SOUBORNÝ REFERÁT

Selective Decontamination of the Digestive Tract: Why Don't We Apply Evidence in Practice?

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Summary

Selective decontamination of the digestive tract [SDD] has been assessed in 54 randomised controlled trials (RCTs) and nine meta-analyses of RCTs only. The most recent meta-analysis includes 36 RCTS in 6,922 unselected patients, and shows that SDD, including enteral and parenteral antimicrobials, reduces the odds ratio for pneumonia to 0.35 [0.29 to 0.41], and mortality to 0.78 [0.68 to 0.89]. The absolute mortality reduction was 4.8%. This information implies that 5 ICU-patients need to be treated with SDD to prevent one case of pneumonia, and 21 ICU-patients need to be treated to prevent one death. Two recent large RCTs report an absolute mortality reduction of 8%, corresponding to the treatment of 12 patients with SDD to save one life. The 54 RCTs and the nine meta-analyses do not provide data for a link between SDD and antimicrobial resistance. The Cochrane Library meta-analysis reports that SDD does not lead to resistance amongst aerobic Gram-negative bacilli but, even better, the addition of enteral polymyxin/tobramycin to the parenteral antimicrobials reduces resistance compared with the parenteral antibiotics only. This is in line with a previous RCT demonstrating that enteral antimicrobials control extended spectrum beta-lactamase producing *Klebsiella*. Antimicrobial resistance, being a long-term issue, has been evaluated in eight studies monitoring antimicrobial resistance between two and seven years, and bacterial resistance associated with SDD has not been a clinical problem. Costs can hardly be a major concern for a manoeuvre of 6 Euros a day that reduces pneumonia by 65%, and mortality by 22% without antimicrobial resistance emerging in unselected patients. These data support level 1 evidence for SDD, allowing a grade A recommendation. The main reason for SDD not being widely used is the primacy of opinion over evidence.
Key words: **SDD (selective decomination of the digestive tract – infection in the ICU – evidence – CDC labels**

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Introduction

Selective decontamination of the digestive tract (SDD) is a prophylactic strategy designed to prevent or minimise the impact of both endogenous and exogenous infections by potentially pathogenic micro-organisms (PPM) in patients who require intensive care including mechanical ventilation. The purpose of SDD is to prevent or eradicate, if initially present, oropharyngeal and gastrointestinal carriage of PPM, especially aerobic Gram-negative bacilli (AGNB), and also *Staphylococcus aureus* and yeasts, leaving the indigenous flora, which are thought to play a role in the resistance to colonisation, predominantly undisturbed. The overall aim is a reduction in morbidity and mortality without antimicrobial resistance emerging.

Infection in the intensive care unit

Morbidity and mortality due to infection, acquired either before or after admission to the intensive care unit (ICU), is a major problem in intensive care medicine [1]. The key to infection control in the ICU is to appreciate that a limited range of PPMs are involved and that infection with them usually follows a predictable endogenous pattern [2]. PPM are first carried in

Table 1. Potentially pathogenic micro-organisms causing infection during mechanical ventilation [2]

NORMAL PPM carried by previously HEALTHY INDIVIDUALS (%)	
Streptococcus pneumoniae	60
Haemophilus influenzae	25–80
Moraxella catarrhalis	5
Escherichia coli	99
Candida albicans	30
Staphylococcus aureus	30
Sensitive to methicillin (MSSA)	
ABNORMAL PPM carried by INDIVIDUALS WITH UNDERLYING DISEASE	
Klebsiella spp	
Enterobacter spp	
Citrobacter spp	
Proteus spp	one-third
Morganella spp	when APACHE II $\geq$ 20
Serratia spp	
Acinetobacter spp	
Pseudomonas spp	
Staphylococcus aureus	
Resistant to methicillin (MRSA)	

Table 2. Three different types of ICU infection due to 15 potentially pathogenic micro-organisms (PPM) [3]

Type of infection	PPM	Carriage	Time cut-off	Incidence
1. Primary endogenous	Normal/abnormal	Present in admission flora	< one week	c. 55%
2. Secondary endogenous	Abnormal	Not present in admission flora, but acquired and carried later	> one week	c. 30%
3. Exogenous	Abnormal	No carriage at all	Anytime throughout ICU treatment	c. 15%

the oropharynx and gut, before infection of internal organs such as lower airways and blood, develops. There are fifteen common PPMs that cause practically all infections (Table 1). They can be classified into two groups: 'normal', usually carried by previously healthy people, and 'abnormal', usually harboured by individuals with a chronic or acute underlying condition. 'Normal' PPMs include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Escherichia coli*, *Staphylococcus aureus* and *Candida albicans*. The group of 'abnormal' bacteria causing infection on the ICU comprises of eight AGNB and methicillin-resistant *Staphylococcus aureus* [MRSA]. The AGNB are *Klebsiella*, *Enterobacter*, *Citrobacter*, *Proteus*, *Morganella*, *Acinetobacter*, *Serratia* and *Pseudomonas* species. Carriage of AGNB and MRSA in the oropharynx and gastro-intestinal tract of healthy individuals is uncommon. Severity of illness is the most important factor in the conversion of the 'normal' into the 'abnormal' carrier state. In general, abnormal carriage develops early, within the first week of admission to the ICU, when the patient's illness is most severe and the associated immunodepression is maximal.

Exogenous infections should be distinguished from primary and secondary endogenous infections (Table 2). This classification is based on the carrier state of the ICU-patient, which is only detectable using surveillance sample from throat and gut. Exogenous infections are less common (± 15%), but may occur throughout the patient's stay in the ICU, and are caused by 'abnormal' PPM without previous carriage. For example, long-stay patients, particularly those who receive a tracheostomy, are at high risk of exogenous lower airway infections. Purulent lower airway secretions yield a PPM, which has never been previously carried by the patient in the digestive tract flora or indeed in their oropharynx but has probably gained access via the tracheostomy. Causative bacteria are almost always abnormal AGNB such as *Acinetobacter* and *Pseudomonas* species and MRSA. Both surveillance and diagnostic samples yield the same PPM in infections of endogenous development. The most frequent infection in the ICU is primary endogenous infection caused by both 'normal' and 'abnormal' PPM present in the admission flora (± 55%). Primary endogenous infections, in general, occur within the first week of admission to the ICU. If the patient was previously healthy, e. g., trauma and burn patients, patients with pancreatitis and acute liver failure, the bacteria causing early primary endogenous infections of lower airways and blood, are usually the 'normal' PPMs. Abnormal MRSA and AGNB may cause primary endogenous infections, if the patient's defences are impaired by underlying disease. For example, a patient with chronic illness such as diabetes, alcoholism and chronic obstructive pulmonary disease may carry abnormal bacteria in the admission flora. Patients with debilitating conditions, transferred from other hospitals, wards or nursing homes, also have high abnormal carriage rates.

Secondary endogenous infections are invariably caused by 'abnormal' bacteria AGNB and MRSA that are within the ICU environment but are not present in the patient's admission flora. They are first acquired in the oropharynx followed by stomach and gut due to transmission via the hands of health care workers. In the critically ill patient, throat and gut acquisitions invariably lead to abnormal microbial carrier states, termed secondary or super carriage. The subsequent build-up to overgrowth, defined as 10^5 PPM/ml of saliva and/or g of faeces, may take a few days and can then result in colonisation and subsequent secondary endogenous infection of lower airways and blood. One third of ICU infections are secondary endogenous, and in general develop after one week of admission to the ICU.

What is SDD?

SDD is a prophylactic technique to control the three types of ICU-infections due to the 15 PPMs [3]. The practice of SDD has four fundamental features (Table 3).

1. Enteral antimicrobials, in combination with
2. Parenteral antimicrobials given immediately on admission
3. Hand hygiene
4. Surveillance cultures of throat and rectum.

This strategy selectively targets the 15 PPMs, which contribute to morbidity and mortality. By design SDD does not target low level pathogens including anaerobes, viridians streptococci, enterococci and coagulase-negative staphylococci as, in general, they only cause morbidity. The most important feature of SDD is the enteral administration of oral non-absorbable polymyxin E/tobramycin to eradicate the abnormal AGNB. This results in decontamination of the digestive tract. SDD is a manoeuvre designed to convert the 'abnormal' carrier state into the 'normal' carrier state using non-absorbable enteral antimicrobi-

Table 3. Full four component protocol of SDD [3]

Target PPM and antimicrobials	Total daily dose [4 x daily]		
	<5 years	5–12 years	>12 years
1. Enteral antimicrobials			
A. oropharynx			
• AGNB: polymyxin E with tobramycin	2 g of 2% paste or gel		
• Yeasts: amphotericin B or nystatin	2 g of 2% paste or gel		
• MRSA: vancomycin	2 g of 4% paste or gel		
B. gut			
•AGNB: polymyxin E (mg) with	100	200	400
tobramycin (mg)	80	160	320
• Yeasts: amphotericin B (mg) or	500	100	2000
nystatin (units)	2×10^6	4×10^6	8×10^6
• MRSA: vancomycin (mg)	20–40/Kg	20–40/Kg	500-2000
2. Parenteral antimicrobials cefotaxime (mg)	150/Kg	200/Kg	4000
3. Hygiene			
4. Surveillance cultures of throat and rectum on admission, Monday, Thursday			

PPM: potentially pathogenic micro-organisms; AGNB: aerobic Gram-negative bacilli; MRSA: methicillin-resistant *Staphylococcus aureus*

als. Critically ill patients are unable to clear these AGNB due to their underlying disease. Intestinal overgrowth with aerobic Gram-negative bacilli causes systemic immunoparalysis. The reasons for the administration of enteral polymyxin E/tobramycin is that it provides recovery of systemic immunity, and that prevention or eradication of abnormal AGNB in throat and gut effectively controls aspiration and translocation of these microorganisms into the lower airways and blood, respectively. Enteral antimicrobials have been shown to be effective in the control of **secondary endogenous** infections. However, the use of enteral antibiotics alone does not affect primary endogenous and exogenous infections. The second component is the immediate administration of an adequate parenteral antimicrobial to control **primary endogenous** pneumonia and septicaemia. Cefotaxime has been used in most randomised controlled trials (RCTs) to cover both 'normal' and 'abnormal' PPMs. In adding enteral to parenteral antibiotics, the original pre-1980s systemic antibiotics, including cefotaxime, remain useful, without the development of antimicrobial resistance. Thirdly, high standards of hygiene are indispensable for reducing hand contamination and subsequent transmission from **'external'** sources. Finally, surveillance samples of throat and rectum, unpopular amongst traditional microbiologists, are taken on admission and twice weekly thereafter, and are an integral component of the SDD protocol. Knowledge of the carrier state allows the compliance and efficacy of this prophylactic protocol to be monitored.

What's the evidence?

Fifty-four randomised controlled trials (RCTs) [4–57] were designed to evaluate SDD in a total of 8,715 patients between 1987 and 2005, and there are nine meta-analyses of the RCTs assessing SDD [58–66]. Thirty-eight RCTs show a significant reduction in infection and four in mortality. All meta-analyses show a significant reduction in infection and 5 out of 9 meta-analyses report a significant mortality reduction. The most complete meta-analysis includes 36 RCTs in 6,922 patients, and shows that SDD reduces the odds ratio for pneumonia to 0.35 (95% confidence interval 0.29 to 0.41), and mortality to 0.78 (95% CI 0.68 to 0.89) [64]. Five ICU patients need to be treated with SDD to prevent one pneumonia, and 21 ICU patients need to be treated to prevent one death. Two recent large RCTs [26, 29] report an absolute mortality reduction of 8% corresponding to the treatment of 12 patients with SDD to save one life.

SDD is a safe method, as the existent data on antimicrobial resistance does not provide a potential link between SDD and antimicrobial resistance. The latest RCT from Amsterdam (The Netherlands) with resistance as primary endpoint reports that SDD does not lead to resistance amongst AGNB, but even better, that the addition of polymyxin/tobramycin to the parenteral antimicrobials reduces resistance compared with the parenteral antibiotic only [26]. Indeed, this latest Dutch RCT evaluating SDD in about 1,000 patients had significantly fewer carriers of multi-resistant AGNB in the patients receiving SDD (16%) than in the control group (26%) [26]. This is in line with a previous RCT demonstrating that enteral antimicrobials control extended beta-lactamase producing *Klebsiella* [13]. SDD was implemented in two American ICUs with endemic vancomycin-resistant enterococci (VRE) [6, 24]. The carriage and infection rates of VRE were low and similar in test and control groups. SDD is not designed to control MRSA. There are seven RCTs conducted in ICUs where MRSA was endemic at the time of the trial, so they report a trend towards higher MRSA infection rates in patients receiving SDD [14, 17, 20, 23, 31, 53, 54]. The addition of enteral vancomycin to SDD is required to control MRSA in ICUs with endemic MRSA [67, 68]. VRE did not emerge in any of the RCTs using enteral vancomycin [8, 21, 28, 29, 37, 46, 67, 68]. Recent literature shows that parenteral antibiotics that do not respect the patient's gut ecology rather than high doses of enteral vancomycin, promotes the emergence of vancomycin-resistant enterococci in the gut [69, 70]. Antimicrobial resistance, being a long-term

Table 4. ICU-interventions that reduce mortality

Intervention	Relative Risk [95% confidence interval]	Absolute Mortality Reduction (%) /95% confidence interval]	Number Needed to Treat	Grade of Recommendation
1. Low tidal volume [79]	0.78 [0.65 to 0.93]	8.8 [2.4 to 15.3]	11	B
2. Activated protein C [80]	0.80 [0.69 to 0.94]	6.1 [1.9 to 10.4]	16	B
3. Intensive insulin [81]	0.44 [0.36 to 0.81]	3.7 [1.3 to 6.1]	27	B
4. Steroids [82]	0.90 [0.74 to 1.09]	6.4 [-4.8 to 17.6]	16	B
5. Selective decontamination [64]	0.65 [0.49 to 0.85]	8.1 [3.1 to 13.0]	21	A

issue, has been evaluated in eight SDD studies monitoring antimicrobial resistance between two and seven years [71–78], and bacterial resistance associated with SDD has not been a clinical problem.

The most recent data showing a survival benefit without bacterial resistance emerging in unselected ICU patient's support level 1 evidence for SDD, allowing a grade A recommendation. Table 4 shows the five evidence based medicine (EBM) manoeuvres showing survival benefit in the critically ill. Only SDD is supported by at least two level 1 investigations [26, 29], the other four [79–82] are supported by only one trial, providing a grade B recommendation. In addition, SDD can be administered to all patients at risk of infection, whilst the other four only in specific subsets of critically ill patients. Finally, SDD reduces antimicrobial resistance amongst AGNB; low tidal volume, activated protein C, intensive insulin and steroids can impossibly impact on this major problem.

Why is SDD not widely used?

The main reason for SDD not being widely used is the *primacy of opinion over evidence*. Two recent surveys into the usage of SDD reveal that it is routinely used in only 4% of UK ICUs [83], but in 24% of Dutch ICUs [84]. The most common reason cited for its non-use (83%) is the belief by UK intensivists that there is a lack of evidence of efficacy and 'it does not work' [83]. The reason for this misconception is multifactorial. However, the longstanding disagreement amongst experts [85, 86] has been an important factor contributing to the confusion. History repeats itself in that Virchow, the expert pathologist of that time [87], heavily opposed Semmelweis' work. Previous experience with thrombolytic drugs indicates a similar pattern, with an undesirable lag between the appearance of meta-analytic evidence and the recommendations of experts. Streptokinase was shown to reduce the risk of death from myocardial infarction by 20% as long ago as 1975. During the following two decades 14 review articles either failed to mention streptokinase or considered it still to be experimental [88], although in this century thrombolytic agents are virtually routine treatment in patients with myocardial infarction.

Concerns expressed by experts about resistance are based on *low level evidence* but have hindered the implementation of SDD. European and American experts state that the most important objection to the widespread use of SDD is the unknown effects on antibiotic resistance in the long term [89, 90]. They invariably refer to their own review articles, the lowest level of evidence [86, 91]. All reviews include the seven RCTs, which were conducted in ICUs where MRSA was endemic at the time of the trial, although there was only a trend towards a higher MRSA infection rate in the patients receiving SDD [14, 17, 20, 23, 31, 53, 54]. A statistically significant trend towards resistance amongst Gram-positive bacteria was found only if including rates of carriage and infection due to low-level pathogens such as enterococci and coagulase-negative staphylococci. Clearly, pneumonia due to these low level pathogens is extremely rare. Similarly, influential authorities including the Center for Disease Control and Prevention do not recommend SDD because of concerns over the development of antibiotic resistance [92]. Additionally, the CDC labels SDD as a high cost > 50 euros strategy [93]. These guidelines are not based on RCTs but on the opinion of the panel, again the lowest level of evidence. More recently, evidence-based medicine is being used by American and Canadian groups [94–96] to develop clinical practice guidelines for the prevention of ventilator-associated pneumonia. The American group concluded that SDD is not recommended because there is ample evidence to suggest that the use of SDD may increase antimicrobial resistance [95]. To support this statement they cited two reviews of groups, which have written repeatedly against SDD [91, 97]. A statement based on expert opinion is misleading and runs contrary to the aims of evidence-based medicine: the best estimate based on an impartial review of all available information [98]. There are two RCTs reporting a significant increase in resistance amongst the target microorganisms of AGNB [40, 53]. Amongst other concerns, the denominator was isolates, samples, or infections and not the patient. Exogenous infections are not controlled by SDD. A transient increase in exogenous lower airway infections due to *Acinetobacter baumannii* was reported from a respiratory unit with a high percentage of tracheotomised patients whilst conducting an RCT on SDD [23, 71]. This observation that the proportion of exogenous infections in SDD trials increases in relation to the reduction in endogenous infections is well recognised. This transient finding is repeatedly used to show that SDD increases resistance amongst AGNB [91]. SDD was

not granted a recommendation by a panel of experts selected by the Canadian Critical Care Trials group and the Canadian Critical Care Society due to their low scoring for safety in terms of antimicrobial resistance and costs of SDD [96]. The panel decided to evaluate not RCTs on SDD but only meta-analyses, none of them providing data for a link between SDD and antimicrobial resistance. Fair enough, the cost--effectiveness of SDD is not yet properly assessed, but costs can hardly be a major concern for a manoeuvre of 6 euros that reduces pneumonia by 65% and mortality by 22% without antimicrobial resistance emerging in unselected ICU patients. The conclusion of the Canadian panel is once again not based on evidence from RCTs but on the opinion of the panel, i. e., the lowest level of evidence. Thus, the assertion that resistance is a problem with SDD is misplaced in an evidence-based analysis [98, 99].

Since its inception, *SDD has rarely received a favourable press*. Indeed, the 1992 report [100] of the first European Consensus conference in Paris, France set the scene by coming down against the use of SDD. In the same vein, although SDD has been a regular feature on the programme of the annual Intensive Care meeting in Brussels, Belgium since 1987, in only three years (1988, 1990, 2003) were speakers invited who viewed it in a favourable light. A greater acceptability for publication of manuscripts that show negative results for SDD compounds its poor reputation – of the 54 randomised trials of SDD, the six showing no benefit [17, 20, 23, 31, 53, 54] were all published by journals of high impact factor. An extreme example is the publication by the *New England Journal of Medicine* of an uncontrolled study where 10% of the study population developed enterococcal pneumonia [101]. It might be questioned whether such a high incidence of such an obscure condition should be taken at face value.

Selective decontamination of the digestive tract has also *never been promoted by pharmaceutical companies*, perhaps because there is little profit in older agents such as cefotaxime, polymyxin E, tobramycin and amphotericin B, which are inexpensive and off patent. Furthermore, SDD is not supported by authoritative-looking data sheets and is not marketed to clinicians in the traditional manner. Paste, gel and suspension are not readily available on the shelf. Hence, the application off SDD requires more effort in terms of commitment and monitoring from the ICU team than is the case with mere systemic administration of the latest antibiotic on the market. The most recent example is the Surviving Sepsis Campaign heavily sponsored by the industry that recommends all EBM interventions that reduce mortality except SDD. SDD at 6 euros a day was considered a high cost strategy by the CDC [93] and Canadian panel of experts [96], whilst the Surviving Sepsis Campaign experts have no problem in recommending activated protein C at a cost of 7,000 euros per patient [102].

Finally, Wazana questions *the interaction of physicians and the pharmaceutical industry* and asks 'is a gift ever just a gift?' [103]. Most opinion leaders have links with the industry and receive grants for the evaluation of new antimicrobial agents both *in vitro* and *in vivo*. The same experts attend national and international meetings at which they chair and report data often promoting these new drugs as first-line antibiotics. The traditionalists on the 'circuit' have relied on the industry to develop new drugs at regular intervals, usually two years following publication of the first case report of super-infections of the currently favoured antibiotic. The realisation that the pharmaceutical industry failed to provide new classes of antibiotics came as a severe blow. Industrialised countries have largely delegated control of drug trials to pharmaceutical companies [104], which places clear limitations on research. However, economic interests seek the best possible financial return, and establishing new potent antibiotics to treat rather than prevent pneumonia is more profitable. Antibiotic usage in the [UK] National Health Service is mainly determined by the pharmaceutical industry. The replacement of piperacillin by piperacillin/tazobactam illustrates that the importance of market forces and financial incentives are placed far above public health needs.

The future

In spite of the powerful anti-SDD movement, SDD is now an EBM protocol. Influential European [105], UK [106] and US [107] societies and institutions acknowledge that SDD is the best-ever evaluated intervention in intensive care medicine that reduces infectious morbidity and mortality. The Agency for Healthcare Research and Quality of the US Department for Health and Human Services considers SDD to be a cheap manoeuvre [107].

Perhaps the most intriguing aspect of the 18 years of clinical research into SDD is the experience that the addition of enteral antibiotics to parenteral antimicrobials may prolong the antibiotic era. Pre-1980s antibiotics are still active so long as they are combined with eradication of aerobic Gram-negative bacilli and MRSA from the gut. An SDD-approach is unlikely to exacerbate the bacterial resistance problem and may be part of the solution, for two reasons. First, SDD based on the concept of the abnormal carrier state is underpinned by surveillance cultures of gut flora. Intensive care units that use SDD have a better knowledge of resistance than those that rely on diagnostic samples (tracheal aspirate and blood). Second, resistance arises in the large numbers of gut bacteria. Small amounts of parenterally administered antibiotics, excreted into the gut, select for resistant bacteria. Elimination of gut overgrowth reduces the likelihood of resistance. We believe that the answer lies not in the development of single, new more potent and expensive systemic antimicrobials but in a radical re-thinking of the philosophy by which antimicrobials are used. In particular, we need to be

much more critical of market-driven health care if we are to find more sustainable solutions to the problems of the ongoing spread of nosocomial, antibiotic-resistant pathogens in the new millennium.

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