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# Selective Decontamination of the Digestive Tract and Selective Oropharyngeal Decontamination in ICU patients: a cost-effectiveness analysis

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**Article summary:**

Article Focus

- Selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) are prophylactic antibiotics used as infection prevention strategy in Intensive Care Units (ICU)
- In a Dutch 13-center study, 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) and with lower incidence of ICU-acquired bacteremia and ICU-acquired colonization of the respiratory tract with multi-resistant bacteria
- This paper describes the costs and effects of SDD and SOD from the healthcare perspective in Dutch ICUs

Key Messages

- Both SDD and SOD were cheaper and more beneficial as compared to standard care and these findings were insensitive to changes in discount rates and extra costs for ventilation days
- SOD, but not SDD, was still dominant (i.e. cheaper and more beneficial) over standard care to current tenfold higher market-prices of the topical components (€40/day for SOD and €400/day for SDD)

Strengths and Limitations.

- 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 using data from a multi-center trial including 5,939 patients
- Baseline differences were present between the three study groups
- Only direct medical costs were included in the analysis and cost data were restricted to health care settings

**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 SOD (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 of 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 were collected on patient-level. 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)-database[18]). For microbiology costs blood cultures, broncheoalveolar 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]

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]

Patients receiving SDD were on average 62.4 (±15.8) years old, compared to 61.4 (±16.3) and 61.4 (±16.2) years for patients receiving SOD and SC, respectively (Table 2). 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 previously [3], 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.

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 price[18] 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.

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.

## 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 trial[3] 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 amphotericine B, which could be alleviated by replacing amphotericine 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 outcome[3], 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 colistin[39]. 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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Contributors: AMdS and MJMB conceived the study. EO, AdW and MJMB designed the study. The SDD-SOD trialist group and AMdS collected the trial data. EO, AdW, MB and MJM analyzed and interpreted the data. EO, MB and MJMB drafted the manuscript and AdW, AMdS and The SDD-SOD trialist group critically revised the manuscript for important intellectual content. All the authors had full access to the data and approved the final manuscript. EO is the guarantor.

Ethical approval: Ethical approval for the trial was granted by the institutional review board at each participating hospital, as published previously (NEJM 2009;360:20). The requirement for informed consent was waived.

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TABLES

| 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

| | | SC N=1,987 | SOD N=1,901 | SDD N=2,032 |
|---|---|---|---|---|
| *Baseline characteristics* | | | | |
| 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) |
| *Clinical outcome ** * | | | | |
| 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) |
| *Resource use* | | | | |
| 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)) | Rectal | 0 | 0 | 7,247 (3.8) |
| | BAL | 263 (1.3) | 221 (1.3) | 253 (1.3) |
| | Sputum | 5,430 (3.7) | 7,467 (4.3) | 8,073 (4.4) |
| | Throat | 431 (2.7) | 6,277 (3.5) | 7,176 (3.8) |
| | 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, Brancheoalveolar 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

| | | SC<br>N=1990 | SOD<br>N=1904 | SDD<br>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<br>(€40,183.93 – €43,697.66) | €40,433.42<br>(€38,837.50 - €42,029.35) | €41,183.12<br>(€39,408.39 - €42,957.85) |

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

*Excluding cefotaxim. Cefotaxim 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, Brancheoalveolar Lavage

| | 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)

| | | 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% | 4.27 (3.96 – 4.57) | 4.02 (3.72 – 4.32) | 4.23 (3.94 – 4.53) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| | +0% | 6.07 (5.58 – 6.55) | 5.62 (5.15 – 6.08) | 5.97 (5.50 – 6.44) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| | +3% | 2.82 (2.63 – 3.01) | 2.68 (2.49 – 2.87) | 2.82 (2.63 – 3.00) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| Sensitivity analysis mechanical ventilation* | BC +15% | €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) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| | + 0% | €38,715.73 (€37,112.32 – €40,319.14) | €37,117.07 (€35,659.90 – €38,574.24) | €37,874.94 (€36,270.73 – €39,479.15) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| | +30% | €45,165.85 (€43,251.01 – €47,080.69) | €43,749.78 (€42,010.47 – €45,489.09) | €44,491.30 (€42,542.03 – €46,440.57) | | SC = dominated by SOD | SC = dominated by SDD | 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) | | SC = dominated by SOD | 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)

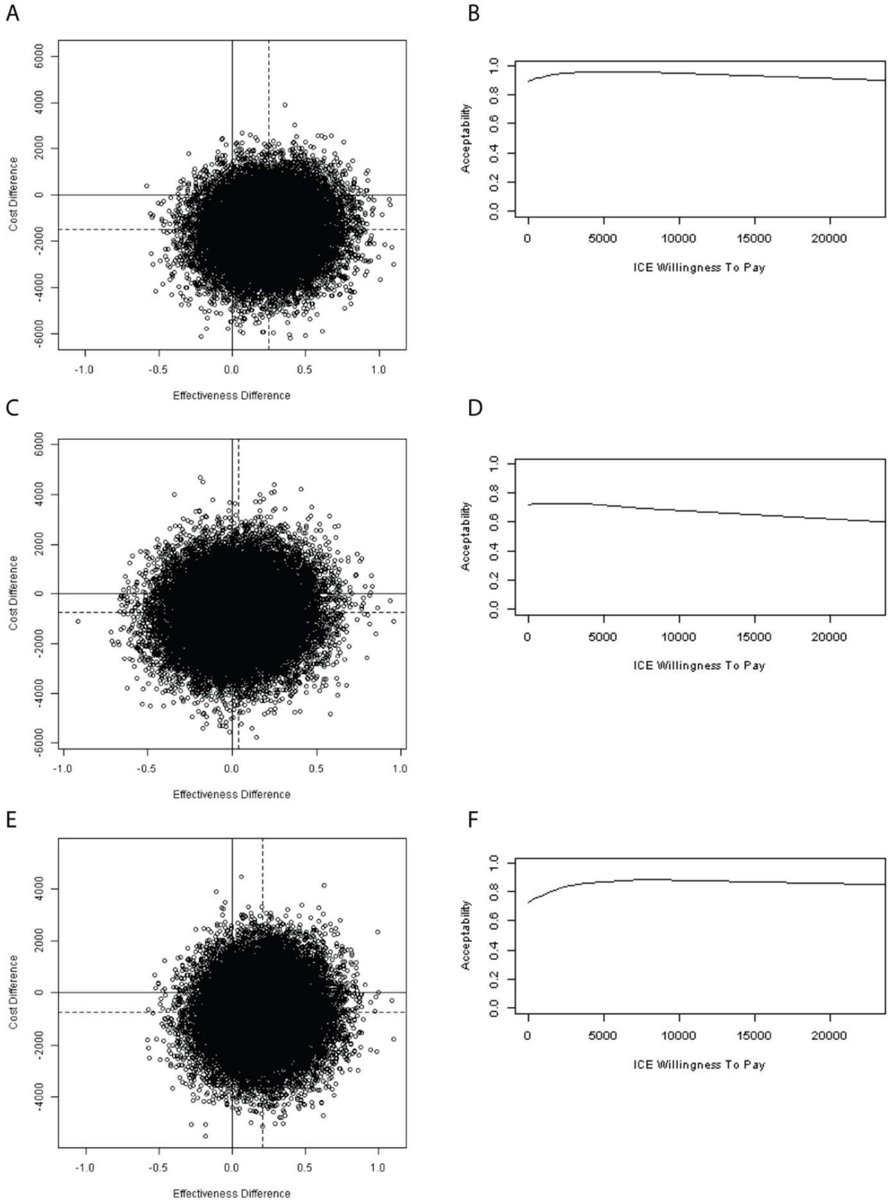


Figure 1: Scatterplot of ICER-pairs based on the results of bootstrap re-sampling technique (25,000 replicates) and cost-effectiveness acceptibility curves for a) and b) SOD vs SC, c) and d) SDD vs SC, e) and f) SOD vs SDD

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

187x251mm (150 x 150 DPI)

| Study design | Item | Page |
|---|---|---|
| 1 | The research question is stated | 5 |
| 2 | The economic importance of the research question is stated | 5 |
| 3 | The viewpoint(s) of the analysis are clearly stated and justified | 5 |
| 4 | The rationale for choosing the alternative programmes or interventions compared is stated | 5 |
| 5 | The alternatives being compared are clearly described | 5,6 |
| 6 | The form of economic evaluation used is stated | 6 |
| 7 | The choice of form of economic evaluation is justified in relation to the questions addressed | 6 |
| | | |
| **Data collection** | | |
| 8 | The source(s) of effectiveness estimates used are stated | 8 |
| 9 | Details of the design and results of effectiveness study are given (if based on a single study) | 5 |
| 10 | Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies) | Na |
| 11 | The primary outcome measure(s) for the economic evaluation are clearly stated | 6 |
| 12 | Methods to value health states and other benefits are stated | 8 |
| 13 | Details of the subjects from whom valuations were obtained are given | Na |
| 14 | Productivity changes (if included) are reported separately | Na |
| 15 | The relevance of productivity changes to the study question is discussed | Na |
| 16 | Quantities of resources are reported separately from their unit costs | 17,19 |
| 17 | Methods for the estimation of quantities and unit costs are described | 6,7 |
| 18 | Currency and price data are recorded | 7 |
| 19 | Details of currency of price adjustments for inflation or currency conversion are given | 7 |
| 20 | Details of any model used are given | Na |
| 21 | The choice of model used and the key parameters on which it is based are justified | Na |
| | | |
| **Analysis and interpretation of results** | | |
| 22 | Time horizon of costs and benefits is stated | 6 |
| 23 | The discount rate(s) is stated | 7 |
| 24 | The choice of rate(s) is justified | 7 |
| 25 | An explanation is given if costs or benefits are not discounted | 7 |
| 26 | Details of statistical tests and confidence intervals are given for stochastic data | 8 |
| 27 | The approach to sensitivity analysis is given | 8 |
| 28 | The choice of variables for sensitivity analysis is justified | 8 |
| 29 | The ranges over which the variables are varied are stated | 8 |
| 30 | Relevant alternatives are compared | Na |

| | | |
|---|---|---|
| 31 | Incremental analysis is reported | 9, 10 |
| 32 | Major outcomes are presented in a disaggregated as well as aggregated form | 21, 22 |
| 33 | The answer to the study question is given | 10 |
| 34 | Conclusions follow from the data reported | 11 |
| 35 | Conclusions are accompanied by the appropriate caveats | 12 |

# Selective Decontamination of the Digestive Tract and Selective Oropharyngeal Decontamination in ICU patients: a cost-effectiveness analysis


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# Selective Decontamination of the Digestive Tract and Selective Oropharyngeal Decontamination in ICU patients: a cost-effectiveness analysis

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**Article summary:**

Article Focus

- Selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) are prophylactic antibiotics used as infection prevention strategy in Intensive Care Units (ICU)
- In a Dutch 13-center study, 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) and with lower incidence of ICU-acquired bacteremia and ICU-acquired colonization of the respiratory tract with multi-resistant bacteria
- This paper describes the costs and effects of SDD and SOD from the healthcare perspective in Dutch ICUs

Key Messages

- Both SDD and SOD were cheaper and more beneficial as compared to standard care and these findings were insensitive to changes in discount rates and extra costs for ventilation days
- SOD, but not SDD, was still dominant (i.e. cheaper and more beneficial) over standard care to current tenfold higher market-prices of the topical components (€40/day for SOD and €400/day for SDD)

Strengths and Limitations.

- 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 using data from a multi-center trial including 5,939 patients
- Baseline differences were present between the three study groups
- Only direct medical costs were included in the analysis and cost data were restricted to health care settings

**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 SOD (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)-database[18]). For microbiology costs blood cultures, broncheoalveolar 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]

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 (±15.8) years old, compared to 61.4 (±16.3) and 61.4 (±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 previously [3], 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.

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 price[18] 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.

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.

**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 trial[3] 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 amphotericine B, which could be alleviated by replacing amphotericine 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 outcome[3], 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 colistin[39]. 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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Contributors: AMdS and MJMB conceived the study. EO, AdW and MJMB designed the study. The SDD-SOD trialist group and AMdS collected the trial data. EO, AdW, MB and MJM analyzed and interpreted the data. EO, MB and MJMB drafted the manuscript and AdW, AMdS and The SDD-SOD trialist group critically revised the manuscript for important intellectual content. All the authors had full access to the data and approved the final manuscript. EO is the guarantor.

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42. Internal Revenue Service.

455 TABLES

| 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] |

456

457 Table 1: Costs used per unit

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

460 * UMCU costs

461

| | | SC<br>N=1,987 | SOD<br>N=1,901 | SDD<br>N=2,032 |
|---|---|---|---|---|
| *Baseline characteristics* | | | | |
| 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) |
| *Clinical outcome ** * | | | | |
| 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) |
| *Resource use* | | | | |
| 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)) | Rectal | 0 | 0 | 7,247 (3.8) |
| | BAL | 263 (1.3) | 221 (1.3) | 253 (1.3) |
| | Sputum | 5,430 (3.7) | 7,467 (4.3) | 8,073 (4.4) |
| | Throat | 431 (2.7) | 6,277 (3.5) | 7,176 (3.8) |
| | 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, Brancheoalveolar 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

| | | SC<br>N=1990 | SOD<br>N=1904 | SDD<br>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<br>(€40,183.93 – €43,697.66) | €40,433.42<br>(€38,837.50 - €42,029.35) | €41,183.12<br>(€39,408.39 - €42,957.85) |

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

*Excluding cefotaxim. Cefotaxim 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, Brancheoalveolar Lavage

| | 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)

| | | 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% | 4.27 (3.96 – 4.57) | 4.02 (3.72 – 4.32) | 4.23 (3.94 – 4.53) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| | +0% | 6.07 (5.58 – 6.55) | 5.62 (5.15 – 6.08) | 5.97 (5.50 – 6.44) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| | +3% | 2.82 (2.63 – 3.01) | 2.68 (2.49 – 2.87) | 2.82 (2.63 – 3.00) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| Sensitivity analysis mechanical ventilation* | BC +15% | €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) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| | + 0% | €38,715.73 (€37,112.32 – €40,319.14) | €37,117.07 (€35,659.90 – €38,574.24) | €37,874.94 (€36,270.73 – €39,479.15) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| | +30% | €45,165.85 (€43,251.01 – €47,080.69) | €43,749.78 (€42,010.47 – €45,489.09) | €44,491.30 (€42,542.03 – €46,440.57) | | SC = dominated by SOD | SC = dominated by SDD | 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) | | SC = dominated by SOD | 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)

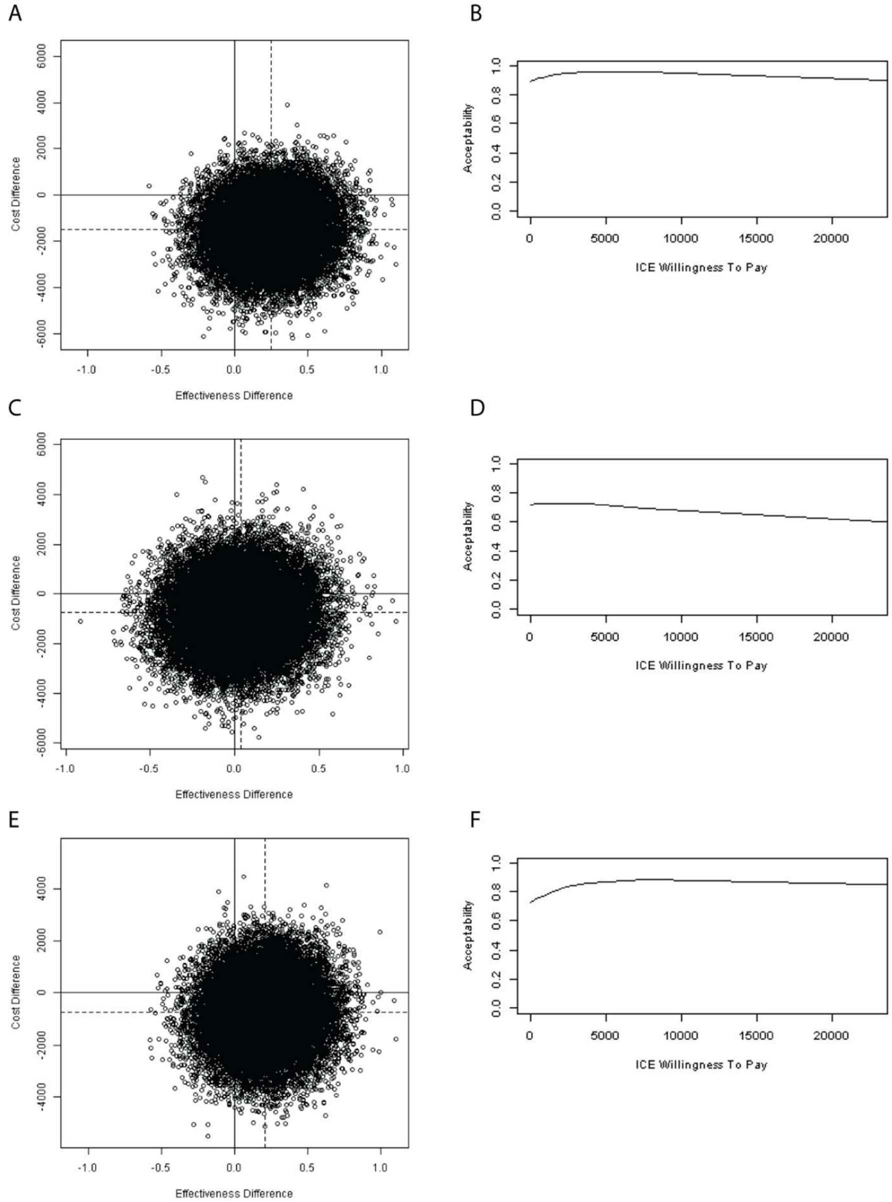


Figure 1: Scatterplot of ICER-pairs based on the results of bootstrap re-sampling technique (25,000 replicates) and cost-effectiveness acceptibility curves for a) and b) SOD vs SC, c) and d) SDD vs SC, e) and f) SOD vs SDD
SOD, selective oropharyngeal decontamination ; SDD selective decontamination of the Digestive tract; SC, standard care
187x251mm (150 x 150 DPI)

| Study design | Item | Page |
|---|---|---|
| 1 | The research question is stated | 5 |
| 2 | The economic importance of the research question is stated | 5 |
| 3 | The viewpoint(s) of the analysis are clearly stated and justified | 5 |
| 4 | The rationale for choosing the alternative programmes or interventions compared is stated | 5 |
| 5 | The alternatives being compared are clearly described | 5,6 |
| 6 | The form of economic evaluation used is stated | 6 |
| 7 | The choice of form of economic evaluation is justified in relation to the questions addressed | 6 |
| | | |
| **Data collection** | | |
| 8 | The source(s) of effectiveness estimates used are stated | 8 |
| 9 | Details of the design and results of effectiveness study are given (if based on a single study) | 5 |
| 10 | Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies) | Na |
| 11 | The primary outcome measure(s) for the economic evaluation are clearly stated | 6 |
| 12 | Methods to value health states and other benefits are stated | 8 |
| 13 | Details of the subjects from whom valuations were obtained are given | Na |
| 14 | Productivity changes (if included) are reported separately | Na |
| 15 | The relevance of productivity changes to the study question is discussed | Na |
| 16 | Quantities of resources are reported separately from their unit costs | 17,19 |
| 17 | Methods for the estimation of quantities and unit costs are described | 6,7 |
| 18 | Currency and price data are recorded | 7 |
| 19 | Details of currency of price adjustments for inflation or currency conversion are given | 7 |
| 20 | Details of any model used are given | Na |
| 21 | The choice of model used and the key parameters on which it is based are justified | Na |
| | | |
| **Analysis and interpretation of results** | | |
| 22 | Time horizon of costs and benefits is stated | 6 |
| 23 | The discount rate(s) is stated | 7 |
| 24 | The choice of rate(s) is justified | 7 |
| 25 | An explanation is given if costs or benefits are not discounted | 7 |
| 26 | Details of statistical tests and confidence intervals are given for stochastic data | 8 |
| 27 | The approach to sensitivity analysis is given | 8 |
| 28 | The choice of variables for sensitivity analysis is justified | 8 |
| 29 | The ranges over which the variables are varied are stated | 8 |
| 30 | Relevant alternatives are compared | Na |

| | | |
|---|---|---|
| 31 | Incremental analysis is reported | 9, 10 |
| 32 | Major outcomes are presented in a disaggregated as well as aggregated form | 21, 22 |
| 33 | The answer to the study question is given | 10 |
| 34 | Conclusions follow from the data reported | 11 |
| 35 | Conclusions are accompanied by the appropriate caveats | 12 |

**Selective Decontamination of the Digestive Tract and Selective Oropharyngeal Decontamination in ICU patients: a cost-effectiveness analysis**

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Keywords: SDD, SOD, Intensive Care, cost-effectiveness, economic evaluation

**Article summary:**

Article Focus

- Selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) are prophylactic antibiotics used as infection prevention strategy in Intensive Care Units (ICU)
- In a Dutch 13-center study, 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) and with lower incidence of ICU-acquired bacteremia and ICU-acquired colonization of the respiratory tract with multi-resistant bacteria
- This paper describes the costs and effects of SDD and SOD from the healthcare perspective in Dutch ICUs

Key Messages

- Both SDD and SOD were cheaper and more beneficial as compared to standard care and these findings were insensitive to changes in discount rates and extra costs for ventilation days
- SOD, but not SDD, was still dominant (i.e. cheaper and more beneficial) over standard care to current tenfold higher market-prices of the topical components (€40/day for SOD and €400/day for SDD)

Strengths and Limitations.

- 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 using data from a multi-center trial including 5,939 patients
- Baseline differences were present between the three study groups
- Only direct medical costs were included in the analysis and cost data were restricted to health care settings

**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 SOD (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)-database[18]). For microbiology costs blood cultures, broncheoalveolar 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]

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 (±15.8) years old, compared to 61.4 (±16.3) and 61.4 (±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 previously [3], 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.

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 price[18] 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.

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.

**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 trial[3] 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 amphotericine B, which could be alleviated by replacing amphotericine 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 outcome[3], 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 colistin[39]. 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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TABLES

| 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

| | | SC<br>N=1,987 | SOD<br>N=1,901 | SDD<br>N=2,032 |
|---|---|---|---|---|
| *Baseline characteristics* | | | | |
| 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) |
| *Clinical outcome ** * | | | | |
| 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) |
| *Resource use* | | | | |
| 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)) | Rectal | 0 | 0 | 7,247 (3.8) |
| | BAL | 263 (1.3) | 221 (1.3) | 253 (1.3) |
| | Sputum | 5,430 (3.7) | 7,467 (4.3) | 8,073 (4.4) |
| | Throat | 431 (2.7) | 6,277 (3.5) | 7,176 (3.8) |
| | 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, Brancheoalveolar 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

| | | SC<br>N=1990 | SOD<br>N=1904 | SDD<br>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<br>(€40,183.93 – €43,697.66) | €40,433.42<br>(€38,837.50 - €42,029.35) | €41,183.12<br>(€39,408.39 - €42,957.85) |

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

*Excluding cefotaxim. Cefotaxim 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, Brancheoalveolar Lavage

| | 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)

| | | 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% | 4.27 (3.96 – 4.57) | 4.02 (3.72 – 4.32) | 4.23 (3.94 – 4.53) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| | +0% | 6.07 (5.58 – 6.55) | 5.62 (5.15 – 6.08) | 5.97 (5.50 – 6.44) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| | +3% | 2.82 (2.63 – 3.01) | 2.68 (2.49 – 2.87) | 2.82 (2.63 – 3.00) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| Sensitivity analysis mechanical ventilation* | BC +15% | €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) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| | + 0% | €38,715.73 (€37,112.32 – €40,319.14) | €37,117.07 (€35,659.90 – €38,574.24) | €37,874.94 (€36,270.73 – €39,479.15) | | SC = dominated by SOD | SC = dominated by SDD | SDD = dominated by SOD |
| | +30% | €45,165.85 (€43,251.01 – €47,080.69) | €43,749.78 (€42,010.47 – €45,489.09) | €44,491.30 (€42,542.03 – €46,440.57) | | SC = dominated by SOD | SC = dominated by SDD | 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) | | SC = dominated by SOD | 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)