Commentary
Selective decontamination of the digestive tract reduces mortality in critically ill patients

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Abstract

Several emotional responses may be invoked in critical care physicians when confronted with selective decontamination of the digestive tract (SDD). Although recent meta-analyses have shown that the use of SDD reduces the occurrence of ventilator-associated pneumonia and improves ICU survival, the effectiveness of SDD has remained controversial. We recently concluded a large randomized, controlled trial on the use of SDD that showed improved survival of ICU patients treated with SDD. A second concern regarding use of SDD has been the fear for the emergence of antimicrobial resistance. Interestingly, a recently published study did not confirm this fear, and our recently finished study even demonstrated a decline in colonization with *P. aeruginosa* and enterobacteriaceae that were resistant against tobramycin, ceftazidime, imipenem and ciprofloxacin. The hopes are that this study will at long last end the debate about the efficacy and safety of SDD in critically ill patients.

Keywords bacterial resistance, intensive care unit acquired infections, pneumonia, selective decontamination of the digestive tract, ventilator-associated pneumonia

Recent meta-analyses have shown that the use of selective decontamination of the digestive tract (SDD) can reduce the occurrence of ventilator-associated pneumonia (VAP) [1–5]. Two of these analyses also demonstrated a significant reduction in intensive care unit (ICU) mortality [4,5]. However, the effectiveness of SDD has remained controversial [6,7]. Although SDD has received considerable attention in European ICUs, North American intensivists have been uniformly resistant to the incorporation of SDD as standard care [8,9]. One of the main concerns is the fear of emergence of selection for resistant organisms. Furthermore, in the guidelines for the prevention of nosocomial pneumonia published in 1997, the Centers for Disease Control and Prevention stated that available data do not justify the routine use of SDD in ICU patients [10].

We recently performed a single-center, prospective, controlled, randomized trial on the use of SDD that showed improved survival of ICU patients treated with SDD [11]. Importantly, the study also demonstrated that colonization with resistant bacteria decreased, which is opposite to the expectation of the skepticists about SDD in intensive care patients.

The concept on which SDD is based

Nosocomial infections are caused by a limited number of potentially pathogenic microorganisms (PPMs) such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Escherichia coli* and *Candida albicans* that are carried by healthy people, and by opportunistic aerobic Gram-negative bacilli such as *Klebsiella*, *Proteus*, *Morganella*, *Enterobacter*, *Citrobacter*, *Serratia*, *Acinetobacter* and *Pseudomonas* species that are present in individuals with underlying pathology.

One method for preventing nosocomial infections by these PPMs is the use of SDD [12]. This technique combines

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ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*; PPM = potentially pathogenic microorganism; SDD = selective decontamination of the digestive tract; VAP = ventilator-associated pneumonia; VRE = vancomycin-resistant entercocci.

Table 1

Selective decontamination of the digestive tract (SDD) schemes and outcomes of prospective randomized trials

Reference	Number of patients	Pulmonary infection incidence (%), control versus SDD	*P* value	Mortality (%), control versus SDD	*P* value
Aerdts *et al.* [14]	88	69.2 vs 5.9	0.0001	15.4 vs 11.8	Not significant
Blair *et al.* [15]	256	34.4 vs 9.7	0.002	21.4 vs 10.5	Not significant
de Jonge *et al.* [11]	934	—[a]	—[a]	22.9 vs 14.8	0.002
Cockerill *et al.* [16]	150	18.6 vs 5.3	0.03	21.3 vs 14.7	Not significant
Jacobs *et al.* [17]	79	9.3 vs 0	< 0.05	53.5 vs 38.8	Not significant
Kerver *et al.* [18]	96	85.1 vs 12.2	< 0.01	32.0 vs 28.5	Not significant
Krueger *et al.* [19]	546	11.1 vs 2.3	0.007	28.6 vs 19.6	Not significant[b]
Palomar *et al.* [20]	83	50.0 vs 17.1	0.005	31.0 vs 24.4	Not significant
Rocha *et al.* [21]	101	46.3 vs 14.9	< 0.001	44.4 vs 21.3	< 0.05[c]
Sanchez-Garcia *et al.* [22]	271	29.3 vs11.5	0.05	47.1 vs 38.9	Not significant
Ulrich *et al.* [23]	100	55.8 vs 14.6	< 0.001	53.8 vs 31.3	< 0.02[c]
Verwaest *et al.* [24]	440	11.4 vs 6.6	< 0.05	16.8 vs 15.5	Not significant
Verwaest *et al.* [24]	440	11.4 vs 7.0	< 0.05	17.6 vs 15.5	Not significant
Winter *et al.* [25]	183	34.8 vs 3.3	< 0.01	43.5 vs 36.3	Not significant

[a] Not evaluated.
[b] Overall intensive care unit mortality was not statistically different, but the mortality was significantly reduced for patients with Acute Physiology and Chronic Health Evaluation II scores of 20–29 on admission.
[c] Not significant on intention-to-treat analysis.

enterally applied, nonabsorbable antibiotics and parenteral antibiotics. The rationale for SDD lies in the appreciation that the majority of ICU infections are caused by the aforementioned pathogens, predominantly the Gram-negative aerobic bacteria. These pathogens may be present prior to admission to the ICU. They give rise to so-called primary endogenous infections. Secondary endogenous infections occur at later time points during the stay in the ICU, are caused by hospital-acquired organisms, and are preceded by colonization of the oropharynx, the stomach and the gut. These infections are much less frequent [13].

The goal of SDD is to prevent, or to eradicate if initially present, oropharyngeal and gastrointestinal carriage of PPMs, especially hospital PPMs, leaving the indigenous flora, which are thought to protect against overgrowth with resistant bacteria, largely undisturbed [13].

SDD classically consists of four aspects. The first is selective eradication of PPMs in the oral cavity by application of orabase, containing nonabsorbable antibiotics (e.g. polymyxin B, tobramycin and amphotericin B), and decontamination of the rest of the digestive tract by local administration (through a nasogastric tube) of the aforementioned antibiotics. Another method is systemic prophylaxis (e.g. cefotaxime) to prevent respiratory infections that may occur early during the

ICU stay, caused by commensal respiratory flora (*S. pneumoniae* and *H. influenzae*). The third aspect is optimal hygiene, to prevent cross-contamination. Finally, regular cultures of throat swabs and faeces are performed (monitoring the effectiveness of SDD).

Studies on SDD

There are presently no studies that have compared the whole regimen, as already described, with regimens using only nonabsorbable antibiotics in the oral cavity and the rest of the digestive tract, or with nonabsorbable antibiotics in the oral cavity alone. We specifically chose to review the trials in which the whole regimen of SDD (oropharyngeal, intestinal and systemic) has been studied since we consider the first three aspects of the original SDD regimen essential to control the three types of infection in ICU patients (primary endogenous infections, secondary endogenous infections and exogenous infections).

Twelve prospective, randomized studies in which SDD is compared with controls (Table 1) [14–25] and five meta-analyses including only prospective studies have been published in the past 15 years. A large prospective, controlled, randomized trial has recently been finished. At present, data from this trial are only available in abstract form [11].

Effects on pneumonia

In the studies in which the original SDD regimen was compared with standard care, the use of SDD significantly reduced the incidence of pneumonia [14–25]. The reduction was independent of the choice of systemic antimicrobial agent, as well as the choice of topical antimicrobial agents, since the effect of SDD on the incidence of pneumonia was found in all the reviewed studies (Table 1).

Remarkably, the incidence of VAP in the control groups varied from 9.3% [17] to 85.1% [18]. One reason for this large variation may be differences in patient populations. Another reason may be the difference in the way in which pneumonia is diagnosed. In some studies, the diagnosis of VAP was made on clinical, radiological and microbiological criteria alone. It can be argued that in these studies the reduction in respiratory tract infections is in fact a reduction in colonization and purulent tracheobronchitis, and not a reduction in pneumonia. Other studies used bronchoscopic techniques, with quantitative cultures that usually cause the incidence of VAP to be one-half of that with the diagnosis made based on clinical, radiological and microbiological criteria. But, also in these studies, the SDD regime still demonstrated a significant reduction in the incidence of pneumonia compared with conventional treatment.

Effects on mortality

Only two of the published studies demonstrated a reduced mortality in SDD-treated patients compared with control subjects [21,23]. In these studies the reported reduction in mortality was found after exclusion of a number of patients. In an intention-to-treat analysis the differences in mortality did not reach significance [4]. Although in all studies but one the number of patients that died in the SDD-treated group was lower compared with the number of patients that died in the control group [14–18,20,22,24,25], a significant effect of SDD on mortality could not be demonstrated. This was due to the small number of patients in those studies (i.e. all these studies were underpowered).

A significant reduction in ICU mortality has been demonstrated in two recent meta-analyses [4,5]. In the analysis by D'Amico et al., the mortality was 24% in SDD-treated patients and was 30% in controls [4]. In addition, one recently published study showed a reduced mortality in patients on SDD in midrange stratum with Acute Physiology and Chronic Health Evaluation II scores of 20–29 on admission [19]. We recently finished a prospective, randomized, controlled study in 934 patients (medical and surgical), presently unpublished, and found a significant reduction in ICU mortality and hospital mortality [11].

Major concerns exist because the majority of studies was performed in a nonblinded fashion. However, the results of the two double-blind studies are comparable with the results of the nonblinded studies in respect to the reduction of the

incidence of VAP (Table 1). Although a double-blind study is the optimal design to determine the efficacy of an intervention, only two of the aforementioned studies were double-blind trials [21,22]. Because surveillance cultures will immediately show which patient is receiving SDD and which patient is not, it is not possible to perform a study in a blinded fashion.

Surveillance cultures are an integral part of microbiology for SDD patients. They are necessary to enable monitoring of the efficacy of SDD and the detection of exogenous infection problems in the ICU. Furthermore, even if it would be possible, the consequence of a blinded study is to create an environment in which both regimens are used at the same time. Under these circumstances the desired effects of SDD would be less because of cross-contamination. This situation has been dealt with in the study of de Jonge et al. [11] by randomly admitting patients to separate units, which were randomized to be using SDD or conventional treatment. Also, as recently shown [26], the inverse relationship between methodological quality score (e.g. blinded versus nonblinded studies) and the benefit of SDD exists for the incidence of VAP, but not for mortality. A well-designed trial can thus be used to demonstrate the effect of SDD on mortality, whether blinded or not.

Effects of SDD on antimicrobial resistance

It has been argued that the use of SDD may lead to the emergence of antimicrobial resistance. However, in none of the published prospective, randomized trials was there a clinically significant harmful effect of SDD in respect to superinfections, nor was there colonization with microorganisms that had acquired resistance to the antibiotics used.

Only two studies adequately analyzed the effects of SDD on antimicrobial resistance [11,19]. The study by Krueger et al. [19] demonstrated no remarkable differences between SDD-treated patients and placebo-treated patients with respect to the isolation of resistant bacteria. Although increasing numbers of patients in both groups became colonized by coagulase-negative staphylococci, enterococci resistant to ciprofloxacin and gentamicin, and oxacillin-resistant coagulase-negative staphylococci, methicillin-resistant S. aureus (MRSA) was rarely isolated. The study by de Jonge et al. demonstrated a decline in colonization with P. aeruginosa and enterobacteriaceae that were resistant against tobramycin, ceftazidime, imipenem and ciprofloxacin [11], which is in contrast with the expectation of the skepticists of SDD. In their study, no colonization with MRSA was found in any patient and the incidence of colonization with vancomycin-resistant entercocci (VRE) was very low (<2%). Colonization with VRE was not influenced by the administration of SDD.

Different effects could clearly have been found in ICUs with a high prevalence of MRSA and VRE. SDD does exert

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selective pressure on MRSA. Indeed, increased colonization with MRSA in SDD-treated patients has been reported in ICUs with endemic MRSA [24,27]. However, no publications exist reporting an increase in hospital outbreaks of MRSA in countries with a low incidence of MRSA carriage in the population. On the contrary, Staphylococcal and *Enterococcus* spp. infections were uncommon and the level of methicillin resistance did not change in a study on the long-term effects of SDD by Hammond and Potgieter [28]. Although no studies showed increased colonization or infection with VRE, it cannot be excluded that SDD has a detrimental effect on VRE in situations were VRE is endemic. On the other hand, the reduced prescription of systemic broad-spectrum antibiotics in SDD-treated patients may also lead to decreased incidence of VRE [22].

Conclusion

Taken together, the results of the individual studies and the meta-analysis indicate a strong protective effect of the original SDD scheme against VAP in critically ill patients. The recent, as yet unpublished, study on SDD from our institution supports the conclusion from the meta-analysis that mortality is also reduced in SDD-treated patients. In hospitals with a low prevalence of VRE and MRSA there is no data that show increased resistance to those organisms. On the contrary, resistance against Gram-negative aerobic bacteria decreased in SDD patients compared with patients receiving standard treatment.

Based on the present data, we recommend using SDD, combining systemic, topical, oropharyngeal and intestinal antibiotics, in critically ill patients. As the concept of SDD has been shown to improve survival, more research is needed to determine the optimal SDD regimen in situations in which VRE and MRSA are endemic.

Competing interests

None declared.

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