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## What is new in selective decontamination of the digestive tract?

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Selective decontamination of the digestive tract (SDD) and selective oropharyngeal decontamination (SOD) are among the few interventions in intensive care medicine that have been shown to improve patient survival, but their use is limited to a minority of European intensive care units (ICUs) (Tables 1, 2) [1].

In addition, when the microbiological data of patients receiving SDD or SOD were compared with those receiving standard care, ICU-acquired bacteremia was significantly reduced for *Staphylococcus aureus*, glucose-non-fermenting Gram-negative rods, and *Enterobacteriaceae* [4]. In particular, the use of SDD was associated with a lower incidence of acquired bacteremia with *Enterobacteriaceae*. Similarly, ICU-acquired candidemia was lower in the SDD group than in the SOD group or standard care group, but the difference was not significant. These findings were confirmed in a recent study comparing SDD and SOD on antibiotic resistance. The incidence of ICU-acquired bacteremia was also lower for aminoglycoside-resistant Gram-negative bacteria in the SDD group [5]. Although the survival rate of ICU patients

remains similar in both studies, the lower incidence of antibiotic resistance and nosocomial bacteremia as consistent findings are in favour of SDD.

Common reasons for the reluctance to use SDD or SOD are related to only a few arguments regularly mentioned in editorials and by expert opinion expressing the fear that their use may promote antibiotic resistance and the possible increase of methicillin-resistant *S. aureus* [15]. These can be summarized as follows:

1. The absence of emergence of resistance is against current microbiological concepts and contradicts the worldwide pandemic of multidrug-resistant microorganisms demonstrated to be directly related to the use of antibiotics. In a recent meta-analysis, no relation was observed between the use of SDD and the development of antimicrobial resistance, thus confirming earlier reports [16]. Recent studies have demonstrated similar findings (Table 2). In a large study showing lower mortality with the use of SDD or SOD compared with standard care, patients treated with SDD and SOD had a significantly lower incidence of carriage and infections with antibiotic-resistant bacteria [4]. Moreover, when compared with SOD, SDD was related with lower rectal carriage of antibiotic-resistant Gram-negative bacteria [5]. By contrast, the continuous application of antibiotics included in the paste, as well as the aerosolized colistin applied in the case of emergence of Gram-negative bacilli in the respiratory samples, may largely contribute to the absence of the documented emergence of resistance (footnote Table 1).
2. One of the main reasons of bacterial resistance to antibiotics is the widespread use of antimicrobial agents. This represents the main reluctance for the use of SDD. Surprisingly, some investigators have even advocated for the use of SOD due to the absence of widespread systemic prophylaxis with cephalosporins

Table 1 Large studies comparing SDD and SOD

| References          | Design   | Results   | Comments  |
|---------------------|--|---|---|
| Krueger [2]         | Single centre, 2 ICUs (Tübingen University Hospital) 30 months. Placebo-randomized standard care (SC) or SDD | ICU mortality<br>SC 23/121 (19 %)<br>SDD 17/120 (14.2 %)<br>RR (95 % CI) 0.885 (0.472–1.659)<br>Infections<br>SC 29 (11.1)<br>SDD 6 (2.3)<br>RR (95 % CI) 0.205 (0.072–0.587)<br>ICU mortality<br>SC 107/468 (22.9 %)<br>SDD 69/466 (14.8 %)<br>RR (95 % CI) 0.65 (0.49–0.85)<br>Acquisition of resistance by Gram-negative pathogens<br>SC 104 (26 %)<br>SDD 61 (16 %)<br>RR (95 % CI) 0.61 (0.46–0.81)<br>ICU mortality<br>SC: 443/1990 (22.3 %)<br>SDD: 440/2045 (21.5 %)<br>SOD: 416/1904 (21.8 %)<br>Bacteremia (any) <sup>b</sup><br>SC: 186/1990 (9.3 %)<br>SDD: 88/2045 (4.3 %)<br>SOD: 124/1904 (6.5 %)<br>Antibiotic-resistant bacteria:<br>Global decrease of antibiotic-resistant bacteria in rectal samples and respiratory samples in point-prevalence surveys performed in 6–8 % of patients<br>ICU mortality<br>SOD: 1165/5881 (19.8 %)<br>SDD: 1138/6116 (18.6 %)<br>ICU-acquired bacteremia<br>SOD: 319/5442 (5.9 %)<br>SDD: 253/5549 (4.6 %)<br>Monthly acquisition of rectal carriage of aminoglycoside-resistant bacteria<br>SOD: 4 %<br>SDD: 7 %<br>$P = 0.046$ | APACHE II $\geq 29$<br>15/23 (62.5 %)<br>14/26 (53.8 %)<br>1.593 (0.767–3.306)<br>Urinary tract<br>60 (22.9)<br>36 (13.6)<br>0.593 (0.357–0.985)<br>146/468 (31.2 %)<br>113/466 (24.2 %)<br>0.78 (0.63–0.99)<br>APACHE II 20–29<br>20/122 (16.4 %)<br>38/115 (33.0 %)<br>0.508 (0.295–0.875)<br>Bloodstream<br>36 (13.7)<br>14 (5.3)<br>0.384 (0.176–0.836)<br>Hospital mortality<br>SC<br>SDD<br>RR (95 % CI):<br>Hospital mortality:<br>632/1990 (31.8 %)<br>665/2045 (32.6 %)<br>584/1904 (30.7 %)<br>SDD vs SOD<br>OR 0.88 (0.76–1.01)<br>OR 0.85 (0.74–0.98)<br>OR 0.65 (0.49–0.85)<br>SDD = SOD mortality<br>OR 0.99 (0.90–1.08)<br>SDD > SOD decreased bacteremia<br>SDD > SOD acquisition of aminoglycoside resistance carriage |
| de Jonge et al. [3] | Single centre (AMC, Amsterdam) 9/1999–12/2001  |   | SDD lowered ICU and hospital mortality  |
| de Smet et al. [4]  | 13 Dutch ICUs cluster-randomized to SC, SDD and SOD. 05/2004–07/2006 5939 ICU patients                       |   | SDD decreased Gram-colonization by Gram-negative pathogens<br>SDD lowered ICU and hospital mortality<br>SDD > SOD decreased bacteremia  |
| Oostdijk et al. [5] | 16 ICUs randomized to 12 months SDD and 12 months SOD or the opposite 08/2009–01/2011                        |   | SDD decreased colonization<br>SDD = SOD mortality<br>SDD > SOD decreased bacteremia<br>SDD > SOD acquisition of aminoglycoside resistance carriage  |

SDD Selective decontamination of the digestive tract. The SDD regimen consists of 4 days of intravenous cefotaxime, the oropharyngeal application (every 6 h) of a paste containing colistin, tobramycin, and amphotericin B, each in a 2 % concentration, and the administration (every 6 h) of a 10-mL suspension containing colistin (100 mg), tobramycin (80 mg as sulfate), and amphotericin B (500 mg) via a nasogastric tube. Topical antibiotics are applied until ICU discharge (Oostdijk EAN et al. JAMA 2014;312:1427–1431). SOD: selective oropharyngeal decontamination. The SOD regimen consists of only the oropharyngeal application (every 6 h) of the paste described above (Oostdijk EAN et al. JAMA 2014;312:1427–1431). During SOD, application of oropharyngeal paste is increased to eight times daily if the first surveillance culture of the throat yields yeasts, until two consecutive surveillance cultures are negative. There are no restrictions in physicians' choices of systemic antibiotic therapy

APACHE II acute physiology and chronic health evaluation II score, ICU intensive care unit, SC standard care, OR odds ratio, RR relative risk, vs versus, 95 % CI 95 % confidence intervals  
<sup>a</sup> During SDD, several adaptations are possible: (1) application of oropharyngeal paste is increased to 8 times daily if the first surveillance culture of the throat yields yeasts, until two surveillance cultures are negative; (2) 5 ml (5 mg) amphotericin B is nebulized 4 times daily if a sputum surveillance culture (not admission culture) yields yeasts, until two sputum cultures become negative; (3) 5 ml (80 mg) colistin is nebulized 4 times daily if a sputum surveillance culture (not admission culture) yields Gram-negative bacteria, until two sputum cultures are negative  
<sup>b</sup> During SDD, it is recommended to avoid antibiotics that have anaerobic activity as much as possible so as to leave the anaerobic flora undisturbed and preserve the so-called colonization resistance. The “to be avoided” antibiotics are penicillin, amoxicillin-clavulanic acid, flucloxacillin, piperacillin, piperacillin ± tazobactam, carbapenem, clindamycin. Metronidazole is the antibiotic of choice when the coverage of anaerobics is intended for clinical reasons

Table 2 Post hoc analyses and secondary studies on SDD and SOD

| References          | Design  | Main results  | Comments   |
|---------------------|---|---|--|
| de Smet et al. [6]  | 2 centres among 13 Dutch ICUs (NEJM 2009)   | Post-ICU rate of nosocomial infection (/1000 days at-risk)<br>SC: 8.3<br>SOD: 11.2<br>SDD: 12.9<br>Respiratory samples ( $n = 2304$ ):<br>Ceftazidime-resistant 10 % (7.6–13.3 %)<br>Tobramycin-resistant 10 % (6.9–12.5 %)<br>Ciprofloxacin-resistant 14 % (10.4–17.0 %)<br>Rectal samples ( $n = 2963$ )<br>Ceftazidime-resistant 6 % (4.7–7.5 %)<br>Tobramycin-resistant 9 % (7.7–11.2 %)<br>Ciprofloxacin-resistant 12 % (9.7–13.5 %)   | No impact of SDD/SOD on post-ICU infection rates   |
| Oostdijk et al. [7] | 13 Dutch ICUs (NEJM 2009)<br>Samples from 6 point-prevalence surveys before, during and after SDD/SOD                           | RR 1.44 (0.87–2.39)<br>RR 1.49 (0.90–2.47)<br>Pre-intervention 10 % (7.6–13.3 %)<br>10 % (6.9–12.5 %)<br>14 % (10.4–17.0 %)<br>Pre-intervention 6 % (4.7–7.5 %)<br>9 % (7.7–11.2 %)<br>12 % (9.7–13.5 %)  | SDD/SOD decreased resistance in respiratory and rectal samples, followed by a rebound effect after stopping it   |
| Benus et al. [8]    | 1 of 13 Dutch ICUs (NEJM 2009)<br>Fluorescent in situ hybridization analysis of the intestinal microbiota                       | Total number of bacteria cultured from the faeces<br>SC: (21 out of 121 patients): $3.7 \times 10^9$ (2.2–6.2)<br>SOD: (19 out of 111 patients): $1.6 \times 10^9$ (0.8–3.4)<br>SDD: (19 out of 86 patients): $1.9 \times 10^9$ (0.9–4.3)<br><i>Enterococcus faecalis</i><br>SC: $2.6 \times 10^6$<br>SOD $7.6 \times 10^6$ $P < 0.05$<br>SDD $69 \times 10^6$ $P < 0.05$<br>Cumulative rate of bacteremia according to respiratory colonization status:<br>SC: 4.5/1000 patient-days<br>SOD: 3.0/1000 patient-days<br>SDD: 3.0/1000 patient-days<br>SDD: 1.0/1000 patient-days in patients remaining colonized by enterobacteriae<br>SDD: 1.0/1000 patient-days in patients successfully decolonized<br>Any bacteremia (except Coagulase-negative<br>SC: 239/1837 (13 %)<br>SOD: 158/1758 (9 %)<br>SDD: 124/1868 (7 %) | SDD/SOD reduced the bacterial count of the faeces  |
| Oostdijk et al. [9] | 13 Dutch ICUs (NEJM 2009) and 1 ICU (UMC Utrecht: 08/2008–08/2010)  | <i>Enterococcus faecium</i> $F. prausnitzii$<br>SC: $6.3 \times 10^6$ $5.5 \times 10^7$<br>SOD $9.8 \times 10^6$ NS<br>SDD $54 \times 10^6$ $P < 0.05$<br>$4.0 \times 10^7$ NS<br>$0.1 \times 10^7$ $P < 0.05$  | SDD/SOD significantly increased enterococci  |
| de Smet et al. [10] | 13 Dutch ICUs (NEJM 2009)<br>Rate of bacteremia and respiratory tract acquisition of microorganisms in patients staying >3 days | Bacteremia with highly-resistant <i>Staphylococci</i> microorganisms<br>19/1837 (0.10 %)<br>20/1758 (1.03 %)<br>NS<br>NNT: 25<br>OR: 0.66 (0.53–0.82)<br>OR: 0.48 (0.38–0.60)<br>NNT: 16<br>8/1868 (0.04 %)<br>Of highly-resistant microorganisms<br>128/881 (15 %)<br>88/886 (10 %)<br>NS<br>OR: 0.46 (0.24–0.88)<br>74/828 (9 %)<br>SDD: 800/828 (97 %)   | SDD decreased bacteremia only in patients successfully decolonized   |
|                     |   | Respiratory tract acquisition of any microorganisms<br>SC: 867/881 (98 %)<br>SOD: 862/886 (97 %)<br>NS<br>OR: 0.65 (0.49–0.87) NNT: 22<br>OR: 0.58 (0.43–0.78) NNT: 18  | SDD > SOD decreased respiratory colonization   |
|                     |   | Respiratory tract acquisition of <i>Enterococcus</i> spp<br>SC: 37/881 (4 %)<br>SOD: 32/886 (3 %)<br>NS<br>OR: 1.44 (1.20–1.74)<br>OR: 1.59 (1.31–1.93)   | SDD > SOD increased respiratory colonization by enterococci <i>Candida</i> spp and <i>Pseudomonas aeruginosa</i> |
|                     |   | Respiratory tract acquisition of tobramycin-resistant non-fermenting Gram-negative pathogens (such as <i>P. aeruginosa</i> )<br>SC: 18/881 (2 %)<br>SOD: 20/886 (2 %)<br>NS<br>OR: 3.02 (1.74–5.20)   |  |

Table 2 continued

| References            | Design  | Main results  | Comments   |  |
|-----------------------|---|---|--|--|
| Oostdijk et al. [11]  | 13 Dutch ICUs (NEJM 2009)<br>Patients receiving SDD with rectal sampling and 1 single centre cohort; UMC Utrecht 01/2008–08/2009  | Proportion of successful decontamination under SDD<br>Patients with digestive enterobacteriaceae at ICU admission<br>Patients with cephalosporin-susceptible microorganisms<br>Patients with cephalosporin-resistant microorganisms<br>Patients with aminoglycoside-susceptible microorganisms<br>Patients with aminoglycoside-resistant microorganisms<br>Patients with any resistant microorganism at ICU entry<br>Patients with any resistant microorganism at ICU discharge<br>28-day mortality in surgical patients<br>SC: 209/973 (21.6 %)<br>SOD: 194/866 (22.6 %)<br>SDD: 191/923 (20.8 %)                                    | 399/507 (79 %)<br>343/430 (80 %)<br>56/77 (73 %)<br>368/457 (81 %)<br>31/50 (62 %)<br>23/109 (21 %)<br>24/109 (22 %)<br>28-day mortality in non-surgical patients<br>335/1016 (33.2 %)<br>308/1038 (30.0 %)<br>349/1111 (31.7 %)<br>Bacteremia in non-surgical patients<br>84/1016 (8.3 %)<br>60/1038 (5.8 %)<br>41/1111 (3.7 %)<br>$P < 0.05$<br>$P < 0.05$<br>$P < 0.05$<br>NS<br>OR: 0.77 (0.63–0.94)<br>OR: 0.85 (0.70–1.03) | SDD less successfully decolonized the digestive tract from resistant microorganisms<br>$P < 0.05$<br>$P < 0.05$<br>SDD decreased mortality in non-surgical patients<br>SDD/SOD decreased bacteremia in all patients                          |
| Melsen et al. [12]    | 13 Dutch ICUs (NEJM 2009)<br>post hoc analysis of surgical ( $n = 2762$ ) versus non-surgical ( $n = 3165$ ) patients   | Bacteremia in surgical patients<br>SC: 86/973 (8.8 %)<br>SOD: 50/866 (5.8 %)<br>SDD: 39/923 (4.2 %)<br>Colistin susceptibility testing<br>Acquisition of rectal colistin-resistant microorganisms<br>Evolution from colistin-susceptible to colistin-resistant SC<br>12.1 %   | OR: 0.97 (0.77–1.22)<br>OR: 0.86 (0.69–1.09)<br>OR: 0.85 (0.70–1.03)<br>$P < 0.05$<br>$P < 0.05$   | SDD decreased mortality in non-surgical patients   |
| Oostdijk et al. [13]  | 9 of 13 Dutch ICUs (NEJM 2009) with colistin susceptibility testing   | Acquisition of rectal colistin-resistant microorganisms<br>Evolution from colistin-susceptible to colistin-resistant SC<br>12.1 %   | OR: 0.85 (0.70–1.03)<br>$P < 0.05$<br>$P < 0.05$   | SDD/SOD decreased bacteremia in all patients   |
| Wittekamp et al. [14] | 5 of 13 Dutch ICUs participating in 2 large studies: I: SC, SOD-I, SDD-I (NEJM 2009) 1007 respiratory and 1093 rectal samples obtained from 1189 patients II: SOD-II, SDD-II (JAMA 2014) 1755 respiratory and 1808 rectal samples obtained from 1865 patients | Tobramycin resistance in rectal samples:<br>1 SDD-I vs SC: RR 0.54 (0.34–0.87)<br>2 SDD-I vs SOD-I: RR 0.46 (0.29–0.72)<br>3 SDD-II vs SDD-I: RR 0.64 (0.40–1.04)<br>4 SDD-II vs SC: RR 0.35 (0.23–0.53)<br>5 SOD-II vs SOD-I: RR 0.56 (0.39–0.78)<br>6 SOD-II vs SC: RR 0.66 (0.47–0.95)<br>Tobramycin resistance in respiratory samples<br>1 SDD-I vs SC: RR 0.61 (0.38–1.00)<br>2 SDD-II vs SC: RR 0.48 (0.32–0.73)<br>3 SOD-II vs SOD-I: RR 0.48 (0.30–0.76)<br>4 SOD-II vs SC: RR 0.42 (0.27–0.64)<br>Colistin resistance in rectal samples<br>1 SOD-II vs SC: RR 0.41 (0.17–0.98)<br>Colistin resistance in respiratory samples | 2.4 (2.5–4.2)/1000 patient-days<br>1.7 % (1.0–2.7)<br>14 %<br>4.2 % <sup>3,4</sup><br>4.5 % <sup>3,4</sup><br>6.6 % <sup>1,2</sup><br>6.7 % <sup>1</sup><br>10.9 %<br>9.7 %<br>5.3 % <sup>2,3</sup><br>4.5 % <sup>3,4</sup><br>1.7 %<br>1.7 %<br>1.7 %<br>1.1 % <sup>1</sup><br>0.9 %<br>2.1 %<br>2.7 %<br>2.8 %<br>1.2 %<br>1.7 %<br>1.1 %<br>1.1 %<br>0.6 %  | Medium-term (24 months) acquisition of colistin-resistance<br>Long-term SDD/SOD (over 7 years) decreased tobramycin resistance in rectal and respiratory samples<br>Long-term SDD/SOD (over 7 years) did not increase resistance to colistin |

SDD selective decontamination of the digestive tract, SOD selective oropharyngeal decontamination, SC standard care, NS not significant, APACHE II acute physiology and chronic health evaluation II score, ICU intensive care unit, OR odds ratio, RR relative risk, vs versus, 95 % CI 95 % confidence interval

and a lower volume of topical antibiotics [4]. Indeed, when SDD was compared with standard care, the use of cephalosporins was increased due to the SDD regimen, but the use of antimicrobial agents was reduced significantly for broad-spectrum penicillins, carbapenems, lincosamides, and quinolones [4]. This was also true for SOD, but the difference with standard care was less pronounced [4].

- Recent SDD/SOD studies were all performed in the Netherlands where antimicrobial resistance is a minor concern with a low reported use of broad-spectrum antibiotics, such as piperacillin/tazobactam, cefepime, and carbapenems. Hence, a more pronounced gradual increase was observed with aminoglycoside-resistant Gram-negative bacteria with SDD [5]. The effects of the prolonged use of SDD and SOD on colistin resistance have been determined in a study performed on two different large ICU cohorts [13]. No association was observed between the use of SDD or SOD and increased acquisition of colistin-resistant Gram-negative bacteria in the respiratory tract. In another study performed on patients colonized with Enterobacteriaceae in the intestinal tract at ICU admission, SDD was shown to eradicate cephalosporin-resistant Enterobacteriaceae from the intestinal tract [11]. These findings are usually related to the fact that the studies are performed in environments with a lower incidence of highly-resistant microorganisms. By contrast, studies performed in countries with a higher incidence of highly-resistant microorganisms have also reported similar effects [17, 18].
- Some observations were performed over a short period of time and resistance may not have been immediately apparent. Hence, a rebound effect after stopping SDD/SOD has been suggested in one of the post hoc analyses, as well as the emergence of colistin-resistant strains during persistent Gram-negative bacteria colonization over the study period (24 months) [13, 7]. Indirect evidence suggests that SDD/SOD is associated with the long-term alteration of the microbiota of the digestive tract and a potential increase in the associated resistome, but this remains largely speculative at

the present time [19]. However, these effects were not confirmed in a very recent report on continuous surveillance of the impact of SDD and SOD up to 7 years [14]. This large study confirmed a continuous reduction of the rate of tobramycin resistance and the absence of emergence of resistance to colistin in both respiratory and rectal samples (Table 2). The occurrence of a rebound effect after the discontinuation of SDD/SOD use in these centres remains to be determined.

In conclusion, SDD and SOD are used in a minority of ICUs, despite the available data on survival benefit. Although antibiotic resistance is not shown to be associated with the use of SDD and SOD in the particular setting of experienced Dutch ICUs, some ecological changes in ICUs have been reported (Table 2). SDD has resulted in lower rectal carriage of antibiotic-resistant Gram-negative bacteria compared to SOD. SDD has demonstrated superiority over SOD, but both are related to a lower use of systemic antibiotics, other than those used during the first 4 days of SDD, and result in a lower mortality in ICU patients compared to standard care. Therefore, SOD can be viewed as a good alternative to SDD. However, the lower rate of bacteremia and bacterial resistance observed with SDD pleads in favor of this regimen. Further studies are planned in higher endemic resistance regions to assess the effect of SDD or SOD on long-term resistance development.

#### Compliance with ethical standards

**Conflicts of interest** JK has received honorarium from B&D and QXV Communications Ltd. PE has no conflict of interest.

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