EDITORIAL

Antipathy against SDD is justified: No

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Exam question: Which intervention targeted at preventing infection and mortality in critical illness has been evaluated positively in 71 randomised controlled trials over 35 years?

Well, of course you know the answer. Indeed, it is the wrong question to ask. The real question is why, given this body of research, has selective digestive decontamination (SDD) not been widely adopted, and why was it excluded from consideration by the most recent iteration of the international Surviving Sepsis Campaign (SSC) guidelines? We will try to unpackage this ‘riddle wrapped in a mystery inside an enigma’ [1].

SDD was excluded from the first iteration of the SSC guidance in 2004. Reasons offered at the time included the view that SDD was not a treatment for sepsis. The illogicality of this approach was immediately evident given the inclusion in the guidelines of prophylaxis for thromboembolic disease and for peptic ulcer disease. Following representations, SDD was included in 2008 and 2012. In 2008 the SSC adopted private polling to minimise bias, developing the ‘GRADE grid’ for that purpose [2]. This revealed two opinion groups: nine respondents weakly in favour and eight weakly opposed. Of the remaining participants, four were neutral, and one strongly opposed, giving SDD a 2B rating (consider using the intervention). This rating was retained for the

2012 guidelines. However, in the most recent iteration in 2016 [3], SDD has been excluded without explanation, presumably being classed amongst a group of interventions of ‘low importance and of low priority to clinicians’. If SDD is indeed of ‘low priority’, is this because of new and important scientific evidence demonstrating that it does not work, or because of deeply held but unfounded anxieties or antipathies? To assist with this analysis, we have summarised current evidence on the effect of SDD on mortality, infection, resistance and the microbiome in Table 1 (references in electronic supplementary material). This includes data from 71 randomised controlled trials, and confirms that SDD reduces mortality, reduces infections, reduces Gram-negative antimicrobial resistance, and does not promote Gram-positive infections. What other intervention in critical care medicine can match this record over 35 years of research?

Attitudes to SDD were explored in an international survey in 2013 of 141 participants which demonstrated substantial equipoise on risks and benefits of SDD, and expressed concerns that SDD might contribute to antimicrobial resistance [4]. A commonly expressed view is that it is wrong to give prophylactic enteral antimicrobials for long periods to critically ill patients to prevent infection; and yet the current approach of treating septic episodes with repeated and prolonged courses of parenteral

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For contrasting viewpoints, please go to <https://doi.org/10.1007/s00134-018-5183-z> and <https://doi.org/10.1007/s00134-018-5198-5>.

Table 1 Summary of the impact of selective decontamination of the digestive tract on morbidity, mortality, resistance, and gut microbiome in critically ill patients

First author	Study design	Reported results/conclusions
Morbidity and mortality		
Liberati A [1]	Systematic review and meta-analysis of 36 RCTs	SDD vs control: respiratory tract infection OR 0.28 (95% CI 0.20–0.38), mortality OR 0.75 (95% CI 0.65–0.87)
Silvestri L [2]	Systematic review and meta-analysis of 51 RCTs	SDD vs control: bacteremia OR 0.63 (95% CI 0.46–0.87), mortality OR 0.74 (95% CI 0.61–0.91)
Price R [3]	Systematic review and network meta-analysis of 18 RCTs	SDD vs control: mortality OR 0.73 (95% CI 0.64–0.84) SOD vs control: mortality OR 0.85 (95% CI 0.74–0.97)
Plantinga NL [4]	Individual patients data meta-analysis of six studies in medical and surgical ICU patients (SDD 7718 patients, SOD 6326 patients, control 3013 patients)	SDD vs standard care/placebo: mortality OR 0.82 (95% CI 0.72–0.93) SOD vs standard care/placebo: mortality OR 0.84 (95% CI 0.73–0.97) SDD vs SOD: mortality OR 0.90 (95% CI 0.82–0.97) SDD and SOD improve hospital and ICU survival compared with standard care with SDD being more effective than SOD
Zhao D [5]	Meta-analysis of 4 RCT including 23822 patients	SDD has higher incidence of ICU-acquired bacteremia, higher carriage of antibiotic-resistant AGNB compared with SDD
Roquilly A [6]	Systematic review and meta-analysis of 30 RCTs of SDD and 24 RCTs of SOD.	SDD vs control: ICU mortality RR 0.78 (95% CI 0.69–0.89) SOD vs control: ICU mortality RR 1.00 (0.84–1.21) SDD reduced mortality and should be considered in critically ill patients at high risk for death
de Jonge E [7]	RCT of 934 patients	SDD decreased ICU and hospital mortality and colonisation with resistant AGNB
de Smet AMGA [8]	Cluster randomized crossover study in 13 Dutch ICUs and including 5939 patients	SDD vs standard care: mortality OR 0.83 (95% CI 0.72–0.97) SOD vs standard care: mortality OR 0.86 (95% CI 0.74–0.99)
Resistance		
Taylor N [9]	Meta-analysis of 5 RCTs including 2631 patients in test group and 2538 patients in control group.	SDD significantly resistance (OR 0.56, 95% CI 0.41–0.78), whilst the regimen of only enteral antimicrobials did not (OR 0.43, 95% CI 0.08–2.45)
Daneman N [10]	Meta-analysis of 64 studies of SDD and SOD in ICU patients	No difference in colonisation/infection with resistant Gram-positive microorganisms, MRSA, and vancomycin-resistant enterococci in SDD versus control group No difference in aminoglycoside resistance and fluoroquinolone resistance among AGNB Reduction of polymyxin-resistant AGNB and third-generation cephalosporin-resistant AGNB in SDD versus control group
de Smet AMGA [11]	Analysis of data from a cluster randomized trial. Bacteremia and respiratory tract colonization with highly-resistant microorganisms was evaluated.	SDD versus SOD: bacteremia OR 0.41 (95% CI 0.18–0.94); respiratory tract colonization OR 0.58 (95% CI 0.43–0.78)
Oostdijk EA [12]	Post-hoc analysis of a cluster randomized trial. Acquisition of colistin-resistant AGNB and conversion from susceptible to resistant AGNB were evaluated in respiratory samples and in rectal swabs.	The rates of acquisition in the respiratory tract of colistin-resistant AGNB were comparable during SDD, SOD and standard care

Table 1 continued

First author	Study design	Reported results/conclusions
Oostdijk EAN [13]	Cluster randomized crossover trial comparing 12 months of SOD (5957 patients) with 12 months of SDD (6040 patients) in 16 Dutch ICUs.	SDD and SOD were associated with low levels of antibiotic resistance. SDD compared with SOD was associated with lower day-28 mortality, reduced length of stay, lower rates of ICU-acquired bacteremia and candidemia, and lower prevalence of rectal carriage of antibiotic-resistant AGNB, but a gradual increase in aminoglycoside-resistant AGNB
Houben AJM [14]	Use of a database from 32 laboratories serving 45 ICUs to identify all Enterobacteriaceae, <i>P. aeruginosa</i> and <i>Acinetobacter</i> spp. isolates from blood and respiratory tract specimens.	There were no trends in antibiotic resistance among blood isolates
		Resistance to cefotaxime/ceftriaxone in respiratory tract isolates increased in intensive care units that did not use SOD/SDD and decreased in those that used SOD/SDD as did resistance to ciprofloxacin
		The use of SOD/SDD was followed by statistically significant reductions in resistance rates for all antimicrobials
Noteboom Y [15]	Prospective cohort study nested within a cluster-randomized crossover study in 16 Dutch ICUs.	Within-host antibiotic resistance acquisition for systemic antibiotics was comparable between SDD and standard care
Wittekamp BHJ [16]	Post-hoc analysis of two consecutive multicenter cluster randomized trials during 7 years in five ICUs.	Tobramycin resistance in respiratory and rectal samples decreased significantly during long-term use of SOD and SDD compared to standard care. Colistin resistance in rectal and respiratory samples did not change compared to standard. The prevalence of colistin and tobramycin resistance among AGNB isolates did not increase during a mean of 7 years of SDD or SOD use
van der Bij AK [17]	Database analysis for rates of <i>S. aureus</i> , <i>E. faecalis</i> , <i>E. faecium</i> isolates, including resistant phenotypes, in blood and respiratory samples of ICU patients from 2008 to 2013.	The use of SDD/SOD was associated with increased rates of <i>S. aureus</i> and <i>E. faecalis</i> isolates, but not with resistant phenotypes. The five-year use of SDD/SOD was not associated with increased isolation of Gram-positive cocci
Leone M [18]	Case-control study over a 6-year period in multiple trauma patients	A relative overgrowth of Gram-positive cocci was observed. Methicillin resistance of <i>Staphylococcus epidermidis</i> was increased, but not <i>Staphylococcus aureus</i> resistance. Resistance of AGNB to beta-lactams and aminoglycosides was the same in SDD patients and control
Heininger A [19]	Five-year prospective observational study in a surgical ICU	MRSA remained stable. Aminoglycoside- and betalactam-resistant AGNB did not increase during SDD. Aminoglycoside resistance of <i>Pseudomonas aeruginosa</i> was 50% below the mean value of German ICUs. The relative frequency of enterococci and coagulase-negative staphylococci was higher than in the German ICUs
Ochoa-Ardila ME [20]	Prospective, 5-year, observational study in medical-surgical ICU	Routine 5-year-use of SDD was not associated with increased antimicrobial resistance
Gut microbiome		Long-term use of SDD was not associated with an increase in acquisition of resistant flora
Benus EF [21]	Analysis of fecal samples of patients enrolled in a multicentre trial	AGNB were significantly reduced by SDD compared to SOD and standard care <i>Faecalibacterium prausnitzii</i> was reduced in SDD regimen compared to SOD and standard care
Buelow E [22]	Evaluation of the impact of SDD on the gut microbiota in 1 ICU patient during and after ICU stay. Evaluation of two common aminoglycoside resistance genes in 12 ICU patients who received SDD	Enterococci increased in SDD group compared to SOD and standard care Hospitalization and administration of SDD has large, but highly individualized, effects on the gut resistome. Selection for transferable antibiotic resistance genes in anaerobic commensal bacteria could impact the risk of transfer of antibiotic resistance genes to opportunistic pathogens

Table 1 continued

First author	Study design	Reported results/conclusions
Buelow E [23]	Comparison of gut microbiota of 10 ICU patients treated with SDD and 10 healthy subjects	<p>Compared with healthy subjects, the microbiota of ICU patients was characterized by lower microbial diversity, lower levels of <i>E. coli</i> and anaerobic Gram-positive butyrate-producing bacteria, and increased abundance of <i>Bacteroides</i> and enterococci</p> <p>Four genes providing resistance to aminoglycosides, macrolides, disinfectants and tetracyclines were more present in ICU patients than in healthy subjects, but genes providing resistance to chloramphenicol and tetracycline were more present in healthy subjects.</p> <p>The risk associated with SDD on selection of antibiotic resistance is limited</p>
<p>RCTs, randomized controlled trials; SDD, selective decontamination of the digestive tract; SOD, selective oropharyngeal decontamination; ICU, intensive care unit; OR odds ratio; RR, risk ratio; CI confidence interval; AGNB, aerobic Gram-negative bacilli; MRSA, methicillin-resistant <i>Staphylococcus aureus</i></p> <p>References to studies are reported in the Electronic Supplementary Material</p>		

antimicrobials can hardly be described as a success from the perspective of antimicrobial resistance. By contrast, a systematic review in 2013 of resistance related to SDD found no relation between the use of SDD and antimicrobial resistance in ICU patients, and concluded that ‘the perceived risk of long-term harm related to selective decontamination cannot be justified by available data’ [5]. This conclusion was confirmed by a 4-year ecological study showing that the introduction of SDD in an ICU is associated with a significant reduction in resistance rates [6], and is reinforced by our summary of current research evidence (Table 1). Those who regard SDD as a resistance risk need to explain why ICUs in the Netherlands, where SDD is widely adopted, use fewer non-SDD antimicrobials and have a much reduced problem with antimicrobial resistance [7, 8] than those countries which rely predominantly on parenteral antimicrobials to prevent or treat nosocomial infections in critically ill patients.

As the traditional SDD regimen does not target MRSA and vancomycin-resistant enterococci, adjustment of the SDD medication by adding vancomycin should be considered in ICUs with a high endemicity of these Gram-positive infections [9, 10]. However, it should be noted that while some studies show an increase in Gram-positive isolates, a meta-analysis did not demonstrate an increase in Gram-positive infections [11].

The argument against SDD has now shifted to the microbiome. A recent study [12] reported the presence of numerous resistance genes in the gut microbiota of ten intensive care patients receiving SDD, compared with healthy individuals. But again, this is the wrong exam question. The real question is how does the gut microbiota of critically ill patients receiving SDD differ from those receiving only parenteral antimicrobials for nosocomial infection, and how do these two groups compare with hospitalised but not critically ill patients, and with a healthy population? Finally, how does the gut microbiota of surviving patients in the first two groups evolve following return to the community?

We hope that the answers to these focused questions might emerge from current research [13]. Researchers have struggled to obtain funding for further international collaborations evaluating SDD, perhaps because funders have noted the large evidence base which already exists in favour of the intervention. However, both the Australian and New Zealand Intensive Care Society (ANZICS) and the Canadian components of this study are now funded, and it is hoped that the UK will also be able to participate. If the SuDDICU study confirms (yet again) the benefits of SDD, then we should stop denying critically ill patients one of the few interventions in intensive care medicine which has been proven to be effective in saving lives and reducing harm. To those of our colleagues who

regard SDD as being of 'low importance and of low priority to clinicians' [3], we feel justified to ask who it is they think they are treating—the clinicians, or our patients?

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-018-5144-6>) contains supplementary material, which is available to authorized users.

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Acknowledgements

We thank Drs. Andy Petros, Hans J. Rommes, and Miguel A. de la Cal for their comments and for reviewing the manuscript.

Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflict of interest.

Received: 26 February 2018 Accepted: 17 March 2018

Published online: 7 June 2018

References

- Churchill W. The Russian enigma. BBC broadcast, 1 October 1939
- Jaeschke R, Guyatt GH, Dellinger P, Schünemann H, Levy MM, Kunz R, Norris S, Bion J, GRADE Working Group (2008) Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. *BMJ* 337:a744. <https://doi.org/10.1136/bmj.a744>
- Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerf B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinhan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP (2017) Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 43:304–377. <https://doi.org/10.1007/s00134-017-4683-6>
- Cuthbertson BH, Campbell MK, MacLennan G, Duncan EM, Marshall AP, Wells EC, Prior ME, Todd L, Rose L, Seppelt IM, Bellinhan G, Francis JJ (2013) Clinical stakeholders' opinions on the use of selective decontamination of the digestive tract in critically ill patients in intensive care units: an international Delphi study. *Crit Care* 17:R266. <https://doi.org/10.1186/cc13096>
- Daneman N, Sarwar S, Fowler RA, Cuthbertson BH, SuDDICU Canadian Study Group (2013) Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. *Lancet Infect Dis* 13:328–341. [https://doi.org/10.1016/s1473-3099\(12\)70322-5](https://doi.org/10.1016/s1473-3099(12)70322-5)
- Houben AJ, Oostdijk EA, van der Voort PH, Monen JC, Bonten MJ, van der Bij AK et al (2014) Selective decontamination of the oropharynx and the digestive tract and antimicrobial resistance: a 4 year ecological study in 38 intensive care units in the Netherlands. *J Antimicrob Chemother* 69:797–804
- de Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS, van der Hoeven JG, Pickkers P, Bogaers-Hofman D, van der Meer NJ, Bernards AT, Kuijper EJ, Joore JC, Leverstein-van Hall MA, Bindels AJ, Jansz AR, Wesselink RM, de Jongh BM, Dennesen PJ, van Asselt GJ, te Velde LF, Frenay IH, Kaasjager K, Bosch FH, van Iterson M, Thijsen SF, Kluge GH, Pauw W, de Vries JW, Kaan JA, Arends JP, Aarts LP, Sturm PD, Harinck HI, Voss A, Uijtendaal EV, Blok HE, Thieme Groen ES, Pouw ME, Kalkman CJ, Bonten MJ (2009) Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med* 360:20–31
- Wittekamp BH, Oostdijk EA, de Smet AM, Bonten MJ (2015) Colistin and tobramycin resistance during long-term use of selective decontamination strategies in the intensive care unit: a post hoc analysis. *Crit Care* 19:113
- de la Cal MA, Cerda E, Van Saene HK, Garcia-Hierro P, Negro E, Parra ML, Arias S, Ballestreros D (2004) Effectiveness and safety of enteral vancomycin to control endemicity of methicillin-resistant *Staphylococcus aureus* in a medical/surgical intensive care unit. *J Hosp Infect* 56:175–183
- Silvestri L, Solidoro A, Milanese M, van Saene HKF, Fontana F, Gregori D, Gullo A (2010) Topical oropharyngeal vancomycin to control methicillin-resistant *Staphylococcus aureus* lower airway infection in ventilated patients. *Minerva Anestesiol* 76:193–202
- Silvestri L, van Saene HKF, Casarin A, Berlot G, Gullo A (2008) Impact of selective decontamination of the digestive tract on carriage and infection due to Gram-positive and Gram-negative bacteria. A systematic review of randomised controlled trials. *Anaesth Intensive Care* 36:324–338
- Buelow E, Bello González TDJ, Fuentes S, de Steenhuijsen Piters WAA, Lahti L, Bayjanov JR, Majoer EAM, Braat JC, van Mourik MSM, Oostdijk EAN, Willems RJA, Bonten MJM, van Passel MWJ, Smidt H, van Schaik W (2017) Comparative gut microbiota and resistome profiling of intensive care patients receiving selective digestive tract decontamination and healthy subjects. *Microbiome* 5:88. <https://doi.org/10.1186/s40168-017-0309-z>
- SuDDICU-ANZ (2015) A crossover, cluster randomised controlled trial of selective decontamination of the digestive tract in intensive care unit patients in Australian and New Zealand. <https://clinicaltrials.gov/ct2/show/NCT02389036>. Accessed 22 Feb 2018