Selective Decontamination of the Digestive Tract
An Answer at Last?

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Selective decontamination of the digestive tract (SDD) is one of the most controversial topics in the treatment of critically ill patients. With the first study published almost 40 years ago,\(^1\) 2 major new contributions appear in this issue of JAMA.\(^2,3\) Unfortunately, these new studies do not close the book on SDD.

Many intensive care unit (ICU)-acquired infections, in particular infections of the respiratory tract, are caused by gram-negative bacteria, *Staphylococcus aureus*, and yeasts, usually resulting from colonization of the upper and lower digestive tracts (mouth, stomach, and intestines). SDD aims to improve patient outcomes by reducing the incidence of ICU-acquired infections through eradicating and preventing colonization of the digestive tract with the aforementioned microorganisms. SDD involves application of topical, nonabsorbable antimicrobial agents (usually colistin, tobramycin, and nystatin) that—selectively—spare the anaerobic flora. Apart from the topical prophylaxis patients receive, intravenous antibiotics, usually with a second- or third-generation cephalosporin, empirically treat respiratory tract infections that may be incubating at the time of ICU admission. The long-standing debate on the use of SDD in critically ill patients is whether benefits for patients have been unequivocally demonstrated and whether the widespread use of antibiotics may increase antibiotic resistance that would outweigh such benefits.

An important new piece of evidence comes from the Selective Decontamination of the Digestive Tract in the Intensive Care Unit (SuDDICU) trial, a large, well-conducted, cluster, crossover, randomized trial in 19 ICUs in Australia and New Zealand, comparing 2791 patients receiving SDD and 3191 patients receiving standard care.\(^4\) Hospital mortality, the primary outcome of the study, occurred in 27.0% of those receiving SDD and in 29.1% of those receiving standard care without SDD. The odds of dying in hospital was 0.91 for SDD patients, reflecting a mortality reduction of 1.7%, with a 95% CI ranging from a reduction of 4.8% to an increase in mortality of 1.3%. Although not statistically significant, the authors conclude that the confidence interval includes a clinically relevant benefit.

These results were included in the newest meta-analysis of SDD by Hammond and colleagues\(^5\) for this, they included trials that randomized patients to SDD and standard care and that determined hospital mortality. They selected 32 randomized clinical trials (RCTs) with a total of 24,389 patients, of which 30 RCTs contributed to the primary outcome. The pooled estimated relative risk for mortality for SDD (compared with standard care) was 0.91 (95% credible interval, 0.82-0.99), with a 99.3% posterior probability (bayesian analysis) that SDD reduced hospital mortality. This corresponds to a 95% probability that implementation of SDD was associated with a reduction in hospital mortality of between 1% and 18%. Beneficial effects were only obtained when pooling studies in which SDD included the intravenous component.

The studies selected for the meta-analysis nicely demonstrate the evolution in clinical trials evaluating SDD over the 40-year period: from a single-center study with 49 individually randomized patients\(^4\) to multicenter studies with thousands of patients randomized in clusters and with crossover of management strategies.\(^2,5-6\) The clustered approach was used in 4 studies,\(^2,5-7\) which together contributed 19,269 patients in the meta-analysis (79%) and account for 32.6% of the pooled estimate. Advantages of a clustered study design, compared with randomization of individual patients, are the capturing of indirect effects, such as reductions in cross-transmission. It also increases feasibility because a waiver of informed consent allows enrollment of all eligible patients, thereby better mimicking the real-world situation if SDD would be implemented. The downside is the possibility of selection bias because even in a clustered approach, someone must determine eligibility for each individual patient based on potentially subjective inclusion criteria, such as an expectation that someone will continue receiving ventilation for a certain period.

The debate on SDD is now enriched with yet another large cluster-randomized study suggesting outcome benefit for ICU patients (albeit without demonstrating a statistically significant effect)\(^3\) and yet another meta-analysis providing more substantial (and statistically significant) evidence of such benefit.\(^3\) Yet, cluster-randomized trials may hamper data interpretation of meta-analyses, potentially leading to an underestimation of the true effect of SDD. In this case, strict application of the meta-analysis study protocol by Hammond and colleagues led in 2 instances to the use of other effect sizes in the meta-analysis than were originally reported. Moreover, it also led to the exclusion of the largest study in the field.

For instance, the study by de Smet and colleagues\(^8\) was a cluster-randomized crossover study that compared standard care vs SDD with an intravenous component (full SDD, as used in the SuDDICU trial) and SDD without intestinal decontamination and without an intravenous component (called selective oropharyngeal decontamination [SOD]). In the crude analysis, there were no statistically significant differences in patient outcomes among the 3 clusters. Yet, there was evidence of selection bias, with patients in standard care having a slightly better prognosis. Therefore, the final analysis was a random-effects logistic-regression model with adjustment for available covariates. This analysis yielded odds ratios for hospital mortality, compared with standard care, of 0.88 (95% CI, 0.76-1.01) for patients receiving SDD.
and of 0.85 (95% CI, 0.74-0.98) for those receiving SOD.\(^5\) In their meta-analysis, Hammond and colleagues chose to join SDD and SOD clusters as a single intervention and to use the crude effect size of a risk ratio of 1.0.

Furthermore, the study by Wittekamp and colleagues\(^6\) compared 3 interventions with standard care: SDD (although without a predefined intravenous component), SOD (as in the study by de Smet et al\(^5\)), and oropharyngeal care with chlorhexidine. All 13 participating sites started with the standard care period, and the 3 interventions were subsequently clustered, crossover randomized. In this study, the adjusted analysis of the comparison between SDD and the standard care baseline period yielded an odds ratio of 0.96 (95% CI, 0.82-1.12) for hospital mortality.\(^6\) For their meta-analysis, Hammond and colleagues chose not to include the standard care baseline period because this was not randomized. Instead, they chose to pool the data from SDD and SOD and to use the chlorhexidine group as the standard care group. Therefore, the effect size used in the meta-analysis was 1.04.

Finally, the largest cluster-randomized crossover study in this field was not included because it lacked a cluster with standard care.\(^8\) This study, performed in the Netherlands, compared 16 clusters with SDD (6040 patients) and SOD (5957 patients), which both had graduated to standard care based on the results of the de Smet et al\(^5\) study. The odds ratio for hospital mortality was 0.86 (95% CI, 0.87-0.94) for patients in the SDD cluster based on mixed-model regression analysis with adjustment for available confounders.

Does the cumulative evidence coming from clinical SDD studies and meta-analyses provide sufficient evidence that SDD improves patient outcomes? The answer is yes, for settings with relatively low prevalence of multidrug-resistant pathogens, such as ICUs in the Netherlands, Australia, and New Zealand,\(^2,5,7,8\) which provide almost all the evidence. Moreover, there is no evidence that implementation of SDD in such settings negatively impacts resistance ecology.\(^2,9,10\)

Does the cumulative evidence coming from clinical SDD studies and meta-analyses also justify widespread implementation of SDD? That requires evaluation of benefits and costs. In the Netherlands, SDD became the recommended standard care for patients with an expected length of mechanical ventilation of at least 48 hours or an expected length of stay in the ICU of at least 72 hours in 2014, which was subsequently supported by a cost-effectiveness analysis.\(^11\) At that time, only a few ICUs outside the Netherlands used SDD,\(^12\) which has most likely not changed since then.

For settings with higher prevalence of multidrug-resistant pathogens, there is only 1 cluster-randomized study, and that did not provide evidence for better patient outcomes.\(^6\)

To conclude, after 40 years of clinical trial experience, important questions regarding the utility of SDD in critically ill patients receiving mechanical ventilation have been answered for settings with a low prevalence of antibiotic resistance. Yet, large-scale studies are still needed to determine effectiveness in specific patient populations and in settings with a high prevalence of multidrug-resistant pathogens.

**REFERENCES**


**Conflict of Interest Disclosures:** None reported.