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REVIEW

# Development of antibiotic resistance related to selective decontamination of the digestive tract

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## Abstract

*Purpose:* To discuss the relevant studies on selective decontamination of the digestive tract (SDD) in intensive care unit (ICU) patients regarding the occurrence of antibiotic-resistant bacteria.

*Findings:* Since the introduction of SDD as a preventive infection measure in the ICU, there have been concerns about inducing antimicrobial resistance. Earlier studies proved that SDD reduces infections without a convincing clinical increase in resistant bacteria, but were not designed to assess this potential problem. In recent years, large prospective studies that were also designed to investigate the occurrence of resistant bacteria during SDD have shown a decrease in antibiotic-resistant Gram-negative bacteria. Increases of resistant Gram-positive bacteria and the increase of colistin resistance during SDD in a setting with an outbreak of extended spectrum beta lactamase producing *Klebsiella pneumoniae* have been reported.

*Conclusion:* SDD reduces colonization, infection and mortality. No convincing overall increase of antimicrobial resistance can be attributed to the use of SDD. The use of SDD in ICUs with low levels of antibiotic resistance can be justified.

## Introduction

It has long been recognized that ICU patients are susceptible to infections, such as respiratory tract infections due to mechanical ventilation. Many of these infections are caused by aerobic Gram-negative bacteria originating from the digestive tract. These nosocomial infections can increase morbidity, mortality and healthcare costs.[1,2] In the late nineteen-sixties, seventies and early eighties, studies initially performed on mice[3] and later in neutropenic leukaemia patients,[4] showed that anaerobic flora played an important role in preventing colonization with aerobic flora. Therefore, the hypothesis was postulated that secondary infections could be prevented by the prophylactic eradication of potential pathogenic bacteria.

Most infections in ICU patients have an endogenous source with the patient's own oropharynx and digestive tract as the main source of infection.[5] Colonization of the oropharynx and digestive tract with aerobic Gram-negative bacteria precedes nosocomial infections. Selective digestive tract decontamination (SDD) was introduced as a measure to prevent colonization with *Staphylococcus aureus*, Gram-negative bacteria and yeasts while leaving anaerobic microflora unchanged.[6] This can be accomplished by the administration of non-absorbable antibiotics to selectively decontaminate the digestive tract and reduce the load of potentially pathogenic bacteria while keeping the anaerobic flora intact. Different SDD strategies have been proposed to prevent secondary infections including adding systemic antibiotics as pre-emptive treatment for infections during the patient's first few days on the ICU. The first study published on SDD in ICU patients reported a study in trauma patients.[6] The result of this trial was a significant reduction in colonization and infection. Since then, many studies, reviews and systematic reviews have been published that address the effectivity and safety of SDD in ICU patients. Several studies using only the oropharyngeal part of the SDD, the so-called SOD (Selective Oropharyngeal Decontamination), have suggested comparable results to SDD in reducing ventilator associated pneumonia (VAP).[7,8]

Although there is evidence that SDD and SOD can reduce morbidity and mortality in ICU patients,[9,10] both these interventions are not widely applied outside the Netherlands. This can be partly explained by the fear of inducing antibiotic resistance in bacteria. A prophylactic, mostly systemic use of antibiotics is associated with increasing antibiotic resistance.[4] Antibiotic resistance is increasing worldwide and thus becoming more of a problem. This increase depends on time and place, the use of antibiotics and the prevalence of different species of bacteria.

The goal of this review is to collect and analyse the evidence regarding the development of antibiotic resistance related to SDD use in the ICU. A Pubmed search was performed for relevant articles published from 1960 until 2013 using the search strategy shown in *table 1*. Additionally, a cross reference search of selected articles was conducted. A historic perspective has been used to show the developments during the last three decades since the first publications on the use of SDD in ICU patients.

## Early studies

In the early eighties, Stoutenbeek and colleagues performed the first study in an ICU administrating SDD to 119 trauma patients after earlier successful application of this technique as a measure for preventing infection in neutropenic leukaemia patients.[4,6] The SDD-regime consisted of decontaminating the oropharynx and the digestive tract with non-absorbable antibiotics (tobramycin, colistin and amphotericin B) next to systemic administration of cefotaxim during the first four days to treat upcoming infections. In this study, the infection rate decreased from 80% in the retrospective studied control group, to 16% in the treatment group.[6] According to the author, the occurrence of resistant microorganisms was rare, but numbers were not reported.

Randomized clinical trials performed by Unertl et al.,[11] Kerver et al.,[12] and Ulrichet al.,[5] also showed a decrease in infections with Gram-negative bacteria. Mortality was either decreased[5,12] or unchanged[11] with equal length of stay in the ICU and duration of mechanical ventilation[5]. Unertl et al. showed that the overall occurrence of resistant pathogens did not increase during SDD when compared with the control group and that no therapeutic problems were posed for the few infections caused by resistant Gram-positive bacteria.[11] No emergence of multiple resistant bacteria was recorded by Kerver et al. during his study. Ulrich et al. used a regime of polymyxin E, norfloxacin and amphotericin B along with systemic trimethoprim until decontamination was achieved. Colonization and overgrowth of resistant micro-organisms did not occur. These studies were performed with relatively small groups and were not designed to assess antimicrobial resistance.

**Table 1.**

| Search strategy | Number of hits |
|---|---|
| ((selective decontamination gut) OR (selective decontamination digestive tract) OR (selective decontamination gastrointestinal tract) OR (SDD) AND ((antimicrobial resistance) OR (antibiotic resistance)) | 223 |
| Clinical trials | 34 |
| Review papers | 65 |
| Case reports | 2 |
| Historical articles | 1 |
| Meta-analysis | 6 |
| Randomized controlled trials | 28 |

In the nineteen-nineties, Rodriguez-Roldan et al. performed the first randomized, double-blind controlled study in Spain in which SDD was compared to a control group.[13] SDD was used without the systemic administration of antibiotics, but concomitant infections were treated with parenteral antibiotics in both groups. The pattern of resistance did not differ between groups, but the groups were very small (13 vs. 15 patients).

Up until this time, most studies had been performed with historical control groups. Aerdts et al. designed a prospective, blinded, randomized trial where a treatment group (TG) consisting of participants on SDD with systemic administration of cefotaxime was compared to two control groups.[14] These two control groups did not receive SDD but received different antibiotic regimes (ampicillin/piperacillin (A/P) vs. cefuroxime plus gentamicin (C/G)) in cases where an infection was suspected. People in the TG were less frequently colonized by Gram-negative bacteria in the oropharynx (TG 0 vs. A/P and C/G >80%) and stomach (TG 24% vs. A/P 94% and C/G 90%), acquired less respiratory tract infections, and had a lower infection related mortality. This was a study with low mortality rates and small numbers of included patients, so it was underpowered to permit conclusions regarding mortality. The development of resistance against the antibiotics used for prophylaxis was not observed. After a limited number of patients had taken part, this study was discontinued because of significant differences in colonization and infection between the treatment and control groups, in favour of the treatment group.[14]

In 1992, Hammond et al. reported the results of her study in South-Africa, a region with a high incidence of resistant microorganisms.[15] There was no significant difference between the SDD and placebo groups in infections overall but there was a reduction of infections with *Enterobacteriaceae* in the SDD group. In this study, mortality, lengths of stay in hospital and ICU stay were similar. Hammond found a significant increase in methicillin resistant *Staphylococcus aureus* (MRSA) and that the application of SDD was more expensive. She later published a study that evaluated the long term effects of SDD on the development of antimicrobial resistance.[16] A comparison was made between isolates in the previous year, during and after the use of SDD with systemic antibiotics. In the SDD group, a reduction was found for the resistance to third generation cephalosporins, the incidence of MRSA infections remained unchanged and there was no increase in microorganisms resistant to aminoglycosides. No long term effects on antimicrobial resistance could be attributed to the use of SDD.[16]

Other studies around that time showed that SDD led to lower rates of infections and colonization with resistant microorganisms. However, there were still concerns about the costs and clinicians were reluctant to implement SDD as oropharyngeal colonization with Gram-positive bacteria

increased.[17] Nonetheless, there were fewer infections with Gram-negative bacteria[17] and no selection of resistant Gram-positive or Gram-negative bacteria occurred in SDD groups.[18,19,20]

In the second half of the nineteen-nineties, several authors did report an increase in resistance associated with the use of SDD. These reports varied from a trend towards more resistance to gentamicin[21] and to polymyxin in the SDD group[22] to an increase of colonization (not infection) with multi-resistant coagulase negative *Staphylococci* (CNS)[23] and an increase in tobramycin-resistant microorganisms.[24] Lingnau et al. reported a shift towards Gram-positive microorganisms, an increase and outbreak in MRSA and an increase in ciprofloxacin resistance of CNS after the introduction of SDD in ICU patients.[25] He also reported on the control of the MRSA outbreak by implementing hygienic measures. These consisted of a change of protocols for hand washing, disinfection and room cleaning protocols, adopting the use of plastic gowns, barrier nursing techniques and motivating nursing staff by educating them on the transmission routes of bacteria. The incidence of pneumonia and mortality increased prior to the above-mentioned hygiene measures but decreased to relatively low values after these measures had been implemented and a decrease in the incidence of MRSA, methicillin-resistant *S. epidermidis* (MRSE), ciprofloxacin-resistant *S. aureus* and ciprofloxacin-resistant *S. epidermidis* was seen concomitantly.[26]

## Recent studies

Around the beginning of the millennium, a few reviews and meta-analyses were published that actually investigated the occurrence of antibiotic resistance associated with the use of SDD. Bonten et al. summarized the findings of 27 prospective randomized studies and six meta-analyses in 2000.[27] Although these studies were difficult to compare due to differences in the application of SDD (SDD or SOD alone) and differences in the antibiotics used, he concluded that SDD is associated with a decrease in the numbers of ventilator-associated pneumonias, but not with improved patient survival, reductions in the duration of ventilation or ICU stay or reductions in antibiotic use. He further stated that the use of SDD is associated with the selection of microorganisms that are intrinsically resistant to the antibiotics used but that studies in the main have been too small and too short to adequately investigate whether SDD will lead to the development of antibiotic resistance.

Concerns were raised over the fact that the increasing use of antibiotics during the last sixty years had led to an increase in antibiotic resistance and that SDD might contribute to further increase of antibiotic resistance.[27] In contrast, Zandstra & van Saene came to the conclusion that the eradication of the reservoir of abnormal bacteria located in the gut by topical non-absorbable antibiotics appears to significantly reduce morbidity, mortality and resistance.[28] His conclusions were to a great extent based on the review of randomized trials by d'Amico et al., cited earlier.[7]

The results of SDD trials have depended on the regime used and the environment where SDD is applied. In regions where the incidence of resistance was low, there was either no difference in the occurrence of resistant microorganisms,[29] or there was a decrease in colonization of Gram-negative microorganisms resistant to ceftazidime, ciprofloxacin, imipenem, polymyxin E or tobramycin.[30] Leone et al. evaluated the effect of SDD on antimicrobial resistance in multiple trauma patients over a six year period.[31] In SDD patients and in control patients, the resistance of *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter* to beta-lactimes and aminoglycosides was the same. He observed a relative overgrowth of Gram-positive cocci and an increase in MRSE but no increase in MRSA.

The use of oropharyngeal or enteral vancomycin during SDD to eradicate *S. aureus* gave rise to the fear of selecting vancomycine-resistant enterococci (VRE). De la Cal et al. investigated whether enteral vancomycine could eradicate MRSA in an endemic setting in Spain.[32] They found that the incidence of MRSA significantly decreased from 31% to 2%. There was an outbreak of VRE during SDD which was self-limiting. *S. aureus* intermediate sensitive to glycopeptides was not observed. About the same time, Silvestri et al. performed a randomized trial to assess the impact of oropharyngeal application of vancomycine on MRSA carrier rates and lower airway infections as well as the emergence of VRE. The study showed that topical oropharyngeal vancomycine was effective in preventing ICU-acquired lower airway infections and preventing secondary carriage due to MRSA in long-term ventilated patients receiving SDD. Neither VRE nor vancomycine-intermediate *S. aureus* was isolated during the study period or in the following year.[33] These studies had a relative short duration.

In 2006, Heininger et al. assessed the distribution of bacterial species and antimicrobial resistance in an ICU during long-term (five years) use of SDD and compared this to national German data.[34] MRSA remained stable in this study, aminoglycoside- and betalactam-resistant Gram-negative rods did not increase and the incidence of *Pseudomonas* resistant to aminoglycosides was lower compared to the mean incidence nationwide.

The relative frequency of enterococci and CNS was higher in the SDD group and this might be of concern.

In 2009 a Cochrane review was published.[10] After the examination of 36 trials, the conclusion was that although there were differences in the SDD regime, differences in patient characteristics, differences in the risk of respiratory tract infection and in the risk of mortality in control groups, there was an overall significant reduction in respiratory tract infections and mortality in patients treated with both topical and systemic antibiotics. Patients treated with topical

antibiotics alone showed reduced incidence of respiratory tract infections but not of mortality. According to the authors of that review,[10] the risk of resistance of antibiotics was appropriately explored only in the trial published in *the Lancet* in 2003 by de Jonge which did not show any such effect.[30]

SDD remained controversial because of conflicting results regarding the occurrence of antibiotic resistance associated with SDD use. To quantify the effects of both SDD and SOD on patient outcome and antibiotic resistance in Dutch ICUs, de Smet et al. designed a cluster-randomized multi-centre study with cross-over design to compare both strategies mutually and to standard care.[35] Systemic administration of cefotaxime during the first four days of admission was part of the SDD regime. Thirteen ICUs participated in this study which enrolled almost 6000 patients and was the largest randomized controlled trial conducted up to that time. This study showed that SDD reduced mortality by 3.5 percentage points and that SOD reduced mortality by 2.9 percentage points compared to standard care. Besides the reduction in mortality, the need for systemic antibiotics decreased in both treatment groups. With regard to antibiotic resistance, the prevalence rates for antibiotic-resistant Gram-negative bacteria were lower during SDD and SOD when compared to standard care and lower during SDD when compared to SOD. SDD and SOD were not associated with increased selection or induction of antibiotic resistance for the antibiotics used for SDD and SOD in the short term.[35]

Nevertheless, Oostdijk et al. reported that SDD and SOD can have marked effects on bacterial ecology in the ICU.[36] Analysing the data from the point-prevalence shown in the previously mentioned study from de Smet et al., she concluded that SDD and SOD lead to an increase in ceftazidime-resistant Gram-negative bacteria. In addition, a considerable rebound effect of ceftazidime resistance in the intestinal tract after discontinuation of SDD was observed in this study. Prevalence rates significantly increased as compared with before and during intervention.[36] Shortcomings of this study were the fact that many patients were only briefly on the ICU (while not using SOD or SDD) and the incidence of antibiotic resistance on the non-ICU hospital wards was unknown. The second shortcoming was the different combinations of ICUs pre, per and post intervention. In contrast, Oostdijk's findings are partly consistent with the results of a five year prospective cohort study conducted in Spain by Ochoa-Ardilla et al., which showed an increase in ceftazidime-resistant (and imipenem-resistant) *P. aeruginosa* during SDD.[37] But this study also demonstrated a reduction in the incidence of *P. aeruginosa* resistant to tobramycin, amikacin and ciprofloxacin and a stable incidence of resistant *Enterobacteriaceae*. The total incidence of antibiotic-resistant bacteria remained stable so the author concluded that long-term use of SDD is not associated with an increase in acquisition of resistant flora.[37] But although the total incidence remained stable, some specific resistant strains might pose a problem. Oostdijk et al. also analysed the rates of colistin resistance during SDD and SOD as this had not been accurately determined. She concluded that during persistent intestinal carriage of Gram-negative bacteria and during intestinal colonization with tobramycin–resistant Gram negative bacteria, the risk of acquiring colistin resistant Gram-negative bacteria and conversion rates to colistin resistance increased. But the overall risk of acquisition of colistin resistant Gram-negative bacteria and conversion rates to colistin resistance were low.[38] In line with the findings of Oostdijk et al., Halaby et al. reported an increase of colistin resistance in extended spectrum beta lactamase producing *Klebsiella pneumoniae* in one ICU in the Netherlands where SDD had been used to control an outbreak.[39]

Another study by de Smet et al. assessed the effectiveness of SDD and SOD for the prevention of respiratory tract colonization and bacteraemia with highly resistant microorganisms in patients after three days on the ICU.[40] Compared with standard care, SDD reduced the rate of acquired highly resistant microorganisms by 38% and SOD by 32%. SDD was associated with a 62% reduction in acquisition rate of cefotaxime-resistant *Enterobacteriaceae* compared with standard care and SOD. The development of bacteraemia acquired in ICUs caused by highly resistant microorganisms was 59% less frequent with SDD than with standard care and 63% less frequent for SDD than with SOD. The author concluded that widespread use of SDD and SOD in intensive-care units with low levels of antibiotic resistance is justified.[40]

## Discussion and Conclusion

During the last sixty years, the prevalence of antibiotic-resistant bacteria has increased and is associated with the use of antibiotics. The change in ecology and notably the global emergence of multi-resistant Gram-negative bacteria is worrisome. Since the 1980s, it has become clear that there is an increase in Gram-negative bacteria producing extended spectrum beta lactamases. Nowadays, Gram-negative bacteria are capable of producing carbapenemases able to hydrolyze carbapenems. It is thus becoming more important to prevent an increase in resistance and to prevent infections with these microorganisms in ICU patients. One of these preventive measures is SDD, which reduces mortality, reduces acquisition of antibiotic-resistant Gram-negative bacteria and can control an outbreak of multi-resistant *Enterobacteriaceae* colonizing the respiratory and intestinal tract.[41] Oostdijk et al. showed that the eradication of intestinal carriage of Gram-negative bacteria led to a lower incidence of bacteraemia, so probably eradication of resistant bacteria reduces both cephalosporin-resistant *Enterobacteriaceae* colonization pressure and thereby the risk of bacteraemia.[42]

SDD probably lowers the incidence of antibiotic resistance by reducing the bacterial load and by reducing the total amount of systemic antibiotics used,[35,41,42] but should be used with great care and superb surveillance in surroundings with higher antibiotic resistance levels. Other important measures such as rational prescribing of antibiotics and strict hygiene measures remain essential. Together they can reduce the chance of transmitting resistant bacteria. In hospitals in the United States, where MRSA prevalent rates are high, universal decolonization with chlorhexidine has been shown to lead to lower MRSA carrier rates and fewers bloodstream infections, as demonstrated by Huang.[43]

Most evidence in favour of SDD arises from the Netherlands and it is not clear whether the results obtained here can be extrapolated to other regions of the world, especially those with a higher baseline incidence of resistance. Yet, studies in South Africa, Spain and France do show similar results,[16,37,31] although the amount of evidence in regions with high MRSA and VRE prevalence is limited. De Jonge published a review in 2005 where he stated that SDD can lower resistance in low MRSA prevalence circumstances, and suggested that more studies are needed to investigate this in regions with higher prevalences of MRSA.[44] A recently published systematic review and meta-analysis by Daneman et al. in 2013, reported that the perceived risk of long-term harm related to selective decontamination cannot be justified by available data.[45]

There are still some unclear issues that deserve to be unravelled. Cost-effectiveness of the use of SDD has only been shown in one study,[46] and more studies on even longer term effects of SDD and SOD on patient and ICU bacterial ecology need to be performed, certainly in surroundings with high levels of antibiotic resistance. These matters will be subjects for research in the near future. In order to investigate this properly, more has to be done than just the surveillance and screening of ICU patients for resistant bacteria alone. For example, a comparison should be made with patients in general hospital wards to get an impression of the development of overall bacterial resistance patterns.

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