Intensive Care Med (2023) 49:984–986
https://doi.org/10.1007/s00134-023-07115-7

EDITORIAL

Selective digestive decontamination- Not sure

Willem Joost Wiersinga*

Selective decontamination of the digestive tract (SDD) is a treatment strategy used to prevent infections in critically ill patients. Since the landmark study by Stoutenbeek and Zandstra demonstrating the beneficial effect of SDD was published in this Journal almost 40 years ago [1], more than 1000 peer-reviewed articles have been published on this subject. However, the clinical value of SDD remains contested with nearly half of all publications being editorials, letters, reviews, and conference proceedings (source: Web of Science). For me, being trained in part on the intensive care unit (ICU) of Zandstra in the OLVG Hospital in Amsterdam, the matter was crystal clear: SDD helps to improve patient outcomes and can even decrease mortality in a setting with a low prevalence of antibiotic resistance [2, 3] while this effect is not seen in a setting with moderate-to-high prevalence of antibiotic resistance [4]. As a result I fully support the Dutch guideline recommendation to use SDD for patients with an expected length of ICU stay of 72 hours or longer [5], whereas I understand that SDD is utilized only sporadically in many other countries.

New insights however make me question if the classical SDD approach is the best way forward. What can be the reason why in the largest and most recent randomized clinical trial so far, the Australian SuDDICU study conducted in an environment of low endemic antibiotic resistance, SDD did not significantly reduce in-hospital mortality [6]? Furthermore, it has been almost two decades since the initial positive SDD trials were carried out in the Netherlands. If they were to be replicated in today's rapidly advancing ICU environment, would we still see the same effect? Can we perhaps better define subgroups of patients that will benefit most from this treatment strategy? And could our novel knowledge on the microbiome help us to design smarter ways of modulating it in critical ill patient to improve outcomes?

SSD is based on the concept of colonization resistance, the mechanism by which a healthy gut microbiota safeguards itself against the invasion of potentially harmful pathogens [7]. In almost all critically ill patients a disruption of the intestinal microbiome is seen characterized by a loss of the butyrate-producing anaerobic intestinal environment, an overgrowth of aerobic pathobionts such as Enterobacteriaceae and an absolute enrichment of opportunistic yeasts capable of causing invasive disease [8]. SSD usually consists of an oral paste and gastric suspension of three nonabsorbed antimicrobial agents (e.g. colistin, tobramycin and amphotericin/nystatin) combined with a short course of systemic antibiotics (e.g. third-generation cephalosporins). Of note, in the above cited study on the effect of SDD in a setting with moderate-to-high prevalence of antibiotic resistance the SDD regime consisted of a mouthpaste with colistin, tobramycin, and nystatin and a gastrointestinal suspension with the same antibiotics without the administration of intravenous antibiotics [4]. Respiratory and rectal surveillance cultures can be used to measure SDD efficacy and to adjust the topical antibiotics in case of resistance. Selective oropharyngeal decontamination (SOD) consists only of the regular topical application of the oral paste. The main aim of SDD is the prevention of ICU-acquired infections, most notably ventilator-associated pneumonia (VAP), caused by the overgrowth of Gram-negative bacteria and yeast from the intestinal tract.

The above mentioned SuDDICU trial which randomized nearly 6000 adults receiving mechanical ventilation in the ICU to SDD or placebo, could not demonstrate any significant difference between the incidence

*Correspondence: w.j.wiersinga@amsterdamumc.nl
Division of Infectious Diseases and Center for Experimental and Molecular Medicine, Department of Medicine, Amsterdam UMC, Location AMC, University of Amsterdam, Meibergdreef 9, Room G2-130, 1105 AZ Amsterdam, The Netherlands

of VAP, ICU-acquired bacteremia or new *Clostridium difficile* infections [6]. It is reassuring to note that this trial, consistent with previous analysis [9], did not reveal any increase in antimicrobial resistance linked to the use of SDD [6]. Although the SuDDICU trial could not demonstrate a significant benefit of SDD, a simultaneously published meta-analysis, which used data from 30 trials including 24,034 participants that contributed to the primary outcome, did show a lower in-hospital mortality associated with the use of SDD among adults ICU-patients treated with mechanical ventilation [10]. What conclusions can be drawn from these observations? Although the SuDDICU study did not unfortunately provide an answer at last, the authors and accompanying editorial both underscore the fact that the confidence interval around the effect estimate of in-hospital mortality includes a clinical important benefit and conclude that the use of SDD may offer the most benefit for certain subsets of patients such as those with trauma [6, 11]. Conceivably, one could envision that in-depth investigation of the microbiome of patients that qualify for SDD can potentially identify certain treatable biologic traits, which could be called enterotypes, of selected patients that will benefit the most of this treatment.

The concept of SDD and the importance of saving the anaerobic bacterial compartment of the intestinal microbiome perfectly fits with the recent finding that early treatment with systemic anti-anaerobic antibiotics in ICU patients is associated with increased mortality [12]. In a cohort study of 3032 critically ill patients in the Unites States, it was found that systemic anti-anaerobic antibiotics led to decreased gut bacterial diversity and an expansion of *Enterobacteriaceae* spp. which was associated with decreased VAP-free survival, infection-free survival and overall survival [12]. In murine models the authors demonstrated that administering anti-anaerobic antibiotics increased vulnerability to Enterobacteriaceae pneumonia [12]. Clearly, the administration of antibiotics can harm the gut microbiota and, paradoxically, elevate the risk of infection.

As an exploratory possibility, a potentially promising and elegant approach to reestablish microbiota-mediated colonization resistance in the critically ill involves the identification of commensal bacterial species that can be developed into next-generation probiotics to reestablish or enhance colonization resistance [7]. Examples include commensal bacteria such as *Blautia producta* that can restore colonization resistance against vancomycin-resistant Enterococcus [13] and *Clostridium scindens*, a bile acid 7a-dehydroxylating intestinal bacterium that is associated with resistance to *C. difficile* infection [14]. Most probably, a mixture of these obligately anaerobic bacteria, perhaps combined with dietary supplements and/or microbiome derived metabolites such as butyrate, will be needed if utilized for the prevention of hospital-acquired infections during critical illness. Vigorous testing for safety besides effectiveness in this vulnerable population will be key in addition to the notion that a one-size-fits-all approach to treating patients with these microbiome modulating compounds will most probably limits its efficacy.

Taken together, 40 years of SDD research have taught us a lot. Although, in my opinion, SDD continues to have a significant positive impact on ICU patient care, we should continue our efforts to evaluate its effects in settings with high antimicrobial resistance rates, identify the patients who will benefit the most, and use our expanding knowledge of the microbiome to assist in restoring the disturbed microbiome in critically ill patients to its prime protective role of colonization resistance. Perhaps, in the near future, we will rephrase SDD as microbiome modulation therapy.

Declarations

Conflicts of interest

The author declare that they have no conflict of interest.

Publisher's Note

Received: 30 March 2023 Accepted: 28 May 2023
Published: 19 June 2023

References

1. Stoutenbeek CP, van Saene HK, Miranda DR et al (1984) The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. Intensive Care Med 10(4):185–192. https://doi.org/10.1007/BF00259435
2. de Jonge E, Schultz MJ, Spanjaard L et al (2003) Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. Lancet 362(9389):1011–1016. https://doi.org/10.1016/S0140-6736(03)14409-1
3. de Smet AM, Kluytmans JA, Cooper BS et al (2009) Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med 360(1):20–31. https://doi.org/10.1056/NEJMoa0800394
4. Wittekamp BH, Plantinga NL, Cooper BS et al (2018) Decontamination strategies and bloodstream infections with antibiotic-resistant microorganisms in ventilated patients: a randomized clinical trial. JAMA 320(20):2087–2098. https://doi.org/10.1001/jama.2018.13765
5. SWAB-Richtlijn: selectieve decontaminatie bij patiënten op de intensive care (herziene versie 2018) 2018 [Accessed 28 Mar 2023]. Available from: https://swab.nl/nl/selectieve-decontaminatie-sdd.
6. Myburgh JA, SuDDICU Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group et al (2022) Effect of selective decontamination of the digestive tract on hospital mortality in critically Ill patients receiving mechanical ventilation: a randomized clinical trial. JAMA 328(19):1911–21. https://doi.org/10.1001/jama.2022.17927
7. Pamer EG (2016) Resurrecting the intestinal microbiota to combat antibiotic-resistant pathogens. Science 352(6285):535–538. https://doi.org/10.1126/science.aad9382

8. Haak BW, Argelaguet R, Kinsella CM et al (2021) Integrative transkingdom analysis of the gut microbiome in antibiotic perturbation and critical illness. mSystems. https://doi.org/10.1128/mSystems.01148-20
9. Daneman N, Sarwar S, Fowler RA et al (2013) Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. Lancet Infect Dis 13(4):328–341. https://doi.org/10.1016/S1473-3099(12)70322-5
10. Hammond NE, Myburgh J, Seppelt I et al (2022) Association between selective decontamination of the digestive tract and in-hospital mortality in intensive care unit patients receiving mechanical ventilation: a systematic review and meta-analysis. JAMA 328(19):1922–1934. https://doi.org/10.1001/jama.2022.19709
11. Bonten M (2022) Selective decontamination of the digestive tract: an answer at last? JAMA 328(23):2310–2311. https://doi.org/10.1001/jama.2022.18623
12 Chanderraj R, Baker JM, Kay SG et al (2023) In critically ill patients, anti-anaerobic antibiotics increase risk of adverse clinical outcomes. Eur Respir J. https://doi.org/10.1183/13993003.00910-2022
13. Kim SG, Becattini S, Moody TU et al (2019) Microbiota-derived lantibiotic restores resistance against vancomycin-resistant *Enterococcus*. Nature 572(7771):665–669. https://doi.org/10.1038/s41586-019-1501-z
14. Buffie CG, Bucci V, Stein RR et al (2015) Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. Nature 517(7533):205–208. https://doi.org/10.1038/nature13828