Commentary

Selective decontamination of the digestive tract: all questions answered?

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Abstract

Although many studies have shown beneficial effects of SDD on the incidence of respiratory tract infections, SDD did not become routine practice because mortality reduction was not demonstrated in individual trials, beneficial effects on duration of ventilation, ICU stay or hospital stay were not demonstrated, cost-efficacy had not been demonstrated, and selection of antibiotic resistance was considered a serious side-effect. A recent study has now shown improved patient survival and lower prevalence of antibiotic resistance in patients receiving SDD. Why could this study show mortality reduction, where all others studies had failed before? And do the microbiological data unequivocally prove protective effects of SDD on emergence of antibiotic resistance? Interestingly, the reported mortality reductions exceeds even the most optimistic predictions from previous meta-analyses, but a clear explanation is not yet evident. The data on antibiotic resistance, however, are rather superficial and do not allow to interpret the underlying epidemiological dynamics. Therefore, the recent findings are provocative and shed new light on the SDD issue, warranting studies confirming its beneficial effects but also addressing several important aspects related to study design.

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

After its first application in intensive care patients in 1984, selective decontamination of the digestive tract (SDD) has been the subject of intense debate between intensivists, infectious disease specialists, microbiologists and methodologists. In 2000, a group of Dutch physicians summarized the scientific evidence on the effects of SDD [1]. They concluded that SDD was associated with a reduction in the incidence of intensive care unit (ICU)-acquired respiratory infections, but improvements in patient survival had not been demonstrated in individual studies. Although several meta-analyses suggested a 20% reduction in ICU mortality, these results should be confirmed in randomized, and preferably double-blind, trials. Significant improvements in outcome with regard to secondary outcomes such as reductions in the duration of ventilation and ICU stay, overall antibiotic use and cost-effectiveness had not been demonstrated. Moreover, the

ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*; SDD = selective decontamination of the digestive tract; VRE = vancomycin-resistant entercocci.

relative importance of the individual components of SDD had not been determined. Finally, selection and emergence of antibiotic-resistant microorganisms was considered an important drawback of the routine use of SDD. Based on these arguments, the routine use of SDD was not advised. What has changed since then?

The first randomized trial on SDD that showed, on intention-to-treat analysis, an impressive reduction in both ICU mortality and hospital mortality for patients receiving SDD has recently been presented [2]. SDD consisted of nonabsorbable antibiotics in the oral cavity and the rest of the digestive tract, systemic prophylaxis with cefotaxime for 4 days intravenously, and nebulization with tobramycin or amphotericin B when tracheal colonization with Gram-negative rods or yeasts occurred. A total of 934 medical and surgical patients were included in the trial, and SDD was associated with a relative reduction of ICU mortality of 36%. This is the highest mortality reduction reported in any individual trial and even exceeds the most positive predictions calculated from meta-analyses for mixed populations. Moreover, patients receiving SDD had a shorter length of ICU stay and fewer patients became colonized with antibiotic-resistant Gram-negative bacteria. Because the study has as yet only been presented in abstract form, it is difficult and premature to draw firm conclusions already. However, the researchers ought to be congratulated with their impressive achievement. Why did this study succeed, where over 30 randomized trials had failed before?

Structural differences between the two study groups are, at first sight, unlikely and, when compared with other studies, the ICU mortality rate in the control group is similar to earlier reported mortality rates. The beneficial effects on patient outcome, however, cannot be explained solely by the larger size, and hence larger power, of the present study. The 36% relative risk reduction of ICU mortality is much larger than in other studies. This reduction in mortality was not restricted to the intensive care period, but persisted throughout the whole period of hospital stay. In fact, a mortality reduction of this magnitude would have resulted in statistically significant mortality differences in several of the earlier studies. It is important to understand the underlying factors leading to this significant mortality reduction to assess the association with systemic or local administered antibiotics.

Importantly, the randomization design in the discussed study was different from the design used in previous studies. Instead of randomizing consecutive patients within a single unit, patients were randomized to either one of two ICU units and SDD was applied to all patients in the so-called SDD ward [2]. It has been argued before that randomization within a single unit would reduce the potential efficacy of SDD (effect modification): decontaminated patients would 'protect' nondecontaminated patients from acquired colonization and subsequent infection, and *vice versa*. However, to what extent can cross-acquisition of microorganisms affect patient outcome? Only a fraction of all colonized patients will develop an infection, and attributable mortality due to ICU-acquired infections is far from 100%. This implies that the role of cross-transmission in infections must have been extremely high in order to create a mortality difference, and can therefore not be considered as an explanation. In this regard, it is unfortunate that the investigators did not use a crossover design. Unmeasured, and perhaps unexpected, structural differences between the two units can therefore not be ruled out.

The dynamics of colonization and infection with antibiotic-resistant pathogens in the ICU are complicated. The proportion of colonized patients can change through admission of patients that are already colonized. In addition, treatment with antibiotics may create resistance by influencing molecular biological mechanisms or selection of pre-existing, but so far undetectable, resistant flora. As the latter events can occur within a patient, they could be considered endogenous colonization. Antibiotic resistance may result from mutations of endogenous chromosomal genes, from the acquisition of resistant genes or from a combination of both events. Nontransferable resistance arises primarily through point mutations in genes encoding the antibiotic target (e.g. β-lactams) or by deregulated expression of a regular process (e.g multidrug efflux pumps, inducible β-lactamases). The frequency of these events depends on the antibiotic pressure, the duration of the therapy and the microorganism.

The first mechanism (resistance through mutations) is relevant for resistance to β-lactam antibiotics (e.g. cephalosporins and carbapenems) and quinolones (e.g. ciprofloxacin), but is of no relevance for resistance based on large genetic elements such as vancomycin resistance in enterococci and methicillin resistance in *Staphylococcus aureus*. Selection of pre-existing flora is relevant for all antibiotic-resistant microorganisms. Finally, antibiotic resistance emerges through spread from patient to patient, usually via the hands of health care workers, which has been called exogenous colonization. The likelihood of cross-transmission is not a linear process, but is influenced by nonadherence of health care workers to hygienic measures and by the proportion of patients colonized with resistant pathogens (i.e. colonization pressure) [3]. An increase in the proportion of the patients being colonized will amplify the risks for cross-transmission.

How can SDD have influenced the dynamics of colonization with antibiotic-resistant microorganisms?

The finding that SDD was not associated with increased colonization with methicillin-resistant *S. aureus* (MRSA) is not surprising in an ICU located in a Dutch hospital. During the study period there was no introduction of MRSA; in addition,

antibiotic treatment in individual patients, therapeutically or for SDD, will not change a methicillin-susceptible *S. aureus* into MRSA. The latter also holds true for vancomycin-resistant entercocci (VRE). In contrast to the situation with respect to MRSA, however, approximately 5% of Dutch patients are colonized with VRE on admission [4]. Recent findings suggest that nosocomial spread and outbreaks with VRE are mainly caused by a specific genogroup of *Enterococcus faecium* characterized by several potential virulence factors [5]. Only two outbreaks with this genotype of VRE have so far occurred in The Netherlands. So, without introduction (or presence) of this strain, SDD will probably not contribute to its emergence.

Resistance to tobramycin is usually plasmid based, whereas resistance to imipenem and quinolones mainly results from chromosomal mutations. All these events (especially chromosomal mutations) can occur during antimicrobial therapy. For correct interpretation of the resistance data of this study [2], it is essential to determine the relative impacts of introduction of resistant strains, of endogenous and exogenous colonization of resistant microorganisms, and of resistance genes. Differences in introduction in either of both wards can be excluded by comparison of colonization rates on admission. Discriminating endogenous and exogenous colonization rates should be performed by genotyping isolates and by investigating horizontal gene transfer associated with resistance.

How could the differences in colonization with antibiotic-resistant Gram-negative bacteria be explained?

First, a higher therapeutic use of intravenous antibiotics in the control population could indeed have created a higher selective pressure for pre-existent resistant bacteria or may have induced more mutations leading to resistance.

Second, SDD may have decreased the total bacterial burden, thereby reducing the colonization pressure and, with equal levels of adherence to infection control measures, reduced the possibilities for clonal spread. This would support the use of SDD to control outbreaks of antibiotic-resistant microorganisms as reported previously [6]. However, it is also possible that there was clonal spread of resistant bacteria in the control ward, whereas tobramycin-resistant bacteria in the non-SDD ward were polyclonal, due to increased selection induced by SDD. If so, the conclusion that SDD prevents emergence of resistance no longer holds true. As adherence to infection control practices was not measured, it is unknown if both units were comparable in this regard. Again, a crossover design could have excluded this possibility. And if clonal spread would have been demonstrated, the question whether enforcement of adherence to infection control practices, without implementation of SDD, could have prevented cross-transmission of pathogens also remains to be determined.

Third, adherence to infection control measures may indeed have been higher in the SDD ward. It is well known that any intervention may, unwillingly, change clinical practice. Just emphasizing the correct use of SDD may have improved compliance with hygienic measures. In fact, this indirect effect of SDD on the awareness of health care workers is frequently put forward as one of the principles of the SDD concept, but has never been quantified. Its contribution to the overall results therefore remains undetermined.

Firm conclusions cannot be drawn from a study published in abstract form only. However, the results of the latest SDD study [2] are important and shed new light on a long-lasting discussion. As for generalization, this impressive mortality reduction should be confirmed in subsequent trials, but it is evident that, from now on, patient survival in the ICU and preferably in hospital should be the primary endpoint of such studies. Also, the design of the study deserves further attention. Randomization of multiple wards in a crossover design is probably to be preferred. In addition, the relative benefits in different patient groups (trauma, surgical or medical, or with low, intermediate or high Acute Physiology and Chronic Health Care Evaluation II scores) should be determined. Moreover, the questions of which part of SDD is most efficient and whether, for example, oropharyngeal decontamination would have the same effects remain to be established. Finally, the role of intravenous prophylaxis, or better pre-emptive therapy, with intravenous cefotaxime has not been elucidated.

The findings with regard to the role of SDD to prevent the emergence of antibiotic resistance are challenging, but too many questions regarding the epidemiology of these bacteria remain unanswered to draw firm conclusions. Also, in terms of development of resistance, the time frame of the study was probably much too short. In hematology departments in The Netherlands, where SDD has now been used for more than 15 years, resistant enteric bacteria have started to emerge only recently [7,8]. Importantly, prevalence of antibiotic resistance in The Netherlands is exceptionally low when compared with most other European and American countries. As a result, the selective effects of antibiotics, both topically and systemically administered, may be completely different in other settings. Therefore, extrapolation of the resistance findings to ICUs in other countries may be dangerous. For now, old concepts on the interaction between antibiotic use and emergence of antibiotic resistance remain undisputed: “the more you use it, the sooner you loose it”. Nevertheless, antibiotics achieve more than causing resistance, and the clinical benefits of SDD will decide on their fate in intensive care patients.

Competing interests

None declared.

References

1. Bonten MJ, Kullberg BJ, van Dalen R, Girbes AR, Hoepelman IM, Hustinx W, van der Meer JW, Speelman P, Stobberingh EE, Verbrugh HA, Verhoef J, Zwaveling JH: **Selective digestive decontamination in patients in intensive care. The Dutch Working Group on Antibiotic Policy.** *J Antimicrob Chemother* 2000, **46**:351-362.
2. de Jonge E, Schultz MJ, Spanjaard L, Bossuyt PM, Vroom MB, Dankert J, Kesecioglu J: **European Society of Intensive Care Medicine, 15th Annual Congress (Barcelona): effects of selective decontamination of the digestive tract on mortality and antibiotic resistance [abstract 30].** *Intensive Care Med* 2002, **28(suppl 1)**:S12.
3. Bonten MJM, Slaughter S, Ambergen AW, Hayden MK, van Voorhis J, Nathan C, Weinstein RA: **The role of 'colonization pressure' in the spread of vancomycin-resistant enterococci. An important infection control variable.** *Arch Intern Med* 1998, **158**:1127-1132.
4. van den Braak N, Ott A, van Belkum A, Kluytmans JAJW, Koeleman JGM, Spanjaard L, Voss A, Weersink AJL, Vandenbroucke-Grauls CMJE, Buiting AGM, Verbrugh HA, Endtz HP: **Prevalence and determination of fecal colonization with vancomycin-resistant enterococcus in hospitalized patients in the Netherlands.** *Infection Control Hospital Epidemiol* 2000, **21**:520-524.
5. Bonten MJ, Willems R, Weinstein RA: **Vancomycin-resistant enterococci: why are they here, and where do they come from?** *Lancet Infect Dis* 2001, **1**:314-325.
6. Brun-Buisson C, Legrand P, Rauss A, Richard C, Montravers F, Besbes M, Meakins JL, Soussy CJ, Lemaire F: **Intestinal decontamination for control of nosocomial multiresistant Gram-negative bacilli: study of an outbreak in an intensive care unit.** *Ann Intern Med* 1989, **110**:873-881.
7. van Belkum A, Goessens W, van der Schee C, Lemmens-den Toom N, Vos MC, Cornelissen J, Lugtenburg E, de Marie S, Verbrugh H, Lowenberg B, Endtz H: **Rapid emergence of ciprofloxacin-resistant enterobacteriaceae containing multiple gentamicin resistance-associated integrons in a Dutch hospital.** *Emerg Infect Dis* 2001, **7**:862-871.
8. Mooij M, Schouten I, Schultsz C, Savelkoul PH, Reinders E, Vos M, van Belkum A, Vandenbroucke-Grauls C: **Drug-resistance associated integrons in ciprofloxacin-resistant *Escherichia coli*.** In *Proceedings of the 42nd International Conference on Antimicrobial Agents and Chemotherapy*. American Society for Microbiology, San Diego, September 2002:124.