

antipsychotic drugs should not be considered free of risk for sudden cardiac death until further data become available.

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## Decontamination of the Digestive Tract in ICU Patients

**TO THE EDITOR:** De Smet and colleagues (Jan. 1 issue)<sup>1</sup> do not address the effects of selective digestive tract decontamination (SDD) in intensive care units (ICUs) on the increasing prevalence of enterococci, which leads to additional use of vancomycin and the emergence of vancomycin-resistant enterococci (VRE). The authors report that in the short term, rates of antibiotic-resistant gram-negative bacteria during SDD or selective oropharyngeal decontamination (SOD) were lower than during standard care. Rates of bacteremia with enterococci were slightly lower during SDD or SOD. However, no data on carriage of enterococci are presented.

In the United States and Europe, the rapid emergence of VRE was preceded by the emergence of ampicillin-resistant *Enterococcus faecium* (AREF).<sup>2</sup> After starting to use SDD in our hospital, as part of the trial reported by de Smet et al., we observed a sharp increase in the prevalence of AREF. After the trial was completed, the prevalence of AREF remained high, and the first serious VRE epidemic in our hospital occurred, involving 30 patients. Eight clinical wards were involved, including four ICUs; one ward was closed for several weeks. Before introducing SOD or SDD in ICUs, decision makers should take into account the possible emergence and amplification of resistant enterococci, especially in low-prevalence settings.

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**TO THE EDITOR:** In their trial of SDD and SOD, de Smet et al. report significant reductions in rates of death and ICU-acquired bacteremia at 28 days. A likely mechanism for this benefit is a reduction in ventilator-associated pneumonia,<sup>1,2</sup> which is associated with a doubling in the rate of death among ICU patients.<sup>3</sup> However, the authors do not provide data on rates of ventilator-associated pneumonia or the use of recommended preventive practices, such as semirecumbent positioning, daily cessation of sedation infusions, and spontaneous-breathing trials, which are frequently combined as part of an evidence-based “ventilator bundle.”<sup>4</sup> If these preventive measures had been used for all patients, the absolute benefit of SDD or SOD in this trial might have been greatly reduced, making these interventions much less attractive, given their associated cost, requirement for additional nursing labor, and potential for antibiotic resistance. These details regarding rates of ventilator-associated pneumonia and the use of preventive measures are also important for understanding the generalizability of these results to ICUs, which have adopted routine use of ventilator bundles.

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**TO THE EDITOR:** According to the report by de Smet et al., a significant reduction in mortality among ICU patients was associated with SDD and SOD. This finding is a two-edged sword, and we are concerned that a balanced perspective has not been provided. First, the implementation of widespread SDD or SOD with the antibiotics used in this study has the potential for causing serious harm to patients, not only because of the emergence of resistance to antibiotics but also because of *Clostridium difficile*-associated colitis.<sup>1</sup> There was no evidence that the patients in this study were followed appropriately or long enough to identify these untoward consequences. Surveillance cultures were obtained only while the patients were in the ICU and undergoing decontamination. Second, it is difficult to generalize these findings. The majority of ICUs around the world are plagued with resistant organisms,<sup>2</sup> and hypervirulent strains of *C. difficile* are now widespread.<sup>3,4</sup> Broad antibiotic use in uninfected patients could be deleterious in these environments.

The study methods must also be carefully considered — specifically, the lack of blinding and the “bundling” of advice regarding the systemic use of antibiotics during periods of decontamination. An impressive reduction in the use of carbapenem and quinolone was observed during the decontamination periods. This makes it impossible to draw any conclusions about the safety or efficacy of these decontamination protocols. Furthermore, the lack of blinding introduces the potential for other serious biases, including subtle differences in ICU management between study periods that may have affected patient outcomes. Blinding with the use of placebo topical and intravenous preparations seems relatively facile. We are concerned that the results of this study may be interpreted superficially and applied with harmful consequences.

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**TO THE EDITOR:** The crossover, cluster-randomized trial by de Smet et al. appears to show reduced mortality with the use of SDD or SOD in critically ill patients but only after adjustment for differences in prognostic factors in the study groups. Although the results are consistent with those of smaller studies,<sup>1-3</sup> the lack of benefit with respect to crude mortality makes the results of this study less compelling. Differences in measured prognostic factors imply a failure of randomization and reflect additional differences in unmeasured factors, for which adjustment cannot be made with the use of regression analysis. Unconcealed study-group assignment allows for selection bias, which was shown in the differential recruitment rates, as discussed, and may have contributed to increased beneficial effects.<sup>4,5</sup> Furthermore, with sequential 6-month intervention periods, seasonal effects on mortality in ICUs may limit the ability to use ICUs of different sizes as their own controls within the overall study, despite the crossover design. The individual randomization of patients with concealment of the study-group assignments and the use of placebo controls<sup>1,3</sup> would have made it considerably more difficult to conduct and complete such a large trial. However, the use of such methods to produce more balanced groups would have yielded more definitive results.

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**TO THE EDITOR:** The study by de Smet et al. has a major flaw. Originally, when the primary end point was in-hospital mortality, which is considered to be the best outcome measure in critically ill patients, the results for SDD and SOD were negative.<sup>1</sup> However, with modification of the statistical analysis and end points, the results became positive for SDD and SOD. While we were enrolling patients in this study, we realized that the groups were dissimilar, since both patients and nurses disliked the mouth paste, which could make doctors reluctant to include seriously ill patients during the SOD period and more willing to include them during the control period. This imbalance is reflected in Table 1 of the article. With correction for this factor, the results became positive. Yet correction factors were determined afterward. We doubt whether a study with these drawbacks — and with significant differences for only half of the end points — justifies the authors' resolute conclusions. In our view, we have another piece of the puzzle but not the final picture.

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1. de Smet AM. First results of the national SDD/SOD trial. Key note lecture presented at the 5th Netherlands Intensive Care Congress, Ede, January 31–February 2, 2007.

**THE AUTHORS REPLY:** Since our study was performed in Dutch ICUs with a low prevalence of antibiotic resistance, our findings may not be applicable to settings with a markedly different bacterial ecology or different practices for preventing ventilator-associated pneumonia. Yet there was no evidence of VRE carriage during the trial, and causality between the trial and the observed VRE outbreak afterward, as mentioned by Meessen et al., remains to be determined. There was also no

evidence of an increase in the rate of *C. difficile* infections during the study or in the 871 patients (in two centers) who were prospectively monitored for nosocomial infections after discharge from the ICU.

Truong et al. question the lack of data regarding the incidence of ventilator-associated pneumonia in our study. We did not monitor such incidence because of the lack of a uniform diagnostic process in 13 different ICUs. The ventilator-bundle approach has not been implemented in the Netherlands as rigorously as it has in the United States, mainly because the cessation of sedation infusions, spontaneous-breathing trials, and the bundle approach itself have never been associated with reductions in the rate of ventilator-associated pneumonia in carefully performed, randomized studies. And although the benefits and feasibility of the semirecumbent position have been questioned,<sup>1</sup> most patients in our study were positioned at 30 degrees for treatment when possible.

Gold and Peleg conclude that it is impossible to draw conclusions because of the observed differences in the use of carbapenem and quinolone. We respectfully disagree. Reduced rates of use of systemic antibiotics (12% with SDD and 10% with SOD in unadjusted analyses) should be considered as an outcome of the interventions. Moreover, avoidance of beta-lactam antibiotics (e.g., carbapenems) was part of the SDD intervention.

Soliman et al. raise the issue of seasonal effects on mortality that would not have been appropriately addressed by the sequential 6-month intervention periods. In fact, there was staggered initiation at the 13 study sites (see the figure in the Supplementary Appendix of the article), which reduced the potential for such an effect. Furthermore, to the best of our knowledge, there is no evidence of seasonality in mortality among adult ICU patients.

Finally, Zijlstra et al. propose an explanation for the baseline difference between the standard-care group and both intervention groups. In their experience, physicians were reluctant to include seriously ill patients when SOD was needed. However, such a bias would have the opposite effect — a lower severity of illness at baseline, rather than the observed higher severity, among patients receiving SDD or SOD — and is also not supported by the data from their own center. The mean ( $\pm$ SD) Acute Physiology and Chronic Health

Evaluation (APACHE II) scores of the patients in their ICU were 16.4±7.5 for 360 patients receiving standard care, 15.7±7.5 for 339 patients receiving SOD, and 16.4±7.7 for 314 patients receiving SDD, with observed inclusion rates of 88%, 91%, and 87% for the three groups, respectively. Their remark that “correction factors were determined afterward” is incorrect, since all variables on case-record forms — which were used throughout the study — were included as covariates.

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## Behavioral Management for Anorexia Nervosa

**TO THE EDITOR:** In their article on behavioral management for anorexia nervosa (Jan. 29 issue),<sup>1</sup> Attia and Walsh state that the Maudsley Method (in which parents take control of refeeding of their child) is the preferred treatment for children and adolescents, but I wonder why they do not recommend it for the 23-year-old woman described in the vignette. For decades, the conventional wisdom was that a “toxic” parent-child relationship caused this disorder. Parents were told to “back off” and were barred from the treatment team.<sup>2</sup> This cruel and inaccurate bias has lingered in psychiatry. Attia and Walsh note that weight restoration is accepted as being paramount for treatment. They also note that inpatient treatment lasts for 18 days, on average, and is associated with a relapse rate of 50% in the first year after hospitalization. When parents are empowered to refeed their child, they do so for as long as it takes, which is usually many months.<sup>3</sup> We await clinical trials using the Maudsley Method in young adults.

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**TO THE EDITOR:** We agree with the authors that structured multidisciplinary behavioral programs that integrate nutritional and psychological treatments are the most promising approaches in the management of anorexia nervosa. However, their

nutritional-support program raises concern. Certainly, priority is given to providing adequate calories,<sup>1</sup> and institutions may opt for different protocols. However, in our experience, patients frequently report considerable difficulties in beginning therapy with such large quantities of solid food (1800 kcal per day); such quantities are probably unrealistic and may be harmful. Patients with anorexia nervosa are at high risk for the refeeding syndrome.<sup>2-4</sup> When similar high-calorie nutritional regimens are enforced, the risk of complications is very high.<sup>1-4</sup> To avoid complications, both current guidelines and expert panels suggest 10 kcal per kilogram of body weight per day for nutritional support during the first 3 days, regardless of the route of administration.<sup>3,4</sup> A cautious increase (by 400 to 500 kcal every 3 days) can then be proposed to obtain a positive energy balance.<sup>1,3</sup> Weight and electrolyte levels should be checked daily to rule out excessive water retention and correct any impairment.

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