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REVIEW

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Selective decontamination of the digestive tract: the mechanism of action is control of gut overgrowth

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Abstract *Purpose:* Gut overgrowth is the pathophysiological event in the critically ill requiring intensive care. In relation to the risk of developing a clinically important outcome, gut overgrowth is defined as $\geq 10^5$ potential pathogens including 'abnormal' aerobic Gram-negative bacilli (AGNB), 'normal' bacteria and yeasts, per mL of digestive tract secretion. Surveillance samples of throat and gut are the only samples to detect overgrowth. Gut overgrowth is the crucial event which precedes both primary and secondary endogenous infection, and a risk factor for the development of de novo resistance. Selective decontamination of the digestive tract (SDD) is an antimicrobial prophylaxis designed to control overgrowth.
Methods: There have been 65 randomised controlled trials of SDD in 15,000 patients over 25 years and 11 meta-analyses, which are reviewed.
Results and conclusions: These trials demonstrate that the full SDD regimen using parenteral and enteral antimicrobials reduces lower airway infection by 72 %, blood stream infection by 37 %, and mortality by 29 %. Resistance is also controlled. Parenteral cefotaxime which reaches high salivary and biliary concentrations eradicates overgrowth of 'normal' bacteria such as *Staphylococcus aureus* in the throat. Enteral polyenes control 'normal' *Candida* species. Enteral polymyxin and tobramycin, eradicate, or prevent gut overgrowth of 'abnormal' AGNB. Enteral vancomycin controls overgrowth of 'abnormal' methicillin-resistant *S. aureus*. SDD controls overgrowth by achieving high antimicrobial concentrations effective against 'normal' and 'abnormal' potential pathogens rather than by selectivity.

Keywords SDD · Mechanism of action · Gut overgrowth · Selectivity · RCTs · Meta-analyses

Introduction

In 1996, Konrad Falke invited us to write an update on selective decontamination of the digestive tract (SDD), in particular, to explain the results of randomised controlled trials (RCTs) not showing a benefit of the technique [1]. He was convinced that negative RCTs teach more than positive ones. Over 50 RCTs had been published up to 2003 when Mervyn Singer encouraged us to write a follow-up. He thought that the reader would benefit if we compared the evidence of efficacy, safety and costs of SDD with traditional parenteral antibiotic-only approach to control infection in the intensive care unit (ICU) [2]. By the end of 2011, there have been 65 RCTs [3–67]

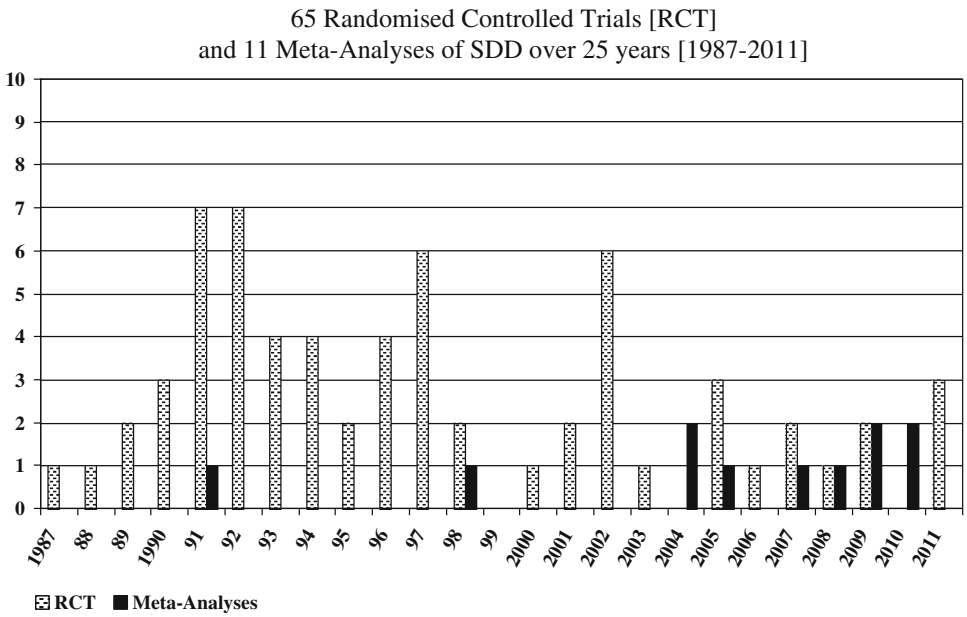

Fig. 1 65 Randomised controlled trials (RCT) and meta-analyses

Table 1 Overview table efficacy of SDD: 65 RCTs and 11 meta-analyses

Author	No RCTs	Sample size	Lower airway infection OR (95 % CI)	Bloodstream infection OR (95 % CI)	Multiple Organ Dysfunction Syndrome OR (95 % CI)	Mortality OR (95 % CI)
Vandenbroucke-Grauls [68]	6	491	0.12 (0.08–0.19)	NR		0.92 (0.45–1.84)
D'Amico [69]	33	5,727	0.35 (0.29–0.41)	NR		0.80 (0.69–0.93)
Safdar [70]	4	259	NR	NR		0.82 (0.22–2.45)
Liberati [71]	36	6,922	0.35 (0.29–0.41)	NR		0.78 (0.68–0.89)
Silvestri [72]	42	6,075	NR	0.89 (0.16–4.95)[a]		NR
Silvestri [73]	51	8,065	NR	0.63 (0.46–0.87)		0.74 (0.61–0.91)
Silvestri [74]	54	9,473				
G −ve			0.07 (0.04–0.13)	0.36 (0.22–0.60)		NR
G +ve			0.52 (0.34–0.78)	1.03 (0.75–1.41)		NR
Silvestri [75]	21	4,902	NR	NR		0.71 (0.61–0.82)
Liberati [76]	36	6,914	0.28 (0.20–0.38)	NR		0.75 (0.65–0.87)
Silvestri [77]	7	1,270	NR	NR	0.50 (0.34–0.74)	0.82 (0.51–1.32)
Silvestri [78]	12	2,252	0.54 (0.42–0.69)[b]	NR		NR

SDD selective decontamination of the digestive tract, *RCT* randomised controlled trial, *No* number, *OR* odds ratio, *CI* confidence interval, *G −ve* Gram-negative, *G +ve* gram-positive, *NR* not reported

[a] Yeast infection

[b] Tracheobronchitis

(Fig. 1) and 11 meta-analyses of only RCTs on SDD [68–78] (Table 1) in approximately 15,000 patients over a period of 25 years. The full protocol using parenteral and enteral antimicrobials has been assessed in one-third of RCTs [5, 10, 11, 16–19, 23, 31, 32, 34, 37, 41, 47, 49, 53, 57–59, 61, 63, 66]. Among the 65 RCTs, 52 are from Europe and 13 from non-European countries (1 South America, 1 China, 2 Africa, 9 North America). The Netherlands (15), Spain (10) and Britain (8) are the leading countries from Europe. All except one meta-analyses are European (1 from The Netherlands and 9 from Italy). Massimo Antonelli convinced us that the time has come to write a third review on SDD. The emphasis would be on the mechanism of action of SDD that underlies the significant reduction of severe infections of lower airways and blood and the survival benefit with resistance being controlled.

Definitions

Carriage or carrier state exists when the same potential pathogen is isolated from at least two consecutive

surveillance samples in any concentration over a period of at least 1 week. Low grade carriage is defined as $<10^5$ potential pathogens per millilitre or gram of digestive tract secretions. High grade carriage or overgrowth is defined as $\geq 10^5$ potential pathogens per millilitre or gram of digestive tract secretions. Overgrowth is a risk factor for developing infection and resistance [79, 80].

SDD is an antimicrobial prophylaxis using parenteral and enteral antimicrobials. It prevents endogenous infections of lower airways and blood and reduces mortality in ICU patients [81].

SDD is based on the observation that critical illness profoundly affects the body flora, both qualitatively and quantitatively, promoting a shift from (1) normal to abnormal carriage, and (2) low to high grade carriage (overgrowth) of 'normal' and 'abnormal' flora [79–81]. There are five microorganisms that belong to the 'normal' flora as they are carried by healthy individuals: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are carried in the throat; *Escherichia coli* is carried in the gut; and *Staphylococcus aureus* and *Candida albicans* are carried in both throat and gut. There are nine 'abnormal' bacteria carried by individuals who suffer from underlying diseases: they include eight aerobic Gram-negative bacilli (AGNB) (*Klebsiella*, *Enterobacter*, *Citrobacter*, *Proteus*, *Morganella*, *Serratia*, *Acinetobacter* and *Pseudomonas* species), and methicillin-resistant *Staphylococcus aureus* (MRSA). 'Abnormal' bacteria are carried in both throat and gut [80]. In 1969, Johanson et al. [82] demonstrated that the main factor associated with oropharyngeal AGNB carriage was the severity of illness. Similarly, Chang et al. [83] showed that in cirrhotic patients the severity of liver disease was independently associated with MRSA carriage.

Detection of gut carriage and overgrowth

The traditional microbiological approach of obtaining and culturing diagnostic samples, such as tracheal aspirate and urine, can never detect overgrowth, as these samples only confirm the clinical diagnosis of infection, and its preceding stage of colonisation. Surveillance samples of throat and gut are the only samples that allow the detection of overgrowth [84]. The standard procedure includes, albeit not mandatory, a broth-enrichment stage to detect very low concentrations of micro-organisms [85, 86].

Critical illness related carriage in overgrowth concentrations (CIRCO)

CIRCO is common on ICU admission [87]. Primary endogenous infections are the most frequent ICU infections (approximately 55 %). They are caused by both normal and abnormal potential pathogens imported into the ICU by the patient's admission flora in overgrowth concentrations. These infections generally occur early, during the first week of ICU treatment. Normal potential pathogens are the etiological agents in previously healthy individuals requiring intensive care following an acute event, such as (surgical) trauma, pancreatitis, acute hepatic failure, and burns. Abnormal bacteria can cause primary endogenous infections in patients with previous underlying disease, such as chronic obstructive pulmonary disease. Patients transferred from another ward/hospital or nursing home belong to this category.

CIRCO often develops during treatment in ICU [88]. Apart from critical illness, opiates, histamine$_2$-receptor antagonists, and antimicrobials promote gut overgrowth by reducing peristalsis [89], increasing the gastric pH >4 [90, 91], and suppressing the normal indigenous, mainly anaerobic, flora required to control abnormal flora [92], respectively. Secondary endogenous infections are invariably caused by the nine 'abnormal' bacteria, accounting for one-third of ICU infections. These infections, generally, occur late, after 1 week of ICU treatment. These abnormal bacteria are first acquired in the oropharynx, and subsequently in stomach and gut. CIRCO readily develops in both oropharynx and gut.

Obviously, CIRCO is not the issue in exogenous infections, i.e. without previous carriage. Exogenous infections (approximately 15 %) are invariably caused by 'abnormal' bacteria, and may occur at any time during ICU treatment. Typical examples are lower airway infection caused by *Acinetobacter* or *Pseudomonas* following the use of contaminated ventilation equipment. Surveillance samples are negative for the potential pathogens that readily appear in diagnostic samples [75] (Table 2).

Table 2 Characteristic features of infections seen in ICU

Type of infection	Potential pathogens	Onset	Incidence (%)	Controlling manoeuvre
Primary endogenous	Normal/abnormal	<1 week	55	Parenteral antimicrobials
Secondary endogenous	Abnormal	>1 week	30	Hygiene + enteral antimicrobials
Exogenous	Abnormal	Anytime during ICU-treatment	15	Hygiene + topical antimicrobials

Gut overgrowth harms the critically ill

Gut overgrowth, in particular of AGNB, has been acknowledged to cause immuno-suppression and generalised inflammation [93]. Gut overgrowth is the crucial event preceding endogenous infections and is a risk factor for the development of de novo antimicrobial resistance. There is a qualitative and quantitative relationship between surveillance cultures of throat and rectum, and diagnostic cultures of lower airway secretions and blood [85, 88].

Dynamics of antibiotic resistance are driven by three mechanisms:

1. Importation. The patient is admitted to the ICU with resistant micro-organisms in overgrowth concentrations in the gut [87];
2. Acquisition from other patients with overgrowth following transmission via the hands of carers. Thirty-three percent of patients admitted as normal carriers to a medical/surgical ICU developed abnormal carriage of multi-drug-resistant *K. pneumoniae* and/or *A. baumannii*, the two abnormal AGNB endemic in the ICU during the study [94]. A higher severity of illness score on admission was a significant risk factor. Similar results were reported by Spanish researchers [95].
3. De novo development. Gut overgrowth has been identified as a risk factor for the development of de novo resistance [96]. The gut of the critically ill patient with microbial overgrowth is the ideal site for the de novo development of new clones, following increased spontaneous mutation, termed hypermutation. In hypermutation, microbial populations start mutating vigorously at random, presumably as an adaptive mechanism that may cause a mutant to arise that would enable them to overcome the unfavourable surroundings, resulting in polyclonality. A high proportion of long-term ICU patients receive parenteral antimicrobials, which are invariably excreted via the bile into the gut. Although low and fluctuating, the antibiotic levels will kill sensitive clones, but allow mutating ones to become resistant to antibiotics [97]. Overgrowth not only promotes mutation but also increases the probability of transfer of genes coding for resistance between micro-organisms.

Each mechanism is responsible for approximately one-third of the resistance problem, the common denominator being overgrowth.

Control of overgrowth

In the mid-1970s, Bodey [98] realised that many systemic antimicrobials may sterilise lungs, blood and bladder but often fail to eradicate identical potential pathogens in overgrowth concentrations from the throat and/or gut.

A classical study by Bodey was the assessment of the old parenteral antifungal 5-fluorocytosine in eradicating *Candida* carriage [98]. He wrote that "5-fluorocytosine has substantially reduced the proportion of patients with persistent fungi in their stools and throats". However, resistance readily occurred. Similarly, systemic prophylaxis with fluconazole also failed to eradicate yeast gut overgrowth [99], probably due to low biliary concentrations of fluconazole [100]. Bodey introduced the enteral administration of polyenes, nystatin and amphotericin B, to control fungal overgrowth [101–103]. Faecal specimens of healthy volunteers contained nystatin concentrations of <100 mg/L of faeces following the daily intake of 8×10^6 units of nystatin [102]. The faecal samples of healthy individuals taking 2,000 mg of amphotericin B daily showed 60 mg/L of faeces of amphotericin B [103]. These faecal levels are due to the high faecal binding of polyenes (Table 3).

Bodey was also the first to assess the enteral antimicrobials polymyxin E and tobramycin in controlling AGNB carriage [104]. The combination of polymyxin [105] and tobramycin [106] was chosen because it covers most abnormal AGNB, including *Pseudomonas* species, and is an in vitro synergistic combination [107]. Compared to polymyxin, tobramycin is less inactivated by mucosal cells, fibres and faeces [108]. Faecal specimens contained tobramycin levels of minimally 100 mg/L of faeces following the daily intake of 300 mg of tobramycin (Table 3) [109]. The faecal samples of individuals taking 600 mg of tobramycin daily showed ≥500 mg/L of faeces [110]. Polymyxin is moderately inactivated by faeces and, hence, faecal concentrations vary. Polymyxin was not detected in one-third of individuals who took 600 mg of polymyxin daily. One-third had faecal levels exceeding 1,000 mg/L of faeces, whereas the remaining individuals showed polymyxin concentrations between 16 and 1,000 mg/L of faeces [111].

Table 3 Antimicrobials selected for SDD to control overgrowth of both 'normal' and 'abnormal' flora

Antimicrobials selected for SDD	Concentrations (mg/L)		
	Saliva	Bile	Faeces
'Normal' flora			
Bacterial overgrowth Cefotaxime	6	20	
Yeast overgrowth amphotericin B			60
or nystatin			<100
'Abnormal' flora			
AGNB overgrowth polymyxin E			16–1,000
with tobramycin			100
MRSA overgrowth vancomycin			3,000–24,000

SDD selective digestive decontamination, *AGNB* aerobic Gram-negative bacilli, *MRSA* methicillin-resistant *Staphylococcus aureus*

At the beginning of the 1980s, Stoutenbeek, in designing the SDD protocol, searched for a parenteral antimicrobial with adequate spectrum and pharmacokinetic properties. Cefotaxime was chosen because:

i. Its spectrum included both 'normal' and most 'abnormal' bacteria [112];
ii. Its pharmacokinetic properties included a high excretion in saliva and bile, possibly associated with eradication of overgrowth [113]. Salivary and biliary samples were obtained from adult patients requiring biliary surgery and receiving 1 g of cefotaxime intravenously four times daily. High concentrations were measured: 6 mg/L of saliva and 20 mg/L of bile (Table 3).

Stoutenbeek subsequently evaluated the decontaminating properties of cefotaxime in trauma patients rendered free from yeasts and AGNB following the administration of enteral amphotericin B and polymyxin E/tobramycin in throat and gut [114]. Cefotaxime was found to eradicate oropharyngeal overgrowth of 'normal' bacteria such as *S. aureus*, *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*. This original finding was confirmed by German researchers [115].

Parenteral antibiotics active against *P. aeruginosa* include ceftazidime, ciprofloxacin, piperacillin-tazobactam and meropenem. None of these anti-pseudomonal agents have ever been shown to clear *P. aeruginosa* from the throat and/or gut following intravenous administration [116, 117].

MRSA endemicity is defined as at least one new case per month of MRSA infection. Under these circumstances, the enteral SDD prophylaxis may be extended by enteral vancomycin. In early 2000, Silvestri et al. [118] observed that parenteral vancomycin failed to clear MRSA carriage from throat and gut, whilst enteral vancomycin eradicated MRSA gut carriage, and was effective in controlling a MRSA outbreak. Two grams of enteral vancomycin lead to faecal vancomycin levels of up to 24,000 mg/L of stool (Table 3) [119]. In contrast, 2 g of parenteral vancomycin were associated with stool vancomycin concentrations varying between 3 and 95 mg/L [120].

The inability to control exogenous infections is an inherent limitation of SDD. Indeed, tracheotomised patients can acquire abnormal bacteria directly into the tracheal site via the tracheostomy, without previous oropharyngeal carriage. A South African SDD RCT, in which there were 24 and 26 exogenous infections due to *A. baumannii* in SDD and controls, respectively, was the first to demonstrate the failure to control exogenous infections [29]. Up to 40 % of patients received a tracheostomy [121, 122]. In 2000, Morar et al. made the original observation that exogenous infections due to abnormal bacteria can be controlled by the topical application of antimicrobials. They prevented exogenous infections in tracheotomised patients by applying 0.5 g of a paste containing 2 % polymyxin E/tobramycin and 4 % vancomycin four times a day onto the tracheostomy [123, 124]. Topical antimicrobials are not part of the routine SDD protocol, but they are added to parenteral and enteral antimicrobials in case of endemicity of exogenous infections.

Clinical impact of SDD using enteral antimicrobials for control of overgrowth

The immuno-suppression reverted to normal in animals which were successfully decontaminated. SDD, after the initial experimental burn injury to rats, decreased sensitivity to a second infectious challenge of *S. pneumoniae* and indirectly decreased the cardiac inflammation and dysfunction associated with a septic challenge [125]. Patients who were free from AGNB following the enteral intake of polymyxin and tobramycin were able to control generalised inflammation [126]. Gut overgrowth of abnormal AGNB is the major source of endotoxin in the human body yielding up to 10 mg of endotoxin per gram of faeces [127]. The enteral antimicrobials of polymyxin/tobramycin significantly reduce the faecal endotoxin load by a factor of 10^4 [128]. It has been suggested that SDD may reinforce the anti-inflammatory effects of corticosteroids [129].

Enteral antimicrobials control overgrowth preventing colonisation and infection of the normally sterile internal organs. As a first step of a pneumonia prevention study, Stoutenbeek et al. [114] administered a 10-ml suspension of polymyxin E 100 mg, tobramycin 80 mg and amphotericin B 500 mg by nasogastric tube four times daily in 17 trauma patients. Ten patients (59 %) developed 13 lower airway infections, 10 primary and 3 secondary endogenous infections. *P. aeruginosa* and *A. baumannii* caused the secondary endogenous and *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. aureus* were responsible for the primary endogenous lower airway infections. SDD of stomach and gut did not affect pneumonia [130].

Stoutenbeek's second step was the assessment of the efficacy of enteral antimicrobials applied in both oropharynx and gut on the pneumonia rate [114]. Twenty-five trauma patients each received daily 2 g of a 2 % polymyxin/tobramycin/amphotericin B paste applied in the oropharynx combined with 40 ml of a solution of the same antimicrobials into the stomach and gut, divided into 4 doses. The pneumonia rate was 52 %; 13 patients developed a total of 13 lower airway infections, all of them were invariably due to 'normal' bacteria. Although the overall reduction was not significant, it was striking that secondary endogenous pneumonias due to 'abnormal' AGNB were completely prevented by the oropharyngeal

decontamination, which eradicated oropharyngeal overgrowth of AGNB [131].

The third and final step of the pneumonia prophylaxis study [114] involved 63 trauma patients, who received enteral antimicrobials in throat/gut combined with parenteral cefotaxime (50–100 mg/Kg/day) to eradicate oropharyngeal overgrowth of 'normal' bacteria. Five patients (8 %) developed exogenous lower airway infections, primary endogenous infections disappeared, and there were no secondary endogenous lower airway infections. Six of the 11 meta-analyses had the endpoint of pneumonia (Table 1) [68, 69, 71, 74, 76, 78], and all invariably demonstrated a significant pneumonia reduction due to both Gram-positive and Gram-negative bacteria. The meta-analysis from the Italian Cochrane Centre demonstrated that enteral and parenteral antimicrobials of SDD reduced lower airway infections by 72 % [odds ratio (OR) 0.28; 95 % confidence interval (CI) 0.20–0.38] [76]. Lower airway infections due to both Gram-negative and Gram-positive bacteria were reduced by 89 % (OR 0.11; 95 % CI 0.05–0.20) and 48 % (OR 0.52; 95 % CI 0.34–0.78), respectively [74]. Interestingly, the use of the full protocol of parenteral and enteral antimicrobials was more effective in reducing Gram-negative lower airway infections than solely enteral antimicrobials (OR 0.07; 95 % CI 0.04–0.13, and OR 0.28; 95 % CI 0.11–0.68, respectively). Additionally, a recent meta-analysis showed that SDD reduces ventilator-associated tracheobronchitis by 46 % (OR 0.54; 95 % CI 0.42–0.69) [78].

In 1989, 5 years after Stoutenbeek published the first SDD study [79], Langer et al. reported their landmark RCT on pneumonia prevention [132]. No statistically different rates of pneumonia or death were found amongst three groups receiving either intravenous cefoxitin, penicillin G, or no antibiotic. Stoutenbeek explained this failure by the omission of oropharyngeal and intestinal antimicrobials [133]. In leaving overgrowth intact, resistance against cefoxitin and penicillin G readily developed followed by lethal superinfections. Liberati et al. [76] confirmed the validity of Stoutenbeek's revolutionary concept that only the combination of parenteral and enteral antimicrobials impacts morbidity and mortality in critically ill ICU patients.

Bloodstream infection was the endpoint of three meta-analyses [72–74] (Table 1). Bloodstream infections due to AGNB were significantly reduced (OR 0.36, 95 % CI 0.22–0.60) [73], fungaemia was also reduced (OR 0.89, 95 % CI 0.16–4.95) but not significantly due to the low event rate in the control group [72]. Although Gram-positive bloodstream infections increased due to the SDD spectrum of activity primarily being against AGNB, this was not significant (OR 1.03, 95 % CI 0.75-1.41) [74].

de la Cal et al. [18] demonstrated that SDD provided a significant survival benefit in burn patients. There are only three RCTs of SDD in burn patients [3, 7, 18]; a recent meta-analysis recruiting 440 patients (289 SDD, 151 controls) showed that SDD significantly reduced mortality by 78 % (OR 0.22; 95 % CI 0.12–0.43; $p < 0.001$) [134].

The largest RCT to date is Dutch, and includes 6,000 patients [19]. It compares SDD and selective oropharyngeal decontamination (SOD), a modified SDD protocol without the parenteral and gut component, with standard care. The main endpoint was mortality. Both SDD and SOD significantly reduced mortality compared to standard care (OR 0.83 $p = 0.02$, and 0.86 $p = 0.045$, respectively). Although this RCT was the first to demonstrate a survival benefit of SOD, the mortality reduction was higher, albeit not significantly, with SDD than SOD. Additionally, a recent meta-analysis, including nine SOD RCTs and 4,733 patients, failed to show any significant reduction in mortality (OR 0.93; 95 % CI 0.81–1.07) [135]. In contrast, an Italian meta-analysis, including only RCTs using the full SDD protocol, showed a mortality reduction of 29 % (OR 0.71; 95 % CI 0.61–0.82) [75]. This effect achieved a 42 % mortality reduction in studies where carriage was eradicated (OR 0.58; 95 % CI 0.45–0.77).

Remarkably, the design of the study determines the magnitude of the survival benefit of SDD. In the study in which all eligible patients received the full SDD protocol, the significant reduction in the OR for mortality was 40 % [17]. If half the patients received SDD due to the RCT design, the significant reduction in the OR for mortality was 29 % [75]. In the most recent Dutch study, one-third of the patients received SDD and reduction in the OR for mortality was still significant, albeit at 17 % [19]. As a practical guideline, SDD should be applied to all ventilated patients of the unit, as mixing non-decontaminated with decontaminated patients still allows transmission of potential pathogens and hence exogenous infections in successfully decontaminated patients.

Impact of SDD on resistance

The main category of potential pathogens in which antimicrobial resistance is a problem in the ICU are AGNB. There are two scenarios:

1. AGNB sensitive to the decontaminating agents polymyxin/tobramycin.

de Jonge et al. [17] conducted an RCT in 934 critically ill adult patients. The in-hospital mortality rate was significantly lower for SDD compared with controls (24 vs. 31 %; $p = 0.002$). Carriage of AGNB resistant to polymyxin E, tobramycin, ceftazidime, ciprofloxacin and imipenem was significantly reduced in SDD patients compared with controls (16 vs. 26 %; $p = 0.001$). Similarly, de Smet et al. [19] showed that there were fewer

patients with AGNB in rectal swabs resistant to the marker antibiotics in the SDD than the SOD group. Additionally, bloodstream infections due to highly resistant pathogens was significantly reduced by SDD compared with SOD (OR 0.37, 95 % CI 0.16–0.85) [136].

2. AGNB resistant to decontaminating agents polymyxin/tobramycin.

- *Serratia* spp are the only potential pathogens intrinsically resistant to polymyxin/tobramycin. In the case of endemic *Serratia*, polymyxin/tobramycin should be replaced by polymyxin/paromomycin or gentamicin [104].
- Extended-spectrum beta-lactamase (ESBL) producing AGNB are often resistant to tobramycin but always sensitive to polymyxin [137]. In the case of endemicity of ESBL-producing AGNB, tobramycin may be replaced by an active aminoglycoside [138].

The concept of exposing vast numbers of critically ill patients to broad-spectrum antibiotics runs counter to existing theoretical models (and dogma) related to the genesis and promotion of antimicrobial resistance in pathogens acquired in the healthcare setting [139]. Indeed, the experts are concerned that SDD may lead to an ecological catastrophe. In contrast, the best evidence is that long-term use of SDD is safe. It actually reduces resistance rather than increasing it [140]. Indeed, traditionalists reject this evidence for four reasons: (1) the absence of resistance is counterintuitive; (2) the evidence comes from ICUs with an unusually low level of resistance; (3) the observation period is too short; and (4) many resistant potential pathogens are not covered by the SDD prophylaxis [141]. We would like to counteract these four arguments [142]. The first argument results from experience of only parenteral, rather than enteral, antibiotic use in the ICU. Critically ill patients invariably have overgrowth of potential pathogens with a high capacity for antimicrobial resistance, exacerbated by the excretion of most parenteral antimicrobials via bile in sublethal concentrations. In contrast, the aim of enteral antimicrobials of the SDD protocol, particularly polymyxin/tobramycin, is the eradication of overgrowth, the major risk factor for the emergence of antimicrobial resistance in particular against cefotaxime. Several European ICUs have implemented SDD for over 20 years. None have reported an outbreak of infection due to micro-organisms resistant to SDD. Finally, SDD has been assessed in ICUs with endemic vancomycin-resistant enterococci and *Aspergillus fumigatus*. Investigators reported no difference between test and control groups [6, 30]. American experts [143] consider the Oostdijk study [144] as proof that SDD causes resistance. However, that study is a point-prevalence survey in which all patients in the unit, whether enrolled or not in the study, were included. This type of ecological study is labelled as a low level evidence study (2C) [145, 146].

SDD use is increasing in Europe, in contrast, its use is uncommon in the United States. We believe the main reason is the "primacy of opinion over evidence" [147, 148]. Indeed, there are opinion leaders who assert that SDD does not provide a survival benefit, whilst it promotes an ecological resistance disaster [148]. The other major impediment to the widespread use of SDD is the lack of support by any pharmaceutical company, explaining why paste, gel and suspension of SDD are not available on the shelf [148].

Selectivity is not required

There is still some uncertainty of how SDD achieves its significant benefits [149]. It now seems clear that 'SDD' was an inappropriate choice of terminology. Rather than selectively removing aerobic bacteria and leaving the anaerobic intestinal microbes unaffected, as the name misleadingly implies, SDD actually works by achieving high antimicrobial concentrations effective against overgrowth of both normal and abnormal flora. It is a contradiction in terms to be both selective and yet achieve effective decontamination or eradication of aerobic overgrowth. However, the term SDD is now so well established that to change it would cause too much confusion. It has been hypothesised that eradication of aerobic overgrowth would lower the rate of oxygen consumption permitting an increase in pO_2 of the gut lumen content from 5 to 60 mmHg: under such conditions, strictly anaerobic micro-organisms can no longer survive even though they may not themselves be sensitive to the decontaminating agents [150].

Future lines of SDD research

Future lines of SDD research may include (1) the impact of the traditional SDD protocol of polymyxin/tobramycin on ICUs to which patients who may carry multi-resistant AGNB are regularly admitted [151]; (2) the impact of polymyxin/tobramycin/vancomycin on ICUs with endemic vancomycin resistant enterococci [6, 30]; (3) the impact of the traditional SDD protocol of polymyxin/tobramycin/amphotericin B on ICUs to which neutropenic patients with mucositis are regularly admitted [152]; and (4) the impact of overgrowth control on the severity of the systemic inflammatory response syndrome [77, 126, 153].

Conclusion

SDD is the most studied manoeuvre in intensive care medicine. There have been 65 RCTs of SDD, in about 15,000 patients, and 11 meta-analyses of RCTs, over a period of 25 years. SDD using parenteral and enteral antimicrobials has been shown to reduce lower airway infection by 72 %, bloodstream infection by 37 %, and mortality by 29 %, with resistance being controlled.

SDD controls overgrowth by achieving high antimicrobial concentrations effective against 'normal' and' abnormal' potential pathogens rather than by selectivity. However, whatever its precise mechanism, withholding SDD from critically ill patients must now surely be ethically questionable given the vast evidence base.

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