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Association Between Selective Decontamination of the Digestive Tract and In-Hospital Mortality in Intensive Care Unit Patients Receiving Mechanical Ventilation

A Systematic Review and Meta-analysis

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IMPORTANCE The effectiveness of selective decontamination of the digestive tract (SDD) in critically ill adults receiving mechanical ventilation is uncertain.

OBJECTIVE To determine whether SDD is associated with reduced risk of death in adults receiving mechanical ventilation in intensive care units (ICUs) compared with standard care.

DATA SOURCES The primary search was conducted using MEDLINE, EMBASE, and CENTRAL databases until September 2022.

STUDY SELECTION Randomized clinical trials including adults receiving mechanical ventilation in the ICU comparing SDD vs standard care or placebo.

DATA EXTRACTION AND SYNTHESIS Data extraction and risk of bias assessments were performed in duplicate. The primary analysis was conducted using a bayesian framework.

MAIN OUTCOMES AND MEASURES The primary outcome was hospital mortality. Subgroups included SDD with an intravenous agent compared with SDD without an intravenous agent. There were 8 secondary outcomes including the incidence of ventilator-associated pneumonia, ICU-acquired bacteremia, and the incidence of positive cultures of antimicrobial-resistant organisms.

RESULTS There were 32 randomized clinical trials including 24 389 participants in the analysis. The median age of participants in the included studies was 54 years (IQR, 44-60), and the median proportion of female trial participants was 33% (IQR, 25%-38%). Data from 30 trials including 24 034 participants contributed to the primary outcome. The pooled estimated risk ratio (RR) for mortality for SDD compared with standard care was 0.91 (95% credible interval [CrI], 0.82-0.99; I^2 = 33.9%; moderate certainty) with a 99.3% posterior probability that SDD reduced hospital mortality. The beneficial association of SDD was evident in trials with an intravenous agent (RR, 0.84 [95% CrI, 0.74-0.94]), but not in trials without an intravenous agent (RR, 1.01 [95% CrI, 0.91-1.11]) (*P* value for the interaction between subgroups = .02). SDD was associated with reduced risk of ventilator-associated pneumonia (RR, 0.44 [95% CrI, 0.36-0.54]) and ICU-acquired bacteremia (RR, 0.68 [95% CrI, 0.57-0.81]). Available data regarding the incidence of positive cultures of antimicrobial-resistant organisms were not amenable to pooling and were of very low certainty.

CONCLUSIONS AND RELEVANCE Among adults in the ICU treated with mechanical ventilation, the use of SDD compared with standard care or placebo was associated with lower hospital mortality. Evidence regarding the effect of SDD on antimicrobial resistance was of very low certainty.

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Selective decontamination of the digestive tract (SDD) is a preventive infection control strategy that usually comprises the administration of nonabsorbable, topical antimicrobial agents to the oropharynx and upper gastrointestinal tract, with or without the administration of a short-term course of broad-spectrum intravenous antibiotics.

Since the 1980s, advocates have encouraged the use of SDD in patients receiving mechanical ventilation in the intensive care unit (ICU), primarily to reduce the incidence of ventilator-associated pneumonia.[1] While a body of evidence suggesting reductions in hospital mortality and ventilator-associated pneumonia exists,[2,3] concerns regarding the effect of SDD on the development of antibiotic resistance have left international guideline panels[4-6] reluctant to recommend SDD and clinicians reluctant to implement in practice.[7,8]

Evidence from randomized clinical trials (RCTs), including the Ecological Effects of Decolonisation Strategies in Intensive Care (RGNOSIS)[9] trial and the Selective Decontamination of the Digestive Tract in Intensive Care Unit Patients (SuDDICU) study have recently added substantive weight to the body of evidence.[10] To provide an updated summary of current evidence, this systematic review and meta-analysis was designed to address whether SDD compared with standard care was associated with reduced hospital mortality and other relevant outcomes including the incidence of antimicrobial-resistant organisms in patients in the ICU treated with mechanical ventilation.

Key Points

Question In adults receiving mechanical ventilation in the intensive care unit, does the use of selective decontamination of the digestive tract (SDD) reduce hospital mortality compared with standard care?

Findings In this systematic review and meta-analysis of 32 randomized trials that included 24 389 participants, there was a 99.3% posterior probability that SDD was associated with reduced hospital mortality compared with standard care (summary risk ratio, 0.91).

Meaning The use of SDD in adults in the intensive care unit treated with mechanical ventilation was associated with lower hospital mortality.

Methods

We conducted a systematic review according to a prespecified published protocol (eAppendix 1 in the Supplement),[11] registered at the International Prospective Register of Systematic Reviews (CRD42022309825), and report the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[12]

Eligibility Criteria

We included RCTs and cluster RCTs that recruited ICU patients, of whom 75% or more were invasively ventilated, and compared the administration of SDD using antibacterial and/or antifungal agents to the upper gastrointestinal tract, stomach, or proximal small bowel with or without the administration of systemic antibiotics to standard care or placebo. Trials that administered only oral antiseptic agents as the intervention were excluded. Trials that included the routine use of topical antiseptic agents were included in the standard care comparator. We included all reports including studies only reported as abstracts, with no language restriction.

Search Strategy

We systematically searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL), from inception to September 12, 2022.

The search strategy included multiple medical subject heading terms and keywords to identify critically ill patients, mechanical ventilation, and selective decontamination of the digestive tract (SDD) or selective oral decontamination, combined with sensitive filters to identify RCTs[13] including cluster and crossover RCTs. We limited the search to adult, human studies. We contacted experts and conducted manual searches of reference lists of included studies and other systematic reviews. eAppendix 2 in the Supplement provides details of the electronic search strategy.

Study Selection

Using the Covidence reference management system,[14] a minimum of 2 investigators independently screened all identified references for inclusion based on the study title and abstract. A minimum of 2 reviewers assessed for inclusion the full text of articles deemed possibly eligible. We resolved disagreement during the review process by discussion or, if necessary, consultation with a third reviewer.

Data Collection

Three investigators independently extracted data from each included trial using a standardized data collection form. We extracted all available data as outlined in the protocol, including characteristics of the included studies, design (RCT or cluster RCT), details of the enrolled population including demographics, illness severity, details of the intervention including oral and systemic agents, dose and duration, and comparison group information including use of topical antiseptics. We did not impute missing data. Continuous variables presented in formats not readily amenable to pooling were converted to mean and SD according to published methods.[15] For the SuDDICU trial,[10] we had access to the study data prior to publication. We resolved discrepancies in the data extracted by discussion or, if necessary, adjudication by a fourth reviewer.

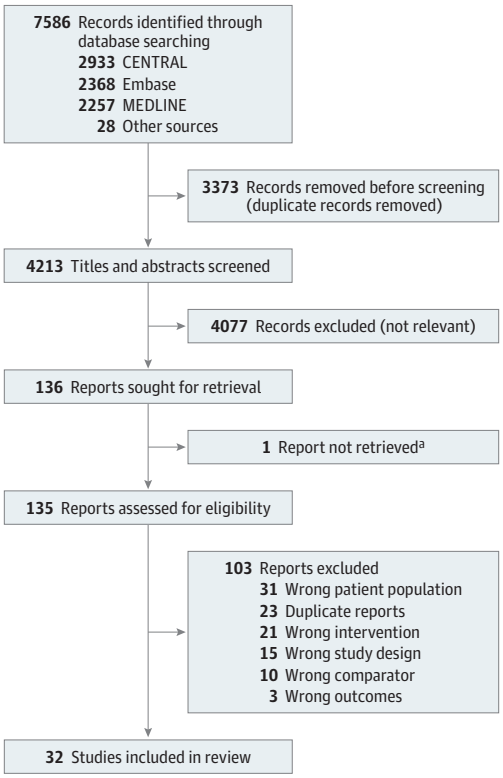
Risk of Bias Assessment

Two investigators with no affiliation with the included trials independently assessed risk of bias for each of the included trials using DistillerSR, a tool assessing risk of bias in RCTs,[16] modified to include items specific to cluster randomized trials developed by 3 of the authors (A.D., N.E.H., G.G.) and reported in eAppendix 4 in the Supplement. Disagreements were resolved by discussion and, if necessary, consultation with a third reviewer.

Outcomes

The primary outcome was hospital mortality. For trials in which hospital mortality was not reported, we used mortality reported

Figure 1. Flow Diagram of Search Strategy and Included Studies



[a] One study identified in previous meta-analyses was not able to be located from primary sources.

at the closest time point to hospital mortality. Mortality was chosen as the primary outcome because it is not prone to ascertainment bias and is a patient-important outcome. Data were also collected for the following secondary outcomes: mortality at longest follow-up, incidence of ventilator-associated pneumonia, duration of mechanical ventilation, and ICU and hospital length of stay. We attempted to collect data regarding the incidence of positive cultures of antimicrobial-resistant organisms and the incidence of *Clostridioides difficile* using data as reported in the included trials, at both a unit level and an individual patient level. We were also able to obtain specific data regarding the incidence of ICU-acquired bacteremia, again as reported in the included trials.

Subgroup Analyses

There were 3 prespecified subgroups for the primary outcome.[11] We compared trials where the intervention consisted of SDD with oral and/or enteral agents only compared with SDD that included oral, enteral, and intravenous agents, with the specified hypothesis that there would be a greater reduction in mortality in trials that included intravenous agents as a component of the intervention. We compared trials conducted in surgical ICUs vs medical ICUs vs trauma ICUs vs mixed population ICUs, with the specified hypothesis that there would be a greater reduction in mortality in trials conducted in surgical ICUs. We also compared individual patient- compared with unit-level randomization (ie, cluster and cluster/cluster-crossover), with the specified hypothesis that there would be a greater reduction in mortality in trials that randomized individual patients. We also performed a post hoc subgroup analysis based on publication date (before or after 2000). When results suggested possible subgroup effects, we used the ICEMAN[17] guidelines to assess their credibility.

Data Synthesis

The primary analysis used a bayesian random-effects model. A bayesian approach was chosen as the primary analytic method because it allows a more nuanced and explicit quantitative summary of the data that is potentially open to more intuitive interpretation by clincians,[18] as well as provides a more robust approach to the estimation of between-study heterogeneity. We performed the primary analysis using vague priors (log of the risk ratio assumed to have a normal distribution with a mean of 0 and an SD of 2) and sensitivity analyses examining treatment effects using weakly informative priors of effect and heterogeneity parameters.[19] The full description of priors is reported in the protocol.[11] In addition, a frequentist random-effects model using Hartung-Knapp-Sidik-Jonkman[20] and Der-Simonian Laird estimates of the between-study variance have been used. Random-effects models for the sensitivity analysis were chosen a priori due to anticipated between-study variation in trial design and implementation of the interventions.[21] We also performed a post hoc pooled secondary analysis limited to studies published as full reports in peer-reviewed journals. Because some of the included trials are cluster-randomized trials, we prospectively adjusted the raw data for the design effect by using an effective sample size approach, defined as the original sample size divided by the design effect.[22] We present results as risk ratios (RRs) for binary outcomes and mean differences (MDs) for continuous outcomes. Along with the pooled estimates of effect sizes and 95% credible intervals (CrIs) for the bayesian meta-analysis, we report 95% CIs for the frequentist model.

We assessed quantitative heterogeneity by reporting the posterior estimates of the heterogeneity parameter (tau) with its 95% CrI and the prediction interval[23] of the intervention pooled effect size and by evaluating the proportion of total variability due to heterogeneity rather than due to sampling error (I^2). Tests for between-subgroup interaction effects were assessed using the Cochran Q statistic.

Small-study effects were assessed by visual assessment of the contour-enhanced funnel plots and formal Egger regression test.

All statistical analyses were performed using R (for the bayesian meta-analysis using the package bayesmeta[24]) and Stata version 17 (StataCorp LLC).

Confidence in the Cumulative Evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the overall certainty of evidence that SDD compared with standard care improves each outcome measure to any degree.[25] We rated certainty in nonzero effects of SDD.

Table. Included Study Characteristics

Source	Design	Centers	Participants	Population	SDD	Control	Ventilated, %	Primary outcome of trial	Mortality time point
Unertl et al,[55] 1987	Individual patient RCT	1	39	Mixed medical surgical	Oral: every 6 h for duration of intubation • Polymyxin B, 15 mg; gentamicin, 24 mg; amphotericin B, 300 mg Enteral: every 6 h for duration of intubation • Polymyxin B, 25 mg; gentamicin, 40 mg	Standard care	100	Colonization and respiratory infection	ICU
Kerver et al,[54] 1988	Individual patient RCT	1	96	Mixed medical surgical	Oral: every 6 h until oropharyngeal and tracheal cultures negative • Polymyxin E, 2%; tobramycin, 2%; amphotericin, 2% Enteral: every 6 h until oropharyngeal and tracheal cultures negative • Polymyxin E, 200 mg; tobramycin, 80 mg; amphotericin B, 200 mg Intravenous: 5 d • Cefotaxime, 50-70 mg/kg/d	Standard care	100	Prevention of colonization	ICU
Ulrich et al,[53] 1989	Individual patient RCT	1	100	Mixed medical surgical	Oral: 4 times/d until potentially pathogenic organism could no longer be isolated • Polymyxin E, 2%; norfloxacin, 2%; amphotericin, 2% Enteral: 4 times/d until potentially pathogenic organism could no longer be isolated • Polymyxin E, 100 mg; tobramycin, 80 mg; amphotericin, 500 mg Intravenous: daily until potentially pathogenic organism could no longer be isolated • Trimethoprim, 500 mg	Standard care	80	Prevention of ICU-acquired infection	ICU
Rodríguez-Roldán et al,[52] 1990	Individual patient RCT	1	28	Mixed medical surgical	Oral: every 6 h • Polymyxin E, 2%; tobramycin or netilmicin, 2%; amphotericin B, 2%	Placebo	100	Colonization and infection in the respiratory system	ICU
Aerdts et al,[51] 1991	Individual patient RCT	1	56	Mixed medical surgical	Oral: 1 g every 6 h • Amphotericin, 2%; norfloxacin, 2%; polymyxin E, 2% Enteral: 4 times/d via nasogastric tube • Polymyxin E, 200 mg; norfloxacin, 50 mg; amphotericin B, 500 mg Intravenous: 3 times/d for 3 d • Cefotaxime, 500 mg	Standard care	100	Lower respiratory tract infection	ICU
Blair et al,[50] 1991	Individual patient RCT	1	331	Mixed medical surgical	Oral: 4 times/d for duration of ICU • Oral polymyxin, 2%; tobramycin, 2%; amphotericin, 2% Enteral: 4 times/d for duration of ICU • Polymyxin, 100 mg; tobramycin, 80 mg; amphotericin, 500 mg Intravenous: 4 d • Cefotaxime, 50 mg/kg/d	Standard care	93	Infection	ICU
Gaussorgues et al,[49] 1991	Individual patient RCT	1	118	Mixed medical surgical	Enteral: 4 times/d for duration of ventilation • Gentamicin, 20 mg; colistin, 36 mg; vancomycin, 50 mg; amphotericin B, 500 mg	Standard care	100	Nosocomial bacteremia	ICU
Pugin et al,[48] 1991	Individual patient RCT	1	79	Surgical	Oral: 6 times daily for duration of ventilation • Polymyxin B sulfate, 37.5 mg; neomycin, 250 mg; vancomycin, 250 mg	Placebo	100	VAP	Hospital
Cockerill et al,[47] 1992	Individual patient RCT	1	150	Mixed medical surgical	Oral: 4 times/d for duration of ICU • Gentamicin, 2%; polymyxin B, 2%; nystatin, 1×10^5 U/g Enteral: 4 times/d for duration of ICU • Gentamicin, 80 mg; polymyxin B, 100 mg; nystatin, 2 million units Intravenous: 3 times/d for 3 d • Cefotaxime, 1 g	Standard care	84.7	Infection rates	Hospital

(continued)

Table. Included Study Characteristics (continued)

Source	Design	Centers	Participants	Population	SDD	Control	Ventilated, %	Primary outcome of trial	Mortality time point
Gastinne et al,[46] 1992	Individual patient RCT	15	445	Mixed medical surgical	Oral: 3 g 4 times/d for duration of ventilation • Colistin sulfate, 2%; tobramycin, 2%; amphotericin B, 2% Enteral: 4 times/d for duration of ventilation • Colistin sulfate, 100 mg; tobramycin, 80 mg; amphotericin B, 100 mg, 4 times/d	Placebo	100	Mortality at day 60	Hospital
Jacobs et al,[45] 1992	Individual patient RCT	1	76	Mixed medical surgical	Oral: 4 times/d for duration of ventilation • Polymyxin E, 2%; tobramycin, 2%; amphotericin, 2% Enteral: 4 times/d for duration of ventilation • Polymyxin E, 100 mg; tobramycin, 80 mg; amphotericin, 500 mg Intravenous: 3 times/d for 4 d • Cefotaxime, 50 mg/kg/d	Standard care	100	Nosocomial pneumonia	ICU
Rocha et al,[44] 1992	Individual patient RCT	1	101	Mixed medical surgical	Oral: 4 times/d for duration of ICU • Polymyxin E, 2%; tobramycin, 2%; amphotericin B, 2% Enteral: 4 times/d for duration of ICU • Polymyxin E, 100 mg; tobramycin, 80 mg; amphotericin, 500 mg Intravenous: 4 d • Cefotaxime, 2 g/d	Placebo	100	Prevention of nosocomial infection in the ICU	ICU
Korinek et al,[43] 1993	Individual patient RCT	2	191	Neurosurgical	Oral: 4 times/d for duration of ventilation (max, 15 d) • Polymyxin E, 2%; tobramycin, 2%; amphotericin, 2%; vancomycin, 2% Enteral: 4 times/d for duration of ventilation (max, 15 d) • Polymyxin E, 100 mg; tobramycin, 80 mg; amphotericin, 500 mg	Placebo	100	Infection rate	Hospital
Langlois-Karaga et al,[42] 1995	Individual patient RCT	1	97	Trauma	Oral: 4 times/d for duration of ventilation or commencement of enteral nutrition • Colistin, gentamicin, amphotericin B Enteral: 4 times/d for duration of ventilation or commencement of enteral nutrition • Colistin, gentamicin, amphotericin B	Placebo	100	Duration of hospitalization and cost of antibiotherapy	NR
Wiener et al,[41] 1995	Individual patient RCT	1	61	Mixed medical surgical	Oral: 4 times/d for duration of intubation • Polymyxin E, 2%; gentamicin, 2%; nystatin, 100 000 units Enteral: 4 times/d for duration of intubation • Polymyxin E, 100 mg; gentamicin, 80 mg; nystatin, 2×10^6 U	Placebo	100	Nosocomial infection	ICU
Quinio et al,[40] 1996	Individual patient RCT	1	148	Trauma	Oral: 15 mL 4 times/d until 24 h post extubation or commencement of enteral feeding • Colistin sulfate, 2%; gentamicin, 2%; amphotericin B, 2% Enteral: 4 times/d until 24 h post extubation or commencement of enteral feeding • Colistin sulfate, 100 mg; gentamicin, 80 mg; amphotericin B, 500 mg	Placebo	100	Nosocomial infection	ICU
Abele-Horn et al,[39] 1997	Individual patient RCT	1	88	Mixed medical surgical	Oral: every 6 h for duration of ventilation • Amphotericin, 2%; tobramycin, 2%; polymyxin E, 2% Intravenous: 3 times/d for 3 d • Cefotaxime, 2 g	Standard care	100	Colonization and infection rates	ICU

(continued)

Results

We retrieved 7586 records. **Figure 1** presents the results of the search and reasons for trial exclusion. The 32 eligible trials[9,10,26-55] included 24 389 participants, most of whom were enrolled in 3 cluster-crossover trials[9,10,27] (18 335/24 389). The **Table** (and eTable 1 in the Supplement) present the characteristics of included trials. One trial was published only as an abstract,[26] all other trials were published in peer-reviewed journals. Apart from the results of the SuDDICU trial,[10] no additional unpublished data were

Table. Included Study Characteristics (continued)

Source	Design	Centers	Participants	Population	SDD	Control	Ventilated, %	Primary outcome of trial	Mortality time point
Palomar et al,[38] 1997	Individual patient RCT	10	83	Mixed medical surgical	Oral: every 6 h for duration of ventilation or 40 d • Polymyxin E, 2%; tobramycin, 2%; amphotericin, 2% Enteral: every 6 h for duration of ventilation or 40 d • Polymyxin E, 2%; tobramycin, 2%; amphotericin, 2% Intravenous: 3 times/d for 4 d • Cefotaxime, 1 g	Standard care	100	Prophylaxis of nosocomial infection	ICU
Verwaest et al,[37] 1997	Individual patient RCT	1	578	Surgical	Oral: 4 times/d for duration of ICU • Ofloxacin, 2%; amphotericin B, 2% or • Polymyxin, 2%; tobramycin, 2%; amphotericin, 2% Enteral: duration of ICU • Ofloxacin, 200 mg, twice daily and amphotericin, 500 mg, 4 times/d or • Polymyxin E, 1 MU; tobramycin, 80 mg; amphotericin, 500 mg Intravenous: for 4 d • Ofloxacin 200 mg OR cefotaxime 1 g 4 times/d	Standard care	100	Colonization, incidence of infection, and mortality	ICU
Sánchez García et al,[36] 1998	Individual patient RCT	5	271	Mixed medical surgical	Oral: every 6 h • Gentamicin, 2%; polymyxin E, 2%; amphotericin B, 2% Enteral: every 6 h • Gentamicin, 80 mg; polymyxin E, 100 mg; amphotericin, 500 mg Intravenous: daily for 3 d • Ceftriaxone 2 g	Placebo	100	VAP	ICU
Bergmans et al,[35] 2001	Individual patient RCT	3	226	Mixed medical surgical	Oral: every 6 h • Gentamicin, 2%; colistin, 2%; vancomycin, 2%	Placebo	100	VAP	Hospital
Krueger et al,[34] 2002	Individual patient RCT	2	527	Surgical	Oral: every 6 h for duration of ICU • Gentamicin, 24 mg; polymyxin B, 15 mg; ± vancomycin, 37.5 mg Enteral: every 6 h for duration of ICU • Gentamicin, 40 mg; polymyxin B, 25 mg; ± vancomycin, 62.5 mg Intravenous: twice/d for 4 d • Ciprofloxacin, 400 mg	Placebo	92.6	Incidence and time at onset of infection, incidence, and time at onset of severe organ dysfunctions and mortality	ICU
Pneumatikos et al,[33] 2002	Individual patient RCT	1	61	Trauma	Oral: continuous infusion of 2 mL/h • Polymyxin E, 73 mg; tobramycin, 73 mg; amphotericin B, 500 mg, in 500-mL 0.9% saline	Placebo	100	Tracheal colonization and VAP	ICU
de Jonge et al,[32] 2003	Individual patient RCT	1	934	Mixed medical surgical	Oral: 4 times/d 0.5 g • Polymyxin E, 2%; tobramycin, 2%; amphotericin B, 2% Enteral: 4 times/d • Polymyxin E, 100 mg; tobramycin, 80 mg; amphotericin B, 500 mg Intravenous: 4 times/d for 4 d • Cefotaxime, 1 g	Standard care	85.3	Acquired colonization by any resistant strain and mortality	Hospital
Camus et al,[31] 2005	Individual patient RCT	3	256	Mixed medical surgical	Oral: 4 times/d for duration of ventilation • Polymyxin E, 45 mg; tobramycin, 30 mg Enteral: 4 times/d for duration of ventilation • Polymyxin E, 75 mg; tobramycin, 50 mg	Placebo	100	Acquired infection	ICU
de La Cal et al,[30] 2005	Individual patient RCT	1	107	Burns	Oral: 4 times/d 0.5 g • Polymyxin E, 2%; tobramycin, 2%; amphotericin B, 2% Enteral: 4 times/d 10 mL • Polymyxin B, 100 mg; tobramycin, 100 mg; amphotericin B, 500 mg Intravenous: 3 times/d for 4 d • Cefotaxime, 1 g	Placebo	76.6	Mortality and endogenous pneumonia	Hospital
Koeman et al,[29] 2006	Individual patient RCT	5	258	Mixed medical surgical	Oral: 0.5 g 4 times/d • Colistin, 2%; chlorhexidine, 2%	Standard care	100	Time to VAP	NR

(continued)

Table. Included Study Characteristics (continued)

Source	Design	Centers	Participants	Population	SDD	Control	Ventilated, %	Primary outcome of trial	Mortality time point
Stoutenbeek et al,[28] 2007	Individual patient RCT	17	401	Trauma	Oral: 0.5 g 4 times/d • Polymyxin E, 2%; tobramycin, 2%; amphotericin B, 2% Enteral: 10 mL 4 times/d • Polymyxin E, 100 mg; tobramycin, 80 mg; amphotericin, 500 mg Intravenous: 4 times/d for 4 d • Cefotaxime, 1 g	Standard care	100	Mortality at 3 mo	ICU
de Smet et al,[27] 2009	Cluster crossover	13	5939	Mixed medical surgical	Oral: 4 times/d • Polymyxin E, 2%; tobramycin, 2%; amphotericin B, 2% Enteral: 4 times/d • Polymyxin E, 100 mg; tobramycin, 80 mg; amphotericin B, 500 mg Intravenous: 4 times/d for 4 d • Cefotaxime, 1 g (SDD group only)	Standard care	91.5	28-d mortality	Hospital
Wittekamp et al,[9] 2018[a]	Cluster crossover	13	6414	Mixed medical surgical	Oral: 4 times/d • Colistin sulfate, 0.19 million units; tobramycin sulfate, 10 mg; and nystatin, 0.1 million units Enteral: 4 times/d • Colistin sulfate, 1.9 million units; tobramycin sulfate, 80 mg; and nystatin, 2.0 million units	Standard care	100	Incidence of ICU-acquired BSI with multidrug-resistant Gram-negative bacteria	Hospital
Papoti et al,[26] 2019[b]	Individual patient RCT	1	72	Mixed medical surgical	Oral: 3 times/d for 10 d • Colistin, fluconazole	Standard care	100	Prevention of infection-related ventilator-associated complications and VAP	ICU
SuDDICU,[10] 2022	Cluster crossover	19	5982	Mixed medical surgical	Oral: every 6 h for duration of ventilation • 0.5 g of oral paste containing colistin, 10 mg; tobramycin, 10 mg; and nystatin, 125 000 international units Enteral: every 6 h • Colistin, 100 mg; tobramycin, 80 mg; and nystatin, 2×10^6 international units Intravenous: daily for 4 d • Third-generation cephalosporin or ciprofloxacin	Standard care	100	Hospital mortality	Hospital

Abbreviations: BSI, bloodstream infections; ICU, intensive care unit; NR, not reported; RCT, randomized clinical trial; SDD, selective decontamination of the digestive tract; VAP, ventilator-associated pneumonia.

[a] Participant number for Wittekamp et al[9] reported as numbers used from chlorhexidine group (control) and SDD/selective oral decontamination groups. The control group for Wittekamp et al was the randomized chlorhexidine group because most sites used this as standard of care prior to randomization.

[b] Published in abstract form only. All other trials from peer-reviewed journals.

obtained directly from study authors. The 32 included trials had a median of 133 trial participants (IQR, 81-366). The median age of participants in the included studies was 54 years (IQR, 44-60), and the median proportion of female trial participants was 33% (IQR, 25%-38%), as shown in eTable 1 in the Supplement.

Risk of Bias

eTable 2 in the Supplement presents the risk of bias assessments. No trials were adjudicated as low risk of bias in all domains. The risk of bias was adjudicated as low for 28 of 30 trials contributing data regarding hospital mortality. We rated down the certainty in other outcomes due to risk of bias as shown in eTable 3 in the Supplement.

Primary Outcome

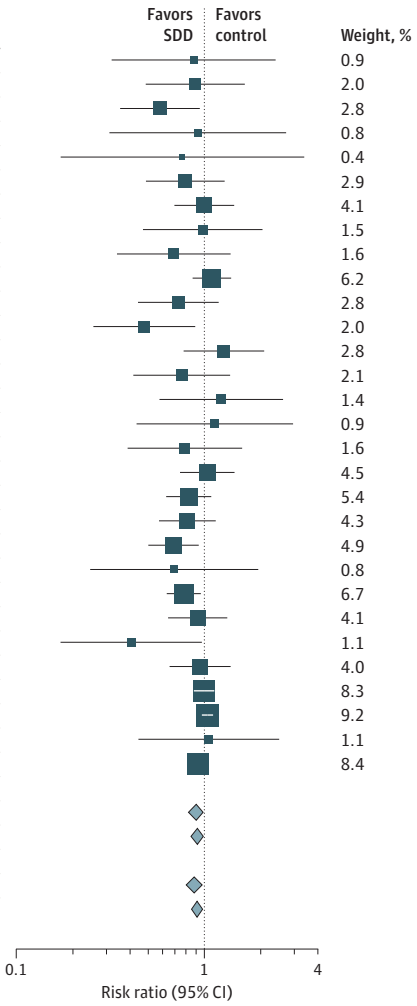
There were 30 trials (24 034 participants) that contributed data to the primary outcome. Ten trials (n = 20 467 participants) reported hospital discharge mortality and 20 (n = 3567 participants) reported mortality at ICU discharge. Using a bayesian random-effects model with vague priors, the pooled estimated RR for hospital mortality for SDD was 0.91 (95% CrI, 0.82-0.99; tau = 0.10; I^2 = 33.9%) compared with standard care, with a 99.3% posterior probability that SDD was associated with lower hospital mortality (**Figures 2**, **3**, and **4**; eTable 4 in the Supplement). The certainty in the evidence was adjudicated as moderate (eTable 3 in the Supplement). The results were similar for the sensitivity analyses using semi-informative priors and the specified frequentist methods (Figures 2 and 4; eTable 4 in the Supplement). There was no evidence of small-study effects on visual inspection of the funnel plot or the Egger test (eFigure 1A in the Supplement).

Subgroup Analysis

The primary outcome of hospital mortality was assessed in 3 a priori subgroups (Figure 4; eFigures 2-4 in the Supplement). There was evidence that the pooled estimate for

Figure 2. Forest Plot for Hospital Mortality for the Comparison Between Selective Decontamination of the Digestive Tract (SDD) Compared With Standard Care

Study	SDD Dead	SDD Alive	Control Dead	Control Alive	Risk ratio (95% CI)[a]	Weight, %
Unertl et al,[55] 1987	5	14	6	14	0.88 (0.32-2.40)	0.9
Kerver et al,[54] 1988	14	35	15	32	0.90 (0.49-1.65)	2.0
Ulrich et al,[53] 1989	15	33	28	24	0.58 (0.36-0.95)	2.8
Rodríguez-Roldán et al,[52] 1990	4	9	5	10	0.92 (0.31-2.73)	0.8
Aerdts et al,[51] 1991	2	15	6	33	0.76 (0.17-3.41)	0.4
Blair et al,[50] 1991	24	137	32	138	0.79 (0.49-1.28)	2.9
Gaussorgues et al,[49] 1991	29	30	29	30	1.00 (0.69-1.44)	4.1
Pugin et al,[48] 1991	10	28	11	30	0.98 (0.47-2.04)	1.5
Cockerill et al,[47] 1992	11	64	16	59	0.69 (0.34-1.38)	1.6
Gastinne et al,[46] 1992	88	132	82	143	1.10 (0.87-1.39)	6.2
Jacobs et al,[45] 1992	14	22	23	20	0.73 (0.44-1.19)	2.8
Rocha et al,[44] 1992	10	37	24	30	0.48 (0.26-0.89)	2.0
Korinek et al,[43] 1993	27	69	21	74	1.27 (0.78-2.09)	2.8
Wiener et al,[41] 1995	11	19	15	16	0.76 (0.42-1.37)	2.1
Quinio et al,[40] 1996	13	63	10	62	1.23 (0.58-2.63)	1.4
Abele-Horn,[39] 1997	11	47	5	25	1.14 (0.44-2.97)	0.9
Palomar et al,[38] 1997	10	31	13	29	0.79 (0.39-1.59)	1.6
Verwaest et al,[37] 1997	89	355	40	167	1.04 (0.74-1.45)	4.5
Sánchez García et al,[36] 1998	51	80	66	74	0.83 (0.63-1.09)	5.4
Bergmans et al,[35] 2001	30	57	59	80	0.81 (0.57-1.15)	4.3
Krueger et al,[34] 2002	52	213	75	187	0.69 (0.50-0.93)	4.9
Pneumatikos et al,[33] 2002	5	26	7	23	0.69 (0.25-1.94)	0.8
de Jonge et al,[32] 2003	113	353	146	322	0.78 (0.63-0.96)	6.7
Camus et al,[31] 2005	39	91	41	85	0.92 (0.64-1.33)	4.1
de La Cal,[30] 2005	6	47	15	39	0.41 (0.17-0.97)	1.1
Stoutenbeen et al,[28] 2007	42	159	44	156	0.95 (0.65-1.38)	4.0
de Smet et al,[27] 2009	1249	2700	632	1358	1.00 (0.88-1.13)	8.3
Wittekamp et al,[9] 2018	1661	2645	782	1326	1.04 (0.97-1.11)	9.2
Papoti et al,[26] 2019	8	27	8	29	1.06 (0.45-2.51)	1.1
SuDDICU,[10] 2022	753	2038	928	2263	0.93 (0.82-1.04)	8.4
Bayesian						
Vague priors					0.91 (0.82-0.99)	
Semi-informative priors					0.92 (0.85-0.99)	
Frequentist						
Sidik-Jonkman					0.88 (0.80-0.97)	
DerSimonian-Laird					0.92 (0.86-0.98)	



The dark blue boxes represent point estimates, and the sizes of the boxes are propotional to the weight. The whiskers represent confidence intervals. For the diamonds, the width represents all trials' pooled estimate confidence interval and the middle point, the point estimate.

[a] Credible intervals for bayesian estimates.

mortality was different (*P* value for the between-subgroup interaction test = .02) for trials that included an intravenous agent as a component of SDD (RR, 0.84 [95% CrI, 0.74-0.94]) compared with those with no intravenous agents (RR, 1.01 [95% CrI, 0.91-1.11]) as shown in eFigure 2 in the Supplement. We judged the credibility of the potential effect modification as moderate to high certainty. There was evidence that the pooled estimate for mortality was different (*P* value for the between-subgroup interaction test = .02) for cluster-randomized (RR, 1.00 [95% CrI, 0.79-1.23]) compared with individual patient (RR, 0.85 [95% CrI, 0.77-0.94]) randomized trials as shown in eFigure 3 in the Supplement. We judged the credibility of the potential effect modification as low. Details of the credibility assessments are presented in eAppendixes 5 and 6 in the Supplement. There was no evidence of a differential estimate of the association with mortality (*P* value for the between-subgroup interaction test = .89) in trials comparing surgical, trauma, and mixed ICU populations, with no data available from medical ICUs (eFigure 4 in the Supplement). Data were not available to permit an assessment of the potential heterogeneity by study design (cluster randomized compared with individual patient randomized trials) on the estimated incidence of positive cultures for antimicrobial-resistant organisms. There was no evidence of a differential association (*P* value for the between-subgroup interaction test = .99) in trials published before or after 2000 (eFigure 5 in the Supplement). The pooled estimate of the association with mortality and uncertainty around the estimate were similar in pooled analysis limited to studies published as full reports in peer-reviewed journals (eFigure 6 in the Supplement).

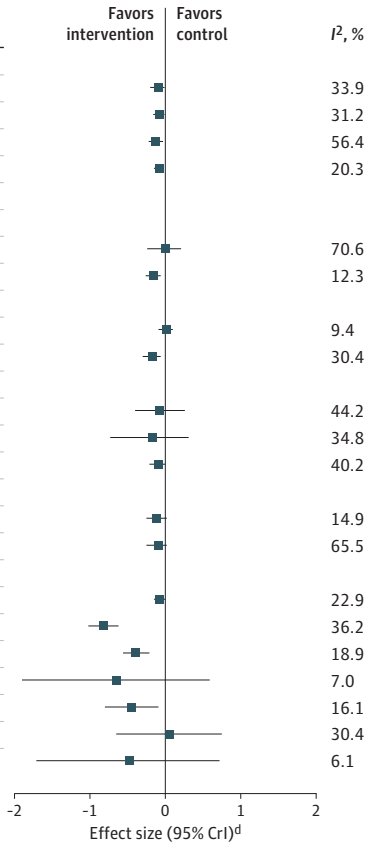
Secondary Outcomes

Figure 3 and eTables 3 and 4 in the Supplement present the results of all secondary outcomes with assessment of small-study

Figure 4. Primary Outcome, Secondary Outcomes, and Subgroup Analyses for the Comparison of Selective Decontamination of the Digestive Tract (SDD) vs Standard Care

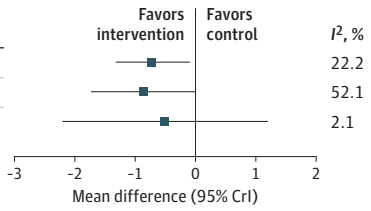
A Binary outcomes

Outcomes	Trials	Participants	Effect size (95% CrI)	I^2, %
Primary outcome: hospital mortality				
Vague priors	30	24 034	-0.09 (-0.20 to -0.01)	33.9
Semi-informative priors	30	24 034	-0.08 (-0.16 to -0.01)	31.2
Hartung-Knapp-Sidik-Jonkman	30	24 034	-0.13 (-0.22 to -0.03)[a]	56.4
DerSimonian-Laird	30	24 034	-0.08 (-0.15 to -0.02)[a]	20.3
Subgroup analysis for the primary outcome				
Study type				
Cluster crossover	3	18 335	0.00 (-0.24 to 0.21)	70.6
Individual patient randomized	27	5699	-0.16 (-0.26 to -0.06)	12.3
Study intervention[b]				
SDD with no IV agent	14	11 037	0.01 (-0.09 to 0.10)	9.4
SDD with IV agent	17	12 997	-0.17 (-0.30 to -0.06)	30.4
Study population[c]				
Surgical ICU	5	1544	-0.08 (-0.40 to 0.26)	44.2
Trauma ICU	4	717	-0.17 (-0.73 to 0.31)	34.8
Mixed population ICU	21	21 773	-0.09 (-0.21 to 0.00)	40.2
Publication year				
1987 to 1999	19	3115	-0.12 (-0.25 to 0.02)	14.9
2000 to 2022	11	20 919	-0.09 (-0.25 to 0.02)	65.5
Secondary outcomes				
Mortality at longest time point	30	24 034	-0.07 (-0.15 to 0.00)	22.9
Incidence of ventilator-associated pneumonia	22	3619	-0.82 (-1.02 to -0.62)	36.2
Incidence of ICU-acquired bacteremia	21	22 076	-0.39 (-0.56 to -0.21)	18.9
Clostridioides difficile infection	3	12 323	-0.65 (-1.90 to 0.59)	7.0
Positive culture of any antimicrobial-resistant organism	5	12 841	-0.45 (-0.80 to -0.09)	16.1
Positive methicillin-resistant *Staphylococcus aureus* culture	5	13 240	0.06 (-0.65 to 0.75)	30.4
Positive vancomycin-resistant enterococcus culture	3	13 287	-0.48 (-1.71 to 0.72)	6.1



B Continuous outcomes

Outcomes	Trials	Participants	Mean difference (95% CrI)	I^2, %
Duration of mechanical ventilation, d[e]	20	20 733	-0.73 (-1.32 to -0.09)	22.2
Intensive care unit length of stay, d[f]	24	23 198	-0.86 (-1.73 to 0.00)	52.1
Hospital length of stay, d[g]	5	18 592	-0.52 (-2.20 to 1.20)	2.1



Subgroup and secondary outcomes are presented based on calculations using vague priors. Full details of the priors are presented in eAppendix 1 in the Supplement. ICU indicates intensive care unit.

[a] Confidence interval.

[b] Total number of trials is 31 because the de Smet et al[27] study contributes both intravenous (IV) and non-IV data. Participant numbers for the control group have been split evenly between the IV and non-IV groups so they remain the same as the main publication (ie, not double counted).

[c] No data in medical ICUs.

[d] The effect size is the log of the risk ratio. The exponent of the values provides the estimated risk ratio, also shown in eFigure 17 in the Supplement.

[e] Median duration of ventilation was 11.8 days (IQR, 8.7-15.1) in the SDD group and 12.5 days (IQR, 8.7-18.0) in the control group.

[f] Median intensive care unit length of stay was 17.2 days (IQR, 12.2-22.0) in the SDD group and 18.9 days (IQR, 12.6-27.0) in the control group.

[g] Median hospital length of stay was 27 days (IQR, 26.3-30.0) in the SDD group and 29 days (IQR, 27-31) in the control group.

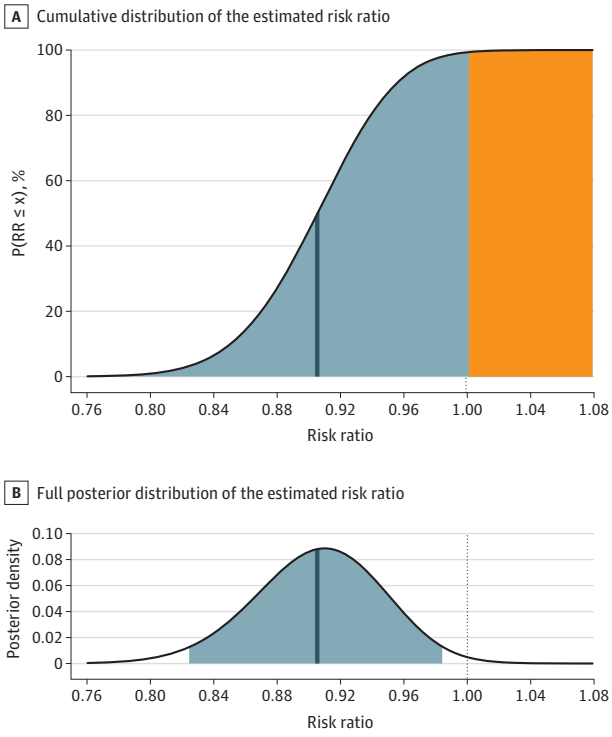
effects presented in eFigure 1B-K in the Supplement. Compared with standard care, SDD was associated with a reduced risk of ventilator-associated pneumonia (RR, 0.44 [95% CrI, 0.36-0.54]; very low certainty; eFigure 7 in the Supplement), a reduced risk of ICU-acquired bacteremia (RR, 0.68 [95% CrI, 0.57-0.81]; low certainty; eFigure 8 in the Supplement), a reduction in the duration of mechanical ventilation (mean difference, −0.73 days [95% CrI, −1.32 to −0.09 days]; moderate certainty; eFigure 9 in the Supplement), and duration of ICU admission (mean difference, −0.86 [95% CrI, −1.73 to 0 days]; low certainty; eFigure 10 in the Supplement). There was no association with duration of hospital stay (mean difference, −0.52 days [95% CrI, −2.23 to 1.20 days]; moderate certainty; eFigure 11 in the Supplement).

The pooled estimated RR for mortality at longest follow-up for SDD compared with standard care was 0.93 (95% CrI, 0.86-1.00) (eFigure 12 in the Supplement). Only 3 trials[28,34,35] provided additional data regarding mortality beyond hospital discharge, 1 completed follow-up at 90 days,[28] 1 at 1 year,[34] and 1 had a median follow-up duration of 3.5 years.[35]

Data were unavailable at a unit level to facilitate a pooled analysis of the association of SDD with the emergence of antimicrobial-resistant organisms; available data are qualitatively summarized in eTable 5 in the Supplement. None of the 3 cluster-randomized trials[9,10,27] reported an increase in positive cultures of antimicrobial-resistant organisms at a unit level.

Of the studies that reported data at an individual patient level, data were available to provide a pooled estimate of the incidence of positive cultures of antimicrobial-resistant organisms (estimated RR, 0.65 [95% CrI, 0.46-0.92]; very low certainty; eFigure 13 in the Supplement), incidence of positive cultures of methicillin-resistant *Staphylococcus aureus* (estimated RR, 1.06 [95% CrI, 0.56-1.98]; very low certainty; eFigure 14 in the Supplement), and vancomycin-resistant enterococcus (estimated RR, 0.62 [95% CrI, 0.18-2.06]; very low certainty; eFigure 15 in the Supplement). The pooled estimated RR for *Clostridioides difficile* was 0.52 (95% CrI, 0.15-1.80; eFigure 16 in the Supplement). eTable 5 in the Supplement summarizes data not amenable to pooling. Fourteen trials[28,31-35,39,40,43,47,48,51,52,55] reported no increase in detection of antimicrobial-resistant organisms from clinical or surveillance cultures, 6 trials[36,37,41,44,50,53] reported an increase in antimicrobial-resistant organisms detected, and 9 trials[26,29,30,38,42,45,46,49,54] did not report the incidence of detection of antimicrobial-resistant organisms.

Figure 3. Cumulative Incidence Plot for the Posterior Probability of the Risk Ratio (RR) for Mortality for Selective Decontamination of the Digestive Tract Compared With Standard Care



A, The cumulative posterior distribution of the estimated RR, with the y-axis corresponding to the probability the RR is less than or equal to the value on the x-axis. The blue area is related to the intervention being beneficial while the orange area is related to an RR greater than 1 (ie, the intervention associated with higher mortality vs the comparator). The bold vertical line indicates the median. B, The full posterior distribution of the estimated RR, with the bold vertical line indicating the median value and the area highlighted in blue indicating the percentile-based 95% credible interval. The dotted lines at an RR of 1 indicate no treatment effect. These panels demonstrate that the probability that selective decontamination of the digestive tract is associated with reduced mortality (to any extent) compared with standard care is more than 99%.

Discussion

In this systematic review and meta-analysis, the use of SDD in patients receiving mechanical ventilation in the ICU is likely associated with a reduced risk of hospital mortality. This reduction in mortality was evident in trials that included an intravenous agent as a component of the intervention. The results provide evidence that the use of SDD may result in a reduced incidence of ventilator-associated pneumonia and ICU-acquired bacteremia; however, this evidence was of lower certainty. It was also found that SDD was probably associated with a small reduction in the duration of mechanical ventilation, but little or no reduction in the duration of ICU admission. There was no evidence that SDD was associated with an increase in the incidence of antimicrobial-resistant organisms; however, the association between SDD and the emergence of antimicrobial-resistant organisms remains very uncertain.

The findings of reduced risk of mortality and incidence of ventilator-associated pneumonia are consistent with the results of a recent Cochrane review.[3] The addition of 2 recent trials[9,10] has more than doubled the sample size, increasing confidence in the primary finding of a reduction in mortality associated with the use of SDD, as well as reporting pooled data for additional outcomes. The use of bayesian methods in this review provides the quantitative framework for clinicians and policymakers to interpret the uncertainty regarding the overall results of recent trials, as they consider the overall risks and benefits of implementing this intervention.[9,10] Concern that the widespread use of broad-spectrum antibiotics might promote antimicrobial-resistant organisms has been a barrier to the adoption of SDD.[7,8] In keeping with previous literature,[7,9] no evidence was found to support the concern, but the available evidence is of very low certainty and is insufficient to rule out that possibility. Methodologically sound, long-term observational studies designed to overcome the limitations identified in the current body of research regarding the ascertainment of the effect of SDD on the development of antimicrobial-resistant organisms is a priority for future research.

Our review has several strengths. The inclusion of recent large trials has substantially increased the number of included

participants, allowing the assessment of a broader range of outcomes than have been previously reported.[3] The use of bayesian and frequentist analyses provides confidence that the results are robust to the methods used to pool data.

Limitations

This study has several limitations. First, consistent with previous trials,[9,27] the prevalence of antimicrobial resistance was uniformly low, consequently, the results may not be applicable in health care settings with a higher rate of antimicrobial resistance. Second, evidence regarding the association of SDD with secondary outcomes, in particular outcomes related to the incidence of antimicrobial-resistant organisms, was adjudicated as very low certainty, largely due to lack of blinding of the health care providers and outcome assessors for these subjective outcomes. The low certainty regarding these outcomes means that these data are not able to resolve the outstanding question regarding the effect of SDD on the incidence of antimicrobial-resistant organisms.

Conclusions

Among adults in the ICU treated with mechanical ventilation, the use of SDD compared with standard care or placebo was associated with lower hospital mortality. Evidence regarding the effect of SDD on antimicrobial resistance was of very low certainty.

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Concept and design: Hammond, Myburgh, Seppelt, Vlok, Adigbli, Finfer, Goodman, Guyatt, Venkatesh, Di Tanna, Delaney.
Acquisition, analysis, or interpretation of data: Hammond, Seppelt, Garside, Vlok, Mahendran, Adigbli, Gao, Santos, Yao, Delaney.
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Critical revision of the manuscript for important intellectual content: All authors.
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Supervision: Hammond, Myburgh, Guyatt, Di Tanna, Delaney.
Other - risk of bias assessment: Gao.

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