Since the recent randomized controlled trial (RCT) on selective decontamination of the digestive tract (SDD) demonstrated a significant reduction in mortality in critically ill adults in intensive care (1), there has been a resurgence of interest in the value of SDD. Nosocomial infection is associated with changes in the gut flora and critical illness profoundly changes body flora, both qualitatively and quantitatively (2), and promotes a shift from 1) normal (3) to abnormal carriage (4, 5) and 2) low to high-grade carriage or gut overgrowth (6).

There are now 65 RCTs and 11 meta-analyses demonstrating a significant reduction in nosocomial pneumonia morbidity and more importantly mortality in adult ventilated patients in intensive care.

We reviewed all RCTs performed in children to determine whether SDD is also effective in children. The use of SDD in pediatrics has been very limited in contrast to the adult experience. This is in part the result of the low rates of infection and mortality in the general pediatric population. The overall mortality rate in pediatric intensive care varies between 5% and 10% (7). Total inhouse mortality (3.74%) can differ a little from outside admissions mortality (3.94%) (8). Crude mortality rates from the Australian and New Zealand 2009 census reported a rate of 2.9% (9). These are low rates compared with the 20% to 30% in adults. There are of course subgroups of children who are at greater risk of infections and also death that might benefit from the use of SDD.

The participants in this systematic review and meta-analysis include children up to the age of 16 yrs who received selective decontamination of the digestive tract and 16 of 165 patients (9.7%) for controls (odds ratio 0.31; 95% confidence interval 0.11–0.87; p = .027). Overall mortality for selective decontamination of the digestive tract was 13 of 170 (7.6%) vs. control, 11 of 165 (6.7%) (odds ratio 1.18; 95% confidence interval 0.50–2.76; p = .70). In three studies (n = 109), infection occurred in ten of 54 (18.5%) patients on selective decontamination of the digestive tract and 24 of 55 (43.6%) in the controls (odds ratio 0.34; 95% confidence interval 0.05–2.18; p = .25).

Conclusions: In the four available pediatric randomized controlled trials, selective decontamination of the digestive tract significantly reduced the number of children who developed pneumonia (Pedia- tric Crit Care Med 2013; 14:89–97).

Key Words: critically ill children; infection; mortality; pediatric; pneumonia; randomized controlled trial; selective decontamination of the digestive tract

Objective: We examined the impact of selective decontamination of the digestive tract on morbidity and mortality in critically ill children.

Data Sources: We searched MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, and previous meta-analyses.

Study Selection: We included all randomized controlled trials comparing administration of enteral antimicrobials in selective decontamination of the digestive tract with or without a parenteral component with placebo or standard therapy used in the controls.

Data Extraction: The primary end point was the number of acquired pneumonias. Secondary end points were number of infections and overall mortality. Odds ratios were pooled with the random effect model.

Data Synthesis: Four randomized controlled trials including 335 patients were identified. Pneumonia was diagnosed in five of 170 patients (2.9%) for selective decontamination of the digestive tract and 16 of 165 patients (9.7%) for controls (odds ratio 0.31; 95% confidence interval 0.11–0.87; p = .027). Overall mortality for selective decontamination of the digestive tract was 13 of 170 (7.6%) vs. control, 11 of 165 (6.7%) (odds ratio 1.18; 95% confidence interval 0.50–2.76; p = .70). In three studies (n = 109), infection occurred in ten of 54 (18.5%) patients on selective decontamination of the digestive tract and 24 of 55 (43.6%) in the controls (odds ratio 0.34; 95% confidence interval 0.05–2.18; p = .25).

Conclusions: In the four available pediatric randomized controlled trials, selective decontamination of the digestive tract significantly reduced the number of children who developed pneumonia (Pediatr Crit Care Med 2013; 14:89–97).
decontamination of the digestive tract. The reason for undertaking the meta-analysis was to assess the four pediatric trials with respect to the primary end point of pneumonia, the secondary end point of overall infection, and finally overall mortality from the available RCTs.

**DATA SOURCES**

**Search Strategy**

RCTs were obtained by searching electronic databases EMBASE and MEDLINE with no restriction on language or gender. Search key words were SDD, selective decontamination of the digestive tract, selective bowel decontamination, and gut decontamination. In addition, the authors searched their personal archives and published meta-analyses on SDD.

Inclusion and Exclusion Criteria. We established inclusion and exclusion criteria before reviewing abstracts and articles. We included all RCTs comparing enteral administration of the SDD antibiotics (opharyngeal, intestinal, or both) with or without a parenteral component with no treatment or placebo in the controls. RCTs with usable information by outcome were finally included in the meta-analysis. Studies were excluded for the following reasons: 1) nonrandomized studies or studies with an inappropriate design; 2) double publications or studies including data extracted from main publication; 3) both study arms received SDD; and 4) studies including neutropenic, stem cell, and bone marrow transplant patients.

**Data Extraction of Outcome Measures**

Three investigators (A.P., L.S., H.vS.) independently retrieved the published findings from each study and compared the sets of data. Any disagreement was resolved by discussion. The following data were sought for each study and recorded on standard collection sheets: specific antimicrobials used and routes; number of patients in each arm; number of patients with pneumonia and infection; and number of deaths.

**Quality Assessment**

The quality of each study was assessed with reference to a predefined list of seven criteria in a scoring system of 0–14 reported originally by Heyland et al (10) and modified by Brazzi et al (11) and Silvestri et al (12). The criteria used here included randomization, study blinding, patient selection, population description, reproducibility, definitions of infection, and carriage (12). The assessment was made by three investigators (A.P., L.S., H.vS.).

**Definitions**

Pneumonia was defined based on the individual clinical and laboratory criteria used by the authors of the selected RCTs, i.e., fever, increased volume and purulence of lower airway secretions, a culture positive for potential pathogens in high concentrations (>105 quantitatively or >2+ semiquantitatively), and the presence of a new or evolving pulmonary infiltrate on the chest radiograph (13).

All other infections were defined according to Centers for Disease Control and Prevention criteria (13).

**Statistical Analysis**

The primary end point was the number of children developing pneumonia during treatment with SDD. Secondary end points were overall infection and mortality. We planned a priori the following subgroup analysis of the three end points: 1) type of regimen used (parenteral plus enteral or enteral only); 2) randomization procedures (adequate or inadequate); and 3) blinding of patients and caregivers to allocated treatment (blinded or unblinded). We hypothesized that the treatment effect would be lower with enteral only regimen, in adequate randomization, and in blinded studies. Randomization was adequate when patients were randomized by telephone or a central office. A study was blinded when both caregivers and outcome assessors were blinded.

Checking for heterogeneity across studies and random-effects meta-analysis were undertaken (14). Results are presented as odds ratio (ORs) with 95% confidence intervals (CIs) using the random effects model. The Cochran Q statistic for heterogeneity was used both for the outcome measures and through subgroup analyses; we considered heterogeneity to be significant if the p value was <.10. F was also evaluated using the formula 100% × (Q−df)/Q where Q is Cochran Q and df the degree of freedom (number of studies −1). Negative values of F are equal to 0%. F <30% indicates mild heterogeneity and 30% to 50% moderate and >50% severe heterogeneity. Computations were performed using EasyMA software (15).

**Data Synthesis**

**Search Findings and Characteristics of the Studies.** The preliminary search identified 153 potentially relevant studies (Fig. 1). Of these studies, 88 were excluded: 64 studies were not randomized, 21 RCTs were double publications, and three RCTs used SDD in both arms. We identified 65 potentially appropriate RCTs of whom 61 were excluded because they were not performed in children. A final sample of only four RCTs, which enrolled a total of 335 patients (170 SDD, 165 controls), was the basis for the systematic review and meta-analysis. One of the four studies was in burn patients only and two of the others were also special populations, cardiac, and liver transplant. However, these are the only four from which some impression of efficacy may be gained (Table 1).

Leclerc and Noizet (16) undertook a systematic review of the four pediatric studies in 2004 but did not undertake a meta analysis of the data they described. We go further and describe the four RCTs (17–20) in terms of quality on a previously devised score. The trials include a varied population ranging from severely burned pediatric patients, to children in pediatric intensive care units, to children undergoing liver transplantation. Quality assessment for all trials using the methods described by Heyland (9), Brazzi (10), and Silvestri (11) resulted in a median score of 9.2 (range, 8.4–9.9). This compares well with previous quality assessment of all the SDD meta-analyses of adult and pediatric data, which resulted in a median score of 9.0 (interquartile range, 8–11) (11). Zobel et al (17) received a score of 10.3, Smith et al 9.7 (18), Ruza et al (19) 7.3, and Barret et al (20) achieved a score of 8.7.
Zobel and colleagues (17) studied 50 children in a cardiac pediatric intensive care unit. All patients were endotracheally intubated and mechanically ventilated. SDD was given to 25 children in a prospective RCT after cardiac surgery in addition to the routine antibiotic regimen and 25 children were controls. During the study, colonization with Gram-negative micro-organisms and yeasts in the oropharynx and digestive and respiratory tracts increased up to 52% in the control group. There was no colonization with these micro-organisms in the treatment group. The rates of acquired secondary infections in the control and treatment groups were 36% and 8%, respectively \((p < 0.025)\). There were no differences in length of intensive care or mortality. The authors concluded that SDD produced a significant reduction of the colonization rate with Gram-negative bacteria and yeasts in critically ill pediatric patients after cardiac surgery and needing intensive care for >3 days. SDD also significantly reduces the Gram-negative infection rate of the respiratory system. However, it did not alter intensive care unit length of stay or mortality rate.

Smith and colleagues (18) undertook the first prospective RCT of short-term SDD in children having orthotopic liver transplantation. Although not specifically documenting that all the children were ventilated, because the patients were liver transplants admitted to the intensive care unit postoperatively, it was assumed both groups were ventilated. Oral and nasogastric SDD, in addition to routine parenteral antibiotics, was given to 18 children having transplants and only routine parenteral antibiotics to the control group of 18. There was no difference in the group’s demographics, intensive care, or hospital length of stay. During the study, 14 Gram-negative infections (intra-abdominal abscess, seven; septicemia, five; pneumonia, one; urinary tract, one) developed in the 36 patients studied. Mortality was not significantly different in the two groups. There were significantly fewer patients with Gram-negative infections in the SDD group: three of 18 patients (11%) vs. 11 of 18 patients (50%) in the control group \((p < 0.001)\). There was also significant reduction in aerobic Gram-negative flora in the stool and pharynx. The authors concluded that short-term postoperative SDD significantly reduces Gram-negative infections in children having orthotopic liver transplantation.

In a prospective, randomized, nonblinded and controlled trial, Ruza et al (18) studied children aged 1 month to 14 yrs who had any manipulation or instrumentation such as mechanical ventilation, vascular cannulation, monitoring of intracranial pressure, thoracic or abdominal drainage, bladder catheterization, peritoneal dialysis, and/or presented a neurologic coma during a >3-day stay in a tertiary pediatric intensive care unit (19). Over a 2-yr period, 226 children were included in the study, the treatment group comprised 116 patients and the control group 110 patients. A total of 164 (73%) children were ventilated, 91 (55.5%) receiving SDD and 73 (44.5%) in the control group \((p < 0.05)\). The treatment group was given colimycin, tobramycin, and nystatin administered orally or through a nasogastric tube, whereas no oropharyngeal decontamination was implemented. Using univariate analysis, SDD did not significantly reduce the incidence of nosocomial infection, the length of stay, or mortality. However, using multivariate analysis, SDD decreased the incidence of respiratory and urinary tract infections, reducing the risk of such infections to one of five and one of three, respectively. Ruza and colleagues (19) concluded that SDD was effective in controlling respiratory and urinary tract infections in children admitted to the pediatric intensive care unit, but it did not reduce the incidence of other types of nosocomial infection.

Finally, Barret et al (20) studied 23 children with severe burns (Table 1). After randomization, SDD was given in a double-blind manner to 11 children and 12 received placebo. The control group received mechanical ventilation for 8 ± 2 days and the SDD group for 14 ± 5 days with no significant difference. Both groups received parenteral antibiotics; the SDD group
also received oral and nasogastric enteral antibiotics including polymyxin E, tobramycin, and amphotericin B. Demographics, hospital course, microbiology results, complications, infectious episodes, and serum levels of interleukin-1β, interleukin-6, interleukin-10, and tumor necrosis factor-α were compared. There was a similar incidence of colonization rates to the wound, sputum, nasogastric aspirates, and feces. The incidence of pneumonia, sepsis, and other complications was also similar in both groups as were serum levels of all cytokines studied. The authors noted a significantly higher incidence of diarrhea \( (p = 0.003) \) in the children who received SDD. They concluded that SDD is not effective in decreasing bacterial colonization and infectious episodes in severely burned pediatric patients.

**PNEUMONIA**

All four RCTs included 335 patients in total (Fig. 2). Pneumonia occurred in five of 170 patients (2.9%) of those who received SDD and in 16 of 165 patients (9.7%) in the control group. This was a significant reduction in the incidence of pneumonia with SDD (OR 0.31; 95% CI 0.11–0.87; \( p = 0.027 \)). Heterogeneity was not observed (chi square = 2.51, \( p = 0.47, I^2 = 0 \)) (Tables 2 and 3).

**INFECTION**

In three RCTs, including 109 children, infections of various origins were confirmed in ten of 54 (18.5%) of those who received SDD and in 24 of 55 (43.6%) children in the control group. SDD had no impact on general infection rates with no overall difference between the groups (OR 0.34; 95% CI 0.05–2.18; \( p = 0.25 \)) (Tables 2 and 3).

**MORTALITY**

The impact of SDD on mortality was analyzed in all four studies. Overall mortality for those who received SDD vs.
those who did not was 13 of 170 (7.6%) and 11 of 165 (6.7%), respectively, demonstrating no reduction in the odds of death (OR 1.18; 95% CI 0.50–2.76; p = 0.70) (Tables 2 and 3).

Subgroup Analysis

Subgroup analyses of type of SDD regimen, randomization, and blinding are shown in Table 4. A significant impact on infections and pneumonia was found with the use of the full protocol of parenteral and enteral antimicrobials rather than solely enteral antimicrobials. A significant impact on pneumonia and overall infection was demonstrated when randomization was adequate and in unblinded studies. The subgroup analyses for mortality were consistent with previous pooled results whether the intervention was parenteral/enteral or enteral, whether the design was blinded or not, and whether the randomization process was adequate or not. The Q and F tests for heterogeneity yielded nonsignificant results in all comparisons.

DISCUSSION

There are very few pediatric studies on the use of SDD in critically ill children. Although there has been a systematic review of the four studies (16), this is the first meta-analysis of these currently available RCTs. The numbers of children included are relatively small, which probably accounts for the lack of significant effect on mortality or overall infection. However, even with relatively few numbers, there is still a significant reduction in pneumonia rates. Using a recognized assessment tool for quality of studies included in meta-analyses, the four studies resulted in a very acceptable median value for quality of the studies.

The new finding of this meta-analysis in pediatrics is that SDD does not significantly reduce overall infections nor mortality. However, there is a significant impact of SDD on reduction of the incidence of pneumonia in critically ill children (OR, 0.34; p = 0.027). Previous reports have demonstrated that the infection rate in children using SDD is very low over a 4-yr period (21).

Furthermore, on subgroup analysis, when the full SDD protocol of enteral plus parenteral antibiotics is used, there is significant reduction in overall infections (OR 0.13 0.04–0.40; p < 0.001). However, this subgroup analysis has to be taken with considerable caution because it involves small numbers of patients. The enteral component of SDD when used alone does not have an impact.

Because invasive mechanical ventilation is a major risk factor for nosocomial pneumonia, it is important to note that in the Zobel et al (17), Smith et al (18), and Barret et al (20) studies, all patients were ventilated and in the Ruza et al (19) study, 73% of the study was ventilated equally distributed. All four pediatric RCTs used noninvasive techniques to diagnose pneumonia consisting of tracheal aspirate and/or sputum. Invasive diagnosis of pneumonia with a protected specimen brush or bronchoalveolar lavage after bronchoscopy is associated with halving the diagnosis of pneumonia (22). However, invasive management does not impact on mortality (23). So using noninvasive techniques in pediatric is a good surrogate measure of diagnosing pneumonia.

We raised the question 15 yrs ago whether mortality or morbidity was the goal to measure quality outcomes against (24). Debate has ensued and morbidity is certainly now recognized.

Table 1. (Continued).

<table>
<thead>
<tr>
<th>Regimen Enteral</th>
<th>Parenteral</th>
<th>Aerobic Gram-Negative Bacilli</th>
<th>Yeasts</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-Negative Bacilli</td>
<td>P, T</td>
<td>A</td>
<td>O, I</td>
<td></td>
</tr>
<tr>
<td>Aerobic Gram-Negative Bacilli</td>
<td>P, T</td>
<td>A</td>
<td>O, I</td>
<td></td>
</tr>
<tr>
<td>Yeasts</td>
<td>P, T</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. (Continued).
as a valuable end point, particularly when it improves quality of care for the patient. Given this acknowledgment, the question has to be asked whether withholding SDD from critically ill children is now justifiable given the extensive adult literature (25) and now the beginnings of a pediatric evidence base, albeit limited? A recent French Consensus Conference recommended SDD as pneumonia prophylaxis in critically ill children (26). Unfortunately, this recommendation has not been implemented. There is still antipathy to SDD from various sectors. Microbiologists and some intensivists dislike the use of such broad-spectrum oral antibiotics and continue to have concerns over emerging resistance. Perhaps more importantly, SDD uses readily available antibiotics and consequently has never been marketed commercially by a large pharmaceutical company and so has not benefited from the persuasive professional marketing techniques available to these agencies. However, if there is a technique or treatment that convincingly demonstrates a reduction in morbidity, should we not use it?

In terms of costs of implementing SDD, a study by Garcia-San Vicente (27) compared two periods of 1 yr: before and after using SDD in the adult intensive care unit. Surveillance cultures did not significantly increase the workload nor the cost of processing the samples. The explanation provided by the authors was that the increase in surveillance samples was offset by the decrease in diagnostic samples such as blood samples, bronchioalveolar lavage, and urine. During the SDD period, they reported an increase in *Pseudomonas aeruginosa* resistance to imipenem, tobramycin, and ciprofloxacin. However, the changes in resistance do not refer to the two periods of study. The author described changes in resistance between 1996 and 2007. The studied periods were 2001–2002 pre-SDD and 2002–2003 post-SDD (28). The authors recognized that their conclusion about *P. aeruginosa* resistance was not well supported (29).

Also the costs during SDD may have been overestimated because surveillance of tracheal and gastric aspirate is not necessary. Costs adjusted for length of stay also confirm that surveillance during SDD is not associated with increased expenditure (26). Although the cost-effectiveness of SDD has not yet been formally calculated, the daily cost of using SDD was estimated at approximately 12 Euros ($16 U.S.) (1).

A study by Oostdijk and colleagues (30) report the emergence of multidrug-resistant bacterial organisms. They conclude that SDD and also selective oral decontamination have marked effects on the bacterial ecology in the intensive care unit with increasing ceftazidime resistance prevalence rates in the respiratory tract and a considerable rebound effect of ceftazidime resistance in the intestinal tract after stopping SDD. However, an alternate explanation was offered for these

### TABLE 2. Data Extracted From Four Randomized Controlled Trials of Selective Digestive Decontamination in Pediatric Population

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Patients With Infection</th>
<th>Patients With Pneumonia</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SDD</td>
<td>C</td>
<td>SDD</td>
<td>C</td>
</tr>
<tr>
<td>Zobel et al (17)</td>
<td>25</td>
<td>25</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Smith et al (18)</td>
<td>18</td>
<td>18</td>
<td>3</td>
<td>11*</td>
</tr>
<tr>
<td>Ruza et al (19)</td>
<td>116</td>
<td>110</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Barret et al (20)</td>
<td>11</td>
<td>12</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

SDD = selective digestive decontamination; C = control; NA = not available.

*Patients with Gram-negative infections.

### TABLE 3. Meta-Analysis of the Impact of Selective Digestive Decontamination on Secondary Endpoints

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Randomized Controlled Trials</th>
<th>No. of Patients</th>
<th>No. of Patients With Outcome</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>p</th>
<th>P^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>4</td>
<td>170</td>
<td>165</td>
<td>0.31 (0.11–0.87)</td>
<td>0.027</td>
<td>0%</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>54</td>
<td>55</td>
<td>0.34 (0.05–2.18)</td>
<td>0.25</td>
<td>4.7%</td>
</tr>
<tr>
<td>Mortality</td>
<td>4</td>
<td>170</td>
<td>165</td>
<td>1.18 (0.50–2.76)</td>
<td>0.70</td>
<td>0%</td>
</tr>
</tbody>
</table>

Odds ratio less than the unit favors treatment; odds ratio above the unit favors controls.
findings. It was pointed out that in Oostdijk’s analysis of resistance all patients, study and nonstudy were included. Abnormal carriage was reported as 5% before, increasing to 15% during and after the trial. However, approximately 70% of the admissions were not actually in the Dutch study conducted by de Smet (31). In contrast, de Smet analyzed surveillance data from only study patients and found the opposite; the proportion of patients with resistant aerobic Gram-negative bacilli to the marker antibiotics, including ceftazidime, was lower with SDD. A study by Ochoa-Ardila (32) have also recently demonstrated that the long-term use of SDD over a 5-yr period in an adult intensive care unit setting does not increase antibiotic resistance.

SDD using parenteral cefotaxime, enteral amphotericin B, polymyxin, and tobramycin does not cover intrinsically resistant methicillin-resistant Staphylococcus aureus. There have been frequent concerns raised about emergence of methicillin-resistant S. aureus as a result of using SDD. Enteral vancomycin

<table>
<thead>
<tr>
<th>End Points</th>
<th>No. of Randomized Controlled Trials</th>
<th>Selective Digestive Decontamination Control</th>
<th>Selective Digestive Decontamination Control</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral plus enteral</td>
<td>2</td>
<td>43</td>
<td>43</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Enteral only</td>
<td>2</td>
<td>127</td>
<td>122</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Randomization adequate</td>
<td>2</td>
<td>43</td>
<td>43</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Randomization inadequate</td>
<td>2</td>
<td>127</td>
<td>122</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
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<td>11</td>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Not blinded</td>
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<td>159</td>
<td>153</td>
<td>4</td>
<td>16</td>
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Infections

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<th>End Points</th>
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<tr>
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<td>11</td>
<td>12</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Not blinded</td>
<td>2</td>
<td>43</td>
<td>43</td>
<td>5</td>
<td>21</td>
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</table>

Mortality

<table>
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<th>End Points</th>
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<th>Selective Digestive Decontamination Control</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>p</th>
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<tr>
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<td>43</td>
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<td>5</td>
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<tr>
<td>Enteral only</td>
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<td>3</td>
<td>159</td>
<td>153</td>
<td>11</td>
<td>10</td>
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</table>

NE = not evaluated as only one study was included.

The Q and p tests for heterogeneity were not significant in all comparisons. Odds ratio < 1 favors treatment; odds ratio > 1 favors controls.
has been added to the traditional SDD protocol in case of endemicity of methicillin-resistant *S. aureus* (33). There are concerns that enteral vancomycin promotes vancomycin-resistant enterococci (34); however, none of the RCTs and long-term studies using enteral vancomycin have ever reported vancomycin-resistant enterococci outbreaks (35–41). This can be explained by the high fecal vancomycin levels between 3000 and 24,000 mg/L after a 2-g enteral dose. In contrast, studies have shown that 2 g parenteral antibiotic that disregards the human ecology and which are excreted by bile in concentrations <3–95 mg/L of feces promote the emergence of vancomycin-resistant enterococci (42).

Demonstrating an overall survival benefit with SDD may be very hard to achieve in pediatrics because the numbers needed to treat are potentially very large given the low mortality rate in pediatric intensive care. A simple sample size calculation assuming a 5% mortality in the control group looking for a 15% reduction in mortality to 4.25% with a 10% type I error or false-positive rate and a 10% type 2 false-negative rate would require a sample size on the order of 27,390 children.

Mechanical ventilation can be seen as a measure of disease severity, defining the need for complex intensive care. The recent Control of Hyperglycemia in Pediatric intensive care trial (CHIP) (43) used as the primary outcome the number of days alive and free from mechanical ventilation within the 30 days after trial entry. The concept of ventilator-free days (VFDs) brings together these two outcomes. A study by Schoenfeld et al (44) define VFDs as: VFD = 0 if the child dies before 30 days; VDF = (30–x) if the child is successfully weaned from ventilator within 30 days (where x is the number of days on the ventilator); or VFD = 0 if the child is ventilated for 230 days. The use of organ failure free days to determine patient-related morbidity surrogate end points in pediatric trials has been supported by influential pediatric trialists in the current low mortality pediatric critical care environment (45). Even for this surrogate marker, 1500 children were needed just to be adequately powered to demonstrate a difference of two VFDs. Death was considered an important outcome, but the study was not powered to detect a difference in mortality.

Extrapolating from adult data into pediatric practice is generally considered inadvisable. However, even if the significant reduction in mortality in adults given SDD is to be ignored, the reduction in pneumonia, which parallels the adult observations, tantalizingly hints at the possibility of a potential reduction in mortality in pediatrics, if studies were to be carried out, which were powered adequately with a large enough total number of children. Until this happens, the potential benefit of a proven maneuver in adults allowing a meta-analysis, which demonstrates a significant reduction in pneumonia rates. SDD significantly reduces the number of children who develop pneumonia. The study by Barret et al (20) could not demonstrate any treatment benefit from SDD in children with severe burns so at this stage, SDD cannot be advocated in this patient population. Furthermore, there was no overall reduction in mortality nor a reduction in overall infection rates, probably because of the small sample size.

However, on the evidence presented, is it not at least worth considering the use of SDD in certain groups of vulnerable children such as those with a high risk of mortality score or those undergoing solid organ transplantation while awaiting evidence of any survival benefit from large multicentered RCTs?

**REFERENCES**


