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COMMENT & RESPONSE

Selective Decontamination of the Digestive Tract and Hospital Mortality in Critically Ill Patients Receiving Mechanical Ventilation

To the Editor The recently published SuDDICU randomized clinical trial[1] confirmed a clinically relevant yet nonsignificant mortality reduction in mechanically ventilated critically ill patients receiving selective digestive decontamination (SDD). We have some comments about this study.[1]

First, the decontamination regimen evaluated in SuDDICU did not differ from previous studies.[2] Selective digestive decontamination, in combination with a short course of intravenous antibiotics, has been evaluated since 1984 and is associated with favorable effects on acquired infection, acquisition of multidrug-resistant microorganisms, and mortality.[3]

Second, the intravenous antibiotic was not given to patients who received curative antimicrobial therapy that covered gram-negative bacteria. As a consequence, cefotaxime, as part of the decontamination protocol, was received by only a fraction of the study patients. In order to assess the additional effect of systemic antibiotics on prevention of mortality, we would like the authors to analyze the subgroup of patients who did not receive curative antimicrobial therapy during the first 4 days after hospital admission. Interestingly, studies of other decontamination regimens, such as selective oropharyngeal decontamination and multiple-site decontamination, which do not include a systemic antibiotic, have shown favorable results with regard to acquired infection, acquisition of multidrug-resistant microorganisms, and mortality.[2-5]

Third, 90-day hospital mortality was an ambitious primary end point. Patients in this study were mechanically ventilated and received SDD for a median of only 7 days. We believe that it is unlikely that a prophylaxis intervention will affect survival at 90 days. Can the authors provide an analysis of survival at day 28?

Although decades of research have confirmed the benefit of SDD, this prophylaxis is only sporadically used outside the Netherlands.[2] Unfortunately, it is unlikely that the SuDDICU trial will increase SDD implementation worldwide. We need to rethink how to increase the implementation of SDD.

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To the Editor A recent trial[1] of critically ill patients in Australia found that SDD had no statistically significant effect on mortality. We question whether SDD was actually delivered in this study.

Selective decontamination of the digestive tract aims to prevent endogenous nosocomial infections by decontaminating the gut from potentially pathogenic bacteria, mainly gram-negative. Selective decontamination of the digestive tract has 4 pillars,[2,3] including (1) a high level of hygiene;

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(2) administration of nonabsorbable, topical antimicrobial agents at a 6-hourly interval to decontaminate the gastrointestinal tract; (3) a short intravenous course of a third-generation cephalosporin to treat any present endogenous infection; and (4) surveillance cultures taken twice weekly of the perineum, throat, and trachea to determine whether decontamination has been effective and to adjust the topical antibiotic in case of resistance. In this way, it is possible to individualize the SDD strategy, which results in a high rate of decontamination.

In this study,[1] surveillance cultures were not obtained and administration of a single dose of SDD was defined as being adherent to protocol. However, as the entire gastrointestinal tract needs to be decontaminated, effective decontamination is achieved only after multiple doses of antibiotics. Therefore, it is unlikely that SDD resulted in decontamination in all patients in this trial or, at best, it is not known. Also, the absence of surveillance cultures prevented adjustment of topical antibiotics for resistant microorganisms in the throat or rectum. In addition, intravenous antibiotics varied in this study, and not all were the recommended choice of a third-generation cephalosporin.

The SuDDICU investigators may refer to their choices as being "pragmatic." However, taking surveillance cultures as part of SDD and adjusting the SDD strategy when necessary is highly feasible and is done in nearly every intensive care unit in the Netherlands that applies SDD.[4]

To summarize, this study did not adhere to 3 of the 4 pillars of SDD. Patients in whom SDD was not delivered cannot benefit from its effects. As a result, we believe that the conclusion of this trial that SDD had no effect on mortality is not justified.

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In Reply The SuDDICU trial[1] was designed to determine whether the administration of SDD as a preventive infection control strategy improved patient-centered outcomes, specifically hospital mortality, in intensive care unit patients receiving mechanical ventilation.

Both Dr Massart and colleagues and Dr Determann and colleagues question the SDD protocol adherence rates and the adequacy of microbiological surveillance in the SuDDICU trial.

The SuDDICU trial was unique in using specifically manufactured, international standard Good Manufacturing Practice–compliant SDD drug preparations. More than 130 000 doses of these preparations were delivered as an oral paste and a gastric suspension of topical antimicrobial agents to 2791 patients. The adherence rates for SDD preparations exceeded 90% in the first week, which was the period when the majority of patients were enrolled in the trial. Specifically, "full" adherence, which occurred if patients received all 4 doses of SDD oral paste and gastric suspension on any day during which they were ventilated over the duration of the trial, was achieved in 2226 of 2791 patients (79.8%). Rates of adherence to SDD and to the trial protocol exceeded those presented in previous trials.[2] The administration rates of intravenous antibiotics with a suitable antimicrobial spectrum accord with the original SDD strategy and included eligible nontrial antibiotics that were administered for clinical reasons. Clinical cure was not adjudicated in the SuDDICU trial, and it is inappropriate to conduct a subgroup analysis using a nonstandard postrandomization variable.

As individual patient consent was waived for patients enrolled in the SuDDICU trial, microbiological surveillance was conducted in accordance with international standards of infection control and antibiotic stewardship at each participating hospital. Additional surveillance cultures, particularly screening rectal and oropharyngeal cultures, were not mandated outside routine clinical practice. The sensitivity and sensitivity of these additional cultures in quantifying enteral "sterilization" has not been established.[3]

For consent reasons, hospital mortality was selected as the index mortality interval, censored at 90 days after enrollment in our study.[1] This is an acceptable mortality interval for critical care randomized clinical trials. Post hoc adjustments for baseline and cluster-level imbalances did not significantly change the primary outcome.

Recent large-scale cluster randomized clinical trials have focused primarily on the development of antimicrobial resistance with mortality rates presented as secondary outcomes.[2,4,5] Interpretation of the SuDDICU trial and its potential effect on clinical practice should consider the pragmatic design and the principal objective to determine the effect of SDD on important patient-centered outcomes. The 2-percentage-point reduction in mortality observed in the SuDDICU trial corresponds to a number needed to treat of 50 to avoid 1 death, which is a clinically important effect size.

The SuDDICU trial contributed greater weight (8.4%) to its accompanying systematic review than any other trial,

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thus providing an important contribution to the conclusion that there is a 99.3% probability that SDD reduces hospital mortality.[6]

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Human Mpox Virus Infection After Receipt of Modified Vaccinia Ankara Vaccine

To the Editor I have some concerns about a recent Research Letter[1] that presented data about human mpox (formerly monkeypox) virus infection after patients received the modified vaccinia Ankara-Bavarian Nordic vaccine (MVA-BN [JYNNEOS]).

First, the US Food and Drug Administration issued an Emergency Use Authorization for the intradermal route of administration with low volume of MVA-BN on August 9, 2022, to expand available vaccine supply.[2] Given that this study[1] enrolled patients from June 28 through September 9, 2022, some of them may have received MVA-BN subcutaneously and others may have received MVA-BN intradermally. However, this information was not provided in the article.[1] The one-fifth dose of MVA-BN given intradermally achieved levels of neutralizing antibodies similar to those produced with standard doses given subcutaneously, but cellular immunity levels were lower.[3] Additionally, in the current outbreak, because concurrent HIV infection is also common among patients with mpox, some patients have a low CD4 cell count. HIV infection may also affect the efficacy of these 2 different MVA-BN vaccination routes. It is of great importance to assess the effects of MVA-BN administered subcutaneously and intradermally. If the protective effects are similar, the current intradermal MVA-BN vaccination recommendation can be maintained. However, if the protective effect of intradermal administration of MVA-BN is lower, MVA-BN vaccination recommendations should be changed to the standard subcutaneous vaccination route. Therefore, it would be helpful if the authors could provide data about human mpox virus infection after receipt of MVA-BN via the subcutaneous and intradermal routes.

Second, information about smallpox vaccination history of patients in this study was not included but is important because first-generation smallpox vaccines provided 85% cross-protection against mpox.[4] However, smallpox vaccination stopped in 1980, and many people do not recall their smallpox vaccination. The smallpox vaccine was administered using the multiple puncture technique with a bifurcated needle. After immunization, vaccinia virus replicates in the dermis, and a papule typically appears at the vaccination site between days 3 and 5. The papule becomes vesicular between days 5 and 8, then pustular, and usually enlarges to maximum size between days 8 and 10. The pustule dries from the center outward and forms a scab that separates between days 14 and 21, leaving a slightly depressed, smooth scar.[5] Therefore, for patients who are uncertain if they received the smallpox vaccine, presence of a residual scar can help confirm smallpox vaccination history.

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