Study Protocol

The effects of SDD and SOD on antibiotic resistance in the ICU: A multi-center comparison.

November 2009
Version 10

Working title: SDD and SOD and antibiotic resistance in the ICU

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List of abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>APACHE</td>
<td>Acute Physiology, Age and Chronic Health Evaluation</td>
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<td>ESBL</td>
<td>Extended Spectrum Beta-Lactamase</td>
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<td>ICU</td>
<td>Intensive Care Unit</td>
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<td>METC</td>
<td>Medical Research Ethics Committee; in Dutch: Medisch Ethische Toetsing Commissie</td>
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<tr>
<td>SOD</td>
<td>Selective Oropharyngeal Decontamination</td>
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<td>SDD</td>
<td>Selective Decontamination of the Digestive tract</td>
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<tr>
<td>UMCU</td>
<td>University Medical Center Utrecht</td>
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<td>WIP</td>
<td>Dutch Workingparty on Infection Prevention; in Dutch: Werkgroep Infectie Preventie</td>
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<tr>
<td>WMO</td>
<td>Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen</td>
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Summary

Introduction: Selective Decontamination of the Digestive tract (SDD) and Selective Oropharyngeal Decontamination (SOD) are equally effective in improving outcome in ICU patients, as demonstrated in a recently performed clustered group-randomized cross-over study in 13 Dutch hospitals [NEJM 2009;360:20]. Whether one of these preventive strategies is favourable with regard to development of antibiotic resistance is yet unknown.

Methods: Multicenter, cross-over comparison study of SDD and SOD in ICU settings using either SDD or SOD for standard care. Results from routinely performed clinical and surveillance cultures will be used to assess development of antibiotic resistance in different ‘marker’ pathogens.

Endpoint: Prevalence of antibiotic resistance.
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 respiratory tract infections have been achieved by prophylactic antibiotic regimens, such as Selective Decontamination of the Digestive tract (SDD) and Selective Oropharyngeal Decontamination (SOD).\(^2,3\) In a recently performed study of the Dutch SDD Trialists Group of 6000 patients SDD and SOD were, as compared to standard care, associated with relative reductions of death at day 28 of 13% and 11%, respectively.\(^4\) This 2% difference in outcome between both intervention groups was not significantly different. In fact, a study of 63,000 patients would be needed to demonstrate superiority of SDD over SOD. Furthermore, there were no differences between SDD and SOD in length of stay in ICU or hospital or overall antibiotic use. Therefore, both preventive measures should be considered equally effective in ICU patients.

Although the manuscript by de Smet et al has not been published yet, it is to be expressed that SDD or SOD will now be recommended as standard of care in Dutch ICUs. No recommendation can be made as of to prefer either of the two regimens.

The difference between both interventions is the absence of intestinal decontamination during SOD and the standard use of cephalosporins for all patients during SDD. It has been hypothesized that eradication of the intestinal Gram negative bacterial flora reduces the likelihood of resistance development in Gram negative bacteria. This hypothesis, though, has never been evaluated and even the before-mentioned study of 4000 patients (2000 patients did not receive SDD or SOD) was underpowered to answer this question.

Therefore, this hypothesis will be investigated with the current protocol. Currently, infection rates with antibiotic resistant Gram negative bacteria are still very low in Dutch hospitals. Nevertheless, the incidence density of antibiotic resistant bacteria in the UMC Utrecht has increased, on average, with 26% in the last 10 years\(^5\). This emergence is most prominent and most relevant in ICUs. Therefore, careful monitoring resistance development through regular surveillance in high risk wards (including ICU) has become an important aspect of the hospital infection control program of the UMCU.

In a yet unpublished subgroup analysis from the previous SDD-SOD-Standard Care study findings suggest that surgical patients benefit more from SDD, whereas non-surgical patients benefit more from SOD. This hypothesis will be further investigated with a
predefined subgroup analysis of surgical and non-surgical patients in the current SDD-SOD study.

**Interventions: SDD and SOD**

**SDD regime**

The SDD regimen is identical to that used in previous trials and will consist of oropharyngeal application (every 6 h) of a paste containing colistin, tobramycin and amphotericin B each in a 2% concentration and administration (every 6 h) of a 10 ml suspension containing 100 mg colistin, 122 mg tobramycin and 500 mg amphotericin B via the nasogastric tube. Topical antibiotics will be applied until ICU-discharge. In addition, cefotaxime (1000 mg, every 6 h) will be administered intravenously during the first four days of study. Cefotaxime will be replaced by ciprofloxacin (twice daily 400 mg) in case of documented cephalosporin allergy.

In patients with tracheostomy the paste will be applied around the tracheostomy. In patients with a duodenal tube or jejunostomy, 5 ml of the suspension will be given via the gastric tube and the remaining 5 ml via the duodenal tube or jejunostomy. Patients with colostoma or ileostoma will receive SDD-suppositories (containing 100 mg colistin, 61 mg tobramycin and 200 mg amphotericin B) twice daily in the distal part of the gut. Patients with a clinical suspicion or documented infection when admitted to ICU will be treated according to standard clinical practice. In these patients cefotaxime will not be added to carbapenems, fluoroquinolones, ceftazidime or piperacillin/tazobactam. The use of ‘colonization resistance impairing antibiotics’, such as amoxicillin, penicillin, amoxicillin-clavulanic acid and carbapenems is discouraged during the SDD period.

Surveillance cultures of endotracheal aspirates, oropharyngeal and rectal swabs will be performed on admission and twice weekly. Based on these surveillance cultures, several adaptations of the SDD regimen are possible: (a) application of oropharyngeal paste will be increased to 8 times daily, if the first surveillance culture of the throat yielded yeasts, until two surveillance cultures are negative; (b) 5 ml (5 mg) amphotericin B will be nebulized 4 times daily if a sputum surveillance culture (not admission culture) yields yeasts, until two sputum cultures become negative; (c) 5 ml (80 mg) colistin will be nebulized 4 times daily if a sputum surveillance culture (not admission culture) yields Gram negative bacteria, until two sputum cultures are negative.
SOD regime

SOD consists of oropharyngeal application of the same paste as used for SDD. In patients with tracheostomy the paste will be applied around the tracheostomy.

Surveillance cultures of endotracheal aspirates and oropharyngeal swabs are performed on admission and twice weekly. Based on these surveillance cultures, adaptation of the SOD regimen is possible: application of oropharyngeal paste is increased to 8 times daily, if the first surveillance culture of the throat yields yeasts, until two surveillance cultures are negative. There are no restrictions in physicians’ choices of systemic antibiotic therapy.

Outcomes

Primary endpoint

- Point prevalence of rectal colonization with specifically defined resistant bacteria (both Gram positive and Gram negative)
- Point prevalence of respiratory tract colonization with specifically defined resistant bacteria (both Gram positive and Gram negative)

Secondary endpoints

- Rate of ICU-acquired bacteraemia caused by antibiotic resistant bacteria, expressed as the rate of ICU-acquired bacteraemia per 100 included patients.
  Antibiotic resistant bacteria are defined, according to the national WIP guidelines. ICU-acquired bacteraemia are defined as those infections documented >48 hours after ICU-admission until 48 hours after ICU-discharge, and microbiologically documented.
- Rate of ICU-acquired bacteraemia caused by antibiotic resistant bacteria, expressed as the rate per 100 ICU-acquired bacteraemia caused by all pathogens.
- Mortality; at day 28, ICU- and in-hospital mortality, 1 year survival.
- Length of ICU-stay
- Predefined subgroup analysis: mortality (28 days-, IC- and in-hospital mortality) in two subgroups: surgical and non-surgical patients.
- Annual use of antibiotics based on pharmacy records.
Methods

Treatment

All ICU’s in the Netherlands participating in the Dutch National Intensive Care Evaluation (NICE) will be invited to participate in this open clustered group-randomized comparison of two equally effective preventive measures. Each ICU will be randomized into one of two study arms (see figure 1), starting either with SDD or SOD for twelve months, with cross-over to the other intervention. Before starting the first study period and after the first period, a wash-out wash-in period (1 month) will be carried out, during which the new treatment (either SDD or SOD) will be implemented, but patient data will not be used for analysis. All patients admitted to ICU with an expected stay of 48 hours in ICU will receive SDD or SOD. Patients with a documented or presumed allergy to any of the components of the SOD or SDD regime will not receive SDD or SOD.

Figure 1: Study design

Randomization

Randomization of the participating ICU will be performed at the pharmacy, using a computerized randomization program and by a person not involved in this project.

Data to be collected

- Anonymized patient-specific data
  - Date of ICU-admission, ICU-discharge, hospital-discharge, ICU- and hospital mortality.
  - Age, gender, APACHE IV score, medical specialty of admission, pre-existent medical conditions.

Of note, these data are already collected for each patient for national benchmarking.
- Microbiological clinical culture results
  - As obtained as part of routine daily clinical practice
- Microbiological surveillance culture results
  - As part of routine practice of SDD and SOD, obtained on admission and twice weekly;
  - As part of point prevalence surveillance to monitor antibiotic resistance. Once a month a rectal swab and respiratory specimen (sputum) will be obtained from all patients in the ICU on a single day (point-prevalence surveys). The exact protocol is defined in a separate manual. Chromogenic agars for screening ESBL producing bacteria will be available for free.
- Aggregated data on unit-wide antibiotic use
  - Obtained from annual reports of hospital pharmacies.

**Informed consent**

As in the previously performed SDD-SOD-Standard Care study, the METC has agreed that this study is not “WMO-plichtig” and thus informed consent is not needed. This is based on the following arguments.

1. With regard to patient outcome, SDD and SOD are equally effective and both will be considered standard of care in Dutch ICUs. The use of both regimens for a certain period of time, as proposed, therefore, should not be considered a deviation from standard care, and could be compared by the temporary restrictive (or favoured) use of certain antibiotics.
2. All patients in ICU will receive either SDD or SOD. Refusal of a patient (or family member) after informed consent would still mean that that patient would receive SDD or SOD as part of standard care. The data of these patients will not be used for this study.
3. Both SDD and SOD are not harmful for patients, as demonstrated in multiple studies in ICU-patients.
4. All data-collection will be anonymous. The patient-specific data that will be collected (age, gender, outcome) are already collected for continuous national benchmarking (without informed consent).
5. No microbiological cultures will be obtained for the sake of the study.
6. Data on antibiotic use will be collected in an aggregated way that cannot be linked to individual patients.
The conditions, as outlined above, are fully compatible with those described recently in the New England Journal of Medicine, in a plea to allow these kind of studies without required informed consent in the US.\textsuperscript{8,9}

As in the previously performed SDD-SOD-Standard Care trial, all patients (or family members) will be asked permission to use medical data for scientific purposes. If this is refused, no patient-specific data (cultures) will be used for analysis. This occurred in 12 out of 6000 patients in the previous study.

Analysis

Study size

A formal power calculation for the incidence of antimicrobial resistance is difficult. Because of the dependency of the data, the usual statistical tests such as Chi square and student-t are inappropriate.\textsuperscript{10} Due to the nature of the study design (which does not preclude post-randomization selection bias) we will take cluster-effects into account and allow for adjustments in imbalances in baseline characteristics between study groups. The analysis plan will conform to CONSORT guidelines for reporting Cluster Randomized Trials.\textsuperscript{11}

Currently, the proportion of patients colonized with Gram-negative multi-resistant bacteria is estimated to be 3%. A documented three times relative reduction between the two groups is considered clinically relevant. At least 1023 patients will be needed per group ($\beta=0.1$, $\alpha=0.05$).\textsuperscript{12} The time needed to enrol this sample size depends on the numbers of ICUs that participate.

A predefined subgroup analysis will be performed for surgical and non-surgical patients with mortality at day 28 after ICU-admission as endpoint.
Reference list


