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Effect of Selective Decontamination of the Digestive Tract on Hospital Mortality in Critically Ill Patients Receiving Mechanical Ventilation
A Randomized Clinical Trial

The SuDDICU Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group

IMPORTANCE Whether selective decontamination of the digestive tract (SDD) reduces mortality in critically ill patients remains uncertain.

OBJECTIVE To determine whether SDD reduces in-hospital mortality in critically ill adults.

DESIGN, SETTING, AND PARTICIPANTS A cluster, crossover, randomized clinical trial that recruited 5982 mechanically ventilated adults from 19 intensive care units (ICUs) in Australia between April 2018 and May 2021 (final follow-up, August 2021). A contemporaneous ecological assessment recruited 8599 patients from participating ICUs between May 2017 and August 2021.

INTERVENTIONS ICUs were randomly assigned to adopt or not adopt a SDD strategy for 2 alternating 12-month periods, separated by a 3-month interperiod gap. Patients in the SDD group (n = 2791) received a 6-hourly application of an oral paste and administration of a gastric suspension containing colistin, tobramycin, and nystatin for the duration of mechanical ventilation, plus a 4-day course of an intravenous antibiotic with a suitable antimicrobial spectrum. Patients in the control group (n = 3191) received standard care.

MAIN OUTCOMES AND MEASURES The primary outcome was in-hospital mortality within 90 days. There were 8 secondary outcomes, including the proportion of patients with new positive blood cultures, antibiotic-resistant organisms (AROs), and *Clostridioides difficile* infections. For the ecological assessment, a noninferiority margin of 2% was prespecified for 3 outcomes including new cultures of AROs.

RESULTS Of 5982 patients (mean age, 58.3 years; 36.8% women) enrolled from 19 ICUs, all patients completed the trial. There were 753/2791 (27.0%) and 928/3191 (29.1%) in-hospital deaths in the SDD and standard care groups, respectively (mean difference, −1.7% [95% CI, −4.8% to 1.3%]; odds ratio, 0.91 [95% CI, 0.82-1.02]; $P = .12$). Of 8 prespecified secondary outcomes, 6 showed no significant differences. In the SDD vs standard care groups, 23.1% vs 34.6% had new ARO cultures (absolute difference, −11.0%; 95% CI, −14.7% to −7.3%), 5.6% vs 8.1% had new positive blood cultures (absolute difference, −1.95%; 95% CI, −3.5% to −0.4%), and 0.5% vs 0.9% had new *C difficile* infections (absolute difference, −0.24%; 95% CI, −0.6% to 0.1%). In 8599 patients enrolled in the ecological assessment, use of SDD was not shown to be noninferior with regard to the change in the proportion of patients who developed new AROs (−3.3% vs −1.59%; mean difference, −1.71% [1-sided 97.5% CI, −∞ to 4.31%] and 0.88% vs 0.55%; mean difference, −0.32% [1-sided 97.5% CI, −∞ to 5.47%]) in the first and second periods, respectively.

CONCLUSIONS AND RELEVANCE Among critically ill patients receiving mechanical ventilation, SDD, compared with standard care without SDD, did not significantly reduce in-hospital mortality. However, the confidence interval around the effect estimate includes a clinically important benefit.

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Visual Abstract

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Supplemental content

Authors and Group Information: The Writing Committee for the SuDDICU Investigators is listed at the end of this article and the SuDDICU Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group are listed in Supplement 5.

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Selective decontamination of the digestive tract (SDD) was originally described in immunocompromised patients with hematological disease[1] and in patients with trauma[2,3] and was extended to critically ill patients treated in intensive care units (ICUs) in the 1980s.[4,5]

Selective decontamination of the digestive tract is the application of topical nonabsorbable antibiotics and antifungal agents to the upper gastrointestinal tract combined with a short course of intravenous antibiotics in patients receiving mechanical ventilation via an endotracheal tube.[6]

The principal aim of SDD is to prevent the development of ventilator-associated pneumonia caused by pathogenic gram-negative bacteria and secondary overgrowth with yeasts from the upper gastrointestinal tract. Selective decontamination of the digestive tract usually consists of an oral paste and gastric suspension of 3 nonabsorbed antimicrobial agents combined with a short course of an intravenous antibiotic with an appropriate antimicrobial spectrum.[5]

Although systematic reviews of published randomized clinical trials have reported that the use of SDD was associated with reductions in interval mortality rates and in the incidence of ventilator-associated pneumonia,[7-10] widespread international use of SDD as standard care remains low.[6,11,12] Clinician uncertainty may relate to concerns about the generalizability of the results of previous randomized clinical trials, weak recommendations about the use of SDD in international clinical practice guidelines,[13] and that use of SDD may increase the prevalence of antibiotic-resistant organisms.[8,14]

To address this uncertainty, the Selective Decontamination of the Digestive Tract in the Intensive Care Unit (SuDDICU) trial was designed to test the hypothesis that adding SDD to standard care would decrease hospital mortality in mechanically ventilated adults in the ICU compared with standard care. An observational evaluation of whether SDD was noninferior to standard care in changes in microbiological ecology was conducted simultaneously.

Key Points

Question Among critically ill patients receiving mechanical ventilation, what is the effect of selective decontamination of the digestive tract (SDD) on hospital mortality?

Findings In this randomized clinical trial that included 5982 patients, SDD compared with standard care without SDD did not result in a significant difference in in-hospital mortality (27.0% vs 29.1%, respectively; odds ratio, 0.91).

Meaning Among critically ill patients receiving mechanical ventilation, SDD did not significantly reduce in-hospital mortality compared with standard care without SDD, although the confidence interval around the effect estimate includes a clinically important benefit.

Methods

Consent

Ethical approval was obtained from human research ethics committees and research governance offices at each site.

Because SDD was implemented as an ICU-wide intervention, a waiver of individual patient consent up to hospital discharge was obtained. For patients in the control group and ecological assessment, a waiver of consent was also obtained because no intervention was offered.

Study Design and Oversight

This was a crossover, cluster randomized clinical trial with a concomitant observational ecological assessment (**Figure 1**). The trial protocol, changes to the trial protocol, and statistical analysis plan are presented in Supplement 1, Supplement 2, and Supplement 3, respectively.[15] The trial was originally planned as an international trial that would include sites outside Australia, in Canada and the United Kingdom. Details of the evolution of the Australian trial are presented in eAppendix 1 in Supplement 4. Data were entered into an encrypted database for statistical analyses conducted at The George Institute for Global Health.

The SDD study drug preparations were manufactured by Verita Pharma (Sydney, Australia) under license from The George Institute for Global Health in accordance with the standards for good manufacturing practice approved by the Therapeutic Goods Administration of Australia.

Trial Participants

Eligible ICUs were general medical and surgical facilities in Australia capable of treating mechanically ventilated adults and able to implement the SDD protocol in all eligible patients. Intensive care units were randomly assigned to adopt an SDD strategy or not for 2 alternating 12-month periods, separated by a 3-month interperiod gap.

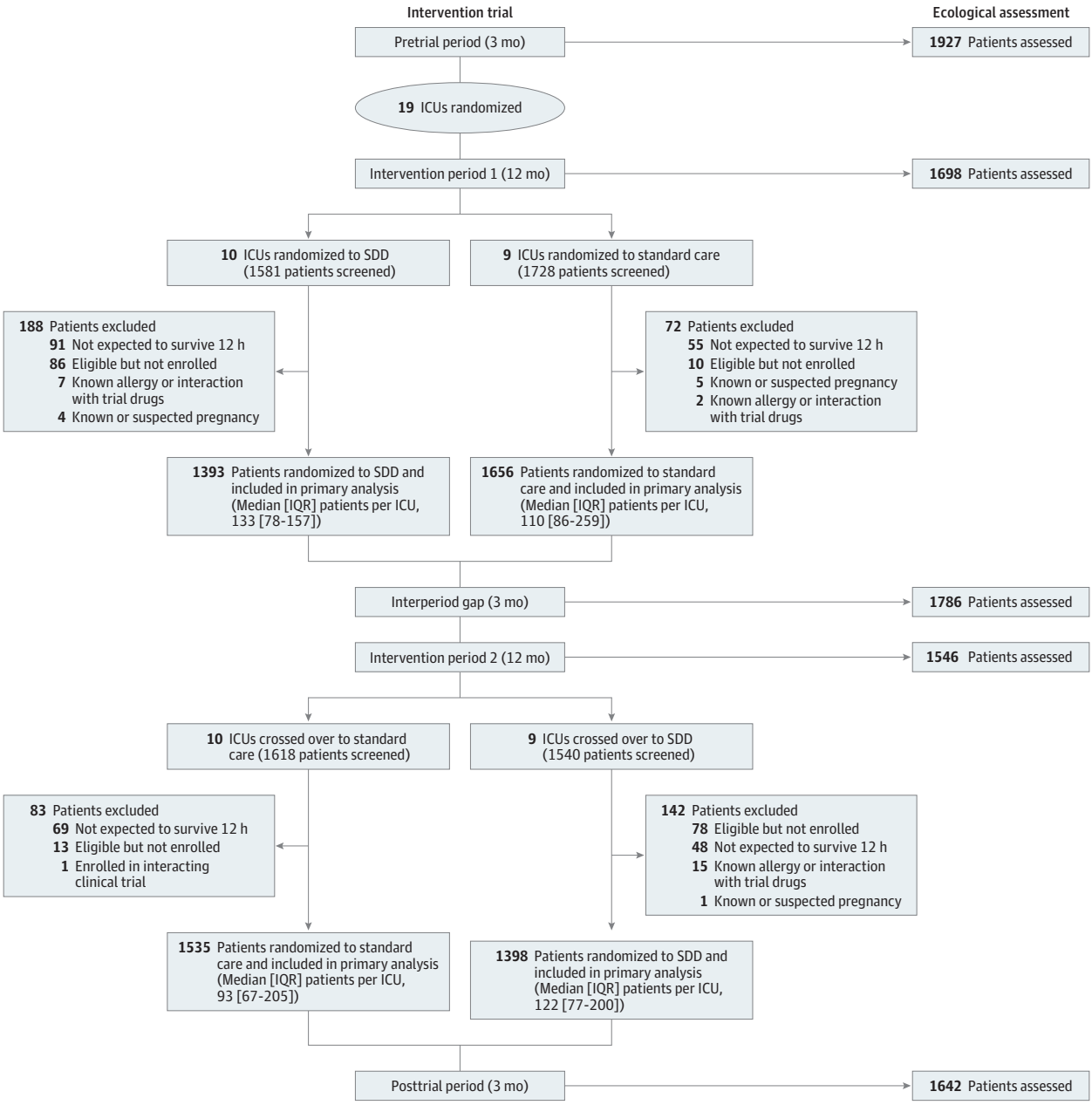
Eligible patients for the intervention periods were those (1) who were mechanically ventilated via an endotracheal tube on admission to the ICU; (2) who underwent ventilation during that admission; and (3) who were predicted to remain ventilated for at least 48 hours. Patients who were previously predicted not to be mechanically ventilated for more than 48 hours but who subsequently required ongoing ventilation were rescreened for recruitment.

For the ecological assessment that was conducted to determine changes in participating ICU microbiological flora, data were collected for 1 full week of each month during five 3-month ecology collection periods: the pretrial period, interperiod gap, and posttrial period and the final 3 months of each 12-month intervention period. During these periods, all patients admitted to participating ICUs regardless of ventilation status, excluding mechanically ventilated patients who were already enrolled in the intervention groups, were included in the ecology assessment.

Randomization

During the 3-month pretrial period, participating ICUs were stratified by size based on their number of beds and then randomly assigned using a computer-generated program written in SAS (SAS Institute Inc) to deliver either SDD plus standard care (SDD group) or to continue standard care in

Figure 1. Participant Flow in the SuDDICU Trial



ICU indicates intensive care unit; SDD, selective decontamination of the digestive tract.

the first 12-month intervention period. The first intervention period was followed by a 3-month interperiod gap, following which ICUs crossed over to the alternate group for a second 12-month period. This was followed by a 3-month posttrial period (eFigure 1 in Supplement 4).

Interventions

Selective decontamination of the digestive tract comprised (1) a 6-hourly topical application of 0.5 g of oral paste containing 10 mg of colistin, 10 mg of tobramycin, and 125 000 IU of nystatin applied to the buccal mucosa and oropharynx; (2) a 6-hourly administration of 10 mL of gastric suspension containing 100 mg of colistin, 80 mg of tobramycin, and 2×10^6 IU of nystatin to the upper gastrointestinal tract via a gastric or postpyloric tube; and (3) a 4-day course of an intravenous SDD-compliant antibiotic (eg, a third-generation cephalosporin or ciprofloxacin), unless already treated with antibiotics with activity against gram-negative bacteria during the first 4 days after enrollment, in which case additional antibiotics were not administered. Details of the SDD drug preparations are presented in eAppendix 2 (sections O to T) in Supplement 4.

The SDD oral paste and gastric suspension were administered as soon as possible from the time of admission to the ICU, if mechanically ventilated on admission, and/or from the time of endotracheal intubation in the ICU and continued for the duration of mechanical ventilation via an endotracheal tube or until day 90, whichever came first. All other treatments, including the administration of antibiotics for prophylactic or therapeutic indications, were at the discretion of treating clinicians in accordance with respective institutional microbiological prescription polices. A list of SDD-compliant antibiotics is presented in eAppendix 3 (section I) in Supplement 4.

Data and Study Management

Data collected at baseline included demographics, admission diagnosis, the Acute Physiology and Chronic Health Evaluation (APACHE) score (a severity of illness score ranging from 0 to 71 [APACHE II][16] or 0 to 299 [APACHE III],[17] with higher scores indicating an increased risk of death), and specific risk factors for infection including prior receipt of oral chlorhexidine and intravenous antibiotics.

For patients treated in ICUs during the SDD intervention period, daily data documenting the delivery of SDD oral paste and gastric suspension were collected for the duration of mechanical ventilation up to 90 days and SDD-compliant antibiotics for 5 days. Adherence in administering the topical components of SDD was reported as the proportion of patients receiving at least 1 eligible SDD dose on a daily basis for the duration of mechanical ventilation.

For all trial participants, doses of all intravenous antibiotics were collected for 28 days. Data recorded daily for 90 days while still in the ICU included the duration of mechanical ventilation, ICU and hospital admission, all new organisms isolated from blood and nonblood cultures, any positive test result for *Clostridioides difficile*, and antibiotic-resistant organisms from all cultures, as defined in eAppendix 2 (section K) in Supplement 4.

For the ecological assessment, data were collected for 1 full week of each month during five 3-month ecology collection periods, the pretrial period, interperiod gap, and posttrial period and the final 3 months of each 12-month intervention period, for all patients admitted to participating ICUs regardless of mechanical ventilation status, excluding mechanically ventilated patients already enrolled in the intervention periods.

Outcome Measures

The primary outcome was all-cause in-hospital mortality within 90 days of enrollment during the index hospital admission.

Clinical secondary outcomes were ICU mortality and days alive and free of mechanical ventilation, ICU admission, and hospitalization through 90 days.

Microbiological secondary outcomes were the results from all new blood cultures; the incidence of new *C difficile* infections; the incidence of predefined antibiotic-resistant organisms from all blood, nonblood surveillance, and clinical cultures; and total antibiotic use, defined in daily defined doses.

Ecological assessment outcomes were the same as microbiological secondary outcomes, except that the outcome for total antibiotic use was excluded from the analysis.

Prespecified additional analyses conducted during this trial, but not included in this report, were a nested cohort microbial metagenomic analysis, a health economic analysis from a health care system perspective, and an updated trial-level systematic review with bayesian meta-analysis that included the results of this trial.

Sample Size Calculation

Based on data from a randomized clinical trial conducted in similar populations in Australia and available at the time of trial design,[18] a total of about 6000 patients from up to 20 Australian ICUs recruiting 150 patients per treatment period, assuming an intracluster correlation coefficient of 0.01 and an interperiod correlation of 0.005, provided at least 80% power to detect a 4.2-percentage-point reduction in hospital mortality from a baseline mortality rate of 29% at an $\alpha = .05$. This projected absolute reduction in mortality was considered to fall within a range between 3.5 and 5.0 percentage points, representing a relative risk reduction between 12 and 17 percentage points and a number needed to treat between 20 and 29, consistent with other randomized clinical trials conducted in the Australian context[18,19] representing a plausible range for a detectable difference.

For the ecological assessment, the original sample size calculation was based on 40 to 50 sites recruiting 110 to 150 patients per period that would provide 80% power to reject a noninferiority margin of 2%.[8] This calculation assumed a base incidence of antibiotic resistance of 10% (as defined in the original study protocol) using an intercluster coefficient of 0.01 and an interperiod coefficient of 0.005 per the mortality analysis. Based on these assumptions, 20 Australian centers had 90% power to reject a noninferiority margin of 3% for antibiotic resistance.

Statistical Analysis

Data were exported to SAS Enterprise Guide version 8.3 for analysis. All patients were analyzed according to their randomization group, regardless of adherence. The primary analysis used all available data with no imputation for missing data.

The primary outcome of death in the hospital within 90 days was analyzed using an individual-level hierarchical logistic regression model, including both a random cluster effect and a random cluster-period effect. The effect of the intervention is presented as the odds ratio for death and the 95% CI, adjusted by the Kenward-Roger correction.[20] Prespecified sensitivity analyses were conducted without the Kenward-Roger correction and by fitting a linear regression at the cluster level[21] and assessing the potential effect of missing data, using a worst-case and best-case scenario (presented in the statistical analysis plan). Adjusted analyses of the primary outcome were conducted using the logistic regression model after adding age, sex, severity of illness, and operative vs nonoperative diagnosis as fixed covariates. Post hoc analyses included calculation of mean risk differences and 95% CIs for the primary outcome (hospital

mortality) and 1 clinical secondary outcome (death within the ICU); secondary analyses included excluding patients who were enrolled less than 1 hour from the time to admission to the ICU; adding prior treatment with oral chlorhexidine and intravenous antibiotics to the model; and presenting the primary outcome for each participating site.

The primary outcome was also examined in 5 prespecified subgroup pairs based on prerandomization age, sex, severity of illness, operative diagnosis, and trauma. Heterogeneity across subgroups was assessed by adding the subgroup variable as well as its interaction with the intervention to the main analysis model.

Analyses of secondary duration outcomes were analyzed as the number of days alive and free of the outcome up to day 90, using a hierarchical linear regression model with the Kenward-Roger correction. Intervention effects were reported as adjusted mean differences and 95% CIs. No adjustments for baseline covariates were made for secondary outcomes. Time to discharge alive from the ICU and the hospital were summarized using cumulative incidence functions treating mortality as a competing risk, censored at day 90. Intervention effects were estimated as hazard ratios and 95% CIs obtained from a cause-specific Cox model, with a fixed effect of treatment and a random site effect. The proportionality assumption was confirmed by visual inspection of the survival curves, given that the test cannot be conducted using a frailty model.

Defined daily doses of antibiotics were defined according to the World Health Organization Collaborating Centre for Drug Statistics Methodology[22] and presented as the mean cumulative daily defined dose for all antibiotics and for each antibiotic over the duration of each intervention period up to 28 days. Absolute differences between groups in mean cumulative daily defined doses were tested post hoc using a hierarchical linear mixed model. Microbiological outcomes and adverse events were reported as proportions and compared between treatment groups using an analysis at the cluster-period level.

The statistical significance threshold for the primary outcome was a 2-sided $P < .05$. For the 4 secondary clinical outcomes, a step-down Holm-Bonferroni approach was prespecified to control the family-wise error rate.[23] All other tests were performed using a 2-sided level of .05. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points were considered exploratory.

Ecological data were assessed using a noninferiority comparison and with a noninferiority margin set at 2%, assuming a base incidence of antibiotic resistance of 10%. An increase of 2% is half the increase in tobramycin resistance reported from a previous cluster randomized clinical trial of SDD[24] and was considered to represent an increase likely to affect the acceptability of SDD.[25,26] Data were analyzed from the 5 study periods using linear regression to model the proportion of events in each cluster and each period, presented as mean proportions and 2-sided 95% CIs (equivalent to a 1-sided 97.5% CI). The main effect of the interventions was estimated as the change, expressed as mean difference and 95% CI (presented as a 1-sided 97.5% CI) in new organisms and antibiotic-resistant organisms isolated from all cultures and new *C difficile* infections from the pretrial period vs the first intervention period and interperiod gap period combined (first comparison), and from the interperiod gap vs the second intervention period and posttrial period combined (second comparison). A $P < .025$ from a 1-sided test of noninferiority indicated that the noninferiority margin of 2% was rejected. To declare noninferiority of SDD compared with standard care, the upper bound of the 95% CI around the absolute risk difference between SDD and standard care needed to be lower than 2%. Post hoc, a sensitivity analysis comparing the change in proportions from the pretrial period and each of the 2 intervention periods was conducted.

One prespecified interim analysis was conducted and reviewed by the data and safety monitoring committee after the completion of the first 12-month intervention period, including day 90 follow-up data at all sites.

Results

Study Sites and Patients

From May 2017 to November 2021, 19 ICUs in 17 hospitals in Australia recruited a total of 14 581 participants, of which 5982 participants were enrolled in the intervention study and 8599 were enrolled in the ecological assessment (Figure 1; eTable 1, eFigure 2, and eFigure 3 in Supplement 4).

Intervention Study

For the first intervention period, 3049 patients were recruited, 1393 (45.7%) in ICUs allocated to SDD and 1656 (54.3%) in ICUs allocated to standard care; for the second intervention period, 2933 patients were recruited, 1398 (47.6%) in SDD ICUs and 1535 (52.3%) in standard care ICUs. The primary outcome was available for all patients, 2791 in the SDD group and 3191 in the standard care group.

There were no significant differences in baseline characteristics between the SDD and standard care groups, respectively, other than the median time from ICU admission and enrollment (16.1 [IQR, 3.5-39.7] hours vs 3.7 [IQR, 0.0-20.5] hours) and the number of participants with prior treatment with oral chlorhexidine (778 [27.9%] vs 526 [16.5%]), receipt of preenrollment intravenous antibiotics (2098 [75.2%] vs 2176 [68.2%]), and receipt of intravenous antibiotics for more than 48 hours prior to randomization (689 [32.5%] vs 600 [27.6%]), (**Table 1**; eTables 2 and 3 in Supplement 4).

Study Treatments and Process Measures

In the SDD group, the proportion of days of mechanical ventilation during which patients received both the SDD oral paste and gastric suspension was 87.1% (eFigure 4 in Supplement 4). The minimum and total number of eligible doses for the SDD preparations are presented in eTable 4 in Supplement 4.

Over the first 4 days, SDD-compliant intravenous antibiotics were administered to 80.0% patients in the SDD group compared with 53.7% patients in the standard care group (eFigure 5, A and B, in Supplement 4).

Table 1. Baseline Participant Characteristics

Characteristics	Selective decontamination of the digestive tract (n = 2791)	Standard care (n = 3191)
Age, mean (SD), y	58.2 (17.1)	58.5 (17.0)
Sex, No. (%)		
Female	1012 (36.3)	1190 (37.3)
Male	1779 (63.7)	2001 (62.7)
ICU admission source, No. (%)		
Emergency department	1119 (40.1)	1170 (36.7)
Admitted following emergency surgery	566 (20.3)	695 (21.8)
Hospital floor (wards)	517 (18.5)	575 (18.0)
Transfer from another hospital	236 (8.5)	314 (9.8)
Transfer from another ICU	189 (6.8)	209 (6.5)
Admitted following elective surgery	164 (5.9)	228 (7.1)
Time from ICU admission to enrollment, median (IQR), h	16.1 (3.5-39.7)	3.7 (0.0-20.5)
APACHE diagnostic category: nonoperative, No. (%)[a]	2061 (73.8)	2268 (71.1)
Admission diagnosis of trauma, No. (%)	378 (13.5)	425 (13.3)
Severity of illness score, median (IQR)[b]		
APACHE II	20.0 (15.0-26.0) [n = 1479]	20.0 (15.0-25.0) [n = 2028]
APACHE III	68.0 (49.0-89.0) [n = 1312]	73.0 (53.0-95.0) [n = 1163]
Comorbidities, No. (%)		
Diabetes	610 (21.9)	743 (23.3)
Systemic steroids	330 (11.8)	405 (12.7)
Immunosuppression	231 (8.3)	279 (8.7)
Prior treatments, No. (%)		
Receiving intravenous antibiotics at enrollment	2098 (75.2)	2176 (68.2)
Receiving intravenous antibiotics for >48 h prior to enrollment	689 (32.5)	600 (27.6)
Use of oral chlorhexidine	778 (27.9)	526 (16.5)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.

[a] The APACHE diagnostic criteria are categorized into nonoperative and operative groups and include prespecified organ system–based criteria with each diagnostic group.

[b] Severity of illness was determined by APACHE scores, ranging from 0 to 71 (APACHE II)[16] or 0 to 299 (APACHE III),[17] with higher scores indicating increased risk of death.

Primary Outcome

At hospital discharge, 753 (27.0%) of 2791 patients allocated to SDD and 928 (29.1%) of 3191 patients allocated to standard care had died (mean difference, −1.7% [95% CI, −4.8% to 1.3%]; odds ratio, 0.91 [95% CI, 0.82-1.02]; P = .12). Findings were similar without the Kenward-Roger correction and adjusting for prespecified covariates (**Table 2**). As all data were available for the primary outcome, sensitivity analyses for missing data did not change the principal analysis (eTable 8 in Supplement 4). Post hoc analyses excluding patients who were enrolled during the first hour after ICU admission (638/2361 [27.0%] vs 577/1889 [30.5%]; odds ratio, 0.85; 95% CI, 0.68-1.06; P = .13) and adjusting for baseline imbalances in chlorhexidine and intravenous antibiotic treatment (odds ratio, 0.91; 95% CI, 0.75-1.11; P = .28) did not significantly alter the analysis (eTable 8 in Supplement 4); hospital mortality at each participating ICU is presented in eTable 9 in Supplement 4.

Clinical Secondary Outcomes

There were no significant between-group differences in ICU mortality (mean difference, −1.4% [95% CI, −3.5% to 0.7%]; odds ratio, 0.92 [95% CI, 0.79-1.08]), the number of days alive and free of mechanical ventilation (mean difference, 2.09 days; 95% CI, −0.35 to 4.53 days), ICU admission (mean difference, 1.75 days; 95% CI, −0.62 to 4.12 days), and hospital admission (mean difference, 1.34 days; 95% CI, −0.89 to 3.58 days) (Table 2). Given that none of the differences were significant at the .05 level, the prespecified Holm-Bonferroni multiplicity correction was not applied. Proximate and underlying causes of death are presented in eTable 10 in Supplement 4. There were no significant between-group differences in the time to death (hazard ratio, 0.93; 95% CI, 0.84-1.02), time to ICU discharge (hazard ratio, 1.05; 95% CI, 0.99-1.11), or time to hospital discharge (hazard ratio, 1.01; 95% CI, 0.95-1.08) (**Figure 2**A; eFigures 8 and 9 in Supplement 4). There was no significant heterogeneity in the effect of intervention assignment on hospital mortality in any of the 5 predefined subgroup pairs (Figure 2B).

Microbiological Secondary Outcomes

During the intervention period, in the SDD and standard care groups, the number of patients with blood cultures collected was 1664 (59.6%) vs 2163 (67.8%), and the number of patients with nonblood cultures collected was 583 (20.9%) vs 1036 (32.5%), respectively (eTables 5 and 6 in Supplement 4). There was a statistically significant reduction in the proportion of patients from whom antibiotic-resistant organisms were cultured (23.1% vs 34.6%; absolute difference, −11.0%; 95% CI, −14.7% to −7.3%) and who had new positive blood cultures (5.6% vs 8.1%; absolute difference, −1.95%; 95% CI, −3.5% to −0.4%) in the SDD group compared with the standard care group. There was no significant difference in the incidence of new *C difficile* infection (0.5% vs 0.9%; absolute difference, 0.24%; 95% CI, −0.6% to 0.1%) between the 2 groups (Table 2).

There was no significant difference in mean cumulative daily defined dose of all intravenous antibiotics administered over the first 28 days (0.81 doses [95% CI, 0.75-0.88] vs 0.85 [95% CI, 0.78-0.91]; mean difference, −0.035; 95% CI, −0.13 to 0.06) (Table 2) and in the overall total daily defined dose (eFigure 6 in Supplement 4) or for each antibiotic class (eFigure 7 in Supplement 4) between the SDD and standard care groups.

Ecological Assessment

Among 8599 patients recruited into the ecological assessment, there were no significant between-group differences in demographics, severity of illness scores, hospital mortality, and microbiological cultures over the five 3-month assessment periods (eTable 11 in Supplement 4). The proportions of

Table 2. Clinical and Microbiological Outcomes and Adverse Events

Outcomes and adverse events	Selective decontamination of the digestive tract (n = 2791)	Standard care (n = 3191)	Difference, % (95% CI)	Odds ratio (95% CI)	*P* value
Primary outcome: in-hospital death within 90 d, No. (%)[a,b]					
Primary analysis[c]	753 (27.0)	928 (29.1)	MD, −1.7 (−4.38 to 1.3)	0.91 (0.82-1.02)	.12
Adjusted analysis[d]				0.92 (0.75-1.11)	.35
Clinical secondary outcomes[b,e]					
Death in the ICU, No. (%)	591 (21.2)	727 (22.8)	MD, −1.4 (−3.5 to 0.7)	0.92 (0.79-1.08)	
Days alive and free of mechanical ventilation					
Mean (SD)	61.9 (36.1)	59.7 (37.1)	MD, 2.09 (−0.35 to 4.53)		
Median (IQR)	83 (18-87)	83 (7-87)			
Days alive and free of ICU admission					
Mean (SD)	58.4 (35.7)	56.4 (36.4)	MD, 1.75 (−0.62 to 4.12)		
Median (IQR)	79 (6-85)	78 (2-85)			
Days alive and free of hospital admission[f]					
Mean (SD)	45.3 (33.4)	44.0 (34.4)	MD, 1.34 (−0.89 to 3.58)		
Median (IQR)	59 (0-76)	57 (0-76)			
Microbiological secondary outcomes[b]					
Any antibiotic-resistant organism found, No. (%)	583 (20.9)	1036 (32.5)	AD, −11.0 (−14.7 to −7.3)		
Any blood organism found, No. (%)	156 (5.6)	259 (8.1)	AD, −1.95 (−3.47 to −0.43)		
Positive for *Clostridioides difficile*, No. (%)	14 (0.5)	29 (0.9)	AD, −0.24 (−0.59 to 0.10)		
Defined daily dose of antibiotics over 28 d, mean (95% CI)[g]	0.81 (0.75-0.88)	0.85 (0.78-0.91)	MD, −0.035 (−0.13 to 0.06)		
Adverse events					
Adverse medication reactions	0	0			
Serious adverse medication reactions	0	0			
Suspected unexpected serious adverse reactions	0	0			
Serious adverse events					
Any event	29 (1.0)	29 (0.9)			
Blocked gastric tube	7 (0.3)	0			
Other[h]	7 (0.3)	0			

Abbreviations: AD, absolute difference; ICU, intensive care unit; MD, mean difference.

[a] Intercluster coefficient for primary outcome is 0.007. There was no significant interaction between treatment and period when analyzing the primary outcome (*P* = .76). No sensitivity analyses for missing data for the primary outcome was performed because there was 100% data available for analyses. Post hoc determination of the intracluster coefficient and interperiod correlation is presented in eTable 7 in Supplement 4. Post hoc sensitivity analyses adjusting the primary outcome for baseline imbalances for prior use of chlorhexidine and intravenous antibiotics are presented in eTable 8 in Supplement 4.

[b] Data were censored at day 90 after enrollment.

[c] Hierarchical model with Kenward-Roger correction.

[d] Analysis adjusted for age, sex, severity of illness, and operative vs nonoperative diagnosis.

[e] Given than none of the differences were significant at the .05 level for the 4 clinical secondary outcomes, the prespecified Holm-Bonferroni multiplicity correction was not applied.

[f] The median time to hospital discharge was 16 days in the selective decontamination of the digestive tract group and 15 days in the standard care group.

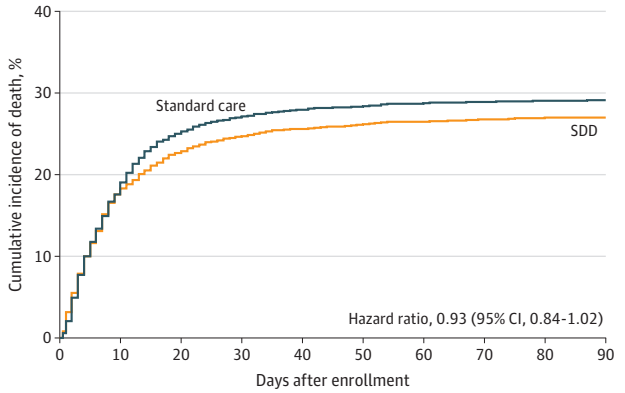
[g] Defined daily doses of antibiotics were defined as the assumed mean maintenance dose per day for a drug used for its main indication in adults according to the World Health Organization Collaborating Centre for Drug Statistics Methodology.[22]

[h] Other serious adverse events were 1 case each of change in kidney function, persistent diarrhea, toxic epidermal necrolysis, persist fever, and elevated creatinine kinase, and 2 skin rashes.

participants with development of antibiotic-resistant organisms, new positive blood cultures, and *C difficile* infections over the five 3-month assessment periods are presented in **Table 3.** For the pretrial period vs the first intervention period and interperiod gap period combined (first comparison) and from the interperiod gap vs the second intervention period and posttrial period combined (second comparison), SDD was noninferior to standard care for the change in the proportion of new positive blood cultures (first comparison: −0.75% vs 0.30%; mean difference, −1.05% [1-sided 97.5% CI, −∞ to 0.47%]; noninferiority *P* < .001; second comparison: −0.90% vs −0.86%; mean difference, 0.04% [1-sided 97.5% CI, −∞ to 1.67%]; noninferiority *P* = .008) and for *C difficile* infections (first comparison: −0.19% vs 0.05%; mean difference, −0.24% [1-sided 97.5% CI, −∞ to 0.18%]; noninferiority *P* < .001; second comparison: 0.03% vs −0.03%; mean difference, −0.05% [1-sided 97.5% CI, −∞ to 0.37%]; noninferiority *P* < .001), but not for the change in proportions with positive

Figure 2. In-Hospital Mortality in the Selective Decontamination of the Digestive Tract and Standard Care Groups

A Probability of in-hospital death within 90 d

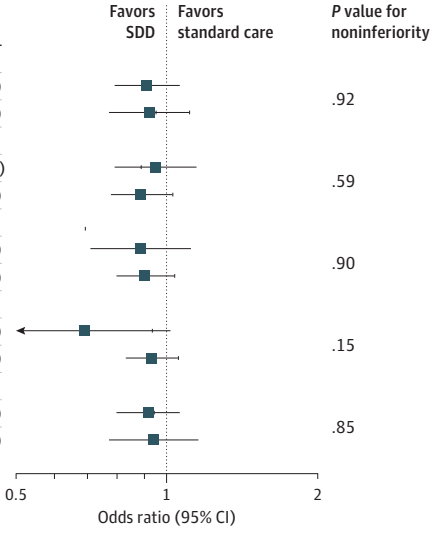


No. at risk

SDD	2791	2300	2158	2103	2077	2063	2052	2045	2039	2038
Standard care	3191	2630	2393	2329	2300	2287	2275	2268	2265	2263

B Subgroup analysis for in-hospital death within 90 d

Subgroup	No./total No. (%) SDD	No./total No. (%) Standard care	Difference, % (95% CI)	Odds ratio (95% CI)	*P* value for noninferiority
Age, y					
≥61	493/1422 (34.7)	613/1660 (36.9)	-2.0 (-5.4 to 1.4)	0.92 (0.79 to 1.06)	.92
<61	260/1369 (19.0)	315/1531 (20.6)	-1.3 (-4.2 to 1.6)	0.93 (0.77 to 1.11)	
Sex					
Female	279/1012 (27.6)	343/1190 (28.8)	-0.7 (-4.9 to 3.6)	0.95 (0.79 to 1.15)	.59
Male	474/1779 (26.6)	585/2001 (29.2)	-2.4 (-5.9 to 1.1)	0.89 (0.77 to 1.03)	
Admission type					
Operative	163/730 (22.3)	229/923 (24.8)	-1.9 (-6.4 to 2.7)	0.89 (0.71 to 1.12)	.90
Nonoperative	590/2061 (28.6)	699/2268 (30.8)	-1.9 (-5.2 to 1.5)	0.91 (0.80 to 1.04)	
Trauma					
Yes	49/378 (13.0)	78/425 (18.4)	-4.2 (-9.8 to 1.3)	0.69 (0.47 to 1.02)	.15
No	704/2413 (29.2)	850/2766 (30.7)	-1.3 (-4.5 to 1.9)	0.93 (0.83 to 1.05)	
APACHE II/III score					
Less than median	556/1425 (39.0)	700/1698 (41.2)	-1.9 (-5.3 to 1.6)	0.92 (0.80 to 1.06)	.85
At or above median	197/1366 (14.4)	228/1493 (15.3)	-0.5 (-3.1 to 2.1)	0.94 (0.77 to 1.16)	



SDD indicates selective decontamination of the digestive tract. Severity of illness was determined by the Acute Physiology and Chronic Health Evaluation (APACHE) scores, ranging from 0 to 71 (APACHE II)[16] or 0 to 299 (APACHE III),[17] with higher scores indicating an increased risk of death. The median APACHE II and APACHE III scores were 20 and 70, respectively. *P* values are from the likelihood ratio test of the interaction term between the subgroup variable and the intervention.

cultures for antibiotic-resistant organisms (first comparison: −3.3% vs −1.59%; mean difference, −1.71% [1-sided 97.5% CI, −∞ to 4.31%]; noninferiority $P = .11$; second comparison: 0.88% vs 0.55%; mean difference, −0.32% [1-sided 97.5% CI, −∞ to 5.47%]; noninferiority $P = .21$) (**Figure 3**). A post hoc sensitivity analysis comparing the pretrial period with each postintervention period did not meaningfully alter the results (eTable 12 and eFigure 10 in Supplement 4).

Adverse Events and Protocol Deviations

Adverse and serious adverse reactions were not notably different between the SDD and standard care groups (Table 2; eTable 13 in Supplement 4). Protocol deviations and valid reasons for not administering SDD interventions are presented in eTables 14 and 15 in Supplement 4.

Discussion

In this crossover, cluster randomized clinical trial, the use of SDD in mechanically ventilated critically ill adults did not significantly reduce in-hospital mortality compared with standard care without SDD, although the confidence interval around the effect estimate includes a clinically important benefit.

The use of SDD did not significantly reduce ICU mortality, the duration of mechanical ventilation, or the duration of ICU and hospital admission. There was a significant reduction in positive blood cultures and cultures of antibiotic-resistant organisms and no significant increase in new *C difficile* infections in patients who received SDD. Overall antibiotic use was not increased in patients receiving SDD.

Table 3. Ecological Assessment Outcomes

	Pretrial period, No./total (%)	Period 1 and interperiod gap, No./total (%)	Intervention crossover	Interperiod gap, No./total (%)	Period 2 and posttrial period, No./total (%)
New infections with antibiotic-resistant organisms from all blood and nonblood cultures[a,b]					
SDD	108/915 (11.8)	184/1719 (10.7)	Standard care	100/874 (11.4)	159/1589 (10.0)
Standard care	94/1012 (9.3)	149/1765 (8.4)	SDD	79/912 (8.7)	136/1599 (8.5)
New positive blood cultures[a]					
SDD	26/915 (2.8)	40/1719 (2.3)	Standard care	26/874 (3.0)	35/1589 (2.2)
Standard care	20/1012 (2.0)	43/1765 (2.4)	SDD	29/912 (3.2)	26/1599 (1.6)
New infections with *Clostridioides difficile*[a]					
SDD	6/915 (0.7)	5/1719 (0.3)	Standard care	2/874 (0.2)	5/1589 (0.3)
Standard care	2/1012 (0.2)	2/1765 (0.1)	SDD	2/912 (0.2)	4/1599 (0.3)

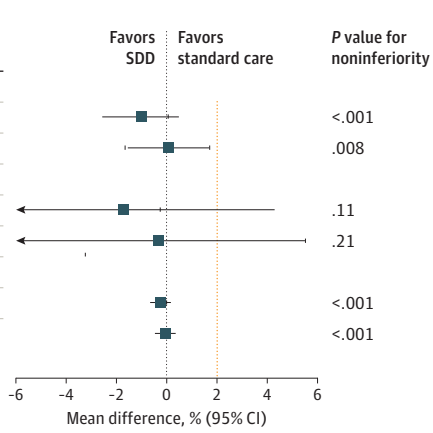
Abbreviation: SDD, selective decontamination of the digestive tract.

[a] Three microbiological outcomes are presented for sites randomized to each intervention period. Proportions of patients were obtained using linear regression to model the proportion of microbiological outcomes in each cluster and each period during the 2 comparative trial periods: pretrial period vs intervention period 1 and interperiod gap combined and interperiod gap vs intervention period 2 and posttrial period combined.

[b] Antibiotic-resistant organisms were defined according to a modification of the Dutch Nosocomial Infection Guidelines (eAppendix 2 [Section G] in Supplement 4).

Figure 3. Ecological Assessment Outcomes

Outcomes	Mean % (95% CI) SDD to standard care	Mean % (95% CI) Standard care to SDD	Mean difference, % (95% CI), SDD – standard care	*P* value for noninferiority
New organisms isolated				
First intervention	−0.75 (−1.94 to 0.44)	0.30 (−0.65 to 1.26)	−1.05 (−2.58 to 0.47)	<.001
Second intervention	−0.90 (−2.09 to 0.29)	−0.86 (−1.97 to 0.25)	0.04 (−1.58 to 1.67)	.008
Antibiotic resistance				
First intervention	−3.30 (−8.17 to 1.58)	−1.59 (−5.12 to 1.94)	−1.71 (−7.73 to 4.31)	.11
Second intervention	0.88 (−3.20 to 4.96)	0.55 (−3.56 to 4.67)	−0.32 (−6.12 to 5.47)	.21
New *Clostridioides difficile* infection				
First intervention	−0.19 (−0.50 to 0.12)	0.05 (−0.23 to 0.32)	−0.24 (−0.66 to 0.18)	<.001
Second intervention	0.03 (−0.28 to 0.33)	−0.03 (−0.31 to 0.26)	−0.05 (−0.47 to 0.37)	<.001



The change in mean proportions of microbiological outcomes between selective decontamination of the digestive tract (SDD) and standard care are presented from the pretrial period vs intervention period 1 and the interperiod gap combined (first intervention) and from the interperiod gap vs intervention period 2 and the posttrial period combined (second intervention). The predefined noninferiority margin of 2% is presented as the red line. The noninferiority margin was rejected for new organisms isolated and *Clostridioides difficile* infection, but not for cultures of antibiotic-resistant organisms, presented by the noninferiority *P* value.

In the ecology assessment, the use of SDD was noninferior to standard care for the development of new positive blood cultures and *C difficile* infections, but not for cultures of new antibiotic-resistant organisms. The use of SDD was not associated with an increased incidence of adverse events.

This pragmatic randomized clinical trial has a number of strengths that include a large study population recruited from multiple ICUs under routine clinical care conditions that assessed the effect of SDD on a robust patient-centered outcome. Second, to our knowledge, the trial used the first mass-produced, commercially manufactured good manufacturing practice–compliant SDD preparation that comprised the antimicrobial components previously identified to reduce the incidence of ventilator-associated pneumonia. Third, the trial was conducted according to a prepublished protocol and statistical analysis plan that included a hierarchical logistic regression model to adjust for the cluster size and a robust assessment of treatment adherence. Fourth, the trial had no loss to follow-up. Fifth, the observed baseline mortality rate of 29% confirms the high acuity of illness severity in the study population. Sixth, microbiological surveillance and antibiotic prescription were conducted in accordance with international practice standards within the context of a pragmatic trial. Seventh, the concurrent observational ecological assessment to evaluate changes in ICU microbiology; specifically, antibiotic resistance over the trial period provides new contextual information about the effect of SDD on unit ecology.

A nonsystematic analysis of patient-level data from selected randomized clinical trials conducted between 2000 and 2017[10] and the current Cochrane Library systematic review[27] reported that SDD was associated with a statistically

significant reduction in hospital mortality compared with standard care, with an absolute risk reduction in mortality that is similar to the point estimate from this trial.

Consistent with the results of this trial, previous randomized clinical trials conducted in environments of low endemic resistance did not report an increase in antibiotic resistance associated with the use of SDD.[5,10,28] A randomized clinical trial conducted in ICUs between 2013 and 2017 with moderate to high baseline rates of antibiotic resistance reported no statistically significant difference in the incidence of new bloodstream infections with multiresistant gram-negative bacteria (the primary outcome) and no significant differences in new highly resistant microorganisms or 28-day mortality between SDD and baseline standard care.[29]

While clinicians will need to consider the primacy of the effectiveness of SDD in improving patient-centered outcomes over the effect on microbiological outcomes, the use of SDD may confer benefits in specific patient populations such as those with trauma,[3] and further trials are needed to confirm benefits in these patients, particularly in environments with high endemic antibiotic resistance.

Limitations

This study had several limitations. First, due its nature, the intervention was unblinded, although this was mitigated by the objective primary outcome and the adoption of SDD as standard care administered to all eligible patients during the intervention period. Second, while more patients were recruited into the standard care group compared with the SDD group, this imbalance is likely due to greater reluctance to recruit patients to the intervention group vs control group when doubt about their duration of ventilation or likelihood of surviving greater than 12 hours existed. Third, while protocol adherence for the use of SDD approached 90% over the duration of the inception period and more than 130 000 doses of SDD were administered, prolonged use of SDD in long-term ventilated patients declined over time due to nonpalatability of the oral paste and reduced access to the upper gastrointestinal tract for the gastric suspension. Fourth, reductions in antibiotic resistance and new blood cultures associated with SDD in the intervention trial may not represent the efficiency of SDD at an individual or institutional level within the context of an effectiveness trial. Fifth, due to the overall low rate of antimicrobial resistance and relatively short period of observation, the ecological assessment had limited power to confirm or refute noninferiority of SDD compared with standard care and did not assess changes in microbiological outcomes at a hospital level or changes in ecology that might be associated with longer-term use of SDD.

Conclusions

Among critically ill patients receiving mechanical ventilation, SDD, compared with standard care without SDD, did not significantly reduce in-hospital mortality. However, the confidence interval around the effect estimate includes a clinically important benefit.

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