Accepted October 2015

REVIEW

Selective decontamination in ICU patients: Dutch guideline

E.A.N. Oostdijk

Department of Medical Microbiology and Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence

E.A.N. Oostdijk – e.a.n.oostdijk@umcutrecht.nl

Keywords - **SDD, SOD, ventilator-associated pneumonia, infection, antibiotic resistance**

Abstract

Selective decontamination of the digestive tract (SDD) and selective oropharyngeal decontamination (SOD) are prophylactic antibiotic regimens used in intensive care units (ICUs) to prevent infections in ICU patients. This guideline, based upon a recently published Dutch Guideline (published at http://www.swab.nl / richtlijnen), summarises relevant literature regarding the effects of SDD and SOD on patient outcome and antibiotic resistance in Dutch ICUs. In conclusion, both SDD and SOD reduce ICU mortality as compared with a control group, yet no difference in survival was found between SDD and SOD. Both strategies are cost-effective. SDD resulted in less ICU-acquired Gram-negative bacteraemia as compared with SOD and control. So far, no increase in antibiotic resistance has been observed.

Introduction

Infections are an important complication in the treatment of patients in the intensive care unit (ICU), increasing morbidity, mortality and healthcare costs.[1] Selective decontamination strategies aim to prevent these infections by decontaminating ICU patients by eradicating colonisation with potential pathogens. Selective decontamination of the digestive tract (SDD) consists of a mouth paste and a suspension administered four times daily via a nasogastric tube into the intestinal tract containing non-absorbable antibiotics with activity against yeasts, *Staphylococcus aureus* and aerobic Gram-negative bacteria, including Enterobacteriaceae and *Pseudomonas aeruginosa*. In addition, systemic prophylaxis, which is usually a third-generation cephalosporin, is given during the first four days of ICU admission. Selective oropharyngeal decontamination (SOD) only consists of the mouth paste. Several cocktails of topical antibiotics have been described, yet the 'classical regimen' contains tobramycin, colistin and amphotericin B.

After the first SDD study in ICU patients in 1984, more than 45 randomised trials have been published. This summarised guideline aimed to provide an overview of the effectivity of SDD and SOD for the Dutch situation, with special consideration of three Dutch trials. In the first study, two ICU wards of the Amsterdam Medical Center (AMC) were compared. In one unit, all eligible patients (n=466) received SDD during a two-year period while the other unit was used as a control ward where none of the 468 admitted patients received SDD.[2] Patients were eligible for inclusion if they had an expected duration of mechanical ventilation of at least 48 hours or an expected length of ICU stay of more than 72 hours. We will refer to this study as the AMC study. The second study was a multicentre, cluster-randomised, cross-over study in 13 ICUs in the Netherlands.[3] All ICUs carried out SDD, SOD and standard care (i.e. no SDD/SOD) for periods of six months with a cross-over period of one month, yet the order of regimens was randomised. Inclusion criteria were the same as for the AMC study. In total, 5939 patients were included: 2045 in the SDD group, 1904 in the SOD group and 1990 in the standard care group. We will refer to this study as the Dutch SDD-SOD study 1. The second Dutch SDD-SOD study was also a cluster-randomised, cross-over study carried out in 16 ICUs with two 12-month study periods comparing SDD with SOD without a control group.[4] All patients with an ICU stay of more than 48 hours were included, resulting in 11,997 inclusions with 6116 patients in the SDD group and 5881 in the SOD group. The SDD and SOD regimens were identical in all three studies and regimens were applied as unit wide interventions as SDD and SOD pursue a change in the bacterial ecology within the unit. In case of individual patient allocation, control group patients might benefit from decontaminated patients admitted to the same ward with regard to protection against acquired colonisation and subsequent infection, and therefore such a design could underestimate the true effect of the intervention.

Effects of SDD and SOD on patient survival

Regarding patient survival during SDD as compared with control group patients, both the AMC study and Dutch SDD-SOD study 1 showed lower mortality rates for SDD patients. In the AMC study relative risk reductions (RRR) were 35% for ICU mortality and 22% for in hospital mortality, resulting in an absolute risk reduction (ARR) of 8.1% and 7% respectively.[2] In the Dutch SDD-SOD study 1, 28-day mortality was the primary endpoint and SDD was associated with an RRR of 13% as compared with the control group with an absolute reduction of 3.5% (*table 1*).[3] Survival benefit was also demonstrated for the SOD group as compared with a control group (RRR of 11% with ARR of 2.9%.(3) One year after ICU admission a significant survival benefit could not be demonstrated with RRR of 4% and 7% for SOD and SDD respectively, as compared with the control group.[5]

The Dutch SDD-SOD study 2 was a head-to-head comparison of SDD and SOD and no differences in mortality between the two interventions were demonstrated. Regarding other clinical endpoints, such as duration of mechanical ventilation or duration of hospital and ICU stay, no differences were obtained either.[4]

An important limitation of cluster randomisation, as used in these three studies, is that inclusion bias might have occurred as ICUs were randomised and not individual patients. In the Dutch SDD-SOD study 1, control group patients had lower APACHE-II scores, were less frequently mechanically ventilated and were more frequently admitted for surgical reasons, all associated with a better outcome. Baseline adjustment resulted in larger differences in patient survival rates in favour of SDD and SOD. In the AMC study and the Dutch SDD-SOD study 2, the two study groups were comparable, yet in these studies residual confounding could not be excluded. Nevertheless, in our opinion these studies provide convincing evidence that SDD and SOD reduce mortality in ICU patients in the Netherlands. Regarding other settings, multiple meta-analyses have been carried out with similar results,[6-8] including the most recent, largest meta-analysis on this topic.[7]

In a post-hoc analysis of the Dutch SDD-SOD study 1 there was evidence of improved survival for surgical patients receiving SDD as compared with SOD.[9] In the Dutch SDD-SOD study 2 a predefined sub-group analysis was therefore performed, but this did not reveal any differences in mortality (28-day, ICU and in-hospital mortality) for SDD as compared with SOD in surgical and non-surgical patients.[3,4] Of note, the definition of a surgical patient differed between study 1 and study 2.

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

Endpoint		SDD versus control RRR	SOD versus control RRR	SDD versus SOD RRR
Mortality	Day 28	13%(3)* (p<0.05)	11%(3)* (p<0.05)	0.01% (p>0.05)(4)
	Intensive care mortality	15%(3)* (p<0.05) 35% (95%CI 15%-51%)(2)	10%(3)* (p<0.05) 33% (95% CI -5%-57%)(12)	2.2% (p>0.05)(4)
	Hospital mortality	9%(3)* (p<0.05) 22% (95%CI 4%-37%)(2)	11%(3)* (p<0.05) 22% (NS)(12)	<0.01% (p>0.05)(4)
	One-year survival	4% (NS)(5)	7% (NS)(5) -1% (NS)(12)	
Infections	ICU-acquired bacteraemia Enterobacteriaceae GNF-GNR *Candida* species Enterococci	56% (95%CI 0.43%-64%)(3) 81% (95%CI 68%-88%)(3) 57% (95%CI 33%-74%)(3) 51% (NS)(3) 15% (NS)(3)	32% (95%CI 14%-47%)(3) 30% (95%CI 2%-50%)(3) 51% (95%CI 13%-73%)(3) 9% (NS)(3) 7% (NS)(3)	35% (95%CI 15%-51%)(3) 72% (95%CI 53%-84%)(3) 12% (NS)(3) 47% (NS)(3) 9% (NS)(3)
	VAP		55% (95% CI 3%-79%)(12)	
Resistance	ICU-acquired bacteraemia with HRMO	59% (95%CI 6%-82%)(17)	-10% (95%CI -105%-41%)(17)	62% (95%CI 15%-83%)(17)
	Acquired respiratory tract colonisation HRMO Tobramycin-resistant GNB Cefotaxime-resistant Enterobacteriaceae Intrinsically colistin resistant GNB Non-intrinsically colistin resistant GNB	42% (95%CI 22%-57%)(17) -21% (NS)(17) 74% (95%CI 39%-88%)(17) 59% (95%CI 43%-71%)(17) 31% (NS)(26)	35% (95%CI 13%-51%)(17) -8% (NS)(17) 1% (NS)(17) 16% (NS)(17) -6% (NS)(26)	11% (NS)(17) -11 (NS)(17) 63% (95%CI 38%-88%)(17) 51% (95%CI 31%-65%)(17) 35% (NS)(26)
	Acquired colonisation with *P. aeruginosa*^			
	Ceftazidime resistant Ciprofloxacin resistant Imipenem resistant Tobramycin resistant	83% (95%CI 23%-96%)(2) 92% (95%CI 39%-99%)(2) 94% (95%CI 51%-99%)(2) -5% (NS)(2)		
	Acquired colonisation with other GNB			
	Ceftazidime resistant Ciprofloxacin resistant Imipenem resistant Tobramycin resistant Polymyxin	19% (NS)(2) 70% (95%CI 37%-85%)(2) 90% (95%CI 19%-99%)(2) 56% (95%CI 26%-73%)(2) -57% (NS)(2)		

NS: non-significant; SDD: selective digestive tract decontamination; SOD: selective oropharyngeal decontamination; RRR: relative risk reduction; 95% CI: 95% confidence interval; ICU: intensive care unit; GNF-GNR: glucose non-fermentative Gram-negative rods; VAP: ventilator-associated pneumonia; HRMO: highly resistant micro-organism(27); GNB: Gram-negative bacteria; *corrected for present baseline differences using a random-effects logistic regression model; ^Acquired colonisation in sputum, throat, rectum, axilla and wounds.

Effects on infection

A one-day point prevalence study in 1265 ICUs revealed that the majority of infections are of respiratory origin.[10] Both SDD and SOD aim to decontaminate the oropharynx to prevent ventilator-associated pneumonia. However, methodological issues are related to ventilator-associated pneumonia as an endpoint. The usual combination of clinical, radiographic and microbiological criteria have a low specificity as other conditions, such as ARDS, may meet these criteria as well.[11] One placebo-controlled trial studying the effectiveness of SOD versus a control group used bronchoalveolar lavage in addition to quantitative cultures.[12] They found that the incidence of ventilator-associated pneumonia was 10.3% in patients receiving SOD as compared with 23.0% in the placebo group, resulting in an RRR of 55% ($p<0.05$).[12] The study was unpowered to detect a difference in mortality. To interpret the results of the various meta-analyses one must take into account the methodological issues as mentioned above.[6,13] To the best of our knowledge no head-to-head comparison has been done for SDD versus SOD regarding ventilator-associated pneumonia.

Bacteraemia on the other hand is a stronger endpoint. Both SDD-SOD study 1 and 2 found a considerable decrease in the incidence of ICU-acquired Gram-negative bacteraemia for SDD and SOD as compared with standard care. In SDD-SOD study 1 incidences were 81% lower for SDD patients and 30% lower for SOD patients. In total 13%, 9% and 7% developed an ICU-acquired bacteraemia in the control group, SOD and SDD respectively, all reaching statistical significance.[3] Similar results were found in SDD-SOD study 2 with odds ratios for SDD versus SOD of 0.77 (95% CI 0.65-0.91) for bacteraemia irrespective the causative agent and 0.42 (95% CI 0.29-0.60) for Enterobacteriaceae.[4] Similar reductions were found in meta-analyses.[8]

Resistance

Controversy exists whether SDD and SOD increase the prevalence of antibiotic resistant bacteria. A recent systematic review included 64 studies and did not show an increased incidence of carriage with resistant pathogens in SDD patients as compared with control group patients.[14] Moreover, they found prevalence of Gram-negative bacilli resistant to polymyxin and third-generation cephalosporins to be significantly lower in the SDD group. Regarding the three Dutch studies, no association could be found between the use of SDD or SOD and resistance (*table 1*). In the AMC study and the Dutch SDD-SOD study 1 a reduction was found in colonisation and infection rates with antibiotic resistant bacteria during SDD compared with control (*table 1*).[2,3] More specifically, acquiring bacteraemia caused by resistant pathogens in the ICU occurred less frequently during SDD as compared with SOD and the control group.[4] Changes in ICU ecology was the primary endpoint of SDD-SOD study 2. Surveillance cultures were obtained once a month from all admitted ICU patients. Regarding intestinal tract colonisation, prevalence of antibiotic resistant Gram-negative bacteria was significantly lower during SDD as compared with SOD, in contrast to respiratory tract colonisation for which no significant differences were found. Trends in time were present for tobramycin-resistant Gram-negative bacteria with an increase of 4% and 7% per month for SOD and SDD respectively.[4] In longitudinal studies in Germany and Spain no increase in resistance was found during the use of SDD.[15,16] Three post-hoc studies of SDD-SOD study 1 and 2 determined the effects of SDD and SOD on colistin resistance. Colistin resistance is feared as colistin has emerged as a last resort antibiotic to combat infections with multi-drug resistant Gram-negative bacteria. It was found that neither SDD nor SOD increased ICU-acquired infection and respiratory tract colonisation with colistin-resistant Gram-negatives.[17-19] For intestinal tract colonisation, acquired colonisation with colistin-resistant Enterobacteriaceae significantly increased if colonisation with an aminoglycoside-resistant Enterobacteriaceae was present.[18]

In all these studies conventional culture methods were used; anaerobic bacteria were not cultured and topical antibiotics may have influenced the culture results. Using metagenomics, an increase in aminoglycoside resistance genes was detected in 13 SDD patients with negative culture results in rectal samples. These resistance genes were found in the non-culturable anaerobic flora located on mobile genetic elements.[20] It is unknown whether resistance genes also increase in ICU patients not receiving SDD.

Other aspects

The overall use of systemic antibiotics was studied in SDD-SOD study 1. It was found that both SDD and SOD resulted in a 10% reduction in the overall use of systemic antibiotics (*table 2*).[3]

Table 2. Difference in antibiotic use in DDD during SDD and SOD as compared with a control group expressed in percentages.

Antibiotic	SDD	SOD
	% vs control	% vs control
Penicillin*	-27.8%(3) +9.0%(2)	-5.3%(3)
Carbapenem ^	-45.7%(3) -77.4%(2)	-25.4%(3)
Cephalosporin#	+86.6%(3) +22.1%(2)	-13.3%(3)
Fluoroquinolone$	-31.4%(3) -42.8%(2)	-14.4%(3)
Lincosamide	-11.6%(3)	+3.4%(3)
Vancomycin	-6.8%(2)	
Other antibiotics	-23.4%(3)	-12.0%(3)
All systemic antibiotics	-11.9%(3)	-10.1%(3)

SDD: selective decontamination of the digestive tract; SOD: selective oropharyngeal decontamination; DDD: defined daily doses
* Amoxicillin, flucloxacillin, piperacillin and tazobactam
^ Imipenem and meropenem
# Cefotaxime, cefamandole, ceftazidime
$ ciprofloxacin

In the AMC study costs of antibiotics were studied and it was demonstrated that SDD resulted in an 11% reduction in costs.[2] Cefotaxime as part of the SDD regimen was included in the analysis in both studies.

One cost-effectiveness analysis was carried out for the Dutch situation. Data from the Dutch SDD-SOD study 1 were used containing medical microbiology data, antibiotic use and length of stay and these costs were compared with life-year gained based on hospital mortality.[21] Both SDD and SOD were cost-saving and more beneficial as compared with the control group. Average savings of costs per patient were €1507 for SOD patients and €758 for SDD patients. Of note, these analyses were done with national prices of antibiotics and prices might differ between hospitals and in time.

Side effects of SDD and SOD are rare. An important side effect is obstruction of the oesophagus with the mouth paste. As described in a case report, the previous dose of the mouth paste should be carefully removed before applying the new dose.[22] Another study described detectable levels of tobramycin systemically due to absorption in the gastrointestinal tract during prolonged use of tobramycin in 83 out of 100 SDD patients.[23] In 12 out of 19 SDD patients with continuous venovenous haemofiltration, tobramycin levels were detected including one toxic level (>3.0 mg/l).[24] Intestinal ischaemia was found to be an important risk factor.

Conclusion

In Dutch ICUs both SDD and SOD reduce ICU mortality and ICU-acquired Gram-negative bacteraemia. No difference in survival was observed between SDD and SDD, although less Gram-negative bacteraemia was found during SDD. Both strategies are cost-effective, with SOD being more cost-effective than SDD. So far, no increase in antibiotic resistance has been observed. Based upon these findings, we recommend the use of SDD or SOD in Dutch ICUs for patients with an expected length of ICU stay of more than 48 hours. A stringent surveillance system to detect antibiotic resistant pathogens should accompany the implementation of SDD and SOD in the ICU. Further studies will focus on the effects of SDD and SOD in other settings with higher levels of antibiotic resistant bacteria and on the effects of SDD and SOD after discharge of the ICU (Bonten and De Jonge, personal communication).

Acknowledgements

Prof. Dr. E. De Jonge, Prof. Dr. B.J. Kullberg, Dr. S. Natsch, Prof. Dr. A.M.G.A. De Smet, Prof. Dr. C.M.J.E. Vandenbroucke-Grauls, Dr. E. Van Der Vorm, Prof. Dr. M.J.M. Bonten

This report is based on the SWAB guideline: Selectieve Decontaminatie published in 2014 on http://www.swab.nl/

Disclosures

The author declares no conflict of interest. No funding or financial support was received.

References

1. Vincent JL. Nosocomial infections in adult intensive-care units. Lancet. 2003;361:2068-77.
2. de Jonge E, Schultz MJ, Spanjaard L, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. Lancet. 2003;362:1011-6.
3. de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med. 2009;360:20-31.
4. Oostdijk EA, Kesecioglu J, Schultz MJ, et al. Effects of decontamination of the oropharynx and intestinal tract on antibiotic resistance in ICUs: a randomized clinical trial. JAMA. 2014;312:1429-37.
5. Oostdijk EA, de Smet AM, Bonten MJ; Dutch SOD-SDD trialists group. Effects of decontamination of the digestive tract and oropharynx in intensive care unit patients on 1-year survival. Am J Respir Crit Care Med. 2013;188:117-20.
6. Liberati A, D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. Cochrane Database Syst Rev. 2009:CD000022.
7. Price R, MacLennan G, Glen J, Su DC. Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: systematic review and network meta-analysis. BMJ. 2014;348:2197.
8. Silvestri L, van Saene HK, Milanese M, Gregori D, Gullo A. Selective decontamination of the digestive tract reduces bacterial bloodstream infection and mortality in critically ill patients. Systematic review of randomized, controlled trials. J Hosp Infect. 2007;65:187-203.
9. Melsen WG, de Smet AM, Kluytmans JA, Bonten MJ. Selective decontamination of the oral and digestive tract in surgical versus non-surgical patients in intensive care in a cluster-randomized trial. Br J Surg. 2012;99:232-7.
10. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302:2323-9.
11. Bonten MJ. Healthcare epidemiology: Ventilator-associated pneumonia: preventing the inevitable. Clin Infect Dis. 2011;52:115-21.
12. Bergmans DC, Bonten MJ, Gaillard CA, al. Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study. Am J Respir Crit Care Med. 2001;164:382-8.
13. Pileggi C, Bianco A, Flotta D, Nobile CG, Pavia M. Prevention of ventilator-associated pneumonia, mortality and all intensive care unit acquired infections by topically applied antimicrobial or antiseptic agents: a meta-analysis of randomized controlled trials in intensive care units. Crit Care. 2011;15:R155.
14. Daneman N, Sarwar S, Fowler RA, Cuthbertson BH. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. Lancet Infect Dis. 2013;13:328-41.
15. Ochoa-Ardila ME, Garcia-Canas A, Gomez-Mediavilla K, et al. Long-term use of selective decontamination of the digestive tract does not increase antibiotic resistance: a 5-year prospective cohort study. Intensive Care Med. 2011;37:1458-65.
16. Krueger WA, Lenhart FP, Neeser G, et al. Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically ill surgical patients: a prospective, stratified, randomized, double-blind, placebo-controlled clinical trial. Am J Respir Crit Care Med. 2002;166:1029-37.
17. de Smet AM, Kluytmans JA, Blok HE, et al. Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. Lancet Infect Dis. 2011;11:372-80.
18. Oostdijk EA, Smits L, de Smet AM, Leverstein-van Hall MA, Kesecioglu J, Bonten MJ. Colistin resistance in gram-negative bacteria during prophylactic topical colistin use in intensive care units. Intensive Care Med. 2013;3:653-60.
19. Wittekamp BH, Oostdijk EA, de Smet AM, Bonten MJ. Colistin and tobramycin resistance during long-term use of selective decontamination strategies in the intensive care unit: a post hoc analysis. Crit Care. 2015;19:113.
20. Buelow E, Gonzalez TB, Versluis D, et al. Effects of selective digestive decontamination (SDD) on the gut resistome. J Antimicrob Chemother. 2014;69:2215-23.
21. Oostdijk EA, de Wit GA, Bakker M, de Smet AM, Bonten MJ; Dutch SOD-SDD trialists group. Selective decontamination of the digestive tract and selective oropharyngeal decontamination in intensive care unit patients: a cost-effectiveness analysis. BMJ Open. 2013;3(3). PubMed PMID: 23468472.

22. Smit MJ, van der Spoel JI, de Smet AM, de Jonge E, Kuiper RA, van Lieshout EJ. Accumulation of oral antibiotics as an adverse effect of selective decontamination of the digestive tract: a series of three cases. Intensive Care Med. 2007;33:2025-6.
23. Oudemans-van Straaten HM, Endeman H, Bosman RJ, et al. Presence of tobramycin in blood and urine during selective decontamination of the digestive tract in critically ill patients, a prospective cohort study. Crit Care. 2011;15:R240.
24. Mol M, van Kan HJ, Schultz MJ, de Jonge E. Systemic tobramycin concentrations during selective decontamination of the digestive tract in intensive care unit patients on continuous venovenous hemofiltration. Intensive Care Med. 2008;34:903-6.
26. Oostdijk EA, Smits L, de Smet AM, Leverstein-van Hall MA, Kesecioglu J, Bonten MJ. Colistin resistance in gram-negative bacteria during prophylactic topical colistin use in intensive care units. Intensive Care Med. 2013;39:653-60.
27. Kluytmans-Vandenbergh MF, Kluytmans JA, Voss A. Dutch guideline for preventing nosocomial transmission of highly resistant microorganisms (HRMO). Infection. 2005;33:309-13.