effect survival in surgical and non-surgical patients (7).

Although SDD and SOD were considered equally effective in ICU patients in the study by De Smet et al.(4), questions about the impact of selection bias, inherent to an open study without individual patient randomization, and long-term ecological effects remained. So far, there is little evidence of increased risks of antibiotic resistance in individual patients receiving SDD or SOD (8), but outbreaks of ESBL-producing bacteria and of Enterobacteriaceae resistant to colistin and aminoglycosides during SDD have been reported (9, 10). We, therefore, evaluated the effects of SDD and SOD on the unit-wide bacterial ecology during a 24-month period, and in addition evaluated the effects on relevant clinical endpoints, antibiotic resistance in individual patients in the ICU-population, as well as in surgical and non-surgical patients separately.

METHODS

Sixteen ICUs, representing all levels (I-III) in the Netherlands (table S1 for more information), participated in this open cluster randomized cross-over study. After randomization each ICU started with either SDD or SOD for twelve months (after a wash-in period of one month), with

a cross-over to the other intervention, after a wash-out wash-in period of one month (Figure 1). In this period the new strategy (either SDD or SOD) was implemented, but patient data were not used for analysis. Randomization was stratified into two strata based on presence or absence of applying selective decontamination in the unit for more than four months prior to the start of the study. Randomization was performed by a pharmacist not involved in the study, using a computerized randomization program. Institutional review board approval was obtained from all participating hospitals and the need for informed consent was waived as both SDD and SOD were considered equally effective and standard of care.

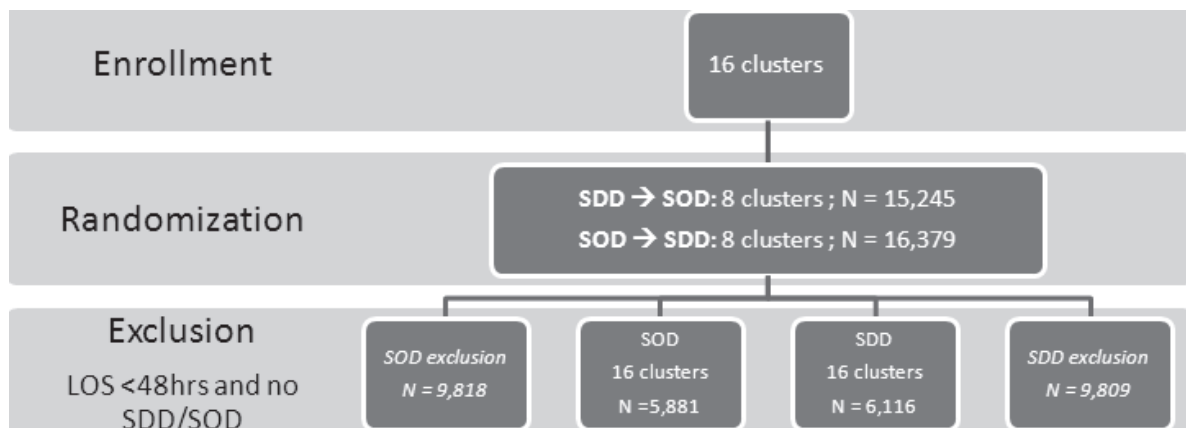


Figure 1

All patients admitted to ICU with an expected ICU-stay of at least 48 hours were eligible to receive SDD or SOD. To minimize inclusion bias all patients that received at least one dosage of SDD or SOD were included, as were all patients with an ICU-stay of at least 48 hours, irrespective whether they received SDD or SOD, and this population is referred to as the eligible study population. CRFs were completed by local research nurses and/or intensivists, and if possible data were obtained via electronic patient data management systems (PDMS).

The SDD and SOD regimens have been described before (3, 4) and consisted of oropharyngeal application (every 6 h) of a paste containing colistin, tobramycin and amphotericin B each in a 2% concentration (in SDD and SOD) and administration (every 6 h) of a 10 ml suspension containing 100 mg colistin, 80 mg tobramycin and 500 mg amphotericin B via the nasogastric tube (in SDD). Topical antibiotics were applied until ICU-discharge. In addition, a third generation cephalosporin (either cefotaxime (n=11) or ceftriaxone (n=5)) was administered intravenously during the first four days in ICU as part of SDD, but not as part of SOD. For more information on the SDD-SOD strategies see supplementary data. Patients with a clinical suspicion or documented infection were treated according to standard clinical practice. The use of ‘colonization resistance impairing antibiotics’, such as amoxicillin, penicillin, amoxicillin-

clavulanic acid and carbapenems was discouraged during the SDD period. Surveillance cultures were obtained to monitor the effectiveness of the regimen and consisted of endotracheal aspirates and oropharyngeal swabs throughout ICU-stay (in SDD and SOD) plus rectal swabs during SDD. Details of surveillance protocols are described in the supplementary index.

The primary endpoint of the study was the unit-wide prevalence of antibiotic resistant microorganisms, determined through monthly point-prevalence surveillance of rectal and respiratory samples in all patients present in the ICU (at 8 am every third Tuesday of the month). Secondary endpoints included day-28 mortality, rates of ICU-acquired bacteraemia and length of ICU-stay. If day-28 mortality could not be determined from hospital databases, a patient was considered to be alive at day-28. Sensitivity analysis was performed, in which all these patients were considered to be dead at day-28 (11).

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

Blood cultures were obtained when bacteraemia was suspected, as part of daily clinical practice. Only patients with a length of ICU-stay of more than 2 days were included in the bacteraemia analyses. Proportions of ICU-acquired bacteraemia were compared during SOD and SDD. Bacteraemia was considered ICU-acquired if the first positive blood culture with a particular species was obtained more than 48 hours after ICU-admission.

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

Data reporting was performed according to CONSORT guidelines for reporting Cluster Randomized Trials.(12) Assuming a prevalence of patients colonized with multi-resistant Gram-negative bacteria of 3% and considering a three-fold relative reduction between both study groups (to 1%) as clinically relevant, 1,023 patients would be needed per group ($\beta=0.1, \alpha=0.05$), when ignoring cluster effects (13). Based on an intracluster correlation coefficient of 0.010, as present in De Smet et al (4), at least 14 clusters would be needed. The primary endpoint, point prevalence of resistant microorganisms in rectal and respiratory tract samples, was analysed using a random-effects poisson regression analysis. Day-28 mortality was analysed with a random-effects logistic-regression model with adjustment for all available relevant covariates (i.e. age, gender, apache 4 score, mechanical ventilation more than 48 hours, and whether surgery was performed in the week preceding ICU-admission). Other secondary endpoints were analysed with Cox regression modelling. A p-value <0.05 is considered to denote statistical significance and all reported p-values are two-sided. Data were analyzed with SPSS version 19.0 (SPSS, Chicago, IL) and R version 2.14.2.

RESULTS

Sixteen ICUs participated and during the 32 cluster-randomized study periods 31,624 patients were admitted, of which 11,997 patients formed the eligible study population; 5,881 during SOD and 6,116 during SDD. Total number of eligible patients per ICU ranged from 201 to 1945 (see table S1). The study groups were comparable regarding age, gender, and need for mechanical ventilation (Table 1). Yet, patients in the SOD arm had higher apache 4 scores (median 75 (inter quartile range 44) versus 73 (IQR 42), $p < 0.01$). In all, 4,713 of 5,881 patients (80.1%) received at least one dosage of SOD and 5,078 of 6,116 patients (83.0%) received at least one dosage of SDD. The mean length of ICU-stay of eligible patients that stayed in ICU for >48 hours but did not receive SDD or SOD patients was 5.1 days and 4.9 days during SOD and SDD, respectively ($p = 0.60$), and ICU-mortality rates of these patients were 6.0% and 4.5% for SOD and SDD, respectively (OR = 1.37 (95% CI 0.90-2.09)).

Primary and secondary endpoints

There were 384 point-prevalence surveys yielding 3,776 rectal swabs. Average numbers of patients included per survey were 156 (IQR 13.5, range 133-168) during SOD and 161 (IQR 15, range 149-181) during SDD. Prevalence of ESBL-producing GNB, and GNB resistant to aminoglycosides, ciprofloxacin, carbapenems and meeting definitions for HRMO (14) in rectal swabs were lower during SDD (Table 2). Prevalence rates were $<1\%$ (and not statistically significant different) for GNB resistant to colistin and for VRE. In time, the prevalence of HRMO tended to increase, though slightly, during SOD and SDD. The most prominent rise was observed for aminoglycoside resistance during SDD (7% per month) which differed statistically significant from the observed increase during SOD (4% per month, $p < 0.05$).

For respiratory tract colonization, 3,651 patients were included in point prevalence surveys, with, on average, 156 (IQR 11.75, range 131-176) and 153 (IQR 15, range 141-1690) patients per month during SOD and SDD, respectively. The prevalence of antibiotic resistant bacteria was markedly lower in respiratory tract samples than in rectal swabs, and there were no statistically significant differences between SOD and SDD and no significant trends in time.

	SOD (n = 5,881)	SDD (n = 6,116)	P-value
Mean age at time ICU admission (95% CI)	63.2 (62.8-63.6)	63.0 (62.6-63.4)	
Median age (range; IQR)	66 (18-110 ; 21)	65 (18-98 ; 21)	0.17
Male sex (%)	3513 (59.8%)	3649 (59.7%)	0.94
Mean apache IV score (95% CI)	79.0 (78.1 – 79.8)	77.4 (76.5 – 78.2)	
Median apache IV (range; IQR)	75 (3-216 ; 44)	73 (3-217 ; 42)	<0.01
Mechanical ventilation (%)	4670 (79.4%)	4835 (79.1%)	0.63
Mechanical ventilion at least 48hrs	3061 (52%)	3109 (50.8%)	0.18
Surgery in week before ICU admission	2213 (37.6%)	2333 (38.2%)	0.55
Specialism			
- surgery	1777 (30.3%)	1840 (30.1%)	0.88
- cardiothoracic surgery	723 (12.3%)	749 (12.3%)	0.94
- neurosurgery	303 (5.2%)	379 (6.2%)	0.01
- neurology	390 (6.6%)	403 (6.6%)	0.93
- internal medicine	1304 (22.2%)	1269 (20.8%)	0.06
- Cardiology	700 (11.9%)	791 (12.9%)	0.09
- Pulmonology	551 (9.4%)	510 (8.3%)	0.05
- Other	120 (2.0%)	168 (2.8%)	0.01
Previous or preexistent condition			
- Chronic coronary insufficiency	689 (11.7%)	737 (12.1%)	0.57
- COPD	996 (16.9%)	1003 (16.4%)	0.43
- Diabetes mellitus	1057 (18.0%)	1136 (18.6%)	0.39
- Chronic dialysis	124 (2.1%)	139 (2.3%)	0.54
- Chronic renal insufficiency	535 (9.1%)	559 (9.1%)	0.93
- Metastasized cancer	350 (6.0%)	280 (4.6%)	<0.01
- Livercirrosis	132 (2.2%)	155 (2.5%)	0.30
- Immunodepression or AIDS	551 (9.4%)	685 (11.2%)	<0.01
Place from which patient was admitted to ICU			
- Home	66 (1.1%)	27 (0.4%)	<0.01
- Emergency department	1801 (30.6%)	1872 (30.6%)	0.99
- Other Dutch ICU	320 (5.4%)	356 (5.8%)	0.37
- Other non-Dutch ICU	14 (0.2%)	10 (0.2%)	0.36
- Nursing home	11 (0.2%)	5 (0.1%)	0.14
- Ward same hospital	3467 (59.0%)	3610 (59.1%)	0.94
- Ward other hospital	108 (1.8%)	110 (1.8%)	0.88
- Other	91 (1.5%)	120 (2.0%)	0.08

Table 1: Baseline characteristics

SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination; ICU, intensive care unit; 95% CI, 95% confidence interval

N patients	HRMO	ESBL	Aminoglycosides#	Ciprofloxacin	Carbapenems*	Colistin [^]	VRE					
Mean (IQR, range)	Perc. of patients (95%. CI)	Trend in time (p-value)	Perc. of patients (95%. CI)	Trend in time (p-value)	Perc. of patients (95%. CI)	Perc. of patients (95%. CI)	Perc. of patients (95%. CI)					
Rectal samples												
SOD	156 (13.5, 12.7% (11.2% - 13.3-168)	0.03 (0.086)	7.7% (6.5% - 8.9%)†	0.03 (0.204)	11.8% (10.3% - 13.2%)†	0.04 (0.046) †	10.3% (8.9% - 11.7%)†	0.01 (0.518)	2.8% (2.0% - 3.5%)†	0.7% (0.3% - 1.1%)	0.2% (0% - 0.4%)	
SDD	161 (15, 149- 181)	7.3% (6.1% - 8.4%)	0.05 (0.052)	4.4% (3.5% - 5.3%)	0.06 (0.087)	5.6% (4.6% - 6.7%)	0.07 (0.017)	5.6% (4.6% - 6.6%)	0.03 (0.320)	1.6% (1.0% - 2.1%)	1.1% (0.7% - 1.7%)	0.6% (0.2% - 0.9%)
Respiratory samples												
SOD	156 (11.75, 3.3% (2.5% - 4.1%)	-0.02 (0.643)	1.3% (0.8% - 1.8%)	-0.08 (0.144)	3.8% (3.0% - 4.7%)	0.02 (0.600)	2.7% (1.9% - 3.4%)	-0.03 (0.441)	1.4% (0.9% - 1.9%)	0.3% (0.0% - 0.5%)		
SDD	153 (15, 141- 169)	2.6% (1.8% - 3.3%)	-0.01 (0.848)	1.3% (0.8% - 1.8%)	0.01 (0.882)	2.7% (2.0% - 3.5%)	0.01 (0.809)	2.5% (1.8% - 3.2%)	-0.02 (0.705)	0.8% (0.4% - 1.2%)	0.6% (0.3% - 1.0%)	

Table 2

Mean proportion of patients colonized with resistant bacteria during SOD and SDD. Chi-square test was used to test for differences between SOD and SDD. Trends in time for 12 months of SOD and 12 months of SDD. A mixed-model poisson regression using random intercept was used to determine trends in time and to test for differences in slopes.

† difference in slope $p < 0.05$ as compared to SDD, # non-susceptible for either tobramycin or gentamycin, * non-susceptible for either imipenem or meropenem, [^]Enterobacteriaceae not intrinsically resistant to colistin,

SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination; IQR, inter quartile range; 95% CI, 95% confidence interval

Day-28 mortality was 25.4% and 24.1% during SOD and SDD respectively (adjusted OR (aOR) 0.963 (95% CI 0.877-1.057) with absolute and relative mortality reductions of 0.7% and 2.8% during SDD as compared to SOD (table 3). For this analysis, the status at day 28, for those that had been discharged from the hospital alive before day 28 (n=6,086), could be retrieved reliably in 5,504 patients (90.4%), and in this group day-28 mortality was 3.3%. Assuming that these other 582 patients had died before day 28, did not change interpretation of the absence of outcome differences between SDD and SOD. ICU-mortality and in-hospital mortality were 19.8% and 27.6% during SOD and 18.6% and 26.6% during SDD, respectively, with corresponding aOR of 0.959 (95% CI 0.865-1.054) and 0.990 (95% CI 0.904-1.084), respectively. Median length of stay in ICU and hospital was determined for patients alive at day-28 and was comparable during SOD and SDD (Table 3). Hazard rates for ICU discharge and hospital discharge were not statistically different.

	SOD (n = 5,881)	SDD (n = 6,116)	Odds ratio or Hazard ratio (95% CI) (P-value)	Adjusted odds (95% CI) (P-value)
ICU mortality	1165 (19.8%)	1138 (18.6%)	0.925 (0.845-1.013) (0.10)	0.959 (0.865-1.054) (0.43)
Hospital mortality	1625 (27.6%)	1629 (26.6%)	0.951 (0.878-1.031) (0.22)	0.990 (0.904-1.084) (0.83)
Day 28 mortality	1494 (25.4%)	1472 (24.1%)	0.931 (0.857-1.011) (0.09)	0.963 (0.877-1.057) (0.42)
Time to outcome for survivors at day-28				
Discharge from ICU <i>Median (IQR)</i>	6 (7)	6 (7)	0.964 (0.924-1.007) (p=0.10)	
Discharge from hospital <i>Median (IQR)</i>	19 (24)	19 (24)	0.958 (0.911-1.008) (p=0.10)	

Table 3 Mortality endpoints and length of stay (days) for survivors at day-28

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

Mixed-model regression analysis was used. Adjusted odds were corrected for age, apache IV, surgery or non-surgery and center.

SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination; ICU, intensive care unit; 95% CI, 95% confidence interval

In the predefined subgroup analysis of surgical (37.8%) and non-surgical patients (62.2%), day-28 mortality for surgical patients was 19.7% and 17.7 % during SOD and SDD, respectively (aORs 0.924 (95%CI 0.782-1.091)). For non-surgical patients day-28 mortality was 28.8% and 28.0% for SOD and SDD, respectively, with corresponding a OR 0.990 (95% CI 0.885-1.108). In total, 5442 SOD- and 5549 SDD-patients had an ICU stay more than two days (table 5). Blood cultures per patientday were 0.13 and 0.12 during SOD and SDD, respectively. The proportion of patients developing ICU-acquired bacteremia with Enterobacteriaceae was lower during SDD

(OR 0.42 (95% CI 0.29-0.60), and the difference was most pronounced for *Escherichia coli* (OR 0.33 (95% CI 0.18-0.62)). In addition, significant reductions in ICU-acquired bacteremia were observed for aminoglycoside resistant gram-negative bacteria (OR 0.54 (95% CI 0.31-0.97)), including Enterobacteriaceae and glucose-non-fermenting Gram-negative rods (e.g. *Pseudomonas* spp.) during SDD. Proportions of patients developing ICU-acquired bacteremia with colistin-resistant gram-negatives, vancomycin-resistant *Enterococci* and methicillin-resistant *S. aureus* were below 0.2% during SOD and SDD. Time till ICU-acquired bacteremia was comparable during SOD and SDD.

	SOD non-surgical (n = 3668)	SDD non-surgical (n = 3779)	SOD surgical (n = 2213)	SDD surgical (n = 2333)
ICU mortality	827 (22.5%)	816 (21.6%)	338 (15.3%)	321 (13.8%)
Unadjusted OR (95% CI)	0.946 (0.848-1.055)		0.885 (0.750-1.044)	
Adjusted OR (95% CI)	0.972 (0.859-1.100)		0.961 (0.797-1.161)	
Hospital mortality	1117 (30.5%)	1130 (29.9%)	508 (23.0%)	498 (21.3%)
Unadjusted OR (95% CI)	0.974 (0.882-1.076)		0.911 (0.792-1.048)	
Adjusted OR (95% CI)	1.005 (0.899-1.123)		0.979 (0.836-1.148)	
Day 28 mortality;	1057 (28.8%)	1058 (28.0%)	437 (19.7%)	413 (17.7%)
Unadjusted OR (95% CI)	0.960 (0.868-1.062)		0.874 (0.753-1.015)	
Adjusted OR (95% CI)	0.990 (0.885-1.108)		0.924 (0.782-1.091)	

Table 4: subgroup analysis. Surgical patients received surgery one week before ICU-admission. Mixed-model regression analysis was used. Adjusted odds were corrected for age, apache IV, surgery or non-surgery and center. SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination; ICU, intensive care unit; 95% CI, 95% confidence interval

Completeness of monthly point prevalence surveillance studies was 92.2% for rectal swabs and 89.5% for respiratory samples, ranging from 81.4% to 98.6% per ICU for rectal samples and from 71.4% to 98.3% for respiratory samples. The accuracy of patient inclusion was 97.5% (ranging from 91% to 100% per center), meaning that 97.5% of the patients that should have been included were indeed included. Accuracy of CRF data was 96.0% for admission and discharge dates and 97.4% for ICU- and hospital-mortality. There were no statistically significant differences between SOD and SDD periods.

Both SDD and SOD were temporarily interrupted or changed as part of control programs for nosocomial outbreaks, due to ampicillin-resistant *Enterococci* (six weeks interruption of SOD in one hospital) or ESBL-producing bacteria (in 1 hospital SOD was replaced by SDD for four weeks). These outbreaks occurred in different hospitals.

There were no reported adverse effects of SDD or SOD. Rejection of the mouthpaste after detubation occurred most frequently and SDD was discontinued in one patient because of a clinical suspicion of Stevens-Johnson syndrome, which was attributed to intravenous administration of beta-lactam antibiotics.

	SOD	SDD	P-value	Odd ratio SDD-SOD (95% CI)
Total number of patients with LOS >2days	5442	5549		
Total number of patients with LOS >2days with at least one blood culture	2662 (49%)	2741 (49%)		
Cultures/patientday	0.13	0.12		
Any positive bloodculture	319 (5.9%)	253 (4.6%)	0.002	0.77 (0.65-0.91)
<i>Enterobacteriaceae</i>	97 (1.8%)	41 (0.7%)	<0.001	0.42 (0.29-0.60)
<i>Escherichia coli</i>	39 (0.7%)	13 (0.2%)	<0.001	0.33 (0.18-0.62)
<i>Klebsiella</i> spp	22 (0.4%)	12 (0.2%)	0.085	0.54 (0.27 – 1.10)
<i>Enterobacter</i> spp	10 (0.2%)	7 (0.1%)	0.465	0.70 (0.27-1.83)
Other <i>Enterobacteriaceae</i>	29 (0.5%)	9 (0.2%)	0.001	0.31 (0.15-0.65)
<i>GNF-GNR</i>	27 (0.5%)	25 (0.5%)	0.778	0.92(0.54-1.60)
<i>Pseudomonas aeruginosa</i>	20 (0.4%)	23 (0.4%)	0.650	1.15 (0.63-2.10)
<i>Acinetobacter</i> spp	3 (0.1%)	1 (0%)	0.375	0.33 (0.04-3.20)
<i>Stenotrofomonas malthophilia</i>	4 (0.1%)	2 (0.0%)	0.453	0.50 (0.09-2.73)
<i>Enterococcus</i> spp	154 (2.8%)	151 (2.7%)	0.853	0.98 (0.78-1.23)
<i>Staphylococcus aureus</i>	28 (0.5%)	17 (0.3%)	0.099	0.61 (0.33-1.11)
<i>Candida</i> spp and other yeasts	48 (0.9%)	33 (0.6%)	0.093	0.69 (0.44-1.07)
Resistant GNB*				
HRMO	31 (0.6%)	23 (0.4%)	0.273	0.74 (0.43 – 1.27)
ESBL	8 (0.1%)	5 (0.1%)	0.404	0.62 (0.20-1.91)
Aminoglycosides#	33 (0.6%)	18 (0.3%)	0.035	0.54 (0.31 – 0.97)
Colistin^	0	4 (0.1%)	0.125	na
VRE	3 (0.1%)	0	0.125	na
MRSA	1 (0%)	1 (0%)	1	1.00 (0.06-15.97)
Time to bacteremia	Median (days) (range – IQR)	Median (days) (range – IQR)	P-value	
<i>Enterococcus</i> spp	10 (3-41; 9)	10 (3-52; 10)	0.518	
GNB*	10 (3-114; 13)	11 (3-68; 17)	0.638	

Table 5: Incidences of ICU-acquired bacteremia for patients with a length of ICU-stay of more than 2 days. *Enterobacteriaceae and glucose non-fermenting Gram-negative rods; # non-susceptible for either tobramycin or gentamycin, ^for Enterobacteriaceae not intrinsically resistant to colistin, VRE, Vancomycin-resistant *Enterococcus* spp, MRSA, methicillin-resistant *Staphylococcus aureus*

SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination; LOS, length of ICU stay; IQR, inter quartile range; 95% CI, 95% confidence interval; GNB gram negative bacteria including Enterobacteriaceae and GNF-GNR; HRMO, highly resistant micro-organisms

DISCUSSION

In this cluster-randomized cross-over study of 11,997 patients the use of SDD and SOD during 24 months in 16 ICUs in the Netherlands was associated with persistently low prevalence levels of antibiotic resistant bacteria. Moreover, intestinal decontamination and routine intravenous treatment with third-generation cephalosporins did not confer additional benefit to oropharyngeal decontamination for the most relevant clinical endpoints, such as patient survival and length of stay.

During the study period there was a gradual increase in intestinal carriage with aminoglycoside resistant Gram-negative bacteria, which was most pronounced during SDD. Long-term effects of SDD have not been studied extensively, but increasing resistance during SDD was not observed in two other longitudinal studies in Germany and France.(15, 16) The German study was a 5-year prospective observational study in a single tertiary care surgical ICU (15), and the French study was a retrospective case-control study also in a single tertiary care center with patients studied over a six year period (16). Yet, both single-center studies may have been underpowered to detect the time trend as observed in our study. In another longitudinal analysis of clinical culture results from Dutch ICUs using (n=17) or not using SDD/SOD (n=13) over a four year period yielded an increasing trend of tobramycin resistant Enterobacteriaceae, approaching statistical significance, in ICUs not using SDD/SOD. This trend was not apparent in ICUs using SDD/SOD. [Houben et al, submitted].

The increase in aminoglycoside resistance as observed in the current study is of potential importance and could result from the selective effects of tobramycin on antibiotic resistance genes in the human microbial flora, with proliferation of resistance genes in the anaerobic flora. Others have shown that the human microbiome indeed acts as a reservoir for antibiotic resistance genes (17, 18) and it is possible that during SDD mobile genetic elements are transferred from the anaerobic flora to aerobic potential pathogens after discontinuation of SDD, increasing the risks of emergence of resistance in time. Metagenomic approaches and studies addressing carriage with antibiotic resistant bacteria after discontinuation of SDD and SOD are needed to further investigate these hypotheses.

Furthermore, resistance to aminoglycosides increases the likelihood of acquisition of colistin resistance (19). Colistin is becoming more and more important as a last-resort antibiotic, due to increasing infection rates with Gram-negative bacteria resistant to carbapenem antibiotics in many parts of the world. The findings of the present study confirm and extend previous results on the epidemiology of colistin resistance in Dutch ICUs using SDD or SOD (19). The prevalence of resistance to colistin was less than 1.1% and 0.6% in rectal swabs and respiratory samples, respectively, during SDD, and even lower during SOD and only four bacteraemias occurred with colistin resistant gram-negatives (all during SDD). Yet, emergence of bacteria with acquired resistance to the antibiotics used in SDD and SOD can occur in settings with failing

infection control (10). Prophylactic administration of colistin on a daily basis in many patients simultaneously, as in SDD and SOD, must, therefore, be accompanied with careful monitoring of both aminoglycoside and colistin resistance, and containment strategies should be developed prospectively and implemented immediately when cross-transmission of resistant bacteria is demonstrated or highly suspected.

This study confirms previous observations that intestinal decontamination is important in preventing ICU-acquired bacteremia with gram-negative bacteria, especially Enterobacteriaceae, with no increased risk of bacteremia caused by enterococci [de Smet, Oostdijk]. Yet, under the circumstances tested with low levels of antibiotic resistant bacteria, this reduction in ICU-acquired bacteremia was not associated with detectable effect in patient outcome.

The current study has several limitations. There was no control group of ICUs not applying SDD or SOD, as this was considered unethical in the Netherlands after previous studies demonstrating improved patient survival due to SDD and SOD. (3, 4). In addition, five ICUs used ceftriaxon instead of cefotaxime for systemic prophylaxis during SDD, but both agents have a similar spectrum of activity and the variation reflects clinical practice.

Strengths of the study include its size and design, allowing evaluation of the unit-wide effects of both interventions. Cluster randomized trials are susceptible to inclusion bias, and in this study the decision to initiate SDD and SOD in individual patients was made by physicians. We aimed to minimize the potential of bias by including all patients that received SDD or SOD and all patients with a length of stay of at least 48 hours in ICU that did not receive SDD or SOD, which accounted for 17% of the study population. Baseline characteristics were comparable for both study groups, with the exception of the mean Apache 4 scores, which were higher during SOD. It is unlikely that this resulted from inclusion bias, which was supported by the fact that adjudication of results with all covariates related to a patients' prognosis did not change the results of crude analyses.

As the most important clinical outcomes, i.e., survival and length of stay in ICU and in hospital, were comparable for SOD and SDD, and as SDD is more costly for medication and microbiological monitoring, the costs-benefit ratio of SOD is more beneficial, as was suggested previously (20). Costs of amphotericin B increased substantially, increasing the daily costs considerably, especially of SDD. Nystatin could be a – cheaper – alternative, if demonstrated equally effective in preventing yeast colonization.

CONCLUSION

This multi-center cross-over study including nearly 12,000 patients did not reveal differences in survival or length of stay between unit-wide application of SOD and SDD, and demonstrated persistently low levels of antibiotic resistance prevalence during a 24-month period. The gradual increase of intestinal carriage with aminoglycoside resistant bacteria, which was most pronounced

during SDD, underscores the need of careful microbiological monitoring. These, and previous results of lack of increased antibiotic resistance during SDD and SOD, support the need of evaluation of these measures in settings with different bacterial ecology.

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SUPPLEMENTARY TABLES

Hospital	Start study	End study	Level	Order	Inclusions SOD	Inclusions SDD
Flevo Ziekenhuis Almere	1 August 2009	1 september 2011	1	SDD-SOD	194	168
Rijnstate Arnhem	1 November 2009	1 December 2011	2	SOD-SDD	337	378
Rijnland Ziekenhuis Leiderdorp	1 November 2009	1 December 2011	2	SOD-SDD	194	206
Groene Hart Ziekenhuis Gouda	1 November 2009	1 December 2011	1->2 (feb '11)	SOD-SDD	196	225
Haga Den Haag	1 December 2009	1 January 2012	3	SOD-SDD	446	504
Catharina Eindhoven	1 December 2009	1 January 2012	2	SDD-SOD	343	342
Deventer Ziekenhuis Deventer	1 December 2009	1 January 2012	2	SOD-SDD	261	237
Sint Lucas Andreas Ziekenhuis Amsterdam	1 January 2010	1 February 2012	2	SDD-SOD	169	174
BovenIJ Amsterdam	1 January 2010	1 February 2012	1	SDD-SOD	225	206
Leids Universitair Medisch Centrum Leiden	1 February 2010	1 March 2012	3	SDD-SOD	758	755
Antonius Ziekenhuis Sneek	1 March 2010	1 April 2012	1	SDD-SOD	163	180
Diakonessenhuis Utrecht	1 April 2010	1 May 2012	2	SDD-SOD	265	216
Universitair Medisch Centrum Utrecht Utrecht	1 May 2010	1 June 2012	3	SOD-SDD	934	1011
Academisch Medisch Centrum Amsterdam	1 June 2010	1 July 2012	3	SDD-SOD	911	987
Nij Smellinghe Drachten	1 September 2010	1 Oktober 2012	1	SOD-SDD	107	94
Maastricht Universitair Medisch Centrum Maastricht	1 January 2011	1 February 2013	3	SOD-SDD	378	433

Table 1: participating hospitals with level of ICU-care (level 1 is lowest, level 3 is highest level of ICU-care). SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination; ICU, intensive care unit

SUPPLEMENTARY DATA

Adjustment study regimen

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 consecutive surveillance cultures were negative. There are no restrictions in physicians' choices of systemic antibiotic therapy.

Based on these surveillance cultures, several adaptations of the SDD regimen are 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) colistin was nebulized 4 times daily if a sputum surveillance culture (not admission culture) yielded Gram negative bacteria, until two sputum cultures are negative.

Chapter 5

*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 and 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 was used during consecutive periods of 6 months (NEJM 2009;360:20).

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.

Measurements and Main Results: During SDD average proportions of patients with intestinal colonization with GNB resistant to either ceftazidime, tobramycin or 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 $\leq 6\%$ for all three antibiotics, but increased gradually (for ceftazidime; $p < 0.05$ for trend) during intervention and to levels $\geq 10\%$ 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 1984¹, 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 pneumoniae* and *Haemophilus influenzae* 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 methicillin-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 a day. SOD consisted only of the oropharyngeal application of the 2% mixture of these antibiotics.

An expanded microbiological methods description can be found in the online supplement.

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 combined, 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 centres were pooled according to study period and specific time point. Similarly, for the analysis of respiratory tract colonization SDD and SOD were combined, 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 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.

A

	1	2	3	NC
A	Standard care	SOD	SDD	829
B	Standard care	SDD	SOD	192
C	SOD	Standard care	SDD	451
D	SOD	SDD	Standard care	424
E	SDD	Standard care	SOD	538
F	SDD	SOD	Standard care	529

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-intervention period	Intervention period	Post-intervention period	
A	Standard care (2)	SOD (2)	SDD (2)	
B	Standard care (2)	SDD (2)	SOD (2)	
C	Standard care (2)	SDD (2)	SOD (2)	
D		SOD (2)	SDD (2)	Standard care (2)
E			SDD (2)	Standard care (2)
F			SDD (3)	SOD (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. * The results from the SOD periods from centres conducting study order C and E were not used for further analysis (grey).

NC: number of cultures taken; (n) number of centres 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. (orange).

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 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 correlation¹⁸. 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 ($44.5 \pm 1.5\%$; range 42% - 51%) and 6.1% lower during SOD ($38.3 \pm 1.6\%$; range 37% - 50%) and 19.6% lower during SDD ($24.9 \pm 1.4\%$; range 22% - 33%). In the respiratory tract, growth was lower during both SDD ($17.7 \pm 1.3\%$; range 15% - 27%) and SOD ($22.1 \pm 1.5\%$; range 13% - 26%), as compared to standard care ($42.5 \pm 1.7\%$; 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 online data supplement).

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 (Beta-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.

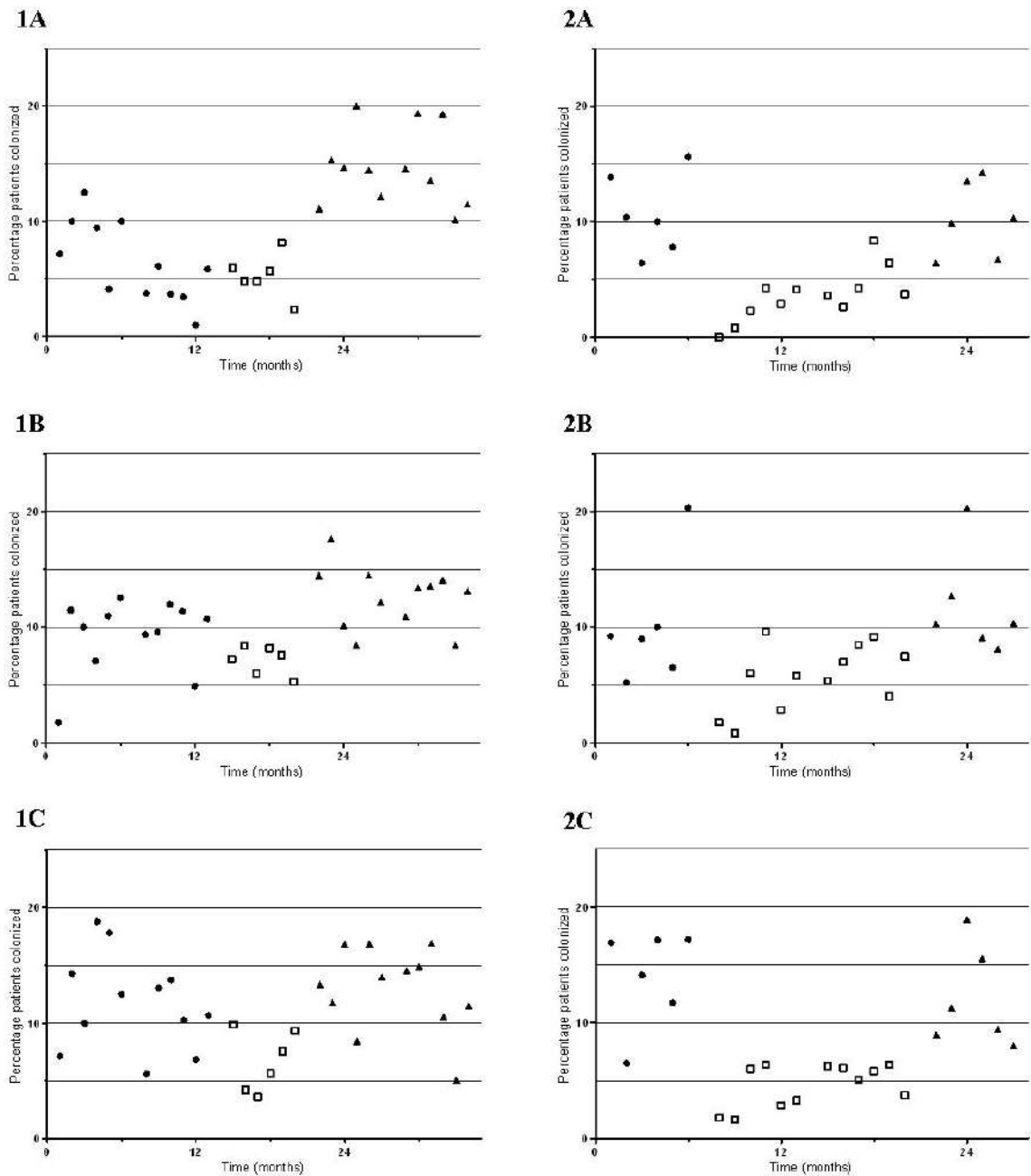


Figure 1: Percentage of patients colonized with Gram- negative rods before, during and after the use of SDD during monthly point prevalence surveillance studies of (1) rectal samples and (2) respiratory samples. (●) pre intervention period; (□) intervention period; (▲) post intervention period for three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

	Average prevalence per period (mean (95% CI))			Change in prevalence during period (Beta-coefficient (P-value))		
	Pre	Inter- vention	Post	Pre	Inter- vention	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; Intervention: intervention period; Post: post-intervention period.
NS: not significant. Beta-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.

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.

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

Table 3: Number and percentage of Gram-negative isolates and species with conferred resistance to ceftazidime, tobramycin or tobramycin obtained from rectal en respiratory tract samples during all monthly point prevalence surveys. Ceftazidime (CFT), ciprofloxacin (CIP), tobramycin (TOB).

Respiratory tract colonization

The prevalence rates of antibiotic resistant micro-organisms 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 resistant bacteria 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 *P. 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 ($p = 0.26$).

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.

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*.

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 before¹⁴ 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. The overall use of systemic antibiotics has been reported previously⁵ but are also provided in the supplementary data.

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 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, and isolates were not genotyped precluding determination of the relevance of clonal spread. And as there were no “control” ICUs with similar point prevalence measurements but without interventions, we could not determine time effects of resistance levels in the absence of interventions.

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 anonymized 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 analysis 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 variability²⁶ 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, most prominent for ceftazidime resistance. 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, systematic as well as the effects of less cephalosporin use during SDD, in order to determine the most “cost-beneficial” infection control measure from an ecological perspective for ICU patients.

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SUPPLEMENTARY DATA:

Microbiologic method

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.

Overall antibiotic use

During the study performed by De Smet et al, the median number of defined daily doses of systemic antibiotics was determined for the patients included in the study. De Smet et al found that the use of systemic antibiotic agents per patient day did not differ significantly among SDD, SOD and standard-care periods, although the overall volume of DDDs was, as compared to standard care, 11.9% and 10.1% lower during SDD and SOD, respectively (NEJM 2009;360:20).

	Average prevalence (mean (95% CI))					
	<i>Ceftazidime</i>		<i>Tobramycine</i>		<i>Ciprofloxacin</i>	
	Pre	Post	Pre	Post	Pre	Post
Rectal tract						
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 combined 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 6

Colistin resistance in gram-negative bacteria during prophylactic topical colistin use in intensive care units

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ABSTRACT

Purpose: Topical use of colistin as part of Selective Digestive Decontamination (SDD) and Selective Oropharyngeal Decontamination (SOD) has been associated with improved patient outcome in intensive care units (ICU), yet little is known about the risks on colistin resistance. We quantified effects of selective decontamination on acquisition of colistin-resistant GNB using data from a cluster-randomized study and a single-centre cohort.

Methods: Acquisition of colistin-resistant GNB and conversion from susceptible to resistance in GNB was determined in respiratory samples (from patients receiving SDD (n=455), SOD (n=476), or standard care (SC) (n=315)), and in rectal swabs from 1,840 SDD-patients. Genotyping of converting isolates was performed where possible.

Results: In respiratory tract acquisition rates of colistin-resistant GNB were comparable during SDD, SOD, and SC and ranged from 0.7-1.1/1,000 patient-days at risk. Rectal acquisition rates during SDD were <3.3/1,000 days at risk. In patients with respiratory tract GNB carriage, conversion rates were 3.6 and 1.1/1,000 patient-days at risk during SDD and SC, respectively ($p>0.05$). In patients with rectal GNB carriage conversion rates during SDD were 5.4 and 3.2/1,000 days at risk and 15.5 and 12.6/1,000 days at risk when colonized with tobramycin-resistant GNB.

Conclusions: Acquisition rates with colistin-resistant GNB in respiratory tract were low and comparable with and without topical use of colistin. Rates of acquisition of colistin-resistant GNB during SDD were - in ICUs with low endemicity of antibiotic resistance - <2.5/1,000 days at risk, but were five-fold higher with during persistent GNB colonization and 15-fold higher during carriage with tobramycin-resistant GNB.

INTRODUCTION

Due to a world-wide emergence of multi-resistant gram-negative bacteria (GNB) colistin has become increasingly important as a last resort antibiotic, especially for patients in Intensive Care Units (ICU).(1-6) Besides its use for intravenous treatment, colistin is used topically in two infection prevention regimens in ICU; Selective Oropharyngeal Decontamination (SOD) and Selective Decontamination of the Digestive Tract (SDD). Both consist of a mixture of topical antibiotics (usually colistin, tobramycin and amphotericin B) applied in the oropharynx every six hours throughout ICU-stay. SDD also consists of a suspension containing the same antibiotics administered via a nasogastric tube to decontaminate the intestinal tract and of a 4-day course of systemic cefotaxime to prevent early ICU-infections.(7) Both regimens aim to prevent colonization and infection with so-called potentially pathogenic micro-organisms, such as Enterobacteriaceae(8), and were associated with a 10-13% reduction in day-28 mortality as compared to standard care.(9)

The effects of SDD and SOD on colistin resistance have not been determined rigorously, although some data suggest that prolonged use induces colistin resistance.(10, 11) As the benefits of SDD and SOD on patient outcome must be carefully balanced against the risks of antibiotic resistance, we quantified the rates of colistin resistance among GNB in the intestinal and respiratory tract of patients receiving SDD or SOD in Dutch ICUs.

MATERIALS AND METHODS

Setting, design and population

We used data from two cohorts (Table 1). The first cohort comprised patients participating in a Dutch 13-center cluster-randomized trial conducted between May 2004 and July 2006, in which the effectiveness of SDD and SOD as compared to standard care (SC) was determined.(9) Characteristics of the ICUs are listed in table S3. In the current analyses we included only ICUs where during the period of study susceptibility to colistin was determined for at least 80% of GNB, as colistin testing was not protocolized (see supplementary data; table S1 and S2). Cohort 2 was a single-center observational study of all ICU-patients consecutively admitted to a tertiary care center in the Netherlands (University Medical Center Utrecht) between Jan 2008 and Aug 2009. SDD was standard of care during this period.

For both cohorts, patients were eligible to receive SDD or SOD when the expected length of mechanical ventilation was >48 hours or the expected ICU stay >72hrs. All SDD/SOD-patients with a length of ICU-stay of >48 hours and with at least two respiratory or at least two rectal swab samples were included in the analyses. The details of the SDD- and SOD-regimen have been reported previously(9) (see also supplementary information). In both cohorts data were collected anonymously and the need for informed consent was waived by the local Institutional Review

Boards.

Microbiological methods

Surveillance cultures were obtained on admission and twice weekly as part of SDD (rectal and respiratory samples) and SOD (respiratory samples only). Surveillance cultures were not routinely obtained during SC in all participating hospitals. In addition, during all three study periods (i.e. SC, SOD and SDD) sputum cultures were obtained if infection was suspected. The presence of *Acinetobacter* spp (AC), *Pseudomonas* spp (PS), *Enterobacter* spp (EB), *Escherichia coli* (EC) or *Klebsiella* spp (KS) was determined in samples from sputum, throat, and bronchoalveolar lavage. Intestinal colonization was defined as the isolation of EC, KS, or EB from rectal swabs. We did not include PS and AC in the analyses of the rectal samples because we considered them as primarily respiratory tract pathogens. The microbiological methods have been described in the supplement. (Supplementary data, table S1 and table S2).

Definitions of colonization

Colonization on admission was defined as growth with any of the marker GNB in the first culture obtained within 48 hours after ICU-admission. Acquisition of colonization was defined as growth of one of the marker pathogens in samples obtained after two days in ICU in the absence of growth in the first 48 hrs. Duration of colonization with GNB was determined for all patients and colonization periods started and ended at midpoint between two consecutive cultures. Colonization ended when two consecutive culture results were negative. If the last or penultimate culture obtained in ICU grew GNB, the patient was considered to be colonized until ICU-discharge.

We determined rates of colonization with colistin-resistant GNB on admission and acquired during ICU-stay, and we determined three colistin-resistance conversion rates. We defined colistin-resistance conversion as a documented shift from colistin susceptibility to colistin resistance within a single bacterial species, during a single ICU-admission. Conversion rates were expressed as events per 1,000 patient days at risk. We calculated three different conversion rates using three different denominators: 1) the total number of patient days at risk (*total conversion rate*); 2) the period of carriage with colistin susceptible GNB (*GNB conversion rate*); 3) and the period of tobramycin-resistant gram-negative colonization (*tobramycin resistant conversion rate*). Patients were considered to be at risk until ICU-discharge, acquisition of, or conversion to colistin resistance.

Data from respiratory tract cultures obtained in cohort-1 allowed comparison of acquisition and conversion rates in patients receiving standard care, SOD, and SDD. Acquisition and conversion rates of colistin resistance were determined in rectal samples of patients receiving SDD in cohort-1 and -2.

Genotyping

To distinguish conversion from selection of other resistant isolates and cross-transmission, available isolates from patients with conversion events were genotyped. From those patients all stored isolates, colistin susceptible and resistant, from all culture sites belonging to the same species and obtained during the same ICU-admission were genotyped. The DiversiLab (DL) system (bioMérieux) was used for *E. coli*, *Klebsiella* spp and *Enterobacter* spp.(12, 13) Isolates with >95% similarity were considered to be identical.

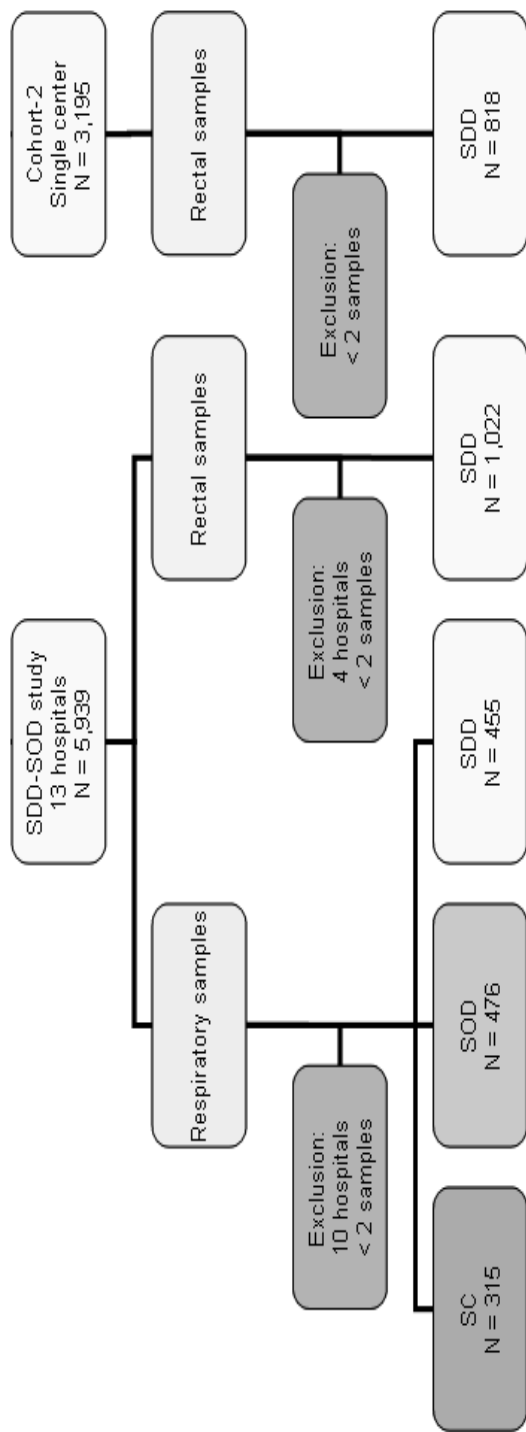
RESULTS

Respiratory tract colonization

From the multi-centre study, three ICUs were eligible for the analysis of colistin resistance in respiratory tract samples as during SC, SOD and SDD >80% of the obtained marker isolates were tested for colistin (see supplementary data; table S1). In all, 1,246 patients were included; 315 during SC, 476 during SOD, and 455 during SDD (table 1) comprising 6,454, 7,536, and 7,658 patient days, respectively. In total 6,466 respiratory tract cultures were obtained. Culture frequency was lower during SC (0.25 per patient day) than during SOD and SDD (0.32 and 0.32 per patient day, respectively ($p < 0.01$ compared to SC)) (table 1). At least one period of GNB colonization during ICU was documented in 44% of the patients receiving SC, as compared to 33% during SOD and 31% during SDD. Four patients received intravenous colistin treatment (three in SC, one in SOD) and one patient (during SC) received aerosolized colistin treatment. Two (0.6%), two (0.4%), and four (0.9%), patients were colonized with colistin-resistant GNB at ICU-admission during SC, SOD, and SDD respectively. There were 18 events of acquisition of colistin resistant GNB, corresponding to acquisition rates of 0.8, 1.1, and 0.7 per 1,000 days at risk during SC, SOD, and SDD, respectively (table 1). Median number of days from ICU admission to acquisition of colistin resistant GNB were 16, 8 and 12 during SC, SOD, and SDD, respectively ($p > 0.05$).

There were in total 12 conversions from colistin susceptible to resistant GNB (1.0%) (species: 1 (8%) EC, 4 (31%) KP, 4 (31%) EB, and 3 (23%) PS). Total conversion rates were 0.5, 0.5, and 0.7 per 1,000 patient-days at risk during SC, SOD, and SDD respectively. In patients with documented episodes of GNB colonization, conversion rates to colistin resistance were 1.1, 2.6, and 3.6 per 1,000 colonized patient-days at risk for SC, SOD, and SDD, respectively ($p > 0.05$ for SDD vs SC; $p > 0.05$ for SC vs SOD). None of these patients that had received colistin for therapeutic reasons acquired colistin resistant GNB.

In 8 out of 12 colistin conversions tobramycin resistance was present (62%). In four patients tobramycin and colistin resistance were demonstrated simultaneously in the same culture.



	Respiratory tract colonization			Rectal colonization		
	SC	SOD	SDD	SDD Cohort-1	SDD Cohort-2	
N patients	315	476	455	1022	818	
N patient days	6454	7536	7658	17145	12942	
N cultures	1611	2382	2473	4740	4158	
Cultures per patient day	0.25 *#	0.32	0.32	0.28	0.32	
N patients with GNB	139 (44%)	155 (33%)	140 (31%)	373 (36%)	443 (54%)	
N patients with colistin I/R	7 (2.2%)	10 (2.1%)	9 (2.0%)	55 (5.4%)	16 (2.0%)	
	(1.0 – 4.3%)	(1.1 – 3.7%)	(1.0 – 3.6%)	(4.2 – 7.0%)	(1.2 – 3.2%)	
On admission	2 (0.6%)	2 (0.4%)	4 (0.9%)	14 (1.4%)	1 (0.1%)	
Acquired	5 (1.6%)	8 (1.7%)	5 (1.1%)	41 (4.0%)	15 (1.8%)	
Acquisition rate / 1,000 pat days (95% CI)	0.8 (0.3 – 1.8)	1.1 (0.5 – 2.1)	0.7 (0.2 – 1.6)	2.4 (2.5 – 4.2)	1.2 (0.7–2.0)	
Median time to acquisition	16 (range 3–37, IQR 5)	8 (range 4–36, IQR 6)	12 (range 4–63, IQR 18)	9 (range 3–86 IQR 11)	19 (range 4–50, IQR 31)	
COL S-R conversion (95% CI)	3 (1.0%) (0.2 – 2.6%)	4 (0.8%) (0.3 – 2.0%)	5 (1.1%) (0.4 – 2.4%)	17 (1.7%) (1.0 – 2.7%)	9 (1.1%) (0.6 – 2.1%)	
Median LoS of converters	37 (range 22–38, IQR 8)	26 (range 20–32, IQR 9)	16 (range 15–121, IQR 12)	19 (range 3–268, IQR 41)	30 (range 8–65, IQR 38)	

	19 (range 14-37, IQR 12)	14 (range 7-18, IQR 7)	12 (range 4-63, IQR 18)	5 (range 2-71, IQR 3)	19 (range 6-50, IQR 30)
Median time to conversion	0.5	0.5	0.7	1.0	0.7
Conversion rate / 1,000 pat days	1.1	2.6	3.6	5.4	3.2
Conversion rate / 1,000 pat days with GNB colonization	NA	NA	NA	15.5	12.6

Table 1: Colistin resistance during SDD, SOD and Standard Care (SC): data collection and results

Respiratory tract colonization: number of patients colonized with spp, *Pseudomonas* spp, *Enterobacter* spp, *Escherichia coli* or *Klebsiella* spp in respiratory tract samples

Rectal tract colonization: number of patients colonized with *Enterobacter* spp, *Escherichia coli* or *Klebsiella* spp in rectal tract samples

Col S-R conversion: number of patients that were colonized with Gram-negative bacteria that converted from susceptible to colistin to colistin resistant within a single bacterial species

Conversion rate: number of conversions per 1,000 patient days at risk

Colonized conversion rate: number of conversions per 1,000 colonized patient days

LoS, length of ICU stay; SDD, Selective Decontamination of the Digestive Tract; SOD, Selective Oropharyngeal Decontamination; SC, Standard Care; NA, not applicable

p < 0.05 for SC vs SDD * p < 0.05 for SC vs SOD

Intestinal colonization

From the multi-centre study, nine ICUs were included as these ICUs tested >80% of the isolates for colistin (see supplementary data; table S2). From these nine ICUs, 1,022 SDD-patients were included yielding 17,145 patient days and 4,740 rectal culture results (0.28 per patient day). 373 Patients (36%) had at least one sample that grew EC, KS or EB, hereafter referred to as gram-negative bacteria (GNB). Colistin resistance on admission was demonstrated in 14 patients (1.4%). In cohort-2, a total of 4,158 rectal swabs were obtained in 818 patients, comprising 12,942 patient days (0.32 culture per patient day) and 443 (54%) patients had ≥ 1 culture with EC, KS or EB. Colistin resistance on admission was demonstrated in one patient (0.1%). Acquisition rates of colistin resistant GNB in rectal swabs during SDD were 3.2 and 1.2 / 1,000 patient-days at risk in cohort-1 and -2, respectively. Conversion from colistin susceptibility to resistance occurred in 17 patients (1.7%) in cohort-1 (12 EC (71%), 4 KP (24%), and 1 EB (6%)) and in 9 patients (1.1%) in cohort-2 (4 EC (44%), 2 KS (22%), and 3 EB (33%)), corresponding to rates of 5.4 and 3.2 per 1,000 colonized patient-days at risk in cohort-1 and -2, respectively. Median time to conversion was 5 days (range 2-71, IQR 3) and 19 days (range 6-50; IQR 30) in cohort-1 and -2, respectively. Sixteen of 26 conversions (62%) were co-resistant to tobramycin; 8 in cohort-1 and 8 in cohort-2. In 15 episodes (94%) tobramycin resistance was present before conversion to colistin resistance occurred. Eighty and 53 patients in cohort-1 and -2, respectively, were colonized, at any time during ICU-admission, with tobramycin resistant GNB (7.8% and 6.5% respectively). Conversion rates from colistin susceptible to resistant GNB during carriage with tobramycin resistant GNB were 15.5 and 12.6 for cohort-1 and -2, respectively. Intestinal colonization with *Pseudomonas* spp or *Acinetobacter* spp occurred in 145 of the patients in CH-1 (76 patients (52%) were also carrier of EC, KS or EB) and in 102 patients in CH-2 (64 (63%) were also carrier of EC, KS or EB). Colistin resistance was present in 5 and 3 patients in CH-1 and CH-2 respectively, all *Pseudomonas* spp.

Genotyping

Twenty-nine isolates of GNB from five episodes of conversion were available for genotyping (Table 2). In all episodes the difference in MICs was confirmed with E-testing. Based on genotyping it appeared that in two of five conversions episodes susceptible and resistant isolates belonged to different genotypes.

Patient number	ICU admission	ICU discharge	Sampling date	Site	Species	Resistance	MIC	Cluster
1	17-11-2008	20-1-2009	17-11-2008	Pleural fluid	<i>Enterobacter cloacae</i>	S	0,064	1
1			17-11-2008	Rectum	<i>Enterobacter cloacae</i>	S	0,064	1
1			11-12-2008	Sputum	<i>Enterobacter cloacae</i>	S	0,125	1
1			5-1-2009	Rectum	<i>Enterobacter cloacae</i>	R	64	1
1			12-1-2009	Throat	<i>Enterobacter cloacae</i>	S	0,064	1
1			12-1-2009	Sputum	<i>Enterobacter cloacae</i>	S	0,125	1
1			14-1-2009	Rectum	<i>Enterobacter cloacae</i>	R	64	1
1			14-1-2009	Rectum	<i>Enterobacter cloacae</i>	R	64	1
2	1-5-2009	23-6-2009	1-5-2009	Abdominal fluid	<i>Klebsiella pneumoniae</i>	S	0,125	2
2			15-6-2009	Rectum	<i>Klebsiella pneumoniae</i>	R	42	3
2			16-6-2009	Rectum	<i>Klebsiella pneumoniae</i>	R	32	3
3	17-1-2009	25-2-2009	18-1-2009	Throat	<i>Enterobacter cloacae</i>	S	0,094	4
3			19-1-2009	Sputum	<i>Enterobacter cloacae</i>	S	0,094	4
3			26-1-2009	Sputum	<i>Enterobacter cloacae</i>	S	0,064	4
3			26-1-2009	Sputum	<i>Enterobacter cloacae</i>	S	0,094	4
3			16-2-2009	Rectum	<i>Enterobacter cloacae</i>	R	8	4
3			16-2-2009	Rectum	<i>Enterobacter cloacae</i>	R	8	4
3			19-2-2009	Rectum	<i>Enterobacter cloacae</i>	R	16	4
4*	7-5-2009	10-5-2009	7-5-2009	Rectum	<i>Escherichia coli</i>	S	0,094	5
4*			7-5-2009	Rectum	<i>Escherichia coli</i>	S	0,125	5
4*	12-5-2009	24-5-2009	no isolates	no isolates	no isolates	no isolates	no isolates	no isolates
4*	27-5-2009	9-7-2009	2-6-2009	Rectum	<i>Escherichia coli</i>	R	8	6
4*			16-6-2009	Rectum	<i>Escherichia coli</i>	R	4	6
4*			30-6-2009	Rectum	<i>Escherichia coli</i>	R	4	6
4*			30-6-2009	Rectum	<i>Escherichia coli</i>	R	3	6
4*			7-7-2009	Rectum	<i>Escherichia coli</i>	R	4	6
5	7-7-2009	2-8-2009	13-7-2009	Rectum	<i>Escherichia coli</i>	S	0,125	7
5			13-7-2009	Rectum	<i>Escherichia coli</i>	S	0,125	7
5			23-7-2009	Rectum	<i>Escherichia coli</i>	R	8	7
5			28-7-2009	Rectum	<i>Escherichia coli</i>	R	4	7

Table 2: Genotype results; isolates obtained from patients colonized with colistin susceptible and resistant strains during SDD. Minimal inhibitory concentrations were determined using E test. S, susceptible; R, resistant
 * patient was admitted to ICU three times; second ICU admission no isolates were stored.

DISCUSSION

SDD and SOD are among the few infection prevention measures with documented benefits on patient outcome in ICU patients.(9, 14) Yet, antibiotic resistance development will be critical for the safety of these interventions when used routinely.(15) We have demonstrated, using two large cohorts of ICU-patients, that the prolonged use of colistin as part of SDD and SOD was not associated with increased acquisition of colistin resistant GNB in the respiratory tract. Moreover, acquisition rates of colistin resistant GNB in the intestinal tract during SDD ranged from 1.2 to 3.2 per 1,000 patient-days at risk. The overall conversion rate from colistin susceptibility to resistance in the intestinal tract was below 1 conversion per 1,000 patient-days at risk. During SDD, though, these conversion rates ranged from 3.2 to 5.4 per 1,000 days of colonization with GNB and from 15.5 to 12.6 per 1,000 days of colonization with tobramycin-resistant GNB.

Only two other studies determined the effects of SDD on colistin resistance.(14, 16) In one study, also performed in the Netherlands, proportions of patients acquiring GNB resistant to polymyxin were 0.3% and 0% in those receiving SDD or not, respectively.(14) In the other study, from Germany, none of 175 patients in the SDD-group acquired polymyxin resistant *E. coli* or *Klebsiella* spp as compared to 4 of 171 patients in the placebo group.(16) Obtained surveillance cultures included rectal and respiratory tract samples in both studies. Associations between prolonged intravenous colistin use and development of colistin resistance have been reported from settings with high levels of carbapenemase-producing GNB.(17-19)

Few studies have quantified the association between antibiotic exposure and resistance development within individual patients. Recently Ong et al. quantified for several classes of antibiotics the risk of resistance development in *P. aeruginosa* and *Enterobacter* spp. in ICU patients not receiving SDD or SOD. Especially the use of meropenem appeared to be strongly associated with the development of meropenem resistance in *P. aeruginosa* with an adjusted hazard rate of 11.1 (95% CI 2.4 – 51.5), corresponding to 23 events of resistance acquisition per 1,000 patient days at risk. (20) Based on these findings we conclude that the rates of resistance acquisition for frequently used antibiotics were considerably higher than for acquisition of colistin resistance during topical use of this agent.

The present study adds further to our knowledge on the effects of SDD and SOD on antibiotic resistance in Dutch ICU-patients. On a patient level, SDD- and SOD-treated patients had significantly lower incidences of carriage and infections with antibiotic resistant bacteria as compared to patients receiving standard care, yet colistin was not part of the marker antibiotics in that study.(9) In a subsequent analysis the risks of acquiring respiratory tract carriage with GNB intrinsically resistant to colistin (i.e. *Proteus* spp and *Serratia* spp) was lower during SDD (7%) as compared to standard care (15%) (OR 0.41 (95% CI 0.29 – 0.57)) or SOD (13%) (OR 0.49 (95% CI 0.35 – 0.69)).(21)

The strength of the present study is the use of two different, both large ICU-cohorts, comprising more than 30,000 cultures. Absence of surveillance cultures during standard care resulted in an almost 25% lower culture frequency during this period, which may have led to an underestimation of the true acquisition rate in these patients. This would further support absence of excessive acquisition of respiratory tract colonization with colistin resistant GNB during SDD or SOD. Another strength is that conversion from colistin susceptibility to resistance was actually documented through genotyping. Consecutively obtained isolates could be analyzed from five patients, which lends support to the hypothesis that prolonged colistin use can induce colistin resistance.

A limitation of our study is the lack of a uniform colistin susceptibility testing method in the first cohort. Five hospitals used disk diffusion for susceptibility testing, which is considered suboptimal since colistin diffuses poorly in agar. In one study, though, sensitivities of this method ranged from 80% - 100% for *E. coli*, *K. pneumoniae* and *Enterobacter* spp(22). Three hospitals used automated susceptibility testing systems, which appeared to be highly reliable when compared to broth dilution tests.(22) In fact, for the 29 isolates available for genotyping, E-tests confirmed the susceptibility testing results of automated systems. Furthermore, we decided to use data only from those ICUs in which at least 80% of the isolates were tested for colistin resistance. This implied that three and nine of 13 ICUs were eligible for inclusion for the analysis of respiratory tract and intestinal tract carriage, respectively. Although this might have introduced bias, overall resistance rates of included and excluded units did not differ extensively (data not shown). In fact, inclusion of colistin susceptibility data from these units would definitely bias findings, as testing was performed only in selected isolates.

Although the overall risk of acquisition of colistin resistant GNB and conversion rates to colistin resistance were low, and comparable between standard care and SDD, our findings identified the circumstances in which this risk is higher. The conversion rate was about five-fold higher during persistent intestinal carriage with GNB, and about 15-fold higher during intestinal colonization with tobramycin-resistant GNB.

In contrast to facilitating resistance, SDD has been used successfully as a control measure in outbreak situations with ESBL-producing GNB.(23, 24) Also in a mice model intestinal colonization with carbapenemase-producing *K. pneumoniae* was effectively eradicated with intestinal administration of polymyxin E and gentamicin, without rebound colonization after discontinuation.(25)

Based on the present study we continue to recommend SDD or SOD in settings with low levels of antibiotic resistance, as both measures are associated with improved patient outcome. However, considering the global emergence of ESBL-producing and carbapenemase-producing GNB both measures should be accompanied with careful monitoring of tobramycin and colistin resistance in GNB. We recommend screening twice a week throughout ICU stay and to treat patients with documented carriage with colistin resistant GNB with barrier precautions.(26) It is yet

not possible to provide evidence-based recommendations for using SDD in patients colonized with a multi-resistant GNB only susceptible for colistin. In theory, continuing of SDD might increase the risk on a pan-resistant strain. On the other hand, high intraluminal levels of topical antibiotics exceed minimum inhibition concentrations of resistant pathogens, leading at least to temporary suppression which reduces the risk of overgrowth and cross-transmission. Further studies with detailed microbiological surveillance are needed to determine the ecological safety of SDD and SOD in ICU patients.

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SUPPLEMENTARY DATA

SDD and SOD regimen:

SDD and SOD were indicated for all adult patients with an expected duration of mechanical ventilation of more than 48 hours and with an expected length of ICU-stay >72 hours. The SDD regimen in CH-1 was identical to the SDD regimen in CH-2 and consisted of the oropharyngeal application and intestinal administration of a mixture of non-absorbable antibiotics (colistin, tobramycin and amphotericin B) four times daily until ICU-discharge. Additionally, all SDD-patients received intravenously 4 g cefotaxime per day during the first four days of the regimen. SOD consisted only of the oropharyngeal application of the same mouth paste as used during SDD. The total amount of colistin administered per dose of SDD was 100mg in the suspension and 100mg in the mouth paste. On top of that, if GNB were present in sputum cultures colistin could be nebulized (during SDD) and in case of upper respiratory tract colonization, the frequency of the oropharyngeal application could be intensified to eight times daily (during SDD and SOD).

Microbiological methods

Clinical cultures were obtained as part of daily practice and were processed using standard microbiological techniques. Rectal and throat samples, obtained as part of SOD and SDD, were inoculated onto MacConkey agar supplemented with tobramycine and cefotaxime. Sputum samples were inoculated onto McConkey-agar plates and bloodagar plates, both without antibiotics and onto MacConkey agars supplemented with tobramycin or cefotaxime and grown for 48 hours at 37°C. If growth was detected automated determination and susceptibility testing was performed according to standard laboratory procedures. Species identification and susceptibility testing of GNB was performed using automated laboratory systems; Phoenix (Becton Dickinson and Co, Sparks, MD, USA) or Vitek-2 (bioMérieux S.A. Marcy-l'Etoile, France). There was no uniform method of colistin susceptibility testing.(22) Three hospitals used automated susceptibility testing systems (VITEK-2 (BioMérieux S.A. Marcy-l'Etoile, France) or Phoenix (Becton Dickinson and Co, Sparks, MD, USA)) with interpretive breakpoints: susceptible MIC \leq 2 μ g/ml, and resistant MIC \geq 4 μ g/ml. One hospital used the colistin Etest (AB Biodisk, Solna, Sweden) performed and interpreted according to the manufacturer's procedures. Four hospitals used disk diffusion with MH agar and disks containing 150 μ g polymyxin B, and overnight incubation at 37 in ambient air (Rosco, Taastrup, Denmark). Isolates with growth inhibition zones \geq 20 mm were considered susceptible and isolates with inhibition zones of \leq 16 were considered susceptible. One hospital used the agar incorporation method using MH agar with a concentration of 2 μ g/ml colistin. Isolates were considered resistant if growth was detected after overnight incubation at 37 in ambient air.

Center	1	2	3	4	5	6	7	8	9	10	11	12	13
SDD	N GNB	130	94	58	73	91	7	147	167	519	225	142	81
	N col	124	69	39	59	20	69	69	57	435	145	0	66
	Percentage	95%	73%	67%	81%	47%	76%	100%	47%	34%	84%	64%	0%
SOD	N GNB	148	222	24	124	55	91	106	250	350	344	173	198
	N col	137	140	13	79	16	57	73	79	336	203	2	172
	Percentage	93%	63%	54%	64%	29%	63%	100%	0%	32%	96%	59%	1%
SC	N GNB	398	248	18	6	43	71	284	391	481	537	192	164
	N col	364	1	0	0	0	71	137	2	441	95	16	61
	Percentage	91%	0%	0%	0%	0%	21%	100%	48%	1%	92%	18%	8%
Total	Percentage	92%	37%	52%	68%	26%	49%	100%	38%	90%	40%	4%	67%

Table S1: Proportion of respiratory cultures positive for gram negative bacteria (GNB) where colistin testing was performed, per hospital during SDD, SOD and Standard Care (SC). GNB: *Acinetobacter* spp, *E.coli*, *Enterobacter* spp, *Klebsiella* spp, *Pseudomonas* spp.
Dark grey: excluded from further analysis. Light grey: included in further analysis.

Center	1	2	3	4	5	6	7	8	9	10	11	12	13	
SDD	N GNB	22	87	34	48	21	87	3	102	66	522	182	13	38
	N col	20	86	32	44	12	82	3	62	52	515	175	0	38
	Percentage	91%	99%	94%	92%	57%	94%	100%	61%	79%	99%	96%	0%	100%

Table S2: Proportion of rectal cultures positive for gram negative bacteria (GNB) where colistin testing was performed, per hospital during SDD.
GNB: *E. coli*, *Enterobacter* spp, *Klebsiella* spp
Dark grey: excluded from further analysis. Light grey: included in further analysis.

	Center	Type	Data included in analysis
Cohort 1	1	University	Respiratory and intestinal tract
	2	Teaching	Intestinal tract
	3	Non-teaching	Intestinal tract
	4	Teaching	Intestinal tract
	5	Teaching	None
	6	Teaching	Intestinal tract
	7	Teaching	Respiratory and intestinal tract
	8	Teaching	None
	9	Teaching	None
	10	University	Respiratory and intestinal tract
	11	University	Intestinal tract
	12	University	None
	13	Teaching	Intestinal tract
Cohort 2	1	University	Intestinal tract

Table S3: characteristics of the participating Intensive Care Units

Chapter 7

*Modelling antibiotic resistance of Gram-negative
bacteria during Selective Digestive tract
Decontamination in Intensive Care Units*

ABSTRACT

Introduction: Selective Digestive tract Decontamination (SDD) is a prophylactic antibiotic regimen consisting of topical antibiotics (tobramycin (TOB), colistin (COL) and amphotericin B) applied in oropharynx and intestinal tract throughout Intensive Care Unit (ICU)-stay, combined with a 4-day course of cefotaxime (CTX). SDD exerts continuous antibiotic pressure of TOB and COL and was associated with 87% increase in cephalosporin use (compared to standard care (SC)) (de Smet NEJM 2009). Yet, in Dutch ICUs, SDD was also associated with 38% lower acquisition rates of antibiotic resistance of Gram-negative bacteria (AR-GNB). Using data from this study we investigated the dynamical interactions between antibiotic pressure (systemic and topical antibiotics) and admission rates of AR-GNB using a mathematical model.

Methods: 1911 patients had at least 1 rectal culture result and the admission and acquisition rate of AR-GNB was determined for TOB+COL, CTX and TOB+COL+CTX. Parameters of the model were estimated by MCMC-simulations using uninformative priors. All available data on duration of stay with corresponding culture dates and results were used at an individual patient level. Posterior parameter estimates were applied to the same model without SDD antibiotic pressure (α_1), without decontamination (ρ) and with a 47% reduction in CTX antibiotic pressure (α_2). Sensitivity analyses were performed by adding various parameters of cross-transmission to the model.

Results: 102 patients were colonized with AR-GNB (93 CTX, 5 TOB+COL and 6 TOB+COL+CTX). Median and 95% credibility intervals for overall resistance prevalence were 3.3% (2.6-4.0) during SDD and 7.0% (5.7-8.7) during SC. If the admission prevalence would increase 5-fold, mimicking settings with high endemicity of antibiotic resistance, overall resistance would be 12.6% and 26.1% during SDD and 26.4% and 50.0% during SC. Adding cross-transmission as a separate parameter to the model, resulted in overall resistance rates of 15% and 39% in low endemic setting for SDD and SC respectively and of 38% and 63% respectively in high endemic settings. Increasing the importance of cross-transmission, resulted in higher rates of overall resistance and smaller differences between SDD and SC.

Conclusion: The model accurately reflects the observed beneficial effects of SDD on antibiotic resistance in Dutch ICUs, as compared to SC. The model also demonstrates that the beneficial effects remain with higher admission prevalence. Cross transmission reduces the beneficial effects, but SDD still outperforms SC.

INTRODUCTION

With a prevalence of ICU-infections of up to 50% and with mortality rates for affected patients doubling those of non-infected patients, prevention of ICU-acquired infections is an important goal of intensive care medicine.(1) One of the many studied preventive measure is Selective Decontamination of the Digestive Tract (SDD), in which colonization with so-called potential pathogens in the oropharynx and intestinal tract is modulated in order to prevent ICU-acquired infections.(2) SDD consists of a mixture of non-absorbable antibiotics (tobramycin (TOB), colistin (COL) and amphotericin B) applied in oropharynx and intestinal tract four times a day throughout ICU-stay, combined with a 4-day course of cefotaxime (CTX). There is strong evidence of lower rates of ICU-acquired infections during SDD(3) and in the two largest trials performed so far significant reductions in day-28 mortality and ICU-mortality were achieved in Dutch ICUs.(4, 5)

A feared adverse effect of SDD is the emergence of antibiotic resistance. As ICUs are considered to be the hot zones of antibiotic resistance in hospitals, controversy exists whether patients admitted to ICU should be exposed to the continuous antibiotic pressure of TOB and COL. Furthermore, SDD was associated with a 87% increase in cephalosporin use (compared to SC). (4) On the contrary, though, SDD was associated with lower acquisition rates of antibiotic resistant micro-organisms in the respiratory tract (5, 6), and with comparable acquisition rates of colistin-resistant micro-organisms, as compared to SC, in Dutch ICUs.(7) Yet, these findings originate from ICUs in the Netherlands, settings with low endemicity of antibiotic resistance. The question, therefore, remains how SDD performs in ICUs with higher baseline prevalence of antibiotic resistant bacteria.

Mathematical modelling has previously been used to disentangle specific roles of different acquisition routes in nosocomial epidemiology. In the present study we have used detailed microbiology data from multiple ICUs and a mathematical model to predict transmission dynamics of antibiotic-resistant Enterobacteriaceae (GNB) in ICUs with and without routine use of SDD, in settings with low and high prevalence of antibiotic-resistant GNB.

METHODS

We used data from patients receiving SDD during a cluster-randomized cross-over study in 13 ICUs the Netherlands.(4) Asymptomatic rectal carriage was determined by screening on ICU-admission and twice weekly. Rectal swabs were inoculated onto McConkey-agar plates and bloodagar plates, both without antibiotics and grown for 48 hours at 37°C. Isolates were further determined using standard microbiological techniques and 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. Only patients with at least one rectal culture result were included in the current analysis. Admission and acquisition rates of AR-GNB were determined for resistance to third-generation cephalosporins (either to ceftazidime, cefotaxim or ceftriaxone (CTX)), colistin (COL), tobramycin (TOB)) and for combined resistance to CTX+TOB+COL. All Enterobacteriaceae were grouped.

Model

A compartmental model was developed, inspired by previous work from Lipsitch et al(8) (Figure 1). We assumed all patients to be colonized with Enterobacteriaceae at ICU-admission, and patients enter the model in one of four compartments based on their colonization status: colonized with susceptible GNB (box S, probability η_s), colonized with CTX-resistant GNB (box R₂, probability η_2), colonized with TOB+COL resistant GNB (box R₁ via η_1), or colonized with bacteria resistant to CTX, TOB and COL (box R₁₂, via η_{12}). In patients in box S and R₂ colonization can be decolonized with SDD, resulting in a transition to box D (with rate μ when receiving SDD). After decontamination patients remain non-colonized until ICU-discharge due to continuous administration of SDD. Because of the use of both selective and regular culture media (see supplementary data), false negative cultures for patients in box D and S cannot be excluded, and μ cannot be determined accurately for patients moving from S to D. The decontamination rate μ is, therefore, only based on the results of patients moving from box R₂ to D. In addition, in another analysis of these data decolonization of rectal carriage with cephalosporin-resistant GNB was equally effective as for cephalosporin-susceptible GNB.(9) AR-GNB can be acquired during ICU-stay, either through endogenous (selection or horizontal gene transfer) or through exogenous acquisition (cross-transmission), resulting in transition from box S to either box R₁ (facilitated through selective pressure from SDD, α_1) or box R₂ (facilitated through selective pressure from CTX, α_2) and subsequently to R₁₂ (facilitated through selective pressure of CTX and SDD). We compared the SDD-model to a non-SDD model (standard care, SC). During SC patients cannot lose GNB-colonization ($\mu = 0$), there is no SDD-antibiotic pressure ($\alpha_1 = 0$) and CTX antibiotic pressure (α_2) is 47% lower than during SDD.(4) In both models it was assumed that systemic antibiotics do not eradicate bacterial carriage, that resistance is cumulative, i.e., that patients colonized with resistant GNB do not transfer to boxes representing carriage with less resistant GNB, that test characteristics had 100% sensitivity and specificity, and that SDD use did not change length of stay in ICU.

Model parameters were estimated by Markov Chain Monte Carlo (MCMC)-simulations using uninformative priors. All available data on duration of stay with corresponding culture dates and results were used at an individual patient level. One million accepted updates of the MCMC chain were used after a burn-in period of 40,000 accepted updates.

The posterior parameter estimates derived from settings using SDD were applied to the model without SDD ($\alpha_1=0$), without decontamination ($\mu=0$) and with 47% lower CTX antibiotic pressure (α_2).

The endpoint of analyses was the proportion of patients colonized with resistant AR-GNB during SDD and SC, in scenarios with different baseline prevalence of AR-GNB and cross-transmission rates. Cross-transmission (according to the mass-action principle) was investigated at various intensities (R_A values), under the assumption that all bacteria have the same spreading capacity. In simulations with cross-transmission an ICU-size of eight beds and constant discharge rates from all compartments, independent of colonization status, was assumed.

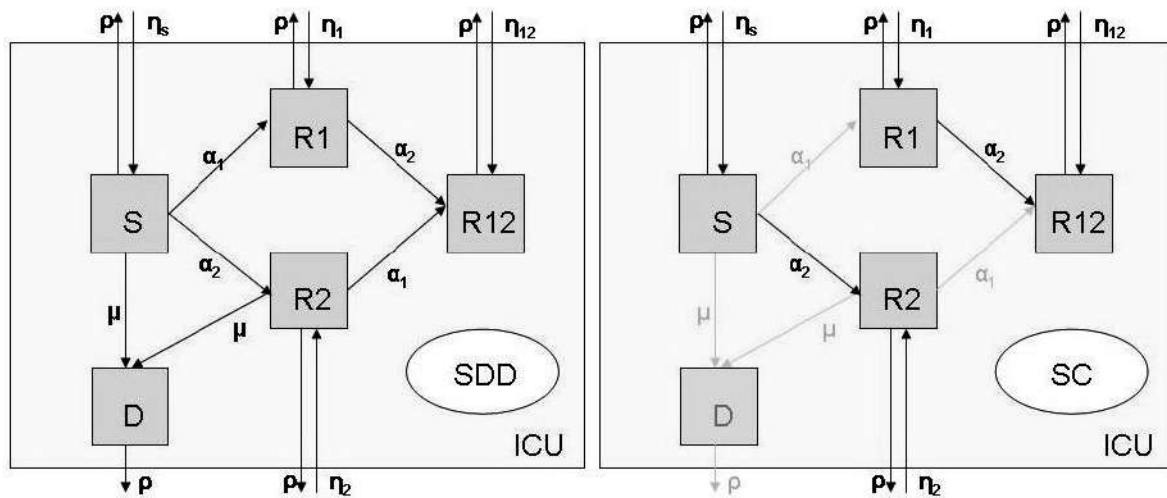


Figure 1: Dynamics of resistance and patient flow in ICU during SDD and SOD
 Patients can enter the model into four compartments based on their admission culture; as being colonized with susceptible Enterobacteriaceae (box S with probability η_s) or being colonized with CTX-resistant GNB (box R2, with probability η_2), TOB+COL resistant GNB (box R1 with probability η_1) or with bacteria resistant for both CTX and TOB+COL (box R₁₂, with probability η_{12}). Patients in box S and in box R₂ can be decontaminated by SDD, resulting in a transition to box D (at rate ρ).

RESULTS

In all, 1,911 patients were included, yielding 7,245 rectal culture results, and 102 were colonized with AR-GNB (with resistance to CTX only (n=93), TOB+COL (n=5) and TOB+COL+CTX (n=6)) (Table 1). The posterior parameter estimates indicate a median overall resistance prevalence of 3.3% (95% credibility intervals 2.6-4.0) during SDD and of 7.0% (95% CI 5.7-8.7) during SC. Increasing the admission prevalence 5-fold, and with $R_0=0$, the median resistance prevalence would be 12.6% (95% CI 10.2-15.4) and 26.1% (95% CI 21.4-30.8) during SDD and SC, respectively (Table2).

Number of patients included	1911		
Length of ICU stay, median (IQR)	9 (10)		
Number of culture days	6958		
Culture frequency (cultures/day)	0.27		
Number of patients colonized with a resistant pathogen	101	At admission	Acquired
R_1^*	5	3	2
R_2^*	93	81	12
$R_{12}^\#$	6	4	2

Table 1: Characteristics of SDD-patients included in the Dutch multi center study (baseline information) SDD, selective decontamination of the digestive tract; ICU, Intensive Care Unit; IQR, inter quartile range; R_1 , Enterobacteriaceae resistant for tobramycin and colistin; R_2 , Enterobacteriaceae resistant for cephalosporins; R_{12} , Enterobacteriaceae resistant for tobramycin, colistin and cephalosporins.

* No patients were in both R_1 and R_2 during the same ICU-stay

3 patients were colonized with R_2 and R_{12} during the same ICU-stay

Allowing cross-transmission increased overall resistance rates (Table 2). Even with high levels of cross transmission, both in low-endemic as in high-endemic settings, the model predicted lower resistance levels during SDD compared to SC. However, if R_0 increases differences in prevalence of resistance between SDD and SC decrease (Figure 2). The maximum difference in the prevalence of resistance between SDD and SC was 26% and 27% in low-endemic and high-endemic settings, respectively, for $R_0 = 1.5$. Removing topical antibiotics from the model (resulting in an ICU not using SDD but with high use of cephalosporins) yielded only subtle differences in the prevalence of AR-GNB in both low and high endemic settings (Figure 3).

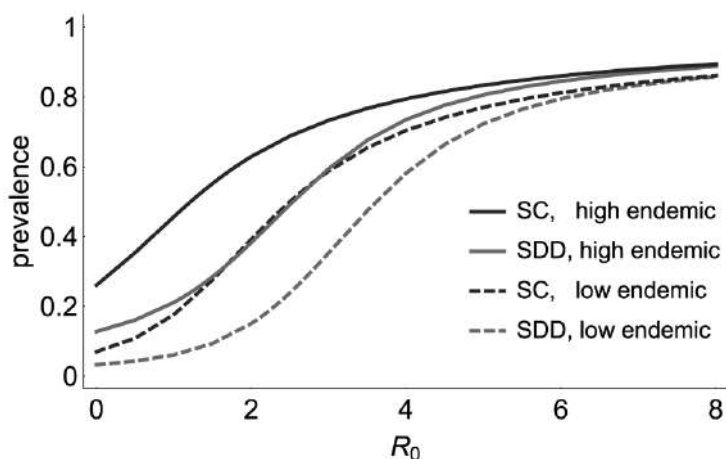


Figure 2: Resistance prevalence in ICU for several parameters of crosstransmission. The lowest two lines represent a low endemic setting. The highest two lines represent a high endemicity setting (i.e. admission prevalence of antibiotic resistant bacteria is 5-fold as high as the low-endemic setting) ICU, intensive care unit; SDD, selective decontamination of the digestive tract; SC, standard care i.e. no-SDD

R_0	Low prevalence			High prevalence		
	SDD Median (95% credibility interval)	SC Median (95% credibility interval)	Perc. posterior values with lower resistance prevalence with SDD than with SC	SDD Median (95% credibility interval)	SC Median (95% credibility interval)	Perc. posterior values with lower resistance prevalence with SDD than with SC
0	3.3 (2.6-4.0)	7.0 (5.67-8.7)	100%	12.6 (10.2-15.4)	26.1 (21.4-30.8)	100%
0.5	4.3 (3.4-5.3)	10.9 (8.9-13.2)	100%	15.9 (12.7-19.5)	35.4 (29.9-40.7)	100%
1	6.0 (4.7-7.7)	17.7 (14.9-20.7)	100%	20.8 (16.6-25.5)	45.8 (40.3-50.8)	100%
1.5	9.3 (6.9-12.1)	27.7 (24.3-31.1)	100%	28.3 (22.4-34.0)	55.4 (50.6-59.5)	100%
2	15.0 (10.9-19.6)	39.3 (36.0-42.4)	100%	38.2 (30.9-44.7)	63.0 (59.1-66.4)	100%
3	35.4 (26.7-42.7)	58.9 (57.0-60.6)	100%	59.7 (52.9-64.5)	73.3 (70.8-75.6)	100%
4	58.5 (50.4-63.5)	70.5 (69.6-71.3)	100%	73.6 (70.2-76.0)	79.5 (77.7-81.1)	100%
6	79.6 (77.9-80.4)	81.2 (80.9-81.5)	100%	84.5 (83.5-85.4)	86.0 (84.9-87.0)	100%
8	85.8 (85.5-86.0)	86.1 (85.9-86.3)	100%	88.7 (88.1-89.4)	89.4 (88.7-90.2)	100%

Table 2: Total resistance prevalence for various cross-transmission values SDD, selective decontamination of the digestive tract; SC, standard care Note that we show the expected prevalence given the parameter values, and that the observed prevalence in a study may differ due to chance effects.

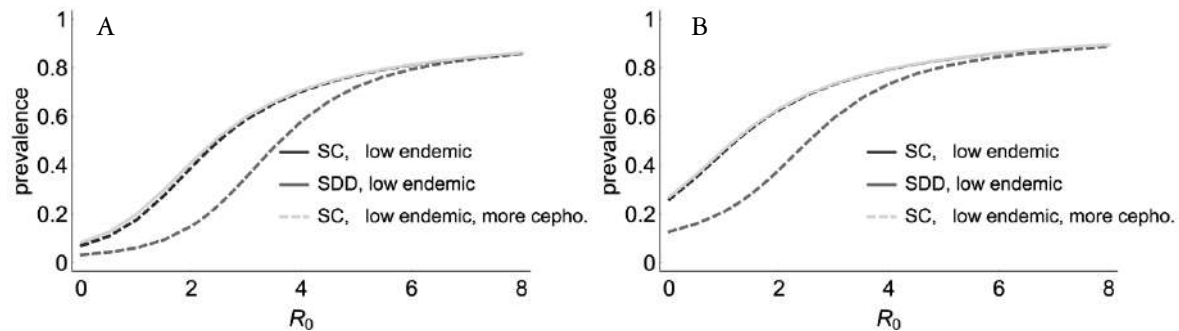


Figure 3: Resistance prevalence in ICU for several parameters of cross-transmission for SDD, no-SDD (SC) and a situation without topical antibiotics but with increased cephalosporin pressure (+85% comparable to SDD).

- A) In a low endemic setting
- B) In a high endemicity setting (i.e. admission prevalence of antibiotic resistant bacteria is 5-fold as high as the low-endemic setting)

ICU, intensive care unit; SDD, selective decontamination of the digestive tract; SC, standard care i.e. no-SDD

DISCUSSION

Using detailed microbiological data and a mathematical model we have investigated the dynamics of antibiotic resistant Enterobacteriaceae in ICU during SDD and standard care. The model confirmed the clinical observations that – in low-endemicity settings - SDD use resulted in a lower prevalence of antibiotic resistant Enterobacteriaceae as compared to standard care,

and predicts that this also accounts for settings with higher levels resistance, even when cross-transmission rates increase.

The reported findings of lower resistance levels during SDD (5, 6), as obtained mainly in settings with low levels of resistance to start with and low rates of cross-transmission, have been considered counterintuitive by many.(10) Yet, the model as applied here confirmed these findings, and even suggests that similar benefits would occur in settings with higher levels of resistance.

Mathematical modelling has previously been used to disentangle the dynamics of nosocomial spread of pathogens.(11) Naturally, the predictive value of a model depends on the accuracy of the data used for parameterization and the sensitivity of the model to the assumptions made. Some of these assumptions need to be discussed. There was information on intestinal carriage with GNB during standard care, as rectal swabs were only obtained as part of SDD. We, therefore, assumed that in the absence of SDD all patients would be colonized with GNB, and that spontaneous eradication did not occur.

In the model eradication of SDD-resistant pathogens could not occur, which was in agreement with the clinical observations in our study cohort. Little is known on the effects of SDD on intestinal and extra-intestinal carriage with multi-resistant bacteria. Yet, SDD was used as part of an infection control strategy to control outbreaks with multi-resistant Enterobacteriaceae(12) and carbapenem-resistant *Klebsiella pneumoniae*.(13) However, usually several measures were implemented simultaneously and it is not possible to quantify the contribution of individual measures.

Heterogeneity among patients with regard to susceptibility for acquiring colonization, e.g. due to systemic antibiotic use, was ignored. Yet, as SDD was used as an ecological intervention we do not expect that this biased our results.(14)

Categorization of patients, as colonized or not, was based on conventional microbiological culture techniques, as used in diagnostic laboratories. Yet, as with any culture-based procedure, there is minimal detection limit, and it remains to be determined whether SDD truly eradicates Gram-negative bacteria from the intestinal tract, or whether resistance genes persist in the non-culturable part of the intestinal microbiome.

Boldin et. al. also used a mathematical model to study the efficacy of barrier precautions and the administration of non-absorbable antibiotics on the prevalence of antibiotic resistant bacteria colonizing the lungs, intestinal tract and skin in ICU-patients.(15) In that model it was assumed that topical antibiotics did not eradicate colonization at the skin and in the lungs, but that they reduced the rate of endogenous transmission of bacteria from the gut to the skin if intestinal colonization was not fully eradicated during ICU-stay. It was concluded that SDD was most beneficial on a ward level if a large proportion of patients was eligible for treatment and if a large proportion of these patients were colonized in the gut, with a high risk of bacterial transmission to the skin. Moreover, the effects of topical antibiotics rapidly declined if cross-transmission increased, which is in line with the findings of the present study.

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Chapter 8

*Selective decontamination of the oropharynx and
the digestive tract and antimicrobial resistance:
a 4-year ecological study in 38 intensive care units
in the Netherlands*

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Marc J.M. Bonten, Akke van der Bij, on behalf of the ISIS-AR study group

ABSTRACT

Purpose: Selective Oropharyngeal Decontamination (SOD) and Selective Digestive Decontamination (SDD) are associated with improved outcome in patients at intensive care units (ICUs), but uncertainty remains on their long-term effects on resistance levels. We determined trends in antibiotic resistance in Gram-negative bacteria in 38 Dutch ICUs with and without SOD/SDD.

Methods: The Infectious Disease Surveillance Information System-Antibiotic Resistance (ISIS-AR) was used to identify all Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter* isolates from blood and respiratory tract specimens from January 2008 until April 2012. Per patient, the last isolate per species per specimen per month was selected to determine cumulative resistance rates (per 100 beds/month) for colistin, tobramycin, ciprofloxacin, ceftazidime and cefotaxime/ceftriaxone in ICUs that continuously used or did not use SOD/SDD or ICUs introducing SOD/SDD. Time trends were analysed by multilevel Poisson regression.

Results: 17 ICUs continuously used SOD/SDD (859 months), 13 did not use SOD/SDD (663 months), and eight ICUs introduced SOD/SDD (223 and 117 months before and after introduction). There were no discernible trends in antibiotic resistance among 637 blood isolates. For the 8,353 respiratory isolates, resistance to cefotaxime/ceftriaxone increased in ICUs that did not use SOD/SDD ($p < 0.001$) and decreased in ICUs that continuously used SOD/SDD ($p = 0.04$), as did resistance to ciprofloxacin ($p < 0.001$). Introduction of SOD/SDD was followed by statistically significant reductions in resistance rates for all antimicrobial agents.

Conclusions: Continuous use of SOD/SDD was associated with decreasing trends in resistance for cefotaxime/ceftriaxone and ciprofloxacin. Introduction of SOD/SDD was associated with reductions in resistance rates for all antimicrobial agents included.

INTRODUCTION

Nosocomial infections, in particular respiratory tract infections, are common in patients treated in intensive care units (ICUs) and are associated with considerable mortality and morbidity [1, 2]. Infections in ICU-patients are most frequently caused by potentially pathogenic microorganisms carried in the throat and gut, present either on ICU-admission or acquired during ICU stay. Selective Oropharyngeal Decontamination (SOD) and Selective Decontamination of the Digestive tract (SDD) are antibiotic prophylaxis strategies used to prevent infections by these microorganisms in ICU-patients.

SOD and SDD both consist of the topical application of non-absorbable antimicrobial agents in the oropharynx. SDD also includes the administration of the same topical agent in the gastrointestinal tract and systemic prophylaxis, usually consisting of a third-generation cephalosporin, during the first three or four days of ICU admission [3, 4]. SOD and SDD result in lower incidences of ventilator-associated pneumonia (VAP) [5], and in ICUs with low levels of antibiotic resistance, SOD and SDD result in better patient outcome [6-8].

Nevertheless, the acceptance of SOD and SDD has remained low, partly because of uncertainties on the long-term effects of both regimens on antibiotic resistance [9, 10]. In theory, SOD and SDD may select for micro-organisms that are intrinsically resistant or acquired resistance to the antibiotics used. However, in most randomized studies patients receiving SOD or SDD had lower carriage rates with antibiotic resistant bacteria than those not receiving any of these interventions [11]. In an ecological study SOD and SDD were both associated with lower unit-wide prevalence of antimicrobial resistance in Gram-negative bacteria during the interventions, but there was an increased prevalence of resistance to ceftazidime in Gram-negative bacteria isolated from rectal swabs after discontinuation of SDD [12].

In the Netherlands, SOD and SDD are used in many but not in all ICUs. Using data from the Dutch Infectious Disease Surveillance Information System - Antibiotic Resistance (ISIS-AR) with 32 participating laboratories serving 45 ICUs, we evaluated trends in antimicrobial resistance in Gram-negative bacteria in ICUs without SOD or SDD and in ICUs using or introducing SOD or SDD in the Netherlands.

METHODS

Setting and interventions

Antimicrobial susceptibility test results (i.e., susceptible [S], intermediate resistant [I] and resistant [R]), and underlying minimal inhibitory concentrations (MICs) of Etests or automated susceptibility testing systems and patient data (i.e., age, gender, specimen site, patient location) of all routinely cultured bacterial species are collected on a monthly basis in the Dutch ISIS-AR

system [13]. Data collection started in January 2008 and currently includes 32 laboratories, serving 45 hospitals with at least one ICU, dispersed over the Netherlands. With approximately 65% of Dutch laboratories and hospitals participating, ISIS-AR is considered representative for clinical antimicrobial susceptibility testing data in the Netherlands.

Information on SOD/SDD use and policy was collected from all ICUs by a structured online questionnaire completed by a clinical microbiologist (complementary data, table 1). For this study, SOD was defined as the application of topical non-absorbable antimicrobials to the oropharynx only; SDD was defined as the application of topical non-absorbable antimicrobials to the oropharynx and/or the gastrointestinal tract in combination with intravenous antibiotics. In the Netherlands, the most frequently used topical antibiotic mixture consists of tobramycin, colistin and amphotericin B applied four times daily until ICU-discharge. (complementary data, table 1) [14].

Isolate selection and antimicrobial susceptibility

From January 2008 until April 2012, we included all isolates of *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp., from blood and lower respiratory tract specimens taken either for clinical or screening purposes. Only isolates from laboratories that submitted complete data to the ISIS-AR database for the whole study period were included (i.e., consistently reporting laboratories). To avoid bias by patients only admitted for a short period of time at an ICU, we excluded patients with only isolates available at two consecutive days, as they probably reflect short-term ICU admissions. To avoid the inclusion of multiple isolates of the same patient, only the last isolate per species per specimen per patient per month was included in the analysis (i.e., cumulative resistance). As antimicrobial susceptibility testing breakpoint guidelines changed in time, we calculated non-susceptibility to colistin, tobramycin, ciprofloxacin, ceftazidime and cefotaxime/ceftriaxone (i.e., if an isolate was non-susceptible to either cefotaxime or ceftriaxone it was considered to be non-susceptible) by reinterpreting available MIC values according to the EUCAST January 2012 guidelines (v2.0, www.eucast.org). If MIC values for an antimicrobial agent were available for less than 80% of all isolates, antimicrobial susceptibility interpretations as reported by the laboratories were used. Since ISIS-AR only collects data on isolates (i.e., positive cultures), the total number of cultures obtained could not be determined.

Analysis

Resistance rates were calculated per 100 patient beds per month. We assumed bed occupancy to be 100% and the total number of beds to be constant in time. Analyses were performed for ICUs that continuously used SOD/SDD or not from January 2008 to April 2012 using all data. For ICUs that introduced SOD or SDD during the period of study, the first month after introduction was excluded from the analyses and resistance rates were calculated before and after the introduction of SOD/SDD with the month of switch fixed at $t=0$ for all ICUs. Trends in

time were analysed by multilevel Poisson regression, taking into consideration the variation between and within ICUs by including those as a level in the model. The number of beds, log-transformed, was used as an offset. All Poisson regression analyses were performed separately for *Enterobacteriaceae* and *P. aeruginosa* isolates. Additionally for colistin, stratified analyses were performed for *Enterobacteriaceae* intrinsically resistant to colistin and *Enterobacteriaceae* that are intrinsically susceptible to colistin according to the EUCAST expert rules [15]. Statistical significance was defined as p-value < 0.05. All data were analysed using SPSS statistical software 19.0 (IBM, Armonk, New York State, United States).

RESULTS

Of the 45 ICUs included in ISIS-AR, complete data for the whole study period was available for 38 ICUs with different levels of care representing all three levels of ICU care available in the Netherlands (complementary data, table 2). Thirteen of the 38 included ICUs did not use SOD/SDD during the study period (accounting for 663 months), and 17 continuously used SOD/SDD (accounting for 859 months) (table 3 and complimentary data, table 2). There were 637 unique blood culture isolates (*Enterobacteriaceae* n=519; *P. aeruginosa* n=107 and *Acinetobacter* spp. n=11) and 8,353 unique respiratory isolates (*Enterobacteriaceae* n=6,339; *P. aeruginosa* n=1,672 and *Acinetobacter* spp. n=342). For ciprofloxacin, ceftazidime, cefotaxime/ceftriaxone and tobramycin, MIC values were available for 91%, 88%, 100% and 94% of isolates, respectively. For colistin, MIC values were available for 73% of isolates. For ICUs that did not use SOD/SDD during the period of study the average rate of resistant isolates per month was 7.3/100 beds for ciprofloxacin (range 2.1 – 13.2/100 beds/month), 6.2/100 beds for ceftazidime (range 1.5 – 10.3/100 beds/month), 5.0/100 beds for cefotaxime/ceftriaxone (range 0.7 – 11.3/100 beds/month), 3.2/100 beds for tobramycin (0 – 6.2/ 100 beds/month) and 6.3/100 beds for colistin (range 3.0 – 11.0/100 beds/month). For ICUs that used SOD/SDD continuously during the period of study, these numbers were 3.5/100 beds for ciprofloxacin (range 0.9 – 6.7/100 beds/month), 3.4/100 beds for ceftazidime (range 0.6 – 7.0/100 beds/month), 3.0/100 beds for cefotaxime/ceftriaxone (range 0.6 – 5.8/100 beds/month), 3.5/100 beds for tobramycin (1.2 – 6.1/100 beds/month) and 5.3/100 beds for colistin (range 2.1 – 10.1/100 beds/month). Figure 1 shows the rate per month per analysis group.

Time Period ^b	No SOD/SDD		SOD ^a		SDD ^a	
	number of ICUs	beds/month	number of ICUs	beds/month	Number of ICUs	beds/month
Q1 2008	21	224	2	58	15	269
Q2 2008	21	224	2	58	15	269
Q3 2008	21	224	2	58	15	269
Q4 2008 ^c	21	219	2	58	15	269
Q1 2009	20	210	2	58	16	283
Q2 2009	20	210	2	58	16	283
Q3 2009	20	210	2	58	16	283
Q4 2009 ^c	20	206	2	58	16	283
Q1 2010 ^c	17	177	4	75	17	292
Q2 2010	17	177	4	82	16	288
Q3 2010	17	177	5	94	15	277
Q4 2010 ^c	16	165	7	108	15	274
Q1 2011 ^c	13	136	9	128	14	258
Q2 2011	13	136	11	139	14	265
Q3 2011	13	136	11	139	14	276
Q4 2011	13	136	11	142	13	265
Q1 2012	13	136	13	161	12	254

Table 3. The average number of intensive care units (ICUs) and beds per month for ICUs with and without selective oropharyngeal decontamination (SOD) or selective decontamination of the digestive tract (SDD) per quartile from January 2008 to April 2012.

^a 9 ICUs switched from SOD to SDD or vice versa during the period of study, see supplementary data, table 2 for detailed information.

^b Q1 January-March; Q2 April-June; Q3 July – September; Q4 October – December

^c 8 ICUs introduced SOD or SDD during the period of study. The time of introduction was December 2008 (n=1), December 2009 (n=1), January 2010 (n=2), October 2010 (n=1), January 2011 (n=3).

Considering resistance in time, for isolates obtained from blood specimens, no discernible trends were observed for all antibiotics studied in ICUs with and without SOD/SDD (data not shown). For Enterobacteriaceae from respiratory samples, the rate of isolates resistant to cefotaxime/ceftriaxone increased with 2% per month and to tobramycin with nearly 1% per month in ICUs that did not use SOD/SDD during the period of study (β 0.019, 95% confidence interval [CI] 0.011-0.026 and β 0.009, 95% CI -0.000-0.002, table 4). In the ICUs that continuously used SOD/SDD there was a trend towards a decrease in the rate of resistance for all antimicrobial agents in Enterobacteriaceae isolates from respiratory samples, with statistical significance reached for ciprofloxacin (β -0.009, 95% CI -0.015 - -0.002) and cefotaxime/ceftriaxone (β -0.006, 95% CI -0.012 - -0.000). For *P. aeruginosa* from respiratory samples, there was a decreasing trend in the rate of isolates resistant to ceftazidime in ICUs without SOD/SDD (β -0.015, 95% CI -0.028- -0.002, table 4). In ICUs with SOD/SDD there was a decreasing trend in the rate of resistance for all antimicrobial agents, which reached statistical significance for ciprofloxacin only (β -0.016, 95% CI -0.027- -0.004).

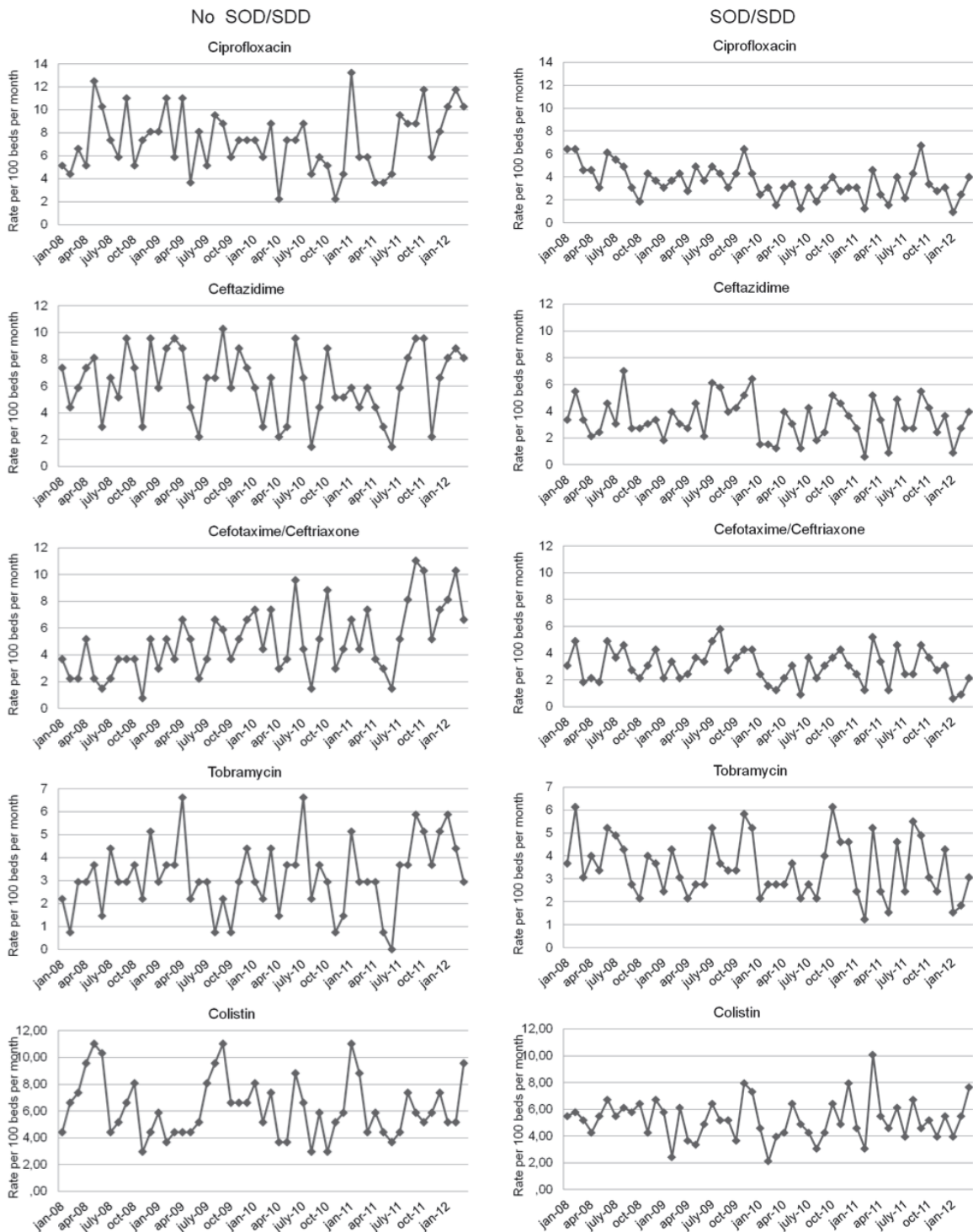


Figure 1: rate per analysis group of resistant isolates from respiratory isolates per 100 bed per month for the 13 intensive care units (ICUs) that did not use SDD/SOD and for the 17 ICUs that used SDD/SOD. SOD, selective oropharyngeal decontamination; SDD, selective decontamination of the digestive tract

Antimicrobial agent	No SOD/SDD		SOD/SDD	
	Coefficient (95% CI) ^a	p-value	Coefficient (95% CI)*	p-value
<i>Enterobacteriaceae</i>				
Ciprofloxacin	0.003 (-0.004 – 0.010)	0.45	-0.009 (-0.015 – -0.002)	0.01
Ceftazidime	0.003 (-0.004 – 0.010)	0.42	-0.006 (-0.012 – 0.001)	0.10
Cefotaxime/ceftriaxone	0.019 (0.011 – 0.026)	<0.001	-0.006 (-0.012 – -0.000)	0.04
Tobramycin	0.009 (-0.000 – 0.019)	0.05	-0.004 (-0.010 – -0.002)	0.24
Colistin	-0.003 (-0.009 – 0.004)	0.38	0.000 (-0.005 – 0.005)	0.96
Colistin IR ^b	-0.004 (-0.010 – 0.003)	0.26	-0.002 (-0.007 – 0.003)	0.34
Colistin non-IR	NA ^c		NA	
<i>Pseudomonas aeruginosa</i>				
Ciprofloxacin	-0.002 (-0.014 – 0.010)	0.73	-0.016 (-0.027 – -0.004)	0.006
Ceftazidime	-0.015 (-0.028 – -0.002)	0.03	-0.003 (-0.014 – 0.009)	0.65
Tobramycin	-0.003 (-0.026 – 0.021)	0.82	-0.003 (-0.020 – 0.014)	0.75
Colistin	NA		0.004 (-0.006 – 0.013)	0.45

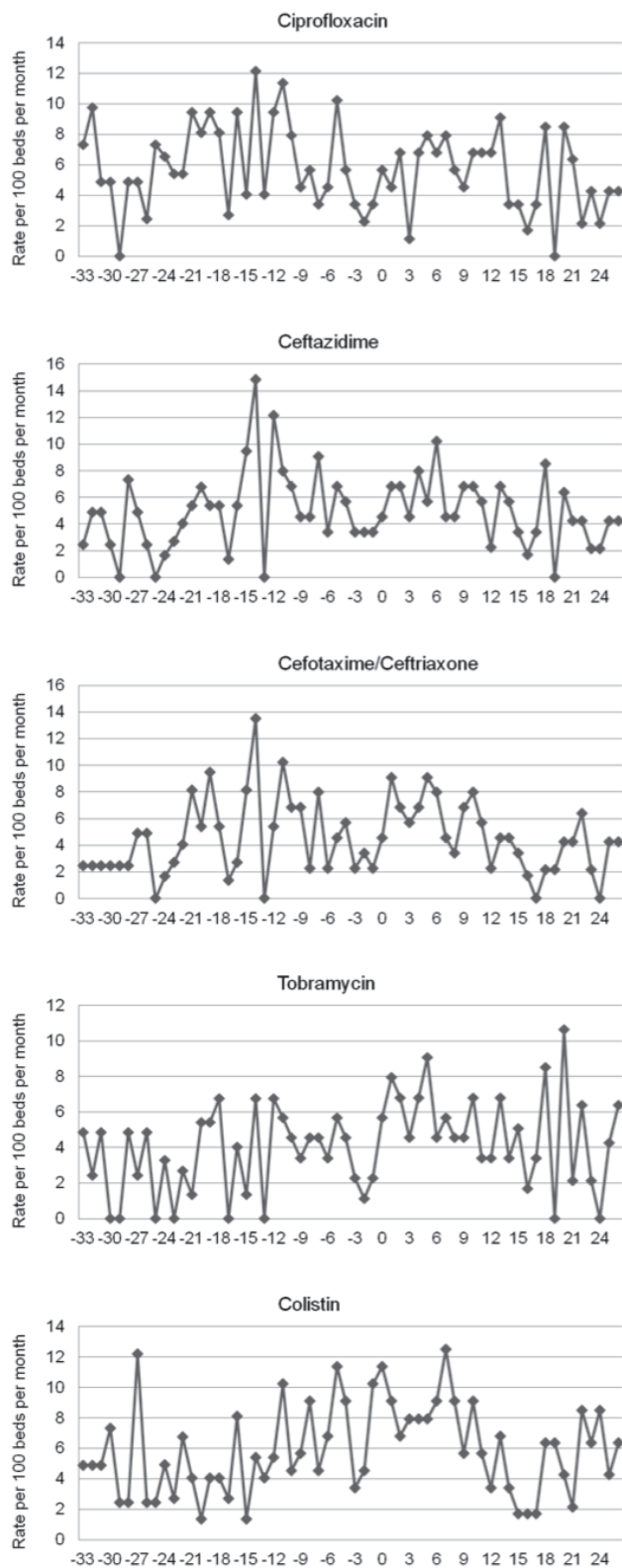
Table 4. Change in the rate of resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates from respiratory tract samples per 100 bed per month for the 13 intensive care units (ICUs) that did not use selective oropharyngeal decontamination (SOD) or selective decontamination of the digestive tract (SDD) and the 17 ICUs that continuously used SOD or SDD from January 2008 to April 2012.

^a Calculated by multilevel Poisson analysis with health care facilities included as a level and the number of beds, log-transformed used as an offset; 95% CI=95% confidence interval.

^b IR – intrinsically resistant

^c NA not available

Eight ICUs introduced SOD (n=6) or SDD (n=2) during the period of study. The duration of data available for analysis before and after the introduction of SOD/SDD ranged from 11 to 36 months and from 14 to 39 months, respectively (table 3 and complimentary data, table 2). For analyses, only those months were included in which data were available from at least four ICUs (≥50% of the ICUs), resulting in periods of 33 and 26 months before and after SOD/SDD introduction, respectively. The number of resistant blood isolates was too small to perform time trends analysis (n<20). Before the introduction of SOD/SDD the rate of *Enterobacteriaceae* from respiratory samples resistant to colistin gradually increased (β 0.025, 95% CI 0.005 - 0.045, table 5), which was followed by statistically significant decreasing trends in resistance rates for all antimicrobial agents after the introduction of SOD/SDD (table 5 & figure 2). No significant time trends were found for *P. aeruginosa* isolates (table 5).



Month	-30	-20	-10	0	10	20
Number of beds	41	74	88	88	88	47
Number of ICUs	4	7	8	8	8	4

Figure 2. Rate of resistant isolates from respiratory isolates per 100 bed per month for the 8 intensive care units (ICUs) that introduced selective oropharyngeal decontamination (SOD) or selective decontamination of the digestive tract from January 2008 to April 2012. The time of SOD or SDD introduction has been fixed for all ICUs at time=0. The rate before the introduction of SOD or SDD is presented before time=0. The rate after the introduction of SOD or SDD is presented after time=0.

Antimicrobial agent	Before SOD/SDD		After SOD/SDD	
	Coefficient (95% CI) ^a	p-value	Coefficient (95% CI)*	p-value
<i>Enterobacteriaceae</i>				
Ciprofloxacin	-0.002 (-0.019 – 0.015)	0.83	-0.048 (-0.082 – -0.014)	0.006
Ceftazidime	0.010 (-0.015 – 0.036)	0.83	-0.050 (-0.082 – -0.019)	0.002
Cefotaxime/ceftriaxone	0.005 (-0.018 – 0.028)	0.65	-0.063 (-0.094 – -0.033)	<0.001
Tobramycin	-0.008 (-0.037 – 0.021)	0.59	-0.049 (-0.080 – -0.017)	0.003
Colistin	0.025 (0.005 – 0.045)	0.01	-0.046 (-0.073 – -0.019)	0.001
Colistin IR ^b	0.022 (0.001 – 0.042)	0.04	-0.049 (-0.078 – -0.020)	0.001
Colistin non-IR	NA ^c		NA	
<i>Pseudomonas aeruginosa</i>				
Ciprofloxacin	-0.004 (-0.024 – 0.015)	0.67	0.008 (-0.015 – 0.032)	0.49
Ceftazidime	-0.002 (-0.024 – 0.021)	0.89	0.020 (-0.006 – 0.046)	0.13
Tobramycin	NA		0.012 (-0.013 – 0.037)	0.35
Colistin	NA		NA	

Table 5. Change in the rate of resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* isolates from respiratory tract samples per 100 bed per month for the 8 intensive care units that introduced selective oropharyngeal decontamination (SOD) or selective decontamination of the digestive tract (SDD), calculated before and after the introduction of SOD/SDD from January 2008 to April 2012.

^a Calculated by multilevel Poisson analysis with health care facilities included as a level and the number of beds, log-transformed used as an offset; 95% CI=95% confidence interval.

^b IR – intrinsically resistant

^c NA not available

For colistin, stratified analyses were performed for *Enterobacteriaceae* that are intrinsically resistant and those that are intrinsically susceptible to colistin. For blood and respiratory isolates, 89 (14%) and 1578 (18%) of isolates belonged to the group of intrinsically resistant *Enterobacteriaceae*, and there were no time trends in the rate of resistance discernible for ICUs with and without SOD/SDD (table 4). In ICUs that introduced SOD/SDD during the study period, there was an increasing trend in the rate of *Enterobacteriaceae* intrinsically resistant to colistin before introduction (β 0.022, 95% CI 0.001 - 0.042), which was followed by a decreasing trend after introduction (β -0.049, 95% CI -0.078 - -0.020, table 5). Among species that are considered intrinsically susceptible to colistin (e.g., *Escherichia coli*, *Klebsiella* spp., *Citrobacter* spp. and *Enterobacter* spp.), only 246 (3%) of all respiratory and 13 (2%) blood isolates were resistant to colistin and these numbers did not allow trend analyses.

DISCUSSION

This ecological study on antimicrobial resistance rates of Gram-negative bacteria in 38 Dutch ICUs using national surveillance data demonstrated a decreasing trend in the rate of resistance for all marker antibiotics in respiratory isolates in ICUs that continuously used SOD/SDD during the 4 years of study, and significant decreases in resistance rates of respiratory isolates for all

marker antibiotics in ICUs that introduced SOD/SDD. In ICUs that did not use SOD/SDD, rates of resistance to cefotaxime/ceftriaxone increased in time. Prevalence of resistance to colistin in Enterobacteriaceae that are intrinsically susceptible was only 3% in respiratory isolates, precluding meaningful time trend analyses. The rate of Enterobacteriaceae intrinsically resistant to colistin decreased after the introduction of SOD/SDD. These results are in line with those from previous studies and a meta-analysis determining resistance in respiratory isolates from individual patients receiving SOD or SDD [6, 7, 11].

Most studies that have been performed on SOD or SDD, like this study, originate from the Netherlands, which is considered a low-prevalence country for antimicrobial resistance [16]. Results of these studies might therefore not be generalizable to countries with a higher level of resistance. However, a recent meta-analysis that showed no association between selective decontamination and resistance included studies from various parts of the world, also from countries in Southern-Europe with a higher baseline prevalence of resistance [11]. Declining rates of antibiotic resistance during daily prophylactic administration of non-absorbable antibiotics in ICU patients seems counterintuitive, but might result from lower nosocomial infection rates [6, 17-19], yielding reductions in the use of systemic antibiotics [6, 11, 20]. However, associations between lower infection rates and less antibiotic prescription have not been reported consistently from SDD studies. Therefore, this issue cannot be answered adequately with available evidence. Another explanation might be the fact that SDD creates a unique environment that prevents overgrowth of resistant mutants because of the combination of very high topical bactericidal antibiotic levels in saliva and faeces, the use of synergistic antibiotic mixtures and the maintenance of colonisation resistance [4, 21].

Colistin resistance remained rare in Gram-negative bacteria intrinsically susceptible to colistin, even though most ICUs with SOD or SDD used colistin as part of the prophylactic regimen since the early 2000s. Previous studies also reported low acquisition rates with colistin-resistant Gram-negative bacteria that were comparable in patients with and without topical use of colistin [7, 22]. Yet, these studies have also demonstrated that colistin resistance can develop, albeit at a low rate, and that the use of SOD or SDD can facilitate clonal spread of Gram-negative bacteria resistant to colistin and tobramycin [23].

Most studies evaluating the effects of SOD or SDD on antibiotic resistance used individual patient data from randomized trials with a median duration of interventions of 16 months [11]. In such studies, patient groups are usually comparable due to randomization with similar screening and culture methods within studies. However, analyses include only those patients that are enrolled, precluding assessment of the effects of SOD or SDD on the unit-wide bacterial ecology. It is unknown which study duration is needed to fully assess the effects of SOD or SDD on the ecology of antimicrobial resistance in ICUs. To our knowledge, there are only two longitudinal ecological studies published, and both did not detect increases in the incidence of resistant bacteria during

5 years of SDD [24, 25]. However, both studies were single-centre studies including one ICU only. A post-hoc ecological analysis of the results of a Dutch 13-center cluster-randomized study demonstrated reduced rates of antibiotic resistance among Gram-negative bacteria during SOD or SDD, yet with an abrupt increase of resistance after discontinuation of SDD, suggesting a rebound effect on resistance in the intestinal tract probably due to the recolonisation of the patient by surrounding microbiological flora [12].

The present ecological study, analyses resistance patterns in time on ICU level, not on patient level, and has a relatively long-term follow-up period on a large number of ICUs. However, the study has some limitations. First, ISIS-AR only collects data on positive cultures and consequently information on the total number of cultures taken or the total number of patients admitted was unavailable. We, therefore, calculated rates using the number of beds per month as denominator. Patient days at risk would have been a better denominator, as incidence densities most accurately reflect the true resistance burden. In our study, the number of beds was assumed to remain stable throughout the period of study. Rates presented might therefore represent either an under or over estimation if the number of hospitalised patients changed in time (e.g., less hospitalised patients will result in less isolates cultured and consequently in an underestimation of the rate found). In our study there was a significant decrease in the number of isolates available in the ISIS-AR database per bed per month in time (β -0.004, 95% CI -0.005 - -0.002, complementary data, table 6). However, the decrease in the number of isolates was only visible in ICUs that used SOD or SDD or ICUs that introduced SOD or SDD, rather reflecting the effects of SOD/SDD on the total number of isolates cultured than a decrease in number of patients. Secondly, individual patient data were not available and, therefore, adjustments for differences between ICUs and patient characteristics, such as severity of illness, could not be made. Third, due to the low number of ICUs that continuously used SOD or SDD during the period of study, we combined these two interventions in our study. When considering blood isolates, the combination of SOD and SDD does not seem clear-cut, since SDD consists of intravenous cefotaxime/ceftriaxone resulting in systemic treatment. However, for respiratory tract isolates combining SOD and SDD is justifiable since both regimens exert effects in the oropharynx, with similar effects on respiratory tract colonization, both with susceptible and resistant bacteria [12, 26]. Fourth, details on microbiological culture procedures, antibiotic susceptibility testing and screening policies were not available and for the ICUs that introduced SOD or SDD during the study period, detection bias might have occurred through a higher frequency of sampling and the use of selective media for detection of micro-organisms resistant to the prophylactic antibiotics. However, this detection bias would have resulted in an increased detection of resistant isolates, which would imply that the observed decrease in resistance rate would have underestimated the true changes in ecology.

Due to these limitations, we did not compare resistance rates and trends between ICUs with and without SOD/SDD. However, this study provides unique information on the trends in antibiotic resistance in ICUs with and without SOD or SDD. In conclusion, these results provide evidence that the use of SOD and SDD is not associated with an increase in resistance rates in time, rather with a reduction in resistant isolates, in ICUs with low endemicity of antibiotic resistance. Studies evaluating the clinical benefits and ecological safety of these measures in settings with different bacterial ecology are warranted.

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COMPLIMENTARY DATA

	SOD 16 ICUs N	SDD 18 ICUs N
Regimen		
Oral topical polymyxin, tobramycin and amphotericin B	15	17
Other oral topical agents	1	1
Gastrointestinal polymyxin, tobramycin and amphotericin B	0	14
Other gastrointestinal agents	0	1
IV cefotaxime during the first 4 days	0	16
IV ceftriaxone during the first 4 days	0	2
Eligibility criteria ^a		
>48 hours ICU admission	3	1
>72 hours ICU admission	4	6
>24 hours intubation	7	5
>48 hours intubation	1	2

Table 1. Background information on the use of selective oropharyngeal decontamination (SOD) or selective decontamination of the digestive tract (SDD) in intensive care units (ICUs) with SOD or SDD

^aData available for 13 ICUs with SOD and 12 ICUs with SDD

ICU	SOD/SDD	Start date SOD/SDD	Months for analysis	Analysis group	Beds	Care level
1	No SOD/SDD		36	Switch group	9	2
	SOD	1-1-2011	14			
2	SOD	1-1-2000	39	SOD/SDD group	34	3
	SDD	1-4-2011	11			
3	SDD	1-1-2000	51	SOD/SDD group	16	2
4	SDD	1-1-2000	3	SOD/SDD group	12	2
	SOD	1-12-2011	47			
5	No SOD/SDD		51	No SOD/SDD group	34	2
6	No SOD/SDD		51	No SOD/SDD group	12	2
7	SDD	1-1-2006	51	SOD/SDD group	32	2
8	No SOD/SDD		24	Switch group	6	2
	SOD	1-1-2010	26			
9	No SOD/SDD		51	No SOD/SDD group	6	2
10	No SOD/SDD		51	No SOD/SDD group	3	1
11	No SOD/SDD		51	No SOD/SDD group	8	2
12	No SOD/SDD		51	No SOD/SDD group	6	1
13	No SOD/SDD		51	No SOD/SDD group	6	1
14	No SOD/SDD		51	No SOD/SDD group	10	2
15	No SOD/SDD		51	No SOD/SDD group	8	2
16	SDD	1-6-1999	51	SOD/SDD group	8	2
19	No SOD/SDD		51	No SOD/SDD group	8	1
20	No SOD/SDD		11	Switch group	14	2
	SDD	1-12-2009	14			
	SOD	1-1-2011	25			
21	No SOD/SDD SDD		24	Switch group	14	2
		1-1-2010	26			
22	No SOD/SDD SOD		33	Switch group	12	2
		1-10-2010	17			
23	SDD	1-4-2003	51	SOD/SDD group	16	2
24	SDD	1-1-2000	51	SOD/SDD group	20	2
25	No SOD/SDD SOD		36	Switch group	8	2
		1-1-2011	14			
26	SDD	1-1-2000	12	SOD/SDD group	7	2
	SOD	1-3-2011	38			
27	SDD	1-1-2000	19	SOD/SDD group	9	2
	SOD	2-8-2010	31			
29	No SOD/SDD		51	No SOD/SDD group	8	1
30	SDD	1-1-2000	51	SOD/SDD group	12	2
31	No SOD/SDD		36	Switch group	12	2
	SOD	1-1-2011	14			
32	SDD	1-1-2000	51	SOD/SDD group	12	2
34	SDD	1-1-2006	51	SOD/SDD group	41	3
38	SDD	1-1-2000	51	SOD/SDD group	36	3
39	SOD	1-1-2008	50	SOD/SDD group	24	3
40	SDD	1-4-2005	4	SOD/SDD group	10	2
	SOD	1-11-2011	46			
41	SDD	1-1-2000	22	SOD/SDD group	14	2
	SOD	1-5-2010	28			

42	SDD	1-1-2000	11	SOD/SDD group	24	3
	SOD	1-4-2011	39			
44	No SOD/SDD		51	No SOD/SDD group	13	2
45	No SOD/SDD		23	Switch group	13	3
	SOD	1-12-2009	12			
	SDD	1-1-2011	15			
46	No SOD/SDD		51	No SOD/SDD group	14	2

Table 2. Overview of intensive care units (ICUs) during the period of study: the use of selective oropharyngeal decontamination (SOD) or selective decontamination of the digestive tract (SDD), the start date of SOD/SDD and the number of months available for statistical analysis, analysis group, number of beds and care level

	Coefficient (95% CI) ^a	p-value
Overall	-0.004 (-0.005 – -0.002)	<0.001
No SOD/SDD group	-0.001 (-0.004 - --0.002)	0.46
SOD/SDD group	-0.004 (-0.007 – -0.002)	<0.001
Switch group	-0.010 (-0.014 – -0.006)	<0.001

Table 6. Change in the number of positive respiratory specimens per 100 bed per month for all three intensive care units (ICUs) analysis groups from January 2008 to April 2012.

^a Calculated by multilevel Poisson analysis with health care facilities included as a level and the number of beds, log-transformed used as an offset; 95% CI=95% confidence interval.

PART III

SDD and intestinal colonization

Chapter 9

*Decontamination of cephalosporin-resistant
Enterobacteriaceae during selective digestive tract
decontamination in intensive care units*

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ABSTRACT

Objectives: Prevalences of cephalosporin-resistant Enterobacteriaceae are increasing globally, especially in Intensive Care Units (ICU). The effect of Selective Digestive tract Decontamination (SDD) on eradication of cephalosporin-resistant Enterobacteriaceae from the intestinal tract is unknown. We quantified eradication rates of cephalosporin-resistant and cephalosporin-susceptible Enterobacteriaceae during SDD in patients participating in a 13-center cluster randomized study and from a single-center cohort.

Methods: All SDD-patients colonized with Enterobacteriaceae in the intestinal tract at ICU-admission were included. Cephalosporin resistance was defined as resistance to ceftazidime, cefotaxim or ceftriaxone and aminoglycoside resistance as resistance to tobramycin or gentamicin. Duration of rectal colonization was determined by screening twice weekly during ICU-stay. Swabs were inoculated on selective media supplemented with tobramycin or cefotaxime.

Results: 507 (17%) of 2,959 SDD-patients with >1 rectal sample were colonized with Enterobacteriaceae at ICU-admission: 77 (15%) with cephalosporin-resistant Enterobacteriaceae and 50 (10%) with aminoglycoside-resistant Enterobacteriaceae. Fifty-six (73%) patients colonized with cephalosporin-resistant Enterobacteriaceae were successfully decontaminated before ICU-discharge, as were 343 (80%) patients colonized with cephalosporin-susceptible Enterobacteriaceae ($p=0.17$). For aminoglycoside-resistance, 31 (62%) patients were decontaminated, as were 368 patients (81%) colonized with aminoglycoside-susceptible Enterobacteriaceae ($p<0.01$). Decolonization was demonstrated after, on average, 4 days if colonized with cephalosporin-susceptible Enterobacteriaceae and aminoglycoside-susceptible Enterobacteriaceae and 5 days if colonized with cephalosporin-resistant Enterobacteriaceae and aminoglycoside-resistant Enterobacteriaceae (logrank test $p=0.053$ for cephalosporin resistance and $p=0.03$ for aminoglycoside resistance). If eradication failed, no associations were found with increased resistance in time ($p>0.05$ for all comparisons).

Conclusions: SDD can successfully eradicate cephalosporin-resistant Enterobacteriaceae from the intestinal tract.

INTRODUCTION

Over the last decade, the epidemiology of antibiotic resistance in Intensive Care Units (ICU) is changing rapidly. Especially the global emergence of (multi-) resistant Gram-negative bacteria (GNB) is worrisome. After the finding of mobile genetic elements conferring resistance to most cephalosporins (Extended spectrum β -lactamases (ESBL)) in the 1980s,¹ GNB are now capable of producing carbapenemases able to hydrolyse carbapenems. As the antibiotic pipeline is virtually empty,² infection prevention is becoming increasingly important, especially in ICU-medicine.

Selective decontamination of the digestive tract (SDD) is a preventive antibiotic strategy aiming to eradicate so-called potential pathogenic micro-organisms (PPMO), such as Enterobacteriaceae, colonizing the respiratory and intestinal tract. SDD consists of topical antibiotics applied in the oropharynx and intestinal tract every six hours throughout ICU-stay and of systemic prophylaxis, usually cefotaxime, which is administered during the first four days after ICU-admission. In Dutch ICUs, SDD was associated with a 13% reduction in day-28 mortality and with a 38% reduction in acquisition with antibiotic-resistant GNB in the respiratory tract, including cephalosporin-resistant Enterobacteriaceae, as compared to standard care.^{3,4} In another study, also from the Netherlands, acquisition rates of cephalosporin-resistant Enterobacteriaceae in the intestinal tract were similarly low in patients receiving and not receiving SDD.⁵ Furthermore, SDD has been successfully used to control an outbreak with multi-resistant Enterobacteriaceae colonizing the intestinal tract in ICU-patients in France.⁶ Moreover, successful eradication of intestinal carriage with Gram-negative bacteria during SDD was associated with lower rates of ICU-acquired bacteremia.⁷ Nevertheless, there is hardly any data on the effects of SDD on eradication of cephalosporin-resistant Enterobacteriaceae from the intestinal tract. Most cephalosporin-resistant Enterobacteriaceae are *in vitro* susceptible to colistin and many are still susceptible to tobramycin. Effective eradication of intestinal carriage with cephalosporin-resistant Enterobacteriaceae could, therefore, reduce both cephalosporin-resistant Enterobacteriaceae colonization pressure in the unit and the risk of ICU-acquired bacteremia for the individual patient. Yet, controversy exists whether SDD can be applied safely to patients colonized with cephalosporin-resistant Enterobacteriaceae in terms of prolonged carriage and cumulating antibiotic resistance as compared to carriage with susceptible Enterobacteriaceae. We, therefore, quantified eradication rates of cephalosporin susceptible and resistant Enterobacteriaceae during SDD.

METHODS

We used rectal culture results from all patients receiving SDD in a Dutch cluster-randomized study comparing SDD to Selective Oropharyngeal Decontamination (SOD) and standard care (i.e. no SDD/SOD) in 13 ICUs from 2004-2006.⁴ In addition, from one participating hospital, data from 19 extra months of SDD use was added from all SDD-patients admitted to ICU

from Jan 2008 until Aug 2009. All patients with an expected length of ICU-stay of >48h were eligible to participate in the trial. The SDD-regimen has been described previously.^{4,5} In short, it consisted of oropharyngeal application of a paste containing colistin, tobramycin and amphotericin B each in a 2% concentration and administration of a 10 ml suspension containing 100 mg colistin, 80 mg tobramycin and 500 mg amphotericin B via a nasogastric tube. Topical antibiotics were applied four times daily until ICU-discharge. In addition, cefotaxime (1000 mg, every 6 h) was administered intravenously during the first four days of study. Rectal carriage with Enterobacteriaceae was determined at admission and twice weekly during ICU-stay. For the present analysis we included all SDD-patients with at least two rectal culture results and with the first sample obtained <2 days in ICU. If colonization with Enterobacteriaceae was present at ICU-admission antimicrobial susceptibility was determined for ceftazidime, cefotaxime and ceftriaxone and isolates being resistant or intermediate resistant (MIC>8mg/L) for any of these agents were considered to be cephalosporin-resistant Enterobacteriaceae. In addition, resistance or intermediate resistance to either tobramycin or gentamicin was determined (MIC>4mg/L) and if present the isolate was considered to be resistant to aminoglycosides. The duration of the first episode of colonization was determined for all patients. Decolonization was defined as two consecutive cultures without growth of the particular colonization defining bacteria. A single negative culture (or a single positive result with another bacterial species) in between two positive cultures was not considered as decolonization. A patient was considered to be colonized with a certain Gram-negative species at discharge if the last culture obtained in ICU grew that particular species. A detailed microbiological methods description can be found in the supplementary data. χ^2 Test was used to test for significant differences. A p-value <0.05 was used to denote statistical significance. Kaplan-Meier analysis was performed to determine differences in colonization duration. Patients were censored when decontamination occurred or when discharged from the ICU. Data were analyzed with SPSS version 15.0 (SPSS, Chicago, IL) and GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, Calif, USA) was used.

RESULTS

In all, 3,187 patients received SDD; at least one rectal sample was obtained from 2,959 patients and 507 were colonized with Enterobacteriaceae at ICU-admission and had at least one follow-up rectal culture result. Of these 507 patients, 77 (15%) were colonized with cephalosporin-resistant Enterobacteriaceae and 50 (10%) with aminoglycoside-resistant Enterobacteriaceae on ICU-admission. Co-resistance occurred in 25 patients (5%). Fifty-six (73%) of the patients colonized with cephalosporin-resistant Enterobacteriaceae were successfully decontaminated before ICU-discharge, as were 343 (80%) of the patients colonized with non-cephalosporin resistant Enterobacteriaceae (p=0.17) (table 1).

	Total	Cephalosporin S	Cephalosporin R	Tobramycin S	Tobramycin R
N patients colonized at ICU-admission	507	430 (85%)	77 (15%)	457 (90%)	50 (10%)
N decontaminated patients	399 (79%)	343 (80%)	56 (73%) ^a	368 (81%)	31 (62%) ^b
Median duration of colonization (days)	4 (2-60; IQR 4)	4 (2-30; IQR 3)	5 (2-60; IQR 5)	4 (2-26; IQR 4)	5.5 (3-60; IQR 5)
Median duration of ICU-stay (days)	11 (3-134; IQR 11)	10 (3-134; IQR 11)	12 (3-77; IQR 10)	11 (3-134; IQR 11)	11.5 (4-82; IQR 9.5)
Median duration of ICU-stay for decontaminated patients (days)	12 (3-134; IQR 13)	12 (4-134; IQR 13)	13 (3-77; IQR 11)	12 (3-134; IQR 13)	12 (4-82; IQR 8)

Table 1

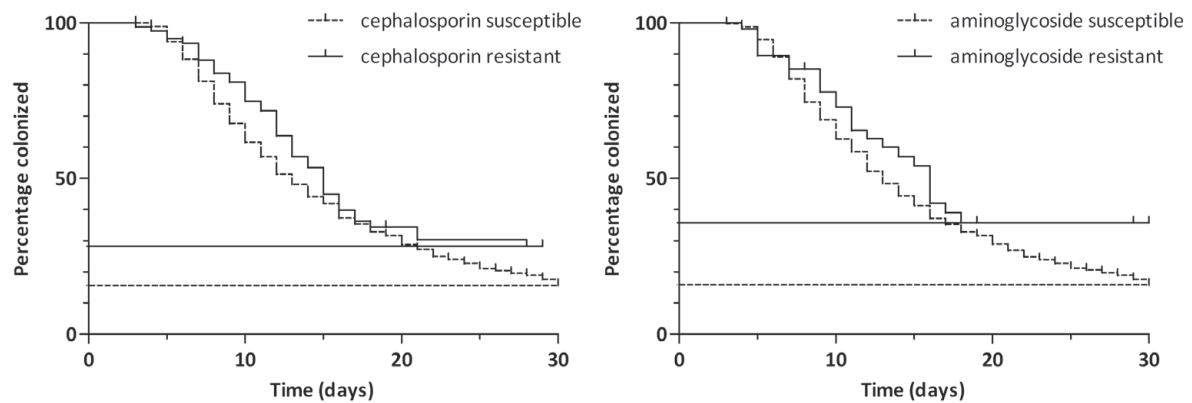
Eradication of cephalosporin and tobramycin resistant Enterobacteriaceae from the intestinal tract using selective decontamination of the digestive tract. Resistance or intermediate resistance to either ceftazidime, cefotaxime or ceftriaxone was used as a marker for cephalosporin resistance.

S, susceptible; R, resistant; ICU, Intensive Care Units; IQR, Interquartile range

^a p value > 0.05 resistant vs non-resistant Enterobacteriaceae

^b p value < 0.05 resistant vs non-resistant Enterobacteriaceae

Among those 50 patients with aminoglycoside resistance 31 (62%) were decontaminated, as were 368 patients (81%) with tobramycin-susceptible Enterobacteriaceae ($p < 0.01$). Decolonization was demonstrated after, on average, 4 days in ICU if colonized with non-cephalosporin resistant Enterobacteriaceae and aminoglycoside-susceptible Enterobacteriaceae and after 5 days if colonized with Enterobacteriaceae resistant to a cephalosporin or aminoglycoside (logrank test for cephalosporin-resistant Enterobacteriaceae $p = 0.053$ and for tobramycin resistance $p = 0.03$) (Figure 1). *Escherichia coli* was the most prevalent species among patients with non-cephalosporin resistant Enterobacteriaceae carriage (78%), but accounted for only 27% of the species among cephalosporin resistant Enterobacteriaceae-colonized patients. In these patients *Enterobacter* spp were most prevalent (43%) (table S1). Eradication was not achieved in 108 patients (21%). To investigate the occurrence of cumulating antibiotic resistance during persistent colonization, resistance to ciprofloxacin, cephalosporins, aminoglycosides and carbapenems (imipenem or meropenem) was determined in the first and in the last culture obtained in ICU from these 108 patients; colonization was demonstrated on admission and discharge in 24 (22%) and 21 (19%) patients, respectively, for ciprofloxacin-resistant Enterobacteriaceae, in 20 (19%) and 23 (21%) patients, respectively, for aminoglycosides, and in 7 (6%) and 9 patients (8%), respectively, for carbapenems. Cephalosporin-resistant Enterobacteriaceae were present in 25 (23%) admission cultures as compared to 24 (22%) discharge cultures. Resistance to >1 of these antibiotic classes in the first and last culture was detectable in 23 (21%) and 24 (22%) patients on admission and discharge, respectively. None of these differences between admission and discharge prevalence were statistically significant (p -values all ≥ 0.6) (table S2).



Day	0	10	20	30	0	10	20	30
Patients at risk S	430	35	4	1	457	41	5	0
Patients at risk R	77	18	5	2	50	12	4	3

Figure 1 Eradication in time for cephalosporin (i.e. ceftazidime, cefotaxime or ceftriaxone) and aminoglycoside (i.e. tobramycin or gentamicin) susceptible and resistant Enterobacteriaceae.

p - value for cephalosporin resistance: 0.05 (Logrank test)

p - value for tobramycin resistance: 0.03 (Logrank test)

DISCUSSION

In this nested post-hoc analysis of a cluster-randomized study supplemented with single center data, SDD appeared to be equally effective in eradicating intestinal carriage of cephalosporin-resistant and cephalosporin-susceptible Enterobacteriaceae, with an average time to eradication of five days and with successful eradication in 80% and 73% of the patients, respectively. Yet, for aminoglycoside-resistant Enterobacteriaceae eradication rates were lower than for susceptible isolates, though the majority of patients were successfully decontaminated in ICU during SDD (62% vs 81% respectively). If eradication failed, no associations were found with increased resistance in time.

We used ceftazidime, cefotaxim and ceftriaxone as marker antibiotics to classify cephalosporin-resistant Enterobacteriaceae. These marker antibiotics can be considered as a proxy for ESBL-production in Enterobacteriaceae. Unfortunately ESBL-production was not confirmed during the period of study to distinguish ESBL-producing Enterobacteriaceae from non-ESBL producing Enterobacteriaceae.

In the analysis we did not take into account the intravenously administered antibiotics as a separate factor as we considered the high intraluminal concentrations of the topical antibiotics to be the most important factor to decontaminate colonized patients. In addition, part of the SDD-regimen is the four-day course of cefotaxime which all patients received. Furthermore, most of the systemic antibiotics with activity against cephalosporin-resistant Enterobacteriaceae are excreted via the kidneys, therefore hardly influencing intestinal decontamination rates.^{8,9} None of the patients received tigecycline, which is mostly excreted in bile, affecting the intestinal flora.¹⁰ Similar rates of effectiveness have been reported from other, though, much smaller studies in specific patient populations. In a paediatric ICU, 23 of 1,101 children (2.1%) were intestinal ESBL-carriers at some point during ICU-admission and received SDD.¹¹ The overall decontamination rate was 54% however no rate was provided for intestinal ESBL-carriage only. In another study all patients detected as ESBL-carriers between 2000 and 2008 received an SDD regimen containing chlorhexidine mouth rinse and oral paramomycin for intestinal decolonization. Of the 18 patients that completed the SDD-strategy, carriage was effectively eradicated in 15 (83%).¹²

The strength of the present study is the size of the study population with 3,187 SDD-patients, all subjected to the same screening schedule. Limitations include the absence of a control population not receiving SDD and the lack of detailed specific patient information to investigate determinants associated with failure of eradication.

Our findings demonstrate successful intestinal decontamination of cephalosporin-resistant Enterobacteriaceae, which may reduce both cross-transmission and infection rates. Failure of eradication was not associated with increased resistance during ICU-stay. In view of the global increase of infections caused by ESBL-producing and carbapenamase-producing bacteria, this approach deserves careful evaluation using stringent surveillance policies to monitor ecological safety.

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SUPPLEMENTARY DATA

Microbiological methods

Rectal samples, obtained as part of SDD, were inoculated onto MacConkey agar supplemented with tobramycin and cefotaxime and grown for 48 hours at 37°C. If growth was detected automated determination and susceptibility testing was performed according to standard laboratory procedures. Species identification and susceptibility testing of GNB was performed using automated laboratory systems; Phoenix (Becton Dickinson and Co, Sparks, MD, USA) or Vitek-2 (bioMérieux S.A. Marcy-l'Etoile, France).

Species	Cephalosporin susceptible	Cephalosporin resistant
<i>Escherichia coli</i>	376 (78%)	22 (27%)
<i>Klebsiella</i> spp	44 (9%)	6 (7%)
<i>Enterobacter</i> spp	11 (2%)	35 (43%)
<i>Proteus</i> spp	31 (6%)	0 (0%)
<i>Citrobacter</i> spp	16 (3%)	12 (15%)
Other	7 (1%)	6 (7%)

Table S1 Species

Number of positive cultures per species during the period of study with susceptibility for or resistance to cephalosporins (ceftazidime, cefotaxime or ceftriaxone)

Patients not decontaminated	108 patients (21%)		
	First culture	Last culture	P value
Ciprofloxacin resistant	24 (22%)	21 (19%)	0.62
Cephalosporin resistant	25 (23%)	24 (22%)	0.87
Aminoglycoside resistant	20 (19%)	23 (21%)	0.61
Carbapenem resistant	7 (6%)	9 (8%)	0.61
Multiresistant > 1 class	23 (21%)	24 (22%)	0.87

Table S2 Resistance in time for patients who are not successfully decontaminated during selective digestive tract decontamination. Multiresistance is present if a micro-organism is resistant to at least two of the antibiotic classes aminoglycosides, carbapenems, cephalosporins or to ciprofloxacin.

Chapter 10

*The role of intestinal colonization with gram-negative
bacteria as a source for intensive care unit-acquired
bacteremia*

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ABSTRACT

Objective: Selective Digestive Tract Decontamination (SDD) aims to eradicate GNB in both the intestinal tract and respiratory tract, and is combined with a 4-day course of intravenous cefotaxime. Selective Oropharyngeal Decontamination (SOD) only aims to eradicate respiratory tract colonization. In a recent study, SDD and SOD were associated with lower day-28 mortality, when compared to standard care (SC). Furthermore SDD was associated with a lower incidence of ICU-acquired bacteremia caused by gram-negative bacteria (GNB). We quantified the role of intestinal tract carriage with GNB and ICU-acquired GNB bacteremia.

Design: Data from a cluster-randomized and a single-center observational study.

Setting: ICUs in the Netherlands.

Patients: Patients with ICU-stay of >48 hours that received SDD (n=2,667), SOD (n=2,166) or SC (n=1,945).

Interventions: SDD or SOD.

Measurements and Main Results: Incidence densities (ID) (episodes/1,000 days) of ICU-acquired GNB bacteremia were 4.5, 3.0 and 1.4 during SC, SOD and SDD, respectively, and the daily risk for developing ICU-acquired GNB bacteremia increased until day 36, 33 and 31 for SDD, SC and SOD, and was always lowest during SDD. Rectal colonization with GNB was present in 26% and 71% of patient days during SDD and SOD, respectively ($p < 0.01$). Irrespective of interventions, ID of ICU-acquired GNB bacteremia was 4.5 during patient days with both intestinal and respiratory tract GNB carriage. This ID reduced with 33% (to 3.1) during days with intestinal GNB carriage only and with another 45% (to 1.0) during days without GNB carriage at both sites.

Conclusions: Respiratory tract decolonization was associated with a 33% and intestinal tract decolonization was associated with a 45% reduction in the occurrence of ICU-acquired GNB bacteremia.

INTRODUCTION

Intensive care unit (ICU)-acquired infections are important complications of the treatment of critically ill patients in ICU (1). Gram negative bacteria (GNB) cause approximately 30% of all episodes of ICU-acquired bacteremia (2), and they have been associated with increased morbidity and mortality (3). Although intestinal colonization with GNB has frequently been considered an important source for ICU-acquired bacteraemia (4), its role has, to the best of our knowledge, never been quantified.

Selective Decontamination of the Digestive tract (SDD) has been proposed as an infection prevention measure for patients in ICU (5). SDD consists of a mixture of topical non-absorbable antibiotics (usually colistin, tobramycin and amphotericin B) applied in the oropharynx and gastrointestinal tract, combined with systemic prophylaxis (usually cefotaxime) during the first four days of ICU-stay. The combination of topical antibiotics administered throughout ICU-stay aims to reduce the incidence of ICU-acquired infections by eradicating colonization with GNB (and *Staphylococcus aureus* and yeasts) both in the oropharynx and the gastro-intestinal tract (6). An alternative to SDD is Selective Oropharyngeal Decontamination (SOD), in which only decontamination of the oropharynx is pursued, by application of the same mouth paste as used in SDD, but without eradicating intestinal colonization and without systemic prophylaxis (7).

In a Dutch multi-center cluster-randomized study, including 5939 patients, both SDD and SOD were, as compared to standard care, associated with an almost equal reduction in day-28 mortality (8). An important difference between SDD and SOD, though, was the reduction in the cumulative incidence of ICU-acquired bacteremia during SDD, which was most apparent for Enterobacteriaceae with odds ratios during SDD of 0.28 (95%CI 0.16–0.47) and 0.19 (95%CI 0.12–0.32) as compared to SOD and standard care, respectively (8).

The differences between SDD and SOD are the systemic prophylaxis with cefotaxime during the first four days in ICU for all patients and intestinal decontamination, both applied during SDD. Of note, during SOD many patients receive intravenous antibiotics during the first four days in ICU for therapeutic reasons. We, therefore, hypothesized that eradication of GNB from the intestinal tract is the cause of the observed reduction in ICU-acquired GNB-bacteremia incidence and aimed to quantify this association.

MATERIAL AND METHODS

Setting, design and population

We used the clinical and microbiological data from the Dutch multi-center cluster-randomized study comparing SDD to SOD and standard care (SC) (8). In addition, we prospectively studied all patients admitted between Aug 2008 and March 2010 to the ICU of the UMC Utrecht, a 1,042 bed tertiary care center in the Netherlands. During this period all adult patients with an expected

length of ICU-stay >48 hours received SDD from Aug 2008 until Aug 2009 and SOD from Sep 2009 until March 2010. Patients that received SDD or SOD in 13 centers of the multi-center study are referred to as cohort-1 (SDD-C1 or SOD-C1) and those that received SDD or SOD in the UMC Utrecht between Aug 2008 and March 2010 are referred to as cohort-2 (SDD-C2 or SOD-C2). In both cohorts data were collected anonymously and the need for informed consent was waived by the local Institutional Review Boards.

The SDD-regimen was identical in both cohorts and has been described previously (8). In short, it consisted of oropharyngeal application of a paste containing colistin, tobramycin and amphotericin B each in a 2% concentration and administration of a 10 ml suspension containing 100 mg colistin, 80 mg tobramycin and 500 mg amphotericin B via a nasogastric tube. Topical antibiotics were applied four times daily until ICU-discharge. In addition, cefotaxime (1000 mg, every 6 h) was administered intravenously during the first four days of study. SOD consisted of the oropharyngeal application of the same paste as used during SDD.

Microbiological methods

From all patients receiving SDD (C1 and C2) and for all SOD-patients from cohort-2, rectal colonization with Enterobacteriaceae or glucose-nonfermenting gram-negative rods (e.g. *P. aeruginosa*) was determined (hereafter referred to as colonization with GNB) by obtaining rectal swabs on admission and twice weekly during ICU-stay. To detect the presence of GNB, for both cohorts rectal swabs were inoculated onto McConkey-agar plates and bloodagar plates, both without antibiotics and grown for 48 hours at 37°C. Isolates from rectal samples and blood cultures were further determined using standard microbiological techniques and 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. Blood cultures obtained for clinical practice were processed according to current clinical practice.

Bacterial colonization and bacteremia with GNB

Rectal colonization with GNB was defined as the isolation of Enterobacteriaceae or glucose-nonfermenting gram-negative rods from a rectal swab. For every SDD-patient (C1 and C2) and for every SOD-patient in cohort-2, the presence of intestinal colonization with GNB was determined for every day in ICU. A colonization period started and ended at midpoint between two consecutive cultures. Colonization ended when a GNB culture result was followed by two consecutive culture results negative for GNB. Correspondingly, in case of a single negative culture for GNB in between two positive cultures, the patient was considered colonized throughout the time period that the three samples had been obtained. If the first culture after ICU-admission grew GNB, the patient was considered to be colonized at ICU-admission. If the last culture obtained in ICU grew GNB, the patient was considered colonized until ICU-discharge. Based on these

definitions, we labelled all patient days as “with” and “without” intestinal GNB colonization. Intestinal colonization could not be determined during SC and SOD-C1.

ICU-acquired bacteremia with GNB was defined as bacteremia occurring at least 48 hours after ICU-admission with growth of either Enterobacteriaceae or glucose-nonfermenting gram-negative rods, without documented bacteremia with the same specie in the first 48 hours of ICU admission. The sampling date of the first positive blood culture was defined as the onset of the bacteremia. Blood sampling was not protocolized and performed when infection was suspected on clinical grounds. ICU-acquired GNB bacteremia was considered “colonized” if bacteremia occurred on a patient-day with intestinal GNB colonization and “non-colonized” if it occurred on a day without intestinal GNB colonization. In the analyses on the effect of intestinal colonization on ICU-acquired GNB bacteremia during SDD, only data from patients with at least one rectal sample analyzed were included.

Analysis

In the analysis, data were pooled for both SDD cohort 1 and 2 and for SOD cohort 1 and 2 (SDD_{total} and SOD_{total}). Incidence densities of ICU-acquired GNB bacteremia were calculated per 1,000 patient-days at risk for SC and SOD_{total} , and for patient-days at risk “with” and “without” intestinal GNB colonization during SDD_{total} . Incidence densities were compared using rate ratios (RRs) with 95% confidence interval (95%CI). Non-parametric data were expressed as median (interquartile range) and the Kruskal-Wallis test was used to test for significant differences. For dichotomous variables the χ^2 test was used. A p-value <0.05 was considered to denote statistical significance and all reported p-values are two-sided.

The Nelson-Aalen method with bacteremia as a time-dependent explanatory variable was used to determine the daily hazard rate for ICU-bacteremia. This is a nonparametric method to estimate the hazard from the cumulative hazard by applying a kernel smoother to the increments (9). The hazard rate is the rate of failure, i.e. rate of bacteremia, in the next day among the remaining ‘at risk’ individuals (10). Patients were censored when discharged or after the first episode of GNB bacteremia. By using hazard plots, both the rate changes over time as well as the magnitude of the failure rate are visualized.

We used a Cox proportional hazard model with colonization status per day as a time-dependent variable to evaluate intestinal colonization as risk factor for ICU-acquired GNB bacteremia allowing for censoring because of ICU-discharge or ICU-mortality. By using a Cox-model, we can determine the rate of ICU-acquired bacteremia in time instead of the cumulative incidence (11). Data were analyzed with SPSS version 12.0 (SPSS, Chicago, IL), GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, Calif, USA) and R version 2.10.1.

RESULTS

In all, 6,778 patients were included; 1,945 in SC (26824 patient-days), 1,853 in SOD-C1 (25,006 patient-days), 1989 in SDD-C1 (26,982 patient-days), 313 in SOD-C2 (3,487 patient-days) and 678 in SDD-C2 (8,412 patient-days). Pooling of the two SOD cohorts (SOD-1 and SOD-2) and the two SDD cohorts (SDD-1 and SDD-2) resulted in a cohort of 2,166 patients with SOD (28,575 patient-days, SOD_{total}) and a cohort of 2,667 patients with SDD (35,394 patient-days, SDD_{total}) (Table 1). Cumulative incidences of ICU-acquired GNB bacteremia were 6.2% (n=121), 4.0% (n=86) and 1.9% (n=52) during SC, SOD_{total} and during SDD_{total}, respectively ($p < 0.001$ for all comparisons). This corresponds to incidence densities of 4.51, 3.01 and 1.43 per 1,000 patient days for SC, SOD_{total} and SDD_{total}, respectively. Rate ratios for the occurrence of ICU-acquired GNB bacteremia were 3.07 (95%CI 2.22 – 4.25) for SDD_{total} vs SC, 2.09 (95%CI 1.48 – 2.95) for SDD_{total} vs SOD_{total} and 1.50 (95%CI 1.14 – 1.98) for SOD_{total} vs SC.

The daily risk for developing ICU-acquired GNB bacteremia increased until day 36, 33 and 31 for SDD_{total}, SC and SOD_{total}, with highest hazard rates per day of 0.0026, 0.0075 and 0.0065 for SDD_{total}, SC and SOD_{total}, respectively (Figure 1). The daily hazard for ICU-acquired GNB bacteremia during SDD_{total} never exceeded the daily risks of SC and SOD_{total}.

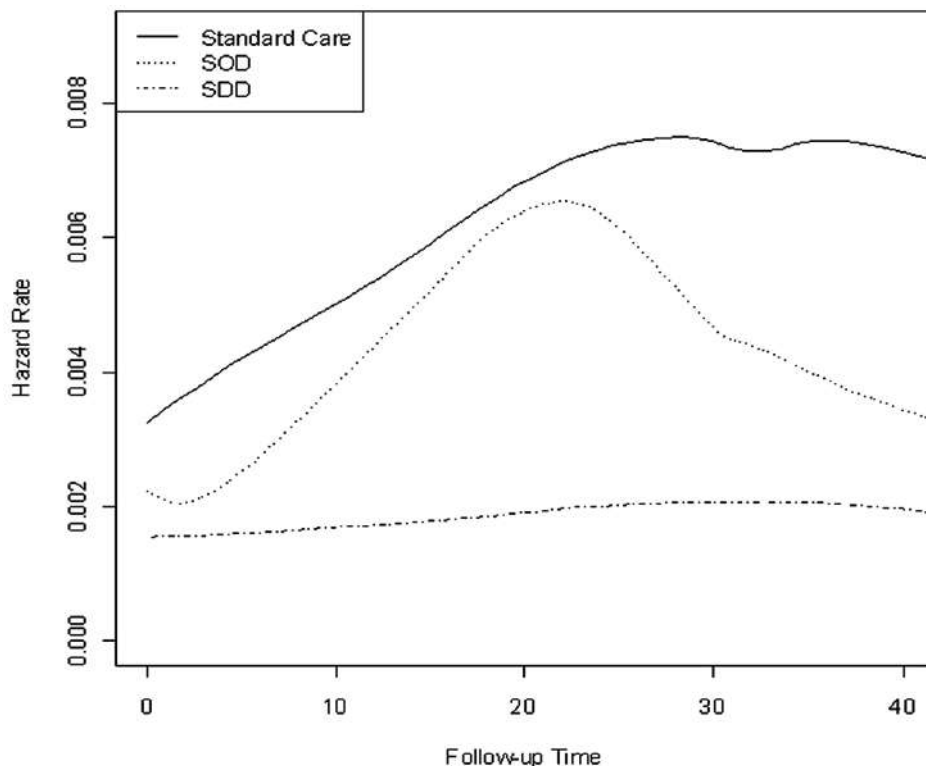


Figure 1: Hazard rate per day for ICU-acquired bacteremia during ICU-stay and number of patients at risk at day 1, 20 and 40. SOD, Selective Oropharyngeal Decontamination; SDD, Selective Decontamination of the Digestive tract; ICU, Intensive Care Unit

At least one rectal sample culture result was available from 2,476 patients (93%) receiving SDD (94% from SDD-C1 and 89% from SDD-C2) and from 259 patients (83%) during SOD-2 (table 1). During SDD, 1,134 (46%) patients had at least one episode of rectal GNB colonization during ICU stay, as compared to 219 (83%) patients during SOD ($p < 0.001$). GNB rectal colonization was present in 8,961 (26%) of all patient-days during SDD_{total} as compared to 2,242 patients-days (71%) during SOD-C2 ($p < 0.001$), and proportions of patients colonized were lower throughout ICU-stay during SDD than during SOD (Figure 2). During SDD, ICU-acquired GNB bacteremia rates were 3.01 and 1.00 per 1,000 patient days for the periods with and without intestinal GNB colonization (rate ratio 3.02 (95%CI 1.75 – 5.20)). In the Cox proportional hazard model, presence of intestinal colonization with GNB was associated with the occurrence of ICU-acquired GNB bacteremia (hazard ratio 2.49; 95% CI 1.29 – 4.80). The median onset of ICU-acquired GNB bacteremia with and without intestinal GNB colonization was day 13 (IQR 15) and day 12 (IQR 14) respectively ($p = 0.7$).

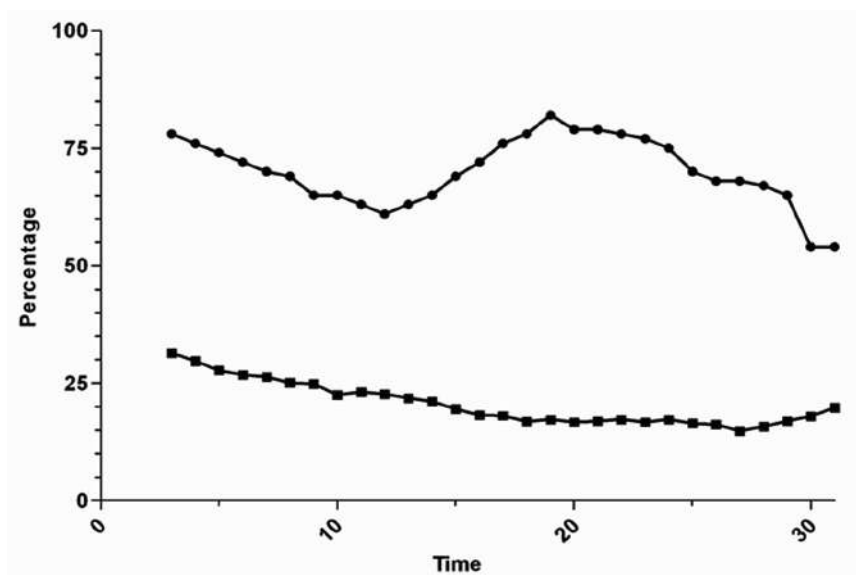
	SC	SOD _{tot}	SDD _{tot}
N patients	1945	2166	2667
Patient-days	26824	28575	35394
N GNB bacteremia	121	86	52
<i>Percentage</i>	(6.2%)	(4.0%)	(1.9%)
<i>95% CI</i>	(5.13 – 7.27)	(3.15 – 4.79)	(1.43 – 2.47)
Median onset (IQR)	10 (11)	13 (15.25)	13 (14)
Incidence density	4.51	3.01	1.43
N patients \geq 1 rectal sample		259	2476
N patients \geq 1 episode of rectal colonization		219 (83%)	1134 (46%)
N Patient days at risk		3163	34011
N Rectal colonization days		2242 (71%)	8961 (26%)
N No rectal colonization days		921 (29%)	25049 (74%)

Table 1

Incidence densities and rate ratios of ICU-acquired GNB bacteremia during Standard Care-, SOD- periods and SDD periods during cohort-1 and cohort-2 (SOD_{tot}, SDD_{tot}). Number of patients and patient-days with GNB colonization during SOD₂ and SDD_{tot}. Median onset in days after ICU-admission.

SC, Standard Care; SOD, Selective Oropharyngeal Decontamination; SDD, Selective Decontamination of the Digestive tract

RR, rate ratio; 95% CI, 95% confidence interval; IQR, interquartile range; SOD₂, SOD period during cohort-2



Day	1	10	20	30
SOD-2	259	103	29	13
SDD-total	2490	1110	450	217

Figure 2: Proportion of SDD-patients and SOD-patients colonized throughout ICU-stay and number of patients at risk at specific time points during SDD cohort-1 and 2 (■); SOD cohort-2 (●) SOD, Selective Oropharyngeal Decontamination; SDD, Selective Decontamination of the Digestive tract; ICU, Intensive Care Unit

Eight patients out of 52 (15%), five colonized and three non-colonized, had ICU-acquired GNB bacteremia within the first four days of ICU-admission. In time, incidence densities of ICU-acquired GNB bacteremia ranged from 0.82 (for non-colonized patient days during SDD) to 3.22 (for SC) per 1,000 patient days during the first ten days in ICU, and then clearly diverged with the lowest rates for non-colonized patient days during SDD_{total} (1.11 and 1.95 between days 10-20 and 20-30, respectively) and with comparable rates during SC, SOD_{total} and for colonized patient days during SDD (ranging from 7.06 and 9.77) (Figure 3).

P. aeruginosa was the most frequent cause of bacteremia during SDD (n = 16; 31%) (table 2). Twenty (38%) of 52 episodes of GNB bacteremia were preceded by rectal colonization with the same species in the week preceding the bacteremia, most frequently being *P. aeruginosa* (n = 7; 35%). Twenty out of 27 (74%) episodes of ICU-acquired GNB bacteremia occurring during colonized patient-days were preceded by rectal colonization with the same pathogen, as were seven out of 25 (28%) episodes occurring during non-colonized patient-days in SDD. In 13 SDD-patients (25%) with GNB bacteremia, no intestinal colonization was detected throughout ICU stay.

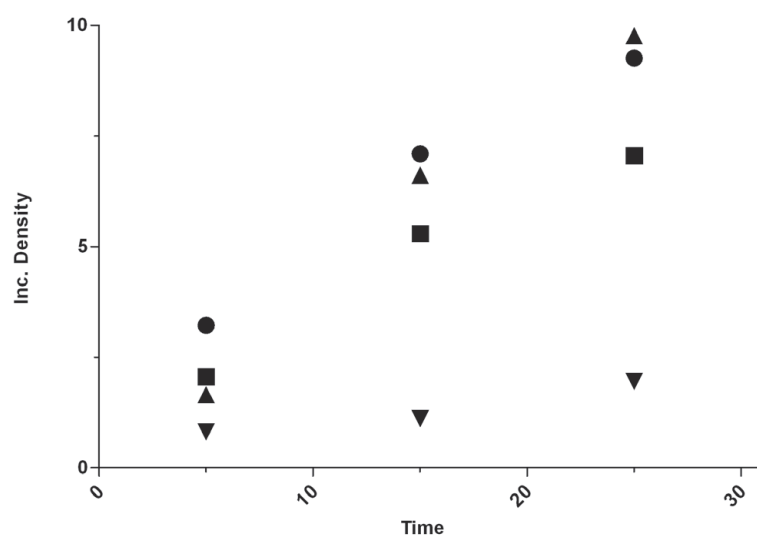


Figure 3:
Incidence densities for ICU-acquired GNB bacteremia per 10 days
(●) Standard Care; (■) SOD_{total}; (▲) SDD_{total} colonized bacteremia; (▼) SDD_{total} non-colonized bacteremia
SOD, Selective Oropharyngeal Decontamination; SDD, Selective Decontamination of the Digestive tract;
ICU, Intensive Care Unit; GNB, Gram-negative bacteria

	SC	SOD _{tot}	SDD _{tot} ICU-bacteremia	SDD _{tot} Prior colonized same species
Episodes	121	86	52	20
<i>P. aeruginosa</i>	25 (21%)	14 (16%)	16 (31%) [#]	7 (35%)
<i>Klebsiella</i> spp	14 (12%)	12 (14%) [#]	6 (12%)*	3 (15%)
<i>E. cloacae</i>	20 (17%)	16 (19%) ^{#†}	8 (15%)	2 (10%)
<i>S. marcescens</i>	5 (4%)	10 (12%)	8 (15%) [#]	4 (20%)
<i>E. coli</i>	27 (22%)	24 (28%) [†]	3 (6%)	2 (10%)
Other species	30 (25%)	13 (15%)*	13 (25%)*	2 (10%)

Table 2
Causative pathogens in ICU-acquired bacteremia during Standard Care, SOD cohort- 1 and cohort- 2 (SOD_{tot}) and SDD cohort-1 and cohort-2 (SDD_{tot}); number of SDD-patients that were colonized in the intestinal tract the week preceding an ICU-acquired bacteremia with the same pathogen (*prior colonized same species*). Number (percent)

SC, Standard Care; SOD, Selective Oropharyngeal Decontamination; SDD, Selective Decontamination of the Digestive tract; ICU, Intensive Care Unit

* Polymicrobial episode 1; # Polymicrobial episode 2; † Polymicrobial episode 3

Respiratory tract colonization with GNB occurred equally frequent among patients with ICU-acquired GNB bacteremia receiving SOD and SDD; 76% of 86 SOD-patients and 67% of 52 SDD-patients ($p = 0.32$) with ICU-acquired bacteremia had at least one episode of respiratory tract colonization with GNB during ICU-stay. Respiratory tract colonization with GNB before onset of bacteremia - with an identical pathogen - was demonstrated in 41% ($n=35$) and 44% ($n = 23$) of SOD and SDD patients, respectively ($p = 1.0$).

In order to quantify the relative roles of intestinal and respiratory tract colonization with GNB for the occurrence of ICU-acquired GNB bacteremia two approaches were used. The most conservative approach is based on the preventive effect of SDD and SOD on GNB bacteremia. Without any selective decontamination regimen, as during SC, the incidence density of ICU-acquired GNB bacteremia was 4.5/1,000 patient days. During SOD and SDD IDs were reduced to 3.0 and 1.4/1,000 patient days, respectively, corresponding to a reduction of 33% by applying oropharyngeal paste and of an additional reduction of 36% by adding SDD-suspension to the SOD-regimen.

The second approach was based, as much as possible, on the actual colonization status of patients. As we could not determine patient days with and without intestinal colonization during SC and patient days with and without respiratory tract colonization in all three study groups some assumptions were needed. Without modulation of the intestinal and respiratory tract flora, as in SC, the incidence density of ICU-acquired GNB bacteremia was 4.5/1,000 patient days. With effective intestinal decontamination (as in 74% of patient days during SDD) and presumed effective respiratory tract decolonization (as observed in >80% of patients with SDD and SOD), the incidence density was 1.0, a reduction of 78%. SDD and SOD equally affect respiratory tract colonization with GNB, and in the presence of intestinal tract colonization with GNB the incidence density of ICU-acquired GNB bacteremia was 3.0/1,000 patient-days in SDD and SOD patients. The 33% incidence density reduction from 4.5 (no modulation) to 3.0 (only modulation of the respiratory tract) can, therefore, only result from respiratory tract decolonization, which suggests that this accounted for 33% of all episodes. As a result, the remaining 45% of the episodes can be attributed to intestinal colonization.

All analyses have also been performed for the cohorts separately (SDD-C1 and SDD-C2; SOD-C1 and SOD-C2), but this did not change interpretation (data not shown).

DISCUSSION

We have demonstrated that intestinal decontamination of GNB was associated with a three-fold reduction in ICU-acquired GNB bacteremia. This reduction was demonstrated among large patient populations receiving either SDD (with intestinal application of non-absorbable antibiotics) or regimens without intestinal decontamination, as well as by demonstration of a similar reduction among patients receiving SDD in which intestinal decontamination had or had not been achieved. Together with the documented similarity in respiratory tract colonization rates among patients with SDD and SOD that developed ICU-acquired bacteremia, the absence of intestinal decolonization during SOD, and the fact that 85% of episodes of ICU-acquired GNB bacteremia occurred after four days in ICU, we estimate that intestinal carriage of GNB is responsible for at least 36% of all episodes of ICU-acquired GNB bacteremia, and that most of these episodes can be prevented. Considering the global emergence of antibiotic-resistant

GNB and the high incidences of ICU-acquired bacteremia intestinal decontamination offers an important target for infection control measures.

In the present study, 38% of episodes of ICU-acquired bacteremia caused by GNB during SDD were preceded by intestinal colonization with the same species during the week before, which is comparable to percentages reported by others in non-SDD settings (12;13). Yet, from these studies it could not be inferred to what extent intestinal carriage with GNB was, instead of other colonized body sites, the source of bacteremia. In ICU patients the colonized respiratory tract has been considered an important source for ICU-acquired GNB bacteremia (14). The urinary tract, contaminated intravascular devices and colonized wounds may also act as sources of ICU-acquired GNB bacteremia, albeit less frequently (4;15). Finally, GNB may cause bacteremia after translocation across the intestinal mucosal barrier, especially when intestinal permeability is increased (3;16). Our ability to compare incidence rates between patients receiving SDD and SOD is crucial to disentangle the respective causal roles of the colonized respiratory and intestinal tract. Respiratory tract decolonization was equally effective during SDD and SOD (8) and we excluded differences in prevalence of preceding respiratory tract colonization among patients with GNB bacteremia that had received SDD or SOD. We also documented that intestinal colonization rates with GNB are three times higher during SOD (75% of the patient days) as compared to SDD (26% of patient days). These findings confirm the results from an earlier study in which SOD hardly affected intestinal colonization with GNB (7). In that study eradication rates for Enterobacteriaceae colonizing the intestinal tract was 11% among patients receiving SOD, which was similar to patients receiving placebo treatment (12%). The final line of evidence is our observation that incidence rates of ICU-acquired GNB bacteremia were comparable during SC, SOD and SDD without intestinal decolonization being achieved.

Our observation that the incidence of ICU-acquired bacteremia was similar in SDD-patients with intestinal colonization as in SOD-patients, and that this risk was 3-fold higher than in SDD-patients without intestinal colonization suggests that successful decontamination of the intestinal tract is essential to achieve maximum benefits from the SDD regimen. Yet, since critical illness is associated with GNB overgrowth, either by decreased intestinal blood flow, decreased intestinal motility or because local and humoral immunity can be reduced (17-21), it is not excluded that this difference in GNB bacteremia incidence between colonized and non-colonized SDD patients resulted from differences in illness severity, rather than from differences in colonization status.

The aim of the short course of cefotaxime, as part of the SDD regimen during the first four days in ICU, is to treat possible “early” ICU-infections caused by respiratory tract commensals, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *S. aureus*. Although this systemic prophylaxis was part of the SDD regimen, and not of the SOD and standard care regimens, we don't think that the differences in intestinal colonization and ICU-acquired bacteremia rates resulted from the intravenous component of SDD. First, almost all patients in the non-SDD periods also received systemic antibiotics during the first four days and, as a result, the total number of defined daily

doses of systemic antibiotics was similar during SOD and SDD (8). Second, cefotaxime has a half life of approximately 1.1 hour and is mainly excreted by the kidneys with hardly any effect on intestinal colonization (22). Yet, the daily risk to acquire gram-negative bacteremia in ICU was highest after day 25 (and median was 10 days), which seems to exclude an important role of cefotaxime in preventing gram-negative bacteremia in ICU. Based on our findings and on the previously documented comparable efficacy of SDD and SOD in reducing day-28 mortality we conclude that the systemic use of cefotaxime during the first four days has no documented benefits concerning relevant endpoints.

Strengths of our study are the size of our study population and the detailed information about intestinal colonization during SDD and SOD. Unfortunately rectal colonization data were not collected during SC. Limitations of our study are the absence of including patient characteristics in the analyses. In the multi-centre study (yielding cohorts SDD-C1, SOD-C1 and SC) there were slight difference in baseline risk between patients receiving standard care and both intervention groups, but not between patients receiving SDD and SOD (8). As compared to SDD and SOD, patients receiving standard care had a slightly better prognosis on admission. Adjustment for these baseline imbalances would have increased the observed incidence differences between standard care versus SDD and SOD. We did not evaluate patient characteristics in the two prospectively studied cohorts of patients receiving SDD and SOD. However, since all patients admitted to ICU received either SDD or SOD (depending on the period of admission) we do not expect clinically relevant differences in patient characteristics between SDD and SOD periods. Another limitation is the use of rectal swabs to determine intestinal colonization. Naturally, rectal swabs are not 100% sensitive to detect intestinal colonization, but it seems unlikely that sensitivity would be different for patients receiving SDD or SOD. Furthermore, apart from the intestinal and respiratory tract, we did not evaluate other sources, such as intravascular devices of the urinary tract as a possible cause of GNB bacteremia. Finally, we added data from a monocentric dataset to those from a multi-center trial. Yet, since the microbiological data from both cohorts were fairly similar (data not shown) and since the monocentric data only accounted for a relatively small proportion of all data, we don't feel that this addition biased our findings.

Our findings add to our understanding of how SDD improves patient outcome in ICU patients. However, the obvious benefit of SDD over SOD in preventing ICU-acquired GNB bacteremia does not easily translate into outcome differences for patients treated with any of both regimens. In fact, the absolute risk reduction in GNB bacteremia of 2.1% corresponds to a number needed to treat of 50 patients to prevent one episode. Yet, even with 100% or 50% attributable mortality due to ICU-acquired GNB bacteremia at least 7,000 and 30,000 patients should be included in a study to reach statistical significance in patient outcome between SDD and SOD. Therefore, the effects of both regimens on antibiotic resistance, rather than the effects on ICU-acquired GNB bacteremia, will be decisive on the ultimate choice of SDD or SOD in Dutch ICUs.

The prophylactic use of antibiotics is controversial, and might increase the occurrence of infections with more resistant strains in the future (23;24). Moreover, the efficacy of SDD and SOD in ICU settings with higher levels of antibiotic resistance than in Dutch ICUs remains to be determined. Notwithstanding these remarks, our findings demonstrate that effective modulation of the Gram-negative intestinal flora could be a very effective measure to reduce incidences of ICU-acquired GNB bacteremia. The rapidly increasing problems of multi-resistant GNB in ICUs worldwide (15) emphasizes the urgent need to further investigate such approaches.

Conclusions

Respiratory tract decolonization was associated with a 33% and intestinal tract decolonization was associated with a 45% reduction in the occurrence of ICU-acquired GNB bacteremia.

The Dutch SOD-SDD trialists group include the following persons and sites:

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PART IV

Other aspects of SDD

Chapter 11

*Effects of decontamination of the digestive tract
and oropharynx in intensive care unit patients
on 1-year survival*

Evelien A.N. Oostdijk, Anne Marie de Smet and Marc J. Bonten,
on behalf of the Dutch SOD-SDD trialists group

Selective Digestive tract Decontamination (SDD) and Selective Oropharyngeal Decontamination (SOD) aim to prevent colonization and subsequent infection in Intensive Care Unit (ICU)-patients by application of non-absorbable antibiotics, either exclusively in the oropharynx (SOD) or through combining oropharyngeal and intestinal application together with a four-day course of systemic antibiotics (SDD).(1) In a cluster-randomized cross-over study comparing 6-month periods of SDD, SOD and Standard Care (SC) in 13 Dutch ICUs between 2004 and 2006, SOD and SDD were, as compared to SC, associated with a statistically significant reduction in day-28 mortality.(2) Based on a random-effects logistic-regression model, odds ratios for death at day-28 were 0.86 (95%CI 0.73 – 1.00) and 0.83 (95%CI 0.71 – 0.97), corresponding to Absolute Risk Reductions (ARR) in day-28 mortality of 2.9% and 3.5% and Number Needed to Treat (NNT) of 34 and 29.(2) It is unknown whether these short-term outcome benefits persist. We, therefore, determined one-year survival in a post-hoc exploratory analysis.

The original study protocol was approved by the institutional review boards of all the participating hospitals and a waiver for informed consent was granted, as described earlier(2). SDD and SOD both consisted of the non-absorbable antibiotics tobramycin, polymyxin E and amphotericin B. During the use of SDD a 2% mixture of these antibiotics was applied in the oropharynx and a suspension (respective doses 80 mg, 100 mg and 500 mg) was administered in the gastrointestinal tract four times daily via a nasogastric tube. Furthermore, for the first four days after ICU admission 1000mg cefotaxime was administered intravenously four times a day. SOD consisted only of the oropharyngeal application of the 2% mixture of these antibiotics. All patients with an expected length of ICU stay more than 72hours or an expected length of ICU-stay more than 48hours were eligible for inclusion. In total, 5,939 patients were included in the trial. For patients who were included twice or more, one-year mortality was determined only once. We audited the collected data by a random check of the one-year survival data by an independent research nurse in 505 (13%) of 3,841 patients who left the hospital alive. Discrepancies between the random check and the original 1 year survival data (n=7 (0.1%)) were resolved in favor of the results of the random check. Twelve patients did not permit the use of and were, therefore, excluded from analysis. For 192 patients data on one-year survival was missing (52 in SC (2.8%), 68 in SOD (3.8%) and 72 in SDD (3.7%)). We assumed these cases to differ from the complete cases systematically and, therefore, excluded these cases to minimize bias over imputing missing values (table 1).(3) With regard to covariates, seven patients had missing APACHE II scores (0.1%), which we considered to be missed at random and as the outcome was binary (high vs low) two sensitivity analyses were performed, in which missing values were replaced by either high APACHE II scores (“worst case scenario”) or low APACHE II scores (“best case scenario”)(4). Parametric data were expressed as means (standard deviation) and non-parametric data as median (interquartile range) and Mann-Whitney U test was used to test for significant differences.

	Standard Care (n = 1810)		Standard Care (n = 52; 2.8%)		SOD (n = 1727)		SOD (n = 68; 3.6%)		SDD (n = 1866)		SDD (n = 72; 3.7%)	
	Complete cases	Outcome missing	Complete cases	Outcome missing	Complete cases	Outcome missing	Complete cases	Outcome missing	Complete cases	Outcome missing	Complete cases	Outcome missing
Median age – yr #	64 (21)	59 (25)	65 (21)	64 (29)	65 (21)	64 (29)	66 (21)	64 (29)	66 (21)	66 (21)	64 (29)	57 (32)
Male sex – no. (%)	1108 (61.2%)	23 (44.2%)	1105 (64.0%)	35 (51.5%)	1105 (64.0%)	35 (51.5%)	1151 (61.7%)	35 (51.5%)	1151 (61.7%)	1151 (61.7%)	39 (54.2%)	39 (54.2%)
Mean APACHE II score	18.7 (8.0)	18.6 (6.7)	19.7 (8.3)	16.5 (7.0)	19.7 (8.3)	16.5 (7.0)	19.7 (7.8)	16.5 (7.0)	19.7 (7.8)	19.7 (7.8)	17.4 (7.6)	17.4 (7.6)
Mechanical ventilation – no (%)	1604 (88.6%)	46 (88.5%)	1633 (94.6%)	59 (86.8%)	1633 (94.6%)	59 (86.8%)	1738 (93.1%)	59 (86.8%)	1738 (93.1%)	1738 (93.1%)	66 (91.7%)	66 (91.7%)
Surgical reason for admission – no (%)	898 (49.6%)	21 (40.4%)	805 (46.6%)	37 (54.4%)	805 (46.6%)	37 (54.4%)	871 (46.7%)	37 (54.4%)	871 (46.7%)	871 (46.7%)	44 (61.1%)	44 (61.1%)
Previous or pre-existent condition												
- cardiovascular disease	890 (49.2%)	25 (48.1%)	820 (47.5%)	22 (32.4%)	820 (47.5%)	22 (32.4%)	947 (50.8%)	22 (32.4%)	947 (50.8%)	947 (50.8%)	28 (38.9%)	28 (38.9%)
- Pulmonary disease	446 (24.6%)	9 (17.3%)	394 (22.2%)	12 (17.6%)	394 (22.2%)	12 (17.6%)	480 (25.7%)	12 (17.6%)	480 (25.7%)	480 (25.7%)	10 (13.9%)	10 (13.9%)
- Diabetes mellitus	268 (14.8%)	12 (23.1%)	245 (14.2%)	7 (10.3%)	245 (14.2%)	7 (10.3%)	259 (13.9%)	7 (10.3%)	259 (13.9%)	259 (13.9%)	6 (8.3%)	6 (8.3%)
- Chronic renal insufficiency	105 (5.8%)	3 (5.8%)	122 (7.1%)	3 (4.4%)	122 (7.1%)	3 (4.4%)	134 (7.2%)	3 (4.4%)	134 (7.2%)	134 (7.2%)	5 (6.9%)	5 (6.9%)
- Malignant solid tumor	182 (10%)	0 (0%)	177 (10.2%)	2 (2.9%)	177 (10.2%)	2 (2.9%)	209 (11.2%)	2 (2.9%)	209 (11.2%)	209 (11.2%)	2 (2.8%)	2 (2.8%)
- Metastized cancer	59 (3.3%)	0 (0%)	55 (3.2%)	1 (1.5%)	55 (3.2%)	1 (1.5%)	67 (3.6%)	1 (1.5%)	67 (3.6%)	67 (3.6%)	1 (1.4%)	1 (1.4%)
- Haematologic cancer	44 (2.4%)	0 (0%)	47 (2.7%)	0 (0%)	47 (2.7%)	0 (0%)	52 (2.8%)	0 (0%)	52 (2.8%)	52 (2.8%)	0 (0%)	0 (0%)
- Immunodepression or AIDS	44 (2.4%)	0 (0%)	45 (2.6%)	0 (0%)	45 (2.6%)	0 (0%)	54 (2.9%)	0 (0%)	54 (2.9%)	54 (2.9%)	1 (1.4%)	1 (1.4%)
- Alcohol or drug abuse	104 (5.7%)	2 (3.8%)	106 (6.1%)	6 (8.8%)	106 (6.1%)	6 (8.8%)	102 (5.5%)	6 (8.8%)	102 (5.5%)	102 (5.5%)	3 (4.2%)	3 (4.2%)

Table 1 Baseline characteristics of the patients included in the one-year analysis and of the patients with missing one-year survival data. Continuous data are expressed as means ± standard deviation (parametric) or medians with interquartile range (non-parametric).

SOD, Selective Oropharyngeal Decontamination; SDD, Selective Decontamination of the Digestive Tract; Apache, Acute Physiology and Chronic Health Evaluation; AIDS, acquired immune deficiency syndrome
age at time of ICU-admission

For dichotomous variables data were expressed as absolute numbers (percentage) and the χ^2 test was used to test for significant differences. A p-value <0.05 was considered to denote statistical significance and all reported p-values are two-sided. Data were analyzed with SPSS version 20 (SPSS, Chicago, IL) and R version 2.14.2 (Lme4-library).

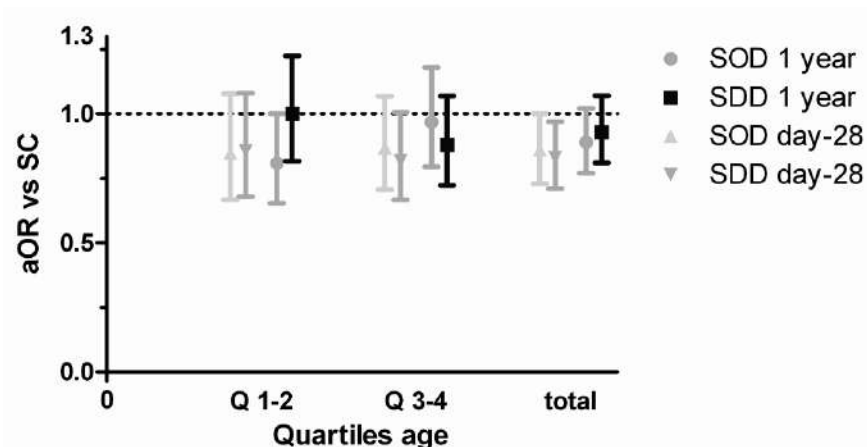
In all 5,403 unique patients were included in the analysis to determine one-year survival; 1,810 patients received SC, 1,727 received SOD and 1,866 received SDD. Crude mortality rates at 1 year were 42.6%, 42.2% and 44.2% for SC, SOD and SDD, respectively. As depicted in table 2, baseline differences were present between the different groups. Patients in the SDD group were older compared to the SOD- and SC-groups and patients in the SC-group had significantly lower APACHE-II scores and were significantly less often mechanically ventilated. Based on a random-effects logistic-regression model adjusted for age (>65 year), sex, APACHE II score (≥ 20), intubation status, medical speciality (surgical vs non-surgical), study site, and study period, adjusted ORs (aOR) for one-year mortality, as compared to SC, were 0.89 (95%CI 0.77 – 1.02) and 0.93 (95%CI 0.81 – 1.07) for SOD and SDD, respectively. These aORs correspond to ARR in 1-year mortality (as compared to 42.6% mortality in SC) of 2.8% for SOD and, 1.8% for SDD with NNT of 35 and 57 for SOD and SDD, respectively. For SOD and SDD combined, aOR for death at 1-year was 0.91 (95%CI 0.80 – 1.03) as compared to SC. As survival differences due to an intervention are bound to decline more rapidly for elderly, we also explored the effects of SOD and SDD on 1-year survival in a stratified analysis for age. For this, patients in the three study groups were subdivided upon the median age into two groups (quartile 1 and 2 versus quartile 3 and 4), yielding three younger study groups with median ages of 53 years for SC and SOD and 54 years for SDD and three older study groups with median ages of 73 for SC and SOD and 74 for SDD. In the younger age group aORs for 1-year survival, as compared to SC, were 0.81 (95%CI 0.65 – 1.00) and 1.00 (95%CI 0.82 – 1.22) for SOD and SDD, respectively and for the older age group 0.97 (95%CI 0.79 – 1.18) and 0.88 (95%CI 0.72 – 1.07) respectively (figure 1). Sensitivity analyses for missing APACHE II scores revealed no relevant changes (data not shown).

Our findings of this post-hoc analysis suggest that the short-term survival benefits associated with SOD and SDD in Dutch ICUs tend to persist up till one year. For SOD, the effect size of the survival benefit was comparable for day-28 and 1-year survival in the younger patients. For SDD the effect size was more stable in older patients. These results provide further evidence of the beneficial effects of SDD and SOD in settings with low-endemicity of antibiotic resistance(5, 6). Whether these effects can also be established in settings with higher levels of antibiotic resistance than in Dutch ICUs remains to be determined, as are the long-term effects on antibiotic resistance development.

	SC (n = 1810)	SOD (n = 1727)	SDD (n = 1866)	P value SC vs SOD	P value SC vs SDD	P value SOD vs SDD
Median age – year #	64 (21)	65 (21)	66 (21)	0.73	0.01	0.01
Male sex – no. (%)	1108 (61.2%)	1105 (64.0%)	1151 (61.7%)	0.09	0.77	0.15
Mean APACHE II score	18.7 (8.0)	19.7 (8.3)	19.7 (7.8)	<0.01	<0.01	0.90
Mechanical ventilation – no (%)	1604 (88.6%)	1633 (94.6%)	1738 (93.1%)	<0.01	<0.01	0.08
Surgical reason for admission – no (%)	898 (49.6%)	805 (46.6%)	871 (46.7%)	0.07	0.08	0.97
Previous or pre-existent condition						
- cardiovascular disease	890 (49.2%)	820 (47.5%)	947 (50.8%)	0.32	0.34	0.05
- Pulmonary disease	446 (24.6%)	394 (22.2%)	480 (25.7%)	0.20	0.45	0.04
- Diabetes mellitus	268 (14.8%)	245 (14.2%)	259 (13.9%)	0.60	0.42	0.79
- Chronic renal insufficiency	105 (5.8%)	122 (7.1%)	134 (7.2%)	0.13	0.09	0.89
- Malignant solid tumor	182 (10%)	177 (10.2%)	209 (11.2%)	0.85	0.26	0.36
- Metastasized cancer	59 (3.3%)	55 (3.2%)	67 (3.6%)	0.90	0.58	0.50
- Haematologic cancer	44 (2.4%)	47 (2.7%)	52 (2.8%)	0.59	0.50	0.91
- Immunodepression or AIDS	44 (2.4%)	45 (2.6%)	54 (2.9%)	0.74	0.38	0.60
- Alcohol or drug abuse	104 (5.7%)	106 (6.1%)	102 (5.5%)	0.62	0.71	0.39

Table 2 Baseline characteristics of the patients included in the one-year analysis. Continuous data are expressed as means \pm standard deviation (parametric) or medians with interquartile range (non-parametric).

SOD, Selective Oropharyngeal Decontamination; SDD, Selective Decontamination of the Digestive Tract; Apache, Acute Physiology and Chronic Health Evaluation; AIDS, acquired immune deficiency syndrome
age at time of ICU-admission



	Standard Care	SOD	SDD
Median age (IQR) Q 1-2	53 (17)	53 (18)	54 (17)
Median age (IQR) Q 3-4	74 (8)	74 (8)	75 (8)
One year survival vs standard care			
Adjusted Odds Ratio (95% CI)	Reference		
Age, lower quartiles (Q 1 and 2)	Reference	0.81 (0.65 – 1.00)	1.00 (0.82 – 1.22)
Adjusted Odds Ratio (95% CI)	Reference		
Age, upper quartiles (Q 3 and 4)	Reference	0.97 (0.79 – 1.18)	0.88 (0.72 – 1.07)
Adjusted Odds Ratio (95% CI)	Reference		
Total (Q 1,2,3,4)	Reference	0.89 (0.77 – 1.02)	0.93 (0.81 – 1.07)

Figure 1: Stratified analysis for age with adjusted Odds ratios for one year mortality for patients in quartile 1 and 2, in quartile 3 and 4 and for all patients. Odds ratios were adjusted for age, sex, APACHE II score (≥ 20), intubation status, medical speciality (surgical vs non-surgical), study site, and study period using a random-effects logistic-regression model.

aOR, adjusted Odds ratios; Q, quartile; IQR, inter quartile range; SDD, Selective Decontamination of the Digestive Tract; SOD, Selective Oropharyngeal Decontamination

Acknowledgements

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Hospital, Dordrecht; Mat van Iterson, Steven F.T. Thijsen, Diakonessen Hospital, Utrecht; Georg H. Kluge, Slotervaart Hospital, Amsterdam; Jacob W. de Vries, Jan A. Kaan, Mesos Medical Center, Utrecht — all in the Netherlands.

SUPPLEMENTARY APPENDIX

Selective Decontamination Regimens

Selective Decontamination of the Digestive Tract (SDD) and Selective Oropharyngeal Decontamination (SOD) both consisted of the non-absorbable antibiotics tobramycin, polymyxin E and amphotericin B. During the use of SDD a 2% mixture of these antibiotics was applied in the oropharynx 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 1000mg cefotaxime was administered intravenously four times a day. SOD consisted only of the oropharyngeal application of the 2% mixture of these antibiotics. All patients with an expected length of ICU stay more than 72hours or an expected length of ICU-stay more than 48hours were eligible for inclusion.

Statistical analysis

Non-parametric data were expressed as median (interquartile range) and the Mann-Whitney U test was used to test for significant differences. For dichotomous variables data were expressed as absolute numbers (percentage) and the χ^2 test was used to test for significant differences. A p-value <0.05 was considered to denote statistical significance and all reported p-values are two-sided.

Data were analyzed with SPSS version 20 (SPSS, Chicago, IL), GraphPad Prism version 5.0 for Windows (GraphPad Software, San Diego, Calif, USA) and R version 2.14.2 (Lme4-library).

	Adjusted Odds Ratio (95% CI)		
	SOD	SDD	SDD and SOD
Excluding cases with missing APACHE II score (n = 7)	0.89 (0.77 – 1.02)	0.93 (0.81 – 1.07)	0.91 (0.80 – 1.03)
Worst case scenario	0.89 (0.77 – 1.02)	0.93 (0.81 – 1.07)	0.91 (0.80 – 1.03)
Best case scenario	0.89 (0.77 – 1.03)	0.93 (0.81 – 1.07)	0.91 (0.81 – 1.03)

Table S1 Sensitivity analyses for missing APACHE II values. For the worst case scenario, 7 missing APACHE II scores were replaced by the worst APACHE II score (i.e. ≥ 20) and for the best case scenario for the best APACHE II score (i.e. < 20).

SOD, Selective Oropharyngeal Decontamination; SDD, Selective Decontamination of the Digestive Tract

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Chapter 12

Selective decontamination of the digestive tract and selective oropharyngeal decontamination in intensive care unit patients: a cost-effectiveness analysis

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ABSTRACT

Objective: To determine costs and effects of Selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) as compared to standard care (i.e. no SDD/SOD (SC)) from a healthcare perspective in Dutch ICUs

Design: A post-hoc analysis of a previously performed cluster-randomized trial (NEJM 2009;360:20).

Setting: 13 Dutch ICUs

Participants: Patients with ICU-stay of >48 hours that received SDD (n=2,045), SOD (n=1,904) or SC (n=1,990).

Interventions: SDD or SOD.

Primary and secondary outcome measures: Effects were based on hospital survival, expressed as crude Life Years Gained (cLYG). The incremental cost effectiveness ratio (ICER) was calculated, with corresponding cost acceptability curves. Sensitivity analyses were performed for discount-rates, costs of SDD, SOD and mechanical ventilation.

Results: Total costs per patient were €41,941 for SC (95%CI €40,184-€43,698), €40,433 for SOD (95%CI €38,838-€42,029) and €41,183 for SDD (95%CI €39,408-€42,958). SOD and SDD resulted in crude LYG of +0.04 and +0.25, respectively, as compared to SC, implying that both SDD and SOD are dominant (i.e. cheaper and more beneficial) over SC. In cost-effectiveness acceptability curves probabilities for cost-effectiveness, compared to standard care, ranged from 89% to 93% for SOD and from 63% to 72% for SDD, for acceptable costs for 1 LYG ranging from €0 to €20,000. Sensitivity analysis for mechanical ventilation and discount rates did not change interpretation. Yet, if costs of the topical component of SDD and SOD would increase tenfold to €400/day and €40/day (maximum values based upon free market prices in 2012), the estimated ICER as compared to SC for SDD would be €21,590 per LYG. SOD would remain cost-saving.

Conclusions SDD and SOD were both effective and cost-saving in Dutch ICUs

INTRODUCTION

Many patients in Intensive Care Units (ICU) are affected by nosocomial infections.¹ These infections are associated with increased mortality and morbidity, and considerable extra costs.² Selective oropharyngeal decontamination (SOD) and selective decontamination of the digestive tract (SDD) are prophylactic antibiotic regimens, that consist of topical antibiotics applied to the oropharynx and the intestinal tract to prevent colonization of gram-negative bacteria, *Staphylococcus aureus* and yeasts. During SOD topical antibiotics are exclusively applied to the oropharynx throughout ICU-stay. During SDD topical antibiotics are applied to the oropharynx but also to the intestinal tract throughout ICU-stay, in combination with intravenous administration of cefotaxime during the first four days in ICU, to pre-emptively treat infections with commensal respiratory tract bacteria.³ SDD has been a widely evaluated but highly controversial intervention in ICU.⁴ Many, but not all, studies reported statistically significant reductions in the incidence of Ventilator-Associated Pneumonia (VAP), but only few were able to demonstrate outcome benefits such as reduced mortality and length of ICU-stay.⁵ In the absence of indisputably documented outcome benefits, the fear for selection of antibiotic resistance has prevailed and SDD has not been recommended in most infection prevention guidelines.⁶⁻⁹ In a cluster-randomized study in 13 Dutch ICUs, SDD and SOD were associated with relative risk reductions of mortality at day 28 of 13% and 11%, respectively, as compared to standard care (i.e. no SDD or SOD).³ Although SOD and SDD are currently widely used in Dutch ICUs, the costs and effects of both regimens have not yet been determined. We, therefore, conducted a cost-effectiveness analysis (CEA), comparing Standard Care, SOD and SDD using data from the Dutch multi-center trial.

METHODS

Data collection

A post-hoc analysis was performed of the cluster randomized crossover trial comparing SOD and SDD to standard care (SC). The trial was conducted in 13 Dutch ICUs and included 5,939 patients (2,045 received SDD, 1,904 received SOD and 1,990 were treated according to SC). All centers were assigned to all three regimens during periods of six months, however, the order of implementation of SC, SOD and SDD was randomized per center.³

SOD and SDD have been described in detail elsewhere.³ In short, SOD consists of a paste applied to the oropharynx, containing polymyxin E, tobramycin and amphotericin B (all in a 2% concentration, applied every 6h). SDD consists, besides of the paste used in SOD, also of a 10 mL suspension of 100 mg polymyxin E, 80 mg tobramycin and 500 mg amphotericin B that is applied via a nasogastric tube, every 6h, and of cefotaxime (1000 mg, every 6h) applied intravenously during the first four days of ICU-admission. The topical antibiotics of both regimens are applied until ICU-discharge. During the trial there were no restrictions to systemic

antibiotic use during SC and SOD. During SDD, the use of antibiotics with anti-anaerobic activity was discouraged. This resulted in a marked increase of cephalosporin use and lower usage of penicillins, carbapenem and clindamycin.³ Surveillance cultures of endotracheal aspirates, oropharynx and rectum were obtained on admission and twice weekly during SDD. During SOD surveillance cultures of endotracheal aspirates and the oropharynx were obtained on admission and twice weekly thereafter. During SC no surveillance cultures were obtained. Clinical cultures were obtained on clinical suspicion of infection in all three periods.

Approach for economic evaluation

We performed a cost-effectiveness analysis (CEA) from a healthcare perspective, hence, only including direct medical costs.¹⁰⁻¹² The time horizon of the study was the period from ICU-admission until hospital-discharge. Life Years Gained (LYG) was used as effectiveness measure. The outcome of the CEA was the incremental cost effectiveness ratio (ICER), expressed as cost per life year gained (LYG). The informal Dutch threshold for cost-effectiveness is €20,000 per LYG.^{13 14} Data from all individual patients were used for analyses. The CEA was performed post-hoc, however, using data that were prospectively collected in Case Report Forms during the trial. Total direct medical costs of the three regimens consisted of three main categories: Length of Stay (LOS), antibiotic use and microbiology costs (table 1). LOS was based on the length of ICU-stay and the number of days on a hospital ward after ICU-discharge. Costs for days in ICU and other hospital days were based upon the Dutch guidelines for costing research in health economic studies.¹¹ Days in ICU were categorized in days with and without mechanical ventilation; days with mechanical ventilation were considered to be 15% more expensive than ICU-days without mechanical ventilation.¹⁵⁻¹⁷ Antibiotic use consisted of the topical components of the SDD and SOD-regimen, hereafter referred to as study medication, and of all systemic antibiotics used in ICU during all periods, including the four days cefotaxime during SDD as part of the SDD-protocol. The price of study medication was €0.87 and €10.48 per day, for SOD and SDD respectively. Costs of systemic antibiotics were based upon prices per Defined Daily Dose (DDD) provided by the Dutch information project on medication and medical devices (Genees-en hulpmiddelen Informatie Project (GIP)-database¹⁸). For microbiology costs blood cultures, bronchoalveolar lavages (BAL), sputum-, throat- and rectal cultures were considered. Rectal cultures were only obtained during SDD as part of SDD-surveillance. Cultures obtained from the other sites were either obtained as part of surveillance (throat- and sputum cultures during SDD/SOD) or as part of daily clinical practice. Microbiological costs were obtained as the internal tariffs applied within the University Medical Center Utrecht. These costs included costs for the microbiological culture, order tariff and extra costs for species determination and susceptibility resistance testing in case of relevant bacterial growth, irrespective of the species. The year 2009 was taken as the reference year for all costs. Costs that were not available for 2009 were corrected for inflation (with respect to 2009) based on the price index.¹¹ An overview of all unit costs used

in the analysis is provided in table 1. LYG were discounted at 1.5% a year, following Dutch guidelines for health economic evaluation.¹⁹ Discounting of costs was not necessary, as all costs occurred within the first year after inclusion.²⁰

Category		Prices per unit
Length of Stay	Day in ICU	€2,183 ¹¹
	Day in hospital ward	€505 ¹¹
	Mechanical ventilation, additional costs	€327.45 ¹⁵⁻¹⁷
Topical antibiotics	Cost of SOD per day	€0.87 ^{3 42}
	Cost of SDD per day	€10.48 ^{3 42}
Microbiology	Blood culture	€11.89 per culture + €12.90 order rate*
	Throat culture	€7.78 per culture + €12.90 order rate *
	Sputum culture	€7.78 per culture + €12.90 order rate *
	Bronchoalveolar lavage	€7.78 per sample + €12.90 order rate *
	Rectum culture	€7.78 per sample + €12.90 order rate *
	Species determination	Extra €13.00 per isolate + €18.52 *
	Resistance profile determination	8.96 per isolate
Antibiotics		According to GIP database ¹⁸

Table 1: Costs used per unit

SOD, selective oropharyngeal decontamination; SDD selective decontamination of the Digestive tract; SC, standard care

* UMCU costs

Analysis

Life Years Gained (LYG) were determined by calculating Life Years Lost (LYL) of the patients who deceased in the hospital, using life tables for the Dutch population combined with age and sex,²¹ with LYG defined as the difference in LYL between regimens. The ICER was defined as the incremental difference between the mean cost of treatment regimens, divided by the incremental difference in mean effect between treatment regimens. To estimate confidence limits for the ICER, bootstrapping (25,000 repeats) was performed, as this does not depend on parametric assumptions about the distribution of the data.^{22 23} Results of the bootstrap procedure were plotted in a cost-effectiveness plane that graphically represents the cost-difference and effect difference between either SDD or SOD and SC, and for SDD versus SOD, for each of the bootstrap replications. Cost-effectiveness acceptability curves (CEAC) were plotted to express the probability that treatment regimens were cost-effective as compared to standard care, for a range of willingness to pay levels for one life year gained (λ).²⁴ The curves display the proportion of bootstrapped ICER-pairs that are cost-effective, meaning that they either fall within the south-east quadrant of the cost-effectiveness plane or remain below the λ threshold in the north-east and south-west quadrants of the plane. Additionally, sensitivity analyses were performed: The discounted results (at 1.5% a year) were compared to results without discounting and to a discount rate of 3% a year; costs for ICU-days with mechanical ventilation were analyzed for 0% and 30% extra per ICU-day

as compared to 15% additional costs in basecase analysis; daily costs of study medication were analyzed with maximum values based upon free market prices in 2012 (€40 for SOD and €400 for SDD). Mann-Whitney U test was used to calculate P-values. P-value <0.05 was considered to denote statistical significance and all reported p-values are two-sided. All analyses were performed using Statistical Package for Social Sciences version 20 (SPSS, Chicago, IL) version 17.0 and R version 2.14.2.

RESULTS

In this cluster-randomized trial 5,939 patients were included; 1,990 patients in the SC group, 1,904 received SOD and 2,045 received SDD. For this post-hoc analysis 19 patients were excluded (3 patients during SC, 3 during SOD and 13 during SDD). Twelve patients declined permission to use clinical data. Seven additional patients were excluded because data on hospital discharge and/or hospital mortality was missing, as reported previously.³

Baseline characteristics differed among the three groups (table 2). Patients receiving SDD were on average 62.4 (\pm 15.8) years old, compared to 61.4 (\pm 16.3) and 61.4 (\pm 16.2) years for patients receiving SOD and SC, respectively. Patients receiving SC had a lower mean APACHE II score (18.6) than those receiving SOD (19.6) and SDD (19.9), and were less likely to be on mechanical ventilation (88.1% for SC vs. 94.2% and 92.9% for SOD and SDD, respectively).

Mean LOS in ICU and in hospital and mean duration of mechanical ventilation did not differ significantly between SC, SOD and SDD. These data differ somewhat from original LOS data reported previously³, which included only data of patients who were alive at day 28.

In all, 7,609 daily doses of study medication were used in the SOD group and 8,068 during SDD, with average numbers of 4.0 doses/day for SOD patients and 3.95 for SDD patients. The average number of DDD of systemic antibiotics during ICU-stay was lowest during SDD with absolute numbers of 33,688 DDDs during SC, 30,299 during SOD and 29,663 during SDD.

	SC N=1,987	SOD N=1,901	SDD N=2,032
<i>Baseline characteristics</i>			
Age, years (mean (SD)) **	61.4 ± 16.2	61.4 ± 16.3	62.4 ± 15.8
Male sex (no (%))	1219 (61.3)	1211 (63.7)	1242 (63.7)
Apache II score (mean (SD)) †*	18.6 ± 7.9	19.6 ± 8.8	19.9 ± 8.9
Mechanical ventilation (no (%)) †*	1,751 (88.1)	1,790 (94.2)	1,888 (92.9)
<i>Clinical outcome **</i>			
Length of MV, days (median (IQR))	6 (9)	7 (8)	6 (9)
Length of stay ICU, days (median (IQR))	8 (11)	9 (9)	9 (10)
Length of stay hospital, days (median (IQR)) ***	15 (23)	15 (22)	15 (21)
<i>Resource use</i>			
Study medication, DDD (total (mean))	0	7,609 (4.0)	8,068 (3.95)
Systemic antibiotics, DDD (total (mean))	33,688 (5.9)	30,299 (6.2)	29,663 (5.2)
Microbiology (total (mean))	0	0	7,247 (3.8)
Rectal	263 (1.3)	221 (1.3)	253 (1.3)
BAL	5,430 (3.7)	7,467 (4.3)	8,073 (4.4)
Sputum	431 (2.7)	6,277 (3.5)	7,176 (3.8)
Throat			
Blood	4,113 (3.7)	4,849 (4.1)	4,461 (4.1)

Table 2: Baseline characteristics, clinical outcomes and resource use of patients
SDD, Selective Decontamination of the Digestive tract; SOD, Selective Oropharyngeal Decontamination; SC, Standard Care; IQR, inter quartile range; DDD, defined daily doses; MV, mechanical ventilation; ICU, Intensive Care Unit; BAL, Bronchoalveolar Lavage

P value <0.05 for: † SC vs SOD; * SC vs SDD; # SOD vs SDD

** Values differ from previously reported values as not all patients could be included in the present analysis

*** Duration in the hospital is the number of days in the hospital after ICU-discharge, for patients who were discharged from the ICU alive

Cost analysis

Average total costs per patient were €41,941 for SC (95%CI €40,184-€43,698), €40,433 for SOD (95%CI €38,838-€42,029) and €41,183 for SDD (95%CI €39,408-€42,958) (Table 3). LOS accounted for approximately 98% of total costs, and these costs were highest for patients during SC. Mean costs per patient for study medication were €3.48 and €41.35 during SOD and SDD, respectively. Mean costs of systemic antibiotics per patient were €358.29 (95%CI €321.34 - €395.24) during SC, €317.65 (95%CI €280.89 - €354.42) during SOD and €439.14 (95%CI €406.69 - €471.59) during SDD ($P < 0.01$ for SDD vs SC and SOD). Mean costs for microbiology cultures were highest for SDD (€ 371.72), as compared to SOD (€287.27) and SC (€220.05) ($P < 0.01$ for SDD vs SC and SOD).

Hospital mortality was 31.8%, 30.7% and 32.3% during SC, SOD and SDD respectively. The difference in hospital mortality for SDD, as compared to reported mortality previously,³ (32.3% vs 32.6%) results from inclusion of outcome data from the twelve patients that declined permission to use clinical (not mortality) data in the main analysis. Estimated life years lost were, on average, 6.07 years for SC patients, 5.62 years for SOD patients and 5.97 years for SDD patients. Effects were discounted with 1.5% a year resulting in life years gained (LYG) of +0.25 years for SOD and +0.04 years for SDD as compared to SC (table 4). SOD resulted in +0.21 LYG when compared to SDD. In the cost-effectiveness plane, point estimates of the differences in costs and effects indicated that both SOD and SDD were beneficial and cheaper (i.e. south-east quadrant) over SC. As depicted in figure 1, SOD and SDD were dominant (i.e. southeast quadrant of plane) in 77.5% and 40.1% of the bootstrap estimates respectively. When comparing SOD vs SDD, SOD dominates SDD in 60.2% of the bootstrap replicates. If only cost aspects were taken into account (i.e. combining the south-east and south-west quadrants), 89.3% and 72.4% of the bootstrap replicates were cheaper than SC during SOD and SDD, respectively. In addition, bootstrap results were graphically displayed in cost-effectiveness acceptability curves showing the probability that a treatment is cost-effective in comparison with another treatment, given a certain threshold value for the willingness to pay for one life year gained. These probabilities varied for values ranging from €0 to €20,000, between 89% and 93% for SOD and between 63% and 72% for SDD (figure 1). For SOD vs SDD, these probabilities varied from 73% to 87%.

In the cost-analysis, €69.59 per one DDD of cefotaxime was used as reference price¹⁸ and average costs of systemic antibiotics were highest during SDD.³ The price of 1 DDD cefotaxime should be €39.37 and €19.07 to balance costs for systemic antibiotics between SDD and SC and SDD and SOD respectively.

	SC N=1990	SOD N=1904	SDD N=2045
Length of Stay			
ICU	€29,553.45 (€28,152.40 - €30,954.49)	€28,684.46 (€27,412.05 - €29,956.87)	€29,069.78 (€27,636.40 - €30,503.16)
Hospital	€8,621.85 (€8,059.10 - €9,184.61)	€7,830.55 (€7,345.91 - €8,315.20)	€7,963.94 (€7,476.75 - €8,451.13)
MV	€3,225.06 (€3,045.61 - €3,404.51)	€3,316.36 (€3,151.14 - €3,481.58)	€3,308.18 (€3,116.09 - €3,500.27)
Total	€41,400.36 (€39,672.04 - €43,128.68)	€39,831.37 (€38,261.92 - €41,400.82)	€40,341.90 (€38,599.66 - €42,084.14)
Study medication	-	€3.48 (€3.47 - €3.49)	€41.35 (€41.07 - €41.62)*
Systemic Antibiotics	€358.29 (€321.34 - €395.24)	€317.65 (€280.89-€354.42)	€439.14 (€406.69-€471.59)
Microbiology			
Rectal swabs	-	-	€102.75 (€97.64 - €107.86)
BAL	€6.44 (€5.42 - €7.46)	€4.70 (€3.92 - €5.49)	€4.77 (€4.01 - €5.53)
Sputum	€114.83 (€106.87 - €122.79)	€135.85 (€127.99 - €143.71)	€117.57 (€110.78 - €124.36)
Throat	€8.12 (€6.39 - €9.84)	€86.66 (€83.07 - €90.25)	€89.65 (€85.68 - €93.63)
Blood	€52.61 (€48.74 - €56.49)	€53.72 (€49.64 - €57.79)	€45.45 (€41.87 - €49.04)
Total	€182.15 (€170.60 - €193.69)	€280.93 (€267.00 - €294.87)	€360.73 (€343.69 - €377.76)
Total	€41,940.79 (€40,183.93 - €43,697.66)	€40,433.42 (€38,837.50 - €42,029.35)	€41,183.12 (€39,408.39 - €42,957.85)

Table 3. Total Costs (2009 €) per patient. Mean (95% confidence interval)

*Excluding ceforaxim. Ceforaxim use is included in total systemic antibiotic use.

SDD, Selective Decontamination of the Digestive tract; SOD, Selective Oropharyngeal Decontamination; SC, Standard Care; MV, mechanical ventilation; ICU, Intensive Care Unit; BAL, Bronchoalveolar Lavage

Sensitivity analyses on mechanical ventilation costs and discount rates did not change the interpretation of results (table 5, figure 1). Yet, daily costs of €10 and €400 for study medication in SOD and SDD resulted in an ICER of €21,590 per LYG for SDD vs SC whereas SOD remained dominant over SC. For all situations, SOD was more effective and cheaper than SDD (table 4 and 5). To stay below the Dutch threshold of €20,000 per life year gained, the maximum daily price for the topical SDD-components should be €375.

	LYG*	Cost difference	ICER
SOD vs SC (95% CI)	+ 0.25 (-0.05 – 0.55)	-€1507.37 (-€3,186.45 – €171.72)	SOD dominates SC
SDD vs SC (95% CI)	+ 0.04 (-0.26 – 0.34)	-€757.67 (-€2,522.56 – €1,007.21)	SDD dominates SC
SOD vs SDD (95% CI)	+ 0.21 (-0.09 – 0.51)	-€749.69 (-€2,439.35 – €939.97)	SOD dominates SDD

Table 4: Outcomes of cost-effectiveness comparisons across groups

* Effects are discounted at 1.5% a year

LYG, life years gained; 95% CI, 95% confidence intervals; SDD, Selective Decontamination of the Digestive tract; SOD, Selective Oropharyngeal Decontamination; SC, Standard Care; ICER, incremental costs effectiveness ratio (costs/LYG)

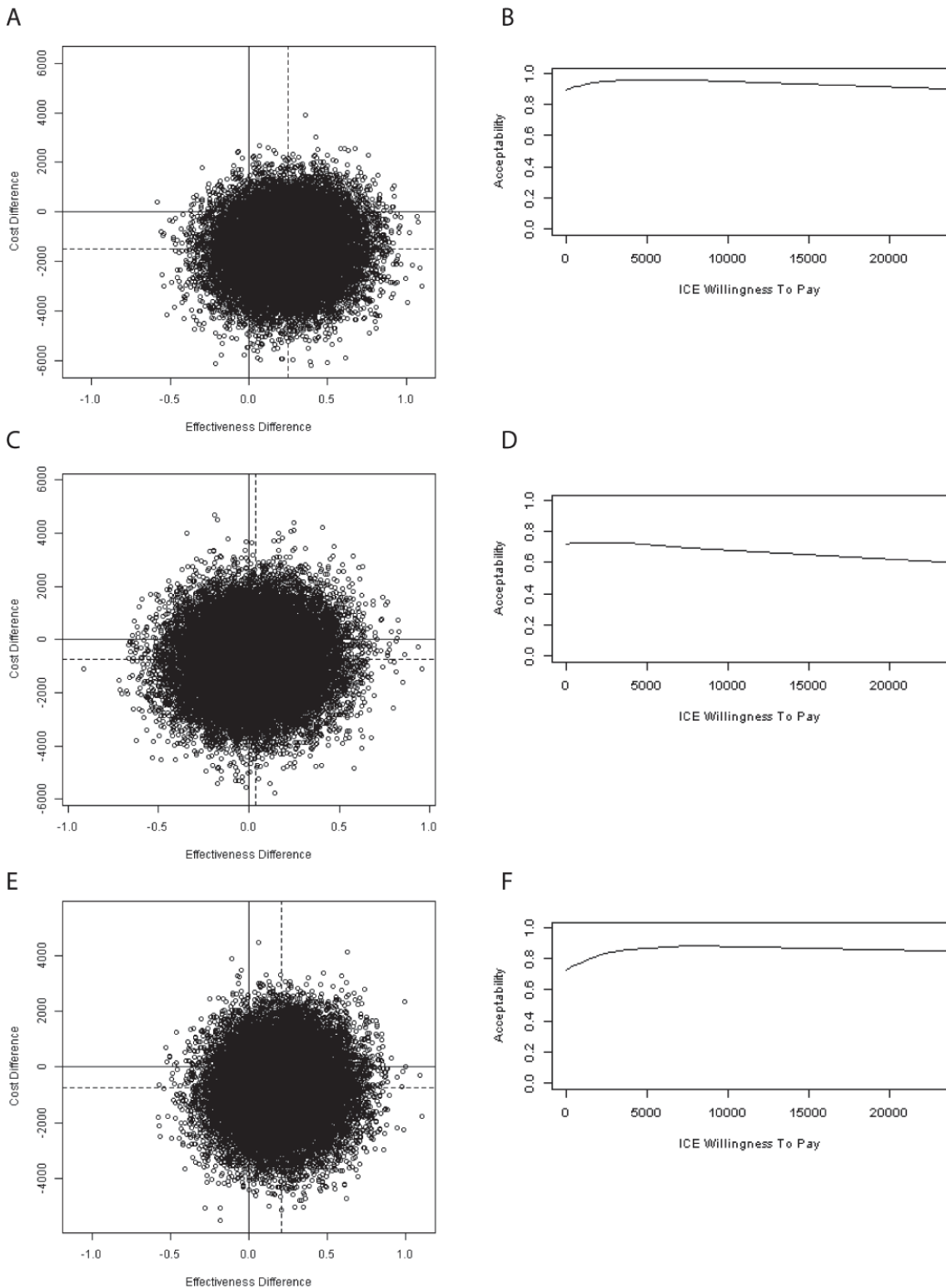


Figure 1: Scatterplot of ICER-pairs based on the results of bootstrap re-sampling technique (25,000 replicates) and cost-effectiveness acceptability curves for a) and b) SOD vs SC, c) and d) SDD vs SC, e) and f) SOD vs SDD
 SOD, selective oropharyngeal decontamination; SDD selective decontamination of the Digestive tract; SC, standard care

	SC	SOD	SDD	ICER analyses SC vs SOD	ICER analyses SC vs SDD	ICER analyses SDD vs SOD
Sensitivity analysis discounting effects (Life years lost)	BC +1.5% +0% +3%	4.27 (3.96 – 4.57) 6.07 (5.58 – 6.55) 2.82 (2.63 – 3.01)	4.02 (3.72 – 4.32) 5.62 (5.15 – 6.08) 2.68 (2.49 – 2.87)	4.23 (3.94 – 4.53) 5.97 (5.50 – 6.44) 2.82 (2.63 – 3.00)	SC = dominated by SOD SC = dominated by SDD SC = dominated by SDD SC = dominated by SDD	SDD = dominated by SOD SDD = dominated by SOD SDD = dominated by SOD SDD = dominated by SOD
Sensitivity analysis mechanical ventilation*	BC +15% +0% +30%	€41,940.79 (€40,183.93 – €43,697.66) €38,715.73 (€37,112.32 – €40,319.14) €45,165.85 (€43,251.01 – €47,080.69)	€40,433.42 (€38,837.50 – €42,029.35) €37,117.07 (€35,659.90 – €38,574.24) €43,749.78 (€42,010.47 – €45,489.09)	€41,183.12 (€39,408.39 – €42,957.85) €37,874.94 (€36,270.73 – €39,479.15) €44,491.30 (€42,542.03 – €46,440.57)	SC = dominated by SOD SC = dominated by SDD SC = dominated by SDD SC = dominated by SDD	SDD = dominated by SOD SDD = dominated by SOD SDD = dominated by SOD SDD = dominated by SOD
Sensitivity analysis price study regimen**		€41,940.79 (€40,183.93 – €43,697.66)	€40,493.15 (€38,996.62 – €42,189.67)	€42,720.23 (€40,943.82 – €44,496.65)	ICER 21,590	SDD = dominated by SOD

Table 5: Sensitivity analysis

Price SOD €40 and SDD €400 per day * Effects are discounted 1.5% a year

BC base case results; SDD Selective Decontamination of the Digestive tract, SOD Selective Oropharyngeal Decontamination, SC Standard Care, ICER incremental costs effectiveness ratio (costs/LYG)

DISCUSSION

This post-hoc analysis of a large cluster-randomized trial performed in 13 Dutch ICUs including 5,920 patients revealed that both SOD and SDD are cost-saving and more effective as compared to standard care. These findings were insensitive to changes in discount rates and extra costs for ventilation days. Furthermore, for SOD, but not for SDD, these findings were insensitive to current (higher) market-prices of the topical components. The probabilities that SOD and SDD are cost-effective for a willingness to pay threshold of €20,000 per life year gained as compared to standard care, were 93% and 63%, respectively.

This is the first head-to-head comparison of the costs and benefits of SDD and SOD and the first comparison of both interventions versus standard care. Strengths of the present study include the large study size and the completeness of data collection.

Limitations of the study are the baseline differences between the three study periods. Patients receiving standard care were younger, had lower APACHE II scores and were less likely to receive mechanical ventilation and, therefore, seemed to have a better prognosis. In the original trial random effects logistic regression modelling was applied to adjust for these differences.³ Here we have used crude data, without any adjustments for baseline differences. Our analysis points at superiority of SOD and SDD when compared to standard care, despite the somewhat more favourable prognosis at the time of ICU-admission of patients receiving standard care. Our findings on the cost-effectiveness of both interventions are, therefore, conservative estimates. Furthermore, patients receiving SOD were, on average, one year younger than those receiving SDD, which may have affected the difference in life years lost between both interventions. Other limitations are the restriction of cost data to the health care setting and the absence of antibiotic and microbiology cost data after ICU-discharge, which could not be obtained retrospectively. Finally, this trial was performed in ICU-settings with low endemicity of antibiotic resistance, which may limit generalizability to other settings.

The main contributor to the total costs was length of stay, which was composed of stay in ICU and hospital after ICU-discharge. The other costs, microbiology and antibiotics, were highest for SDD, which had been reported previously.²⁵ Some, relatively small single-centre studies, also determined the effects of SDD on costs of days in ICU or in the hospital. In a German study SOD with cefotaxime prophylaxis resulted in lower average costs for antibiotic therapy and for days on ventilation than during standard care.²⁶ In a French study of trauma patients both daily ICU-costs as well as mean antibiotic costs, including SDD treatment, were lower during SDD compared to standard care.²⁷ In a Spanish study mean costs of systemic antibiotics were lower and less diagnostic procedures for infections were performed during SDD, compared to standard care, which resulted in a 21% reduction of total costs per survivor in the SDD-treated group.²⁸ Yet, in none of these studies a formal cost-effectiveness analysis was performed.

VAP incidences were not determined in the Dutch SDD-SOD trial³ because of the perceived difficulties in uniformly diagnosing VAP in 13 ICUs. Yet, both SDD and SOD have been associated with reduced incidences of VAP, as compared to standard care.^{5 29} In addition to SDD and SOD there are other preventive measures that have been associated with reductions in the incidence of VAP, such as the use of silver-coated endotracheal tubes and continuous subglottic suctioning. In a large multi-centre randomized controlled trial silver-coated endotracheal tubes were associated with a relative risk reduction of the incidence of VAP of 35.9%, without discernible beneficial effects on patient outcome.³⁰ In a cost-effectiveness analysis of this trial the use of silver-coated tubes, although 45-fold more expensive than normal tubes (\$90 vs \$2 per tube), yielded savings of \$12,840 per episode of VAP prevented.³¹ Continuous subglottic suctioning (CSS) was, in a recent meta-analysis of 13 randomized trials, associated with a 45% reduction in the incidence of VAP (RR 0.55 (95%CI 0.46-0.66), but also without discernible beneficial effects on patient outcome (RR 1.01 (95%CI 0.85-1.20)).³² The intervention appeared cost saving in two studies, saving \$4,992 and €1,176 per episode of VAP prevented.^{33 34} However, these analyses were based on extrapolated costs per episode of VAP, rather than on the true costs generated during the trials. Other widely recommended measures to prevent VAP, such as the semi-recumbent patient position and different bundle approaches have not been associated with documented improvements in patient outcome and have not been evaluated with formal cost-effectiveness analyses.

In conclusion, both SOD and SDD appeared more beneficial and cost saving as compared to standard care and even if the costs of both measures would increase tenfold SOD will remain cost-saving and the incremental cost effectiveness ratio of SDD will be around the Dutch threshold for cost-effectiveness of €20,000 per life year gained. The higher price for medication follows from the higher costs for amphotericin B, which could be alleviated by replacing amphotericin B by nystatin, which has also good antifungal activity in topical application.³⁵ With 1,180 ICU-beds in a country of 16.6 million inhabitants (year 2010), extrapolation of our findings suggests that nationwide implementation of SOD or SDD in ICUs, as occurred after the trial, has saved, per year, 18-36 million euros.

The Dutch multi-centre study on SDD and SOD provided evidence of better patient outcome³, lower antibiotic resistance prevalence in the ICUs,³⁶ lower incidence of ICU-acquired bacteremia and ICU-acquired colonization of the respiratory tract with multi-resistant bacteria,³⁷ effective eradication of intestinal carriage with cephalosporin-resistant Enterobacteriaceae,³⁸ and low rates of resistance development to colistin³⁹. Importantly, these beneficial effects were obtained in ICUs with low levels of antibiotic resistance, reflected by incidence rates of bloodstream infections caused by methicillin-resistant *S. aureus*, vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae of <0.1, <0.1 and 0.5 per 1,000 patient at risk, respectively.³⁷ Whether these benefits can be realized in ICUs with different bacterial ecology remains to be determined,⁴⁰ but given the potential gains careful scientific evaluation is warranted.⁴¹

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PART V

Summary and discussion

Chapter 13

General discussion

Evelien A.N. Oostdijk and Marc J.M. Bonten

THE CONCEPT

In 1971 the concept of colonization resistance was proposed by van der Waaij et al. (1), who suggested a beneficial effect of the anaerobic flora in resisting colonization by aerobic gramnegative bacilli in the digestive tract in ICU patients. Many infections are caused by enteric bacilli, presumably from endogenous origin. Selective decontamination of the digestive tract (SDD) was developed to selectively eliminate the aerobic gramnegative bacilli from the digestive tract, leaving the anaerobic flora unaffected. The first clinical studies with SDD were performed in granulocytopenic patients yielding favorable results.(2) In the early 1980s, Stoutenbeek and coworkers (3) adapted the principle for ICU patients. The full concept of SDD aims to eradicate microorganisms from the intestine, the stomach, and the oropharynx by nonabsorbable antibiotics, which are combined with systemic antibiotic prophylaxis during the first days of ICU admission. In the SDD regimen the combination of colistin and an aminoglycoside are generally used, both are effective against gramnegative bacilli and *Staphylococcus aureus*, non-absorbable and do not affect the anaerobic intestinal flora. Amphotericin B was added to prevent overgrowth with yeasts and systemic prophylaxis to prevent early infections. Since the introduction of this preventive strategy, more than 45 randomized studies and multiple observational studies in a variety of ICU populations have been performed.(4) However, there are large differences in the regimens of SDD that were studied, the endpoints used, and the designs applied.

Several metaanalyses of SDD studies have been published, with more or less comparable results.(5, 6) They generally conclude that SDD decreases the incidence of VAP caused by aerobic gramnegative bacteria with RRRs ranging from 0.40 to 0.78, although reported outcomes regarding prevention of VAP were related to the methodological quality of the individual studies.(7)

As an alternative to SDD, investigators have evaluated the effects of oropharyngeal decontamination alone. (8-10) In a prospective randomized placebocontrolled doubleblind study, 87 patients received topical antimicrobial prophylaxis in the oropharynx and 139 patients received placebo. The aim of the study was to prevent VAP by modulation of oropharyngeal colonization, without influencing gastric and intestinal colonization and without systemic prophylaxis. Oropharyngeal colonization present on admission was eradicated in 75% of the patients (4% among control patients) and only 10% of study patients acquired oropharyngeal colonization, as compared to 61% of control patients. There were no significant differences in gastric and intestinal colonization. This regimen resulted in a RRR for VAP of 0.62 (95% CI 0.26–0.98).(8)

EXPERIENCE WITH SDD/SOD IN THE NETHERLANDS

Most detailed data on the effects of SDD and SOD in ICU-patients come from two studies performed in Dutch ICUs.(9, 11) The ecological setting of these ICUs is characterized by low levels of antibiotic resistance: For instance, prevalence of methicillin-resistance among *S. aureus* isolates was <1%, of vancomycin-resistance among enterococci was <1%, and of extended-spectrum betalactame production among Enterobacteriaceae was <5%.

In the first study two ICU-wards, within a single university hospital, were compared. In one unit all eligible patients (n=466) received during a two-year period SDD and in the other unit none of the 468 admitted patients received SDD.(11) Eligibility was defined as an expected duration of intubation of at least 48 hours or an expected stay in ICU of at least 72 hours if not intubated. The second study was a multi-centre cluster-randomized cross-over study in 13 ICUs in the Netherlands.(9) During study-periods of six months all eligible patients (same criteria as in (11)) in a single unit received SDD, SOD or standard care (no SDD and no SOD), and all three regimens were applied in random order in all participating ICUs. The SDD-regimen was identical in both studies and in both studies interventions were applied for all patients eligible. As SDD and SOD pursue a change in the bacterial ecology within the unit, a study design in which all patients are exposed to the same procedures in time is the best to quantify effectiveness. If patients are individually randomized decontaminated patients may offer some protection against acquired colonization and subsequent infection in those receiving standard care, and vice versa, and this will underestimate true effectiveness.

Effects on patient outcome

In both studies the “classical” SDD regimen (tobramycine, colistine en amphotericine B) was, compared to a control population (no SDD/SOD), and SDD and SOD were associated with reduced mortality. In the cluster-randomised study both SOD and SDD were associated with a lower day-28 mortality. Compared to the control population, the relative risk reduction (RRR) for day-28 mortality was 11% and 13% for SDD and SOD, corresponding to an absolute mortality reduction on day-28 of 2.9% and 3.5% for SDD and SOD (9). The survival benefit one year ICU-admission was less (and no longer statistically significant), being 4% and 7% for SDD and SOD, respectively.(12) In the single-center study the RRR for ICU- and hospital-mortality was 35% and 22%, respectively.(11)

The design of both studies had, undoubtedly, many advantages as compared to a study with randomisation of individual patients, but had, inevitably, also some disadvantages. In a cluster-randomised design individual patients are not randomised, which may facilitate inclusion bias. In the cluster-randomized study patients included in the control population had – at the time of ICU-admission – on average a lower APACHE-II score, were less frequently mechanically ventilated and were more frequently admitted for surgical reasons. All these determinants are

associated with a better prognosis. A random-effects logistic-regression model was used to adjust for these baseline differences, which may not adjust for all confounders. In the single-center study SDD was applied in one ICU-ward only and the availability of beds determined in which ICU a new patient was admitted. Although baseline characteristics were comparable for both groups, residual confounding cannot be ruled out. Nevertheless, both studies provide convincing evidence that SDD and SOD reduce ICU-mortality under the circumstances tested.

Effects on Ventilator-Associated Pneumonia

Both SDD and SOD pursue decontamination of the oropharynx to prevent ventilator-associated pneumonia (VAP). In many studies the incidence of VAP, therefore, was the primary study endpoint, though this comes with major methodological problems. The most widely used combination of clinical, radiographic and microbiological criteria are partly subjective and have suboptimal specificity, as other conditions, such as ARDS, may have a similar clinical presentation. (13) Bronchoalveolar lavage with quantitative microbiological cultures of obtained samples has a higher specificity (14), but this invasive approach is used infrequently for routine diagnostic purposes. The use of subjective criteria for endpoint determination in the absence of blinding may introduce considerable bias. Only few studies quantified the effects of decontamination on VAP incidence using both a double-blind placebo-controlled design and invasive diagnostics with quantitative culturing in all patients with a clinical suspicion of VAP. In one such study, in the Netherlands, the RRR of VAP was 55% when applying SOD ($p < 0.05$). (8) There are several meta-analyses in which SDD and SOD are associated with statistically significant reductions in the incidence of VAP, but the before-mentioned methodological drawbacks apply to almost all individual studies included in these analyses. (5, 6)

Effects on ICU-acquired bacteremia, antibiotic use and costs

In the Dutch multi-center study the RRR of ICU-acquired bacteremia caused by enteric Gram-negative bacteria was, compared to standard care, 81% and 30% for SDD and SOD, respectively. (9) The incidence difference between SDD and SOD also reached statistical significance, and results from a post-hoc analysis suggest that this difference in effectiveness resulted from successful intestinal decontamination, that is pursued during SDD but not during SOD. (15)

In the Dutch multi-center study SDD and SOD were associated with a 10% reduction in systemic antibiotic use, which included the routine use of cefotaxim during the first four days as part of SDD. As part of SDD it is recommended not to prescribe antibiotics with anti-anaerobic activity, which resulted in a decline in the intravenous use of clindamycin, piperacillin-tazobactam and carbapenem antibiotics and in a relative increase of 85% in the use of cephalosporins. (9)

The results of this multi-center study were used to determine the cost-effectiveness of SDD and SOD, in which costs for microbiology, antibiotics and length of stay were compared to the benefits of life years gained, based on hospital mortality data. (16) Both SOD and SDD were associated

with less costs and were more effective than standard care. Per patient SOD and SDD were, on average, €1507 and SDD €758 less expensive. Even if the daily costs of the topical medication would increase tenfold (from €4 to €40 for SOD and from €40 to €400 for SDD) SOD would remain cost-saving. In such a scenario the costs of SDD would be €21,590 per life year gained.

Effects on antibiotic resistance

The benefits of SDD and SOD should be carefully balanced against the potential disadvantages in the short-term, but also in the long-term. These include resistance against any of the antibiotics used and increased transmission of antibiotic-resistant bacteria in general because of the higher antibiotic pressure induced. In a systematic review and meta-analysis of 64 studies there was no evidence of a higher incidence of acquisition of resistance during SDD, as compared to control populations.(4) In the two Dutch studies SDD and SOD were strongly associated with reduced incidences of infection and carriage with antibiotic-resistant bacteria (Table). (9, 11) As compared to SOD, SDD offered better protection against ICU-acquired bacteremia with antibiotic-resistant bacteria and against acquired carriage of the respiratory tract with Gram-negative bacteria intrinsically resistant to colistin and with acquired resistance for third-generation cephalosporins. (17) The latter is quite remarkable, as the use of these antibiotics had increased with 85% during SDD.

The ecological effects of SDD and SOD were determined through monthly one-day point prevalence surveillance of all patients present in any of the 16 participating ICUs.(18) The implementation of SDD/SOD was immediately followed by a decline in the prevalence of antibiotic-resistant Gram-negative bacteria in the respiratory tract, but during the months that the interventions were used the prevalence of ceftazidim resistance increased (β 0.09 ($p < 0.05$)). After discontinuation of SDD/SOD the prevalence returned to pre-intervention levels. Similar observations were made for intestinal carriage: a rapid decline in prevalence after implementation of SDD, and a rapid return to pre-intervention prevalence levels after discontinuation. Only for ceftazidim resistance prevalence levels remained elevated after SDD, as compared to pre-intervention. Stable and low prevalence levels of resistance during SDD were observed in longitudinal studies from Germany and Spain.(19, 20) However, there are also reports of higher prevalence of carriage with Gram-positive bacteria during SDD (21, 22), including MRSA,(23, 24) and of outbreaks with ESBL-producing Gram-negative bacteria. (25, 26)

Endpoint	SDD versus control	SOD versus control	SDD versus SOD
Mortality			
Day 28	RRR 13%(9)* (p<0.05)	RRR 11%(9)* (p<0.05)	
Intensive Care mortality	RRR 15%(9)* (p<0.05)	RRR 10%(9)* (p<0.05)	
Hospital mortality	RRR 35% (95%CI 15% - 51%)(11)	RRR 33% (95% CI -5% - 57%)(8)	
One year survival	RRR 9%(9)* (p<0.05)	RRR 11%(9)* (p<0.05)	
	RRR 22% (95%CI 4% - 37%)(11)	RRR 22% (NS)(8)	
	RRR 4% (NS) ⁴	RRR 7% (NS) ⁴	
		RRR -1% (NS)(8)	
Infections			
ICU-acquired bacteraemia	RRR 56% (95%CI 0.43% - 64%)(9)	RRR 32% (95%CI 1.4% - 47%)(9)	RRR 35% (95%CI 15% - 51%)(9)
Enterobacteriaceae	RRR 81% (95%CI 68% - 88%)(9)	RRR 30% (95%CI 2% - 50%)(9)	RRR 72% (95%CI 53% - 84%)(9)
GNF-GNR	RRR 57% (95%CI 33% - 74%)(9)	RRR 51% (95%CI 13% - 73%)(9)	RRR 12% (NS)(9)
Candida species	RRR 51% (NS)(9)	RRR 9% (NS)(9)	RRR 47% (NS)(9)
Enterococci	RRR 15% (NS)(9)	RRR 7% (NS)(9)	RRR 9% (NS)(9)
VAP		RRR 55% (95% CI 3% - 79%)(8)	
Resistance			
ICU-acquired bacteraemia with HRMO	RRR 59% (95%CI 6% - 82%)(17)	RRR -10% (95%CI -105% - -41%)(17)	RRR 62% (95%CI 15% - 83%)(17)
Acquired respiratory tract colonization	RRR 42% (95%CI 22% - 57%)(17)	RRR 35% (95%CI 13% - 51%)(17)	RRR 11% (NS)(17)
HRMO			
Tobramycine resistant GNB	RRR -21% (NS)(17)	RRR -8% (NS)(17)	RRR -11 (NS)(17)
Cefoxim resistant Enterobacteriaceae	RRR 74% (95%CI 39% - 88%)(17)	RRR 1% (NS)(17)	RRR 63% (95%CI 38% - 88%)(17)
Intrinsically colistin resistant GNB	RRR 59% (95%CI 43% - 71%)(17)	RRR 16% (NS)(17)	RRR 51% (95%CI 31% - 65%)(17)
Non-intrinsically colistin resistant GNB	RRR 31% (NS)(38)	RRR -6% (NS)(38)	RRR 35% (NS)(38)
Acquired colonization with <i>P. aeruginosa</i> ^			
Ceftazidime resistant	RRR 83% (95%CI 23% - 96%)(11)		
Ciprofloxacin resistant	RRR 92% (95%CI 39% - 99%)(11)		
Imipenem resistant	RRR 94% (95%CI 51% - 99%)(11)		
Tobramycine resistant	RRR -5% (NS)(11)		
Acquired colonization with other GNB ^			
Ceftazidime resistant	RRR 19% (NS)(11)		
Ciprofloxacin resistant	RRR 70% (95%CI 37% - 85%)(11)		
Imipenem resistant	RRR 90% (95%CI 19% - 99%)(11)		
Tobramycine resistant	RRR 56% (95%CI 26% - 73%)(11)		
Polymyxine	RRR -57% (NS)(11)		

Table 1. Overview of various endpoints obtained from Dutch randomized studies comparing SDD and/or SOD to control.

SDD, selective digestive tract decontamination; SOD, selective oropharyngeal decontamination; RRR, relative risk reduction; 95% CI, 95% confidence interval; ICU, intensive care; VAP, ventilator associated pneumonia; HRMO, highly resistant micro-organism(39); GNB, gram negative bacteria

* corrected for present baseline differences using a random-effects logistic regression model

PC, persoonlijke communicatie; Effects of Decontamination of the Digestive and Oropharynx in ICU Patients on one-year survival, Oostdijk E.A.N. De Swith A.M.G.A., Bonten M.J.M., On behalf of the Dutch SOD-SDD trialists group, accepted for publication

^ Acquired colonization in sputum, throat, rectum, axilla en wounds

Colistin is an old antibiotic that currently is, worldwide, increasingly being used as a last resort agent to treat infections with multiple antibiotic-resistant Gram-negative bacteria. Little is known about the mechanisms of resistance to colistin, but long-term intravenous treatment is considered an important risk factor.(27) In Dutch ICUs daily use of topical colistin, as in SDD and SOD, was not associated with acquired carriage of colistin-resistant Enterobacteriaceae in the respiratory tract.(28) Observed rates of acquired carriage were 1.1, 0.7 en 0.8 per 1,000 patient days at risk during SOD, SDD and control, respectively. For rectal carriage (only measured during SDD) comparable rates were observed, but the risk increased (to 15,5 per 1,000 patient days at risk) in patients colonized with tobramycin-resistant Enterobacteriaceae.

Eradication or suppression of carriage reduces colonization pressure, and as such SDD has been applied successfully as a control measure (together with other interventions) during outbreaks, for instance in France and the UK.(29, 30) In the Dutch setting, eradication of intestinal carriage with Enterobacteriaceae during SDD was equally successful for strains that were susceptible or resistant to third-generation cephalosporines. Eradication, was less effective, if these bacteria were also resistant to tobramycin.(31) In Israel SDD (with gentamicyn and polymyxin E) was tested in a double-blind placebo-controlled trial for its effectiveness in eradicating carriage with carbapenem-resistant Gram-negatives.(32) Among those that received SDD 61% had a negative rectal culture after two weeks, as compared to 16% in the placebo group (OR 0.13 (0.02-0.74)). All throat cultures were negative after one week in SDD patients, as compared to 14.2% in the placebo group. Nevertheless, after discontinuation of SDD carriage rates rapidly increased again.

Adverse events

The oral paste used in SDD and SOD may cause oesophageal obstruction if not dispelled carefully before application of the next dosage.(33) Furthermore, sustained use of SDD may lead to some absorption of tobramycin from the intestinal tract. For instance, 83 of 100 patients had detectable tobramycin levels in blood ($>0.050\text{mg/L}$),(34) and 12 out of 19 patients that received both continuous venovenous haemofiltration and SDD had detectable tobramycin levels, in one patient being toxic ($>3.0\text{mg/L}$).(35)

The recent large studies performed in Dutch ICUs have provided strong evidence that, in that particular ecological setting, SDD and SOD reduce ICU-mortality, ICU-acquired bacteremia with Gram-negative bacteria, and systemic antibiotic use in a cost-effective manner. During a period of ten years there was no evidence that SDD or SOD were associated with increased resistance in these ICUs. If any, both measures were associated with reductions in systemic antibiotic resistance. These counterintuitive observations might result from the overall lower usage of systemic antibiotics or from the fact that the topical antibiotics are still active against many resistant bacteria. Yet, all studies have used conventional culture techniques that may suffer

from antibiotic carryover effects, and it is currently unknown to what the non-culturable flora is affected by SDD and SOD. In Dutch ICUs SDD and SOD appear equally effective on relevant clinical outcomes, such as survival and length of stay. SDD seems more protective against ICU-acquired bacteraemia and respiratory tract carriage with resistant Gram-negative bacteria, and SOD seems to have a more attractive cost-effectiveness profile.

It is currently unknown to what extent these effects can be achieved in settings with different bacterial ecology. Although successful application has been reported from several, solitary, ICUs across Europe,(22, 36) more studies are needed. The potential threat of enhanced selection of pre-existing multi-resistant pathogens is becoming more important, with the current emergence of carbapenem-resistant pathogens. Nevertheless, if similar effects would be achieved as in Dutch ICUs, these interventions could save 7,000 deaths per year in British ICUs, only.(37) The use of SDD (or SOD) as a measure to control outbreaks with multi-drug resistant bacteria, that could not be controlled with classical infection control measures, should strongly be discouraged, until more data on its ecological safety and effectiveness have been obtained.

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Nederlandse samenvatting (Dutch summary)

Acknowledgements

Curriculum vitae

NEDERLANDSE SAMENVATTING (DUTCH SUMMARY)

Introductie

Infecties vormen een belangrijke complicatie in de behandeling van ernstige zieke patiënten in IC-afdelingen. In West-Europese landen zijn infecties van de luchtwegen het meest prevalent en zijn gram-negatieve bacteriën de meest voorkomende verwekkers. IC-verworven infecties zijn geassocieerd met hogere morbiditeit, sterfte en kosten voor ziekenhuisbehandeling.

Selectieve decontaminatie is een van de vele strategieën die aangewend zijn om het optreden van deze infecties te verminderen. Selectieve Darm Decontaminatie (SDD) bestaat uit een mondpaste en een suspensie voor intestinale toediening met niet-resorbeerbare antibiotica om de tractus digestivus van mond tot anus te ontdoen van potentieel pathogene micro-organismen. Er zijn meerdere combinaties van topicale antibiotica bestudeerd, en het “klassieke” regime bestaat uit tobramycine, colistine en amphotericine B 4dd vanaf IC-opname tot IC-ontslag. Naast de topicale antibiotica krijgen SDD-patiënten gedurende de eerste vier dagen op IC systemische antibiotica, meestal een 3^e generatie cephalosporine. De eerste evaluatie van deze interventie bij IC-patiënten verscheen in 1984(1) en intussen zijn er meer dan 45 gerandomiseerde studies gepubliceerd. In 2001 publiceerde de SWAB haar advies over SDD bij beademde patiënten op de IC, en concludeerde dat het routinematig gebruik van SDD bij deze patiëntengroep niet was aanbevolen.(2) Er waren geen overtuigende bewijzen voor effectiviteit van goed opgezette individuele studies en er was nog veel onduidelijkheid over de risico's met betrekking tot selectie van antibiotica-resistente bacteriën. De noodzaak van goed opgezette studies van voldoende omvang om klinisch relevante eindpunten te evalueren en zorgvuldige analyse van de effecten van SDD op resistentie werd onderstreept.

Twaalf jaar later zijn dergelijke studies in Nederlandse ziekenhuizen verricht en is het aangewezen om het advies met betrekking tot routinematig gebruik van SDD (of andere vormen van selectieve decontaminatie) te heroverwegen. Aangezien de grootste en meest recente studies in Nederland verricht zijn, en aangezien de bacteriële ecologie van Nederlandse IC-afdelingen (met weinig multi-resistente bacteriën) zich niet eenvoudig laat vergelijken met die van IC-afdelingen in veel andere landen is deze aanbeveling grotendeels gebaseerd op de resultaten van twee recente Nederlandse studies. Dit betrof een studie in het Academisch Medisch Centrum, waarin patiënten van twee IC-afdelingen met elkaar werden vergeleken. In de ene afdeling kregen gedurende twee jaar 466 patiënten SDD en in de andere IC werd SDD niet gebruikt en werden 468 patiënten geïncludeerd(3, 4). De tweede studie betrof een cluster-gerandomiseerde cross-over multi-center studie in 13 IC-afdelingen. In elk van de IC-afdelingen kregen patiënten gedurende zes maanden SDD, SOD (alleen orofaryngeale decontaminatie en zonder standaard intraveneuze profylaxe) of geen van beide interventies. In totaal werden 5939 patiënten geïncludeerd (2045 kregen SDD, 194 kregen SOD en 1990 kregen standaard behandeling) en de volgorde van de interventies was per IC-afdeling gerandomiseerd (4). Het SDD-regime was identiek in beide

studies en in beide studies werden de interventies toegepast bij patiënten met een verwachte minimale beademingsduur van 48 uur of een verwachte opnameduur van minimaal 72 uur. In beide studies werd SDD (en SOD) als ecologische interventie in een IC-afdeling geïmplementeerd, en ondergingen alle patiënten in een bepaalde tijdsperiode dezelfde interventie. Hiermee werd voorkomen dat succesvol gedecontamineerde patiënten een beschermend effect hadden op patiënten die geen SDD (of SOD) kregen, en vice versa, waardoor het ware effect van de interventie onderschat zou worden. Daarnaast weerspiegeld een afdelingsbreed toegepaste interventie de situatie wanneer SDD of SOD als routinemaatregel zouden worden toegepast.

Effect op mortaliteit

In beide studies was de “klassieke” SDD (tobramycine, colistine en amphotericine B), vergeleken met een controle populatie (geen SDD/SOD), geassocieerd met lagere sterfte.

In het cluster-gerandomiseerde onderzoek waren SOD als SDD geassocieerd met een relatieve risico reductie (RRR) voor dag-28 sterfte van 11% en 13%, wat overeenkwam met een geschatte absolute mortaliteitsreductie op dag-28 van 2.9% en 3.5% (Tabel 1). Het overlevingsvoordeel 1 jaar na IC-opname was minder groot (en niet meer statistisch significant) en was 4% en 7% voor SDD en SOD. (5) (hoofdstuk 11)

In de Nederlandse multi-center studie waren 2762 chirurgische en 3165 niet-chirurgische patiënten geïncludeerd. In een post-hoc analyse van de patiënten die SDD hadden gekregen, was de IC-sterfte vergelijkbaar in beide groepen, maar waren de totale beademingsduur, IC-opnameduur en ziekenhuis opnameduur significant korter voor chirurgische dan voor niet-chirurgische SDD-patiënten. In niet-chirurgische patiënten was SOD, maar niet SDD, geassocieerd met een lagere sterfte. (6) In de Amsterdamse studie was de RRR voor IC-sterfte 35% en 22% voor ziekenhuissterfte. (3)

De opzet van beide studies had tegengesteld voordeel ten opzichte van een studie met randomisatie van individuele patiënten, maar daardoor ook een aantal nadelen. In de cluster-gerandomiseerde multicenter studie werden individuele patiënten niet gerandomiseerd, waardoor bias in inclusie kan ontstaan. Patiënten in de controlegroep hadden op het moment van inclusie, gemiddeld, een lagere APACHE-II score, werden minder vaak beademd en waren vaker opgenomen vanwege een chirurgische oorzaak. Al deze determinanten zijn geassocieerd met een betere prognose, waarvoor correctie in de analyse noodzakelijk was. In de Amsterdamse studie werd de interventie in één van de twee ICs toegepast en besliste beschikbaarheid van bedden over de toewijzing van patiënten naar een afdeling. Hoewel de baseline patiëntkarakteristieken vergelijkbaar waren, is residuale confounding met deze opzet niet uit te sluiten. Desalniettemin zijn wij van mening dat beide studies overtuigende argumenten aandragen dat SDD en SOD de sterfte van IC-patiënten verminderen. Extrapolatie van de multicenter studie (13 IC-afdelingen met in totaal 197 IC-bedden) naar de landelijke situatie (1100 IC-bedden) zou betekenen dat jaarlijks ruim 700 patiënten minder in Nederlandse IC-afdelingen zouden overlijden.

Effect op andere uitkomst maten

Zowel SDD als SOD streven naar decontaminatie van de oropharynx met als doel beademings-geassocieerde pneumonie te voorkomen. In veel studies is daarom het optreden van beademings-geassocieerde pneumonie het primaire eindpunt, maar hier kleven grote methodologische problemen aan. De doorgaans gebruikte combinatie van klinische, radiologische en microbiologische criteria hebben een lage specificiteit doordat vele andere aandoeningen, zoals ARDS, zich soortgelijk kunnen presenteren.(7) Een broncho-alveolaire lavage in combinatie met kwantitatieve microbiologische kweken heeft een hogere specificiteit maar wordt in weinig Nederlandse IC-afdelingen routinematig gebruikt in het diagnostisch proces. Daarnaast zijn deze criteria deels subjectief en dat kan, in afwezigheid van blinding, bias introduceren.

In één Nederlandse studie is het effect van SOD op het ontstaan van beademings-geassocieerde pneumonie op dubbelblind placebo-gecontroleerde wijze en met hoog specifieke diagnostiek onderzocht. In deze studie ondergingen alle patiënten met een klinische verdenking op beademings-geassocieerde pneumonie een broncho-alveolaire lavage. De RRR van beademings-geassocieerde pneumoniedoor SOD was 55% ($p < 0.05$).⁽⁸⁾ Er zijn verschillende meta-analyses waarin SDD en SOD geassocieerd zijn met significante reducties in incidentie van beademings-geassocieerde pneumonie, maar voor bijna alle individuele studies gelden bovengenoemde methodologische bezwaren.⁽⁸⁾⁽⁹⁾

In de Nederlandse multi-center studie was de RRR van IC-verworven bacteriëmie veroorzaakt door Gram-negatieve darmbacteriën 81% en 30% voor SDD en SOD in vergelijking met de controlepopulatie.⁽⁴⁾ Ook het verschil tussen SDD en SOD was statistisch significant, en resultaten van een post-hoc analyse suggereerden dat dit verschil was toe te schrijven aan de intestinale decontaminatie, die bij SDD wel en bij SOD niet nagestreefd wordt.⁽¹¹⁾ **(hoofdstuk 10)**

In de Nederlandse multi-center studie waren SDD en SOD geassocieerd met een reductie in het gebruik van intraveneuze antibiotica van ongeveer tien procent. Dit was inclusief de vier dagen cefotaxim als onderdeel van SDD. Teneinde de kolonisatieresistentie in stand te houden worden tijdens SDD antibiotica met anti-anaerobe werking zoveel mogelijk vermeden. Dit leidde tot een reductie in het gebruik van clindamycine, piperacilline-tazobactam en carbapenems, maar tot een relatieve toename van 85% in het gebruik van cephalosporines.

De gegevens van de Nederlandse multi-center studie zijn gebruikt om de kosteneffectiviteit van SDD en SOD te berekenen, waarbij kosten van microbiologisch onderzoek, antibioticagebruik en ligduur werden afgezet tegen de baten van gewonnen levensjaren, gebaseerd op ziekenhuis mortaliteit⁽¹²⁾. **(hoofdstuk 12)** Zowel SOD als SDD waren kostenbesparend. Per patiënt was SOD gemiddeld €1507 en SDD €758 goedkoper. Met een vertienvoudiging van de dagelijkse prijs voor SOD (van €4 naar €40) en SDD (van €40 naar €400) zou alleen SOD kostenbesparend blijven. In een dergelijk scenario zouden de kosten van SDD €21,590 per gewonnen levensjaar bedragen.

Effect op antibiotica resistentie

De voordelen van SDD en SOD moeten zorgvuldig afgewogen worden tegen de eventuele nadelen op korte, maar ook op lange termijn. Resistentie van bacteriën tegen de gebruikte antibiotica en toename van verspreiding van antibiotica-resistente bacteriën door hogere antibioticadruk zijn de belangrijkste potentiële gevaren van deze strategieën. In een systematische review en meta-analyse van 64 studies werd geen verhoogde incidentie gevonden van dragerschap met antibiotica resistente bacteriën tijdens SDD ten opzichte van controle.(13) In de twee Nederlandse studies waren SDD en SOD sterk geassocieerd met een reductie in het optreden van infecties en kolonisatie met antibiotica-resistente bacteriën (Tabel).(4)(3) In vergelijking met SOD beschermde SDD beter tegen IC-verworven bacteriëmie met antibiotica-resistente bacteriën en tegen verworven kolonisatie van de luchtwegen met Gram-negatieve bacteriën die intrinsiek resistent zijn voor colistine en die resistentie verworven hebben tegen derde-generatie cephalosporines. Dit is opmerkelijk, want juist die antibiotica werden meer gebruikt gedurende SDD.

De ecologische effecten van SDD en SOD zijn in de Nederlandse multi-center studie bestudeerd middels maandelijks puntprevalentie onderzoeken bij alle op dat moment opgenomen IC-patiënten.(14) (hoofdstuk 5) Na introductie van SDD/SOD was er een onmiddellijke daling in de prevalentie van antibiotica resistente Gram-negatieve bacteriën in de luchtwegen, maar gedurende de interventies nam de prevalentie van ceftazidime resistentie toe (β 0.09 ($p < 0.05$)). Na het stoppen van SDD/SOD keerde de prevalentie terug naar het niveau van voor interventie. Hetzelfde werd waargenomen voor intestinale kolonisatie: een snelle daling van prevalenties tijdens SDD, en een snelle terugkeer naar de prevalenties van voor SDD na het stoppen van de interventie. Alleen voor ceftazidime resistentie steeg de prevalentie na het stoppen van SDD tot boven de prevalentie van de pre-interventieperiode. In longitudinale studies in Duitsland en Spanje werd geen toename van resistentie gevonden tijdens het gebruik van SDD.(17,18)

Colistine is een oud antibioticum dat, mondiaal, steeds vaker wordt ingezet als laatste middel voor infecties met multi-resistente Gram-negatieve bacteriën. Er is nog weinig bekend over resistentie voor colistine, maar langdurig intraveneus colistine gebruik lijkt een belangrijke risicofactor. (15) In een post-hoc analyse van de Nederlandse multi-center studie was het dagelijks gebruik van colistine – in topicale vorm – gedurende SDD en SOD niet geassocieerd met het verwerven van dragerschap met colistine-resistente Enterobacteriaceae in de luchtwegen.(16) (hoofdstuk 6) De incidentie van verworven kolonisatie met colistine-resistente Enterobacteriaceae per 1000 patiëntdagen was 1-3 voor luchtwegen en tractus intestinalis, maar steeg tot 15 bij patiënten die drager waren van tobramycine-resistente Enterobacteriaceae.

Er zijn echter ook meldingen van hogere prevalenties van dragerschap met Gram-positieve bacteriën (19,20), inclusief MRSA,(21,22) en een uitbraak van ESBL-producerende gram-negatievebacteriën (23) gedurende SDD. In één Nederlandse IC-afdeling werd SDD geïmplementeerd als maatregel om een clonale uitbraak met ESBL-producerende *Klebsiella*

pneumoniae te bestrijden. Klassieke infectiepreventie maatregelen waren eerder onvoldoende gebleken. In deze afdeling trad na introductie van SDD een snelle toename op van colistine en tobramycine resistentie bij ESBL-positieve *K. pneumoniae* en infecties met Gram-negatieve bacteriën die intrinsiek resistent zijn voor colistine. Pas na het stoppen van SDD werd de uitbraak gecontroleerd.(24)

Eradicatie (of suppressie) van dragerschap met antibiotica-resistente bacteriën kan bijdragen aan het controleren van een uitbraak. In de multi-center studie was eradicatie van intestinale kolonisatie met Enterobacteriaceae gedurende SDD even succesvol voor bacteriën die wel en niet gevoelig waren voor derde-generatie cephalosporines, maar minder succesvol als deze bacteriën ook nog resistent waren voor tobramycine.(26) (hoofdstuk 9) SDD werd succesvol gebruikt ter controle van ESBL-producerende *Klebsiella pneumoniae* in een Franse en een Engelse IC.(25,27) In Israel was SDD (met gentamycine en polymyxine E) in een dubbel-blind placebo gecontroleerde studie effectief in het onderdrukken van dragerschap met carbapenem-resistente Gram-negatieve bacteriën. (28) Met SDD had 61% een negatieve rectumkweek na 2 weken (versus 16% met placebo, (OR 0.13 (0.02-0.74)) en waren alle keelkweken na een week negatief (versus 14.2% met placebo).

Bijwerkingen

SDD en SOD mondpasta kan de oesofagus obstrueren indien deze niet goed verwijderd wordt voor het aanbrenge van de nieuwe gift.(29) Daarnaast kan bij langdurig gebruik van SDD absorptie van tobramycine uit het maag-darm kanaal plaatsvinden. Zo hadden 83 van 100 patiënten detecteerbare tobramycine spiegels in het bloed (>0.050mg/L)(30), en hadden 12 van 19 patiënten die continue venoveneuzehemofiltratie ondergingen en SDD kregen detecteerbare tobramycine spiegels, die bij één patienteen toxische waarde (>3.0mg/L) bereikte.(31)

Alternatieven

Er zijn geen andere infectie preventie maatregelen voor beademde intensive care patiënten, waarvan vergelijkbare effecten op sterfte of andere relevante eindpunten overtuigend zijn aangetoond. Decontaminatie van de mondholte met chloorhexidine was in een Nederlands multi-center onderzoek geassocieerd met een 40-50% reductie in het optreden van beademings-geassocieerde pneumonie, maar de studie was te klein om een effect op sterfte te kunnen aantonen.(32) Dat is ook de conclusie van een recente meta-analyse: er is wel evidentie voor een beschermend effect op het ontstaan van beademingsgeassocieerde pneumonie, maar niet op reductie van sterfte.(9) Sommige studies hebben een beschermend effect van probiotica op het ontstaan van beademingsgeassocieerde pneumonie gesuggereerd, maar de resultaten van twee meta-analyses spreken elkaar hierin tegen.(34,35) In een Nederlands onderzoek, dat voortijdig afgebroken werd, kon non-inferiority in het voorkomen van IC-verworven infecties met met probiotica, ten

opzichte van SDD, niet aangetoond worden.⁽³⁶⁾ De studie was te klein om effecten op sterfte te kunnen onderzoeken. De onderzoekers concludeerden dat meer studies nodig zullen zijn om effectiviteit van probiotica in preventie van beademings-geassocieerde pneumonie vast te stellen.

Discussie

Twee Nederlandse studies, met in totaal bijna 7000 intensive care patiënten, hebben sterk aannemelijk gemaakt dat SDD en SOD in Nederlandse IC-afdelingen sterfte, IC-verworven bacteriemien met Gram-negatieve bacteriën en systemisch antibioticagebruik verminderen en dat beide interventies kostenbesparend zijn. Gedurende een periode van tien jaar zijn er geen aanwijzingen dat het gebruik van SDD en SOD in Nederlandse intensive care afdelingen tot een toename van resistentie geleid heeft. In de verrichte studies was er zelfs sprake van een minder resistentie, mogelijk door reductie van systemische antibiotica of door de effectiviteit van de lokale antibiotica voor veel resistente bacteriën. Alle microbiologische onderzoeken zijn echter gebaseerd op conventionele kweektechnieken, waarbij een effect van antibiotica in de monsters niet volledig uit te sluiten is. Momenteel wordt onderzocht in hoeverre het niet-kweekbare gedeelte van de darmflora fungeert als een reservoir voor antibiotica resistentiegenen tijdens SDD⁽³⁷⁾ (Bonten persoonlijke communicatie). Daarnaast hebben alle studies zich vooralsnog beperkt tot de effecten van SDD en SOD tijdens de opname op de intensive care. Het optreden van (re-)kolonisatie met resistente flora na ontslag van de intensive care wordt momenteel onderzocht (De Jonge, persoonlijke communicatie).

Op basis van de beschikbare gegevens lijken SDD en SOD even effectief op klinische uitkomsten zoals sterfte en ligduur. SDD heeft een groter beschermend effect dan SOD op het ontstaan van IC-verworven bacteriemien en dragerschap met resistente bacteriën, maar SOD heeft een aantrekkelijker kosten-effectiviteitsprofiel.

Aanbevelingen

Op basis van de geobserveerde effecten in Nederlandse intensive care afdelingen wordt het gebruik van SDD en SOD aanbevolen voor intensive care patiënten met een verwachte beademingsduur van minimaal 48 uur of een verwachte ligduur van minimaal 72 uur. Op dit moment kan geen voorkeur voor een van beide interventies worden uitgesproken. Gebruik van deze interventies dient samen te gaan met nauwkeurige microbiologische surveillance, bij opname en tweemaal wekelijks, van bijzonder-resistente micro-organismen en Gram-negatieve bacteriën met resistentie voor aminoglycosiden of colistine. Een goede hygiëne op de afdeling, blijkend uit afwezigheid van transmissie van bijzonder-resistente micro-organismen, is een voorwaarde voor het implementeren van SDD of SOD. Bij uitbraken met bijzonder-resistente micro-organismen dient (tijdelijke) onderbreking van de regimes overwogen te worden. De bacteriele ecologie van kweekbare en niet-kweekbare micro-organismen moet longitudinaal bestudeerd worden om de lange-termijn effecten van SDD en SOD te kunnen beoordelen.

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