Selective Decontamination of the Digestive Tract and Ventilator-Associated Pneumonia (Part 1)

We read with interest the article “The Pathogenesis of Ventilator-Associated Pneumonia: Its Relevance to Developing Effective Strategies for Prevention,” by Safdar et al.1 We were surprised by 3 completely misleading statements: (1) most but not all selective digestive decontamination (SDD) meta-analyses have found a beneficial effect on ventilator-associated pneumonia (VAP), (2) they found an inconsistent effect on mortality, and (3) recent studies have justified the concern relating to the effect on mortality, and (3) recent studies have justified the concern relating to the potential for promoting antimicrobial resistance with long-term use of SDD. We cannot let this misinformation go uncorrected.

SDD is the best ever evaluated manoeuvre in intensive care medicine.2 Twenty years of clinical research have generated 55 randomized controlled trials (RCTs) and 10 meta-analyses, half of which are from Europe, invariably from Italy, and half from North America, of which two are from Canada and three are from the United States.3–12 One of the American meta-analyses9 was produced by Safdar, the author of the article to which we are responding here. All but one meta-analysis assessed the efficacy of SDD in mixed intensive-care-unit (ICU) populations.

Out of the 10 meta-analyses, the main end point was pneumonia in 7, 3–8, 10 The end points of 2 meta-analyses were yeast end points were 2 meta-analyses were yeast and infections11 and bloodstream infections,12 and the end point of Safdar’s meta-analysis was overall infection and Gram-negative infections in liver-transplant patients.9 Table 1 summarizes the morbidity results of these meta-analyses. The 7 meta-analyses with the end point of pneumonia consistently demonstrated a significant reduction in pneumonia. The most recent Cochrane meta-analysis, published in 2004, with 6,922 patients, showed that SDD using parenteral and enteral antimicrobials reduces the odds ratio for pneumonia to 0.35 (95% confidence interval [CI] 0.29–0.41).10 On average, 5 patients need to receive SDD to prevent one pneumonia. A total of 9,230 patients were available for the first meta-analysis of RCTs that reported bloodstream infections12 (Luciano Silvestri MD, unpublished data). SDD using parenteral and enteral antimicrobials significantly reduced the odds ratio for bloodstream infections, to 0.63 (95% CI 0.46–0.87). Additionally, a protective effect against bloodstream infections due to aerobic Gram-negative bacilli (AGNB) was found, with an odds ratio of 0.44 (95% CI 0.27–0.73). These findings are in strong contrast with Safdar’s claim that not all meta-analyses have found a beneficial effect.

Mortality was the outcome measure in 8 meta-analyses (Table 2).1–7,9,10,12 There was a consistent survival benefit in all but 2 meta-analyses.9,9 The most recent Cochrane meta-analysis of RCTs demonstrated that SDD using parenteral and enteral antimicrobials reduces the odds ratio for mortality to 0.78 (95% CI 0.68–0.89).10 The systematic review of RCTs that reported bloodstream infections and mortality in 9,230 patients13 showed that SDD using parenteral and enteral antimicrobials significantly reduced the odds ratio for mortality, to 0.74 (95% CI 0.60–0.91) (Luciano Silvestri, unpublished data). The number of patients to be treated with SDD to save one life is 21 in the pneumonia meta-analysis.10 Kollef’s meta-analysis of 2,270 surgical/medical patients4 and Safdar’s meta-analysis of 259 liver-transplant recipients did show an impact on mortality, but the impact was not significant, as the sample size was too small.13 Safdar’s claim that there is a very real concern relating to the potential of SDD for promoting antimicrobial resistance is based on 2 editorials, written by the groups of Bonten14 and Daschner,15 who openly oppose SDD. Remarkably, Safdar ignores the largest individual RCT, which had about 1,000 patients, and the primary end point was antimicrobial resistance among AGNB, the target microorganisms of SDD.16 This RCT, published in 2003, and conducted over the years 1999–2001, demonstrated that carriage of AGNB resistant to imipenem, ceftazidine, ciprofloxacin, tobramycin, and polymyxins occurred in 16% of SDD patients, compared with 26% in control patients, with a relative risk of 0.6 (95% CI 0.5–0.8). Fair enough; at this point in time there is no meta-analysis on antimicrobial resistance during SDD available. However, as RCTs have predefined study periods, in general a few years, this type of meta-analysis, although valuable, will not address Safdar’s justified concern with regard to antimicrobial resistance over the long term. The long-term use of SDD has been evaluated in 10 SDD studies, which monitored it between 2 and 9 years, and resistance associated with SDD has not been a clinical problem.17–26 There are 4 possible explanations why SDD reduces resistance among the target bacteria. First, in eradicating abnormal carriage and overgrowth, SDD prevents increased spontaneous mutation. Second, very high topical bactericidal levels in throat and gut eradicate resistant mutants already present. Third, polymyxin E and tobramycin are a synergistic mixture. Fourth, the administration of parenteral antimicrobials is lower in successfully decontaminated patients. These observations are in sharp contrast with the common experience that the introduction of any new potent parenteral antibiotic is associated with superinfections within 2 years.27 We believe that the addition of enteral to parenteral antimicrobials is a promising practice to maintain the usefulness of antimicrobials.

Finally, Safdar refers to the latest fad of SDD antagonists, concerning the relative contribution of the parenteral and enteral components to the reduction of morbidity and mortality.28 The 55 RCTs were not designed to assess the relative effect of the 2 major components of SDD. However, uncertainty of the weight of the parenteral and enteral contribution does not justify withholding a treatment that, in its entirety, has been shown consistently to save lives.

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Table 1.  Main Morbidity Results of the 10 Meta-Analyses of Randomized Controlled Trials of Selective Digestive Decontamination

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Number of RCTs</th>
<th>Aggregate Number of Patients</th>
<th>End Points</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SDD Trialists Collaborative Group</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>1993</td>
<td>22</td>
<td>4,142</td>
<td>Pneumonia</td>
<td>0.33</td>
<td>0.27–0.40</td>
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<td></td>
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<td></td>
<td></td>
<td>Parenteral/enteral</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enteral</td>
<td>0.43</td>
<td>0.33–0.56</td>
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<tr>
<td><strong>Kollef</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1994</td>
<td>16</td>
<td>2,270</td>
<td>Pneumonia</td>
<td>0.145&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.116–0.174</td>
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<tr>
<td><strong>Heyland et al</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>1994</td>
<td>25</td>
<td>3,395</td>
<td>Pneumonia</td>
<td>0.46†</td>
<td>0.39–0.56</td>
</tr>
<tr>
<td><strong>D’Amico et al</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td>1998</td>
<td>33</td>
<td>5,727</td>
<td>Pneumonia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parenteral/enteral</td>
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<td>0.29–0.41</td>
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<td></td>
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<td></td>
<td></td>
<td>Enteral</td>
<td>0.56</td>
<td>0.46–0.68</td>
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<tr>
<td><strong>Nathens et al</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td>1999</td>
<td>11</td>
<td>NR (surgical)</td>
<td>Pneumonia</td>
<td>0.19</td>
<td>0.15–0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bacteremia</td>
<td>0.51</td>
<td>0.34–0.75</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N (medical)</td>
<td>0.45</td>
<td>0.33–0.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bacteremia</td>
<td>0.77</td>
<td>0.43–1.36</td>
</tr>
<tr>
<td><strong>Redman et al</strong>&lt;sup&gt;8&lt;/sup&gt;</td>
<td>2001</td>
<td>NR</td>
<td>NR</td>
<td>Pneumonia</td>
<td>0.31</td>
<td>0.20–0.46</td>
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<td></td>
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<td></td>
<td>Parenteral/enteral</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enteral</td>
<td>0.40</td>
<td>0.29–0.55</td>
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<tr>
<td><strong>Safdar et al</strong>&lt;sup&gt;9&lt;/sup&gt;</td>
<td>2004</td>
<td>4</td>
<td>259 (liver transplant)</td>
<td>Infection overall</td>
<td>0.88†</td>
<td>0.73–1.09</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td>Infection due to AGNB</td>
<td>0.16†</td>
<td>0.07–0.37</td>
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<tr>
<td><strong>Liberati et al</strong>&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>36</td>
<td>6,922</td>
<td>Pneumonia</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parenteral/enteral</td>
<td>0.35</td>
<td>0.29–0.41</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Enteral</td>
<td>0.37</td>
<td>0.29–0.48</td>
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<tr>
<td><strong>Silvestri et al</strong>&lt;sup&gt;11&lt;/sup&gt;</td>
<td>2005</td>
<td>42</td>
<td>6,075</td>
<td>Fungal carriage</td>
<td>0.32</td>
<td>0.19–0.53</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fungal infections</td>
<td>0.30</td>
<td>0.17–0.53</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Fungemia</td>
<td>0.89</td>
<td>0.16–4.95</td>
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<td><strong>Silvestri et al</strong>&lt;sup&gt;12&lt;/sup&gt;</td>
<td>2005</td>
<td>51</td>
<td>9,230</td>
<td>Bloodstream infections</td>
<td>0.63</td>
<td>0.46–0.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bloodstream infections due to AGNB</td>
<td>0.44</td>
<td>0.27–0.73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bloodstream infections due to Gram-positives</td>
<td>0.92</td>
<td>0.59–1.44</td>
</tr>
</tbody>
</table>

RCTs = randomized controlled trials
SDD = selective decontamination of the digestive tract
NR = not reported
AGNB = aerobic Gram-negative bacilli
*Risk difference
†Relative risk

Data from Reference 12 include unpublished data from Luciano Silvestri MD.

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Table 2. Mortality Results of 10 Meta-Analyses of Randomized Controlled Trials of Selective Digestive Decontamination*

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Number of RCTs</th>
<th>Aggregate Number of Patients</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
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<td>SDD Trialists</td>
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<td></td>
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<td>Collaborative Group</td>
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<td>22</td>
<td>4,142</td>
<td>0.80</td>
<td>0.67–0.97</td>
</tr>
<tr>
<td>Kollef</td>
<td>1994</td>
<td>16</td>
<td>2,270</td>
<td>0.051†</td>
<td>0.015–0.089</td>
</tr>
<tr>
<td>Heyland et al</td>
<td>1994</td>
<td>25</td>
<td>3,395</td>
<td>0.87‡</td>
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<td>D’Amico et al</td>
<td>1998</td>
<td>33</td>
<td>5,727</td>
<td>0.80</td>
<td>0.69–0.93</td>
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<td>Nathens et al</td>
<td>1999</td>
<td>11</td>
<td>NR (surgical)</td>
<td>0.60</td>
<td>0.41–0.88</td>
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<td></td>
<td></td>
<td>NR (medical)</td>
<td>0.75</td>
<td>0.53–1.06</td>
</tr>
<tr>
<td>Redman et al</td>
<td>2001</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Safdar et al</td>
<td>2004</td>
<td>4 (liver transplant)</td>
<td>259</td>
<td>0.82†</td>
<td>0.22–2.45</td>
</tr>
<tr>
<td>Liberati et al</td>
<td>2004</td>
<td>36</td>
<td>6,922</td>
<td>0.78</td>
<td>0.68–0.89</td>
</tr>
<tr>
<td>Silvestri et al 11</td>
<td>2005</td>
<td>42</td>
<td>6,075</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Silvestri et al 12</td>
<td>2005</td>
<td>51</td>
<td>9,230</td>
<td>0.74</td>
<td>0.60–0.91</td>
</tr>
</tbody>
</table>

*Only data on the effect of the combination of parenteral and enteral components of SDD are shown, where possible.5,7,10,12

RCTs = randomized controlled trials
SDD = selective decontamination of the digestive tract
NR = not reported
†Risk difference for mortality related to acquired nosocomial infections
‡Relative risk

Data from Reference 12 include unpublished data from Luciano Silvestri MD.


The authors reply:

We agree with Silvestri et al that selective digestive decontamination (SDD) to prevent pneumonia has been extensively studied in the ICU population. More than 50 prospective randomized controlled trials have been conducted and numerous meta-analyses published. Yet, more than 15 years after SDD was proposed as a novel strategy to reduce ICU-acquired infections, basic and very important questions remain unanswered.

First of all, our statement that most but not all clinical trials found a reduction in the incidence of pneumonia with the use of SDD is correct. However, we agree that all meta-analyses of SDD that reported pneumonia as an outcome measure found a beneficial effect. But it is very important to acknowledge that these meta-analyses failed to find a beneficial impact of SDD on other important secondary outcomes: duration of mechanical ventilation and length of hospital stay.

As Silvestri et al acknowledge, SDD has not been found to have a mortality benefit for all patient populations in all of the clinical trials and meta-analyses. Therefore, their statement that it “has consistently been shown to save lives” is not totally supported by the evidence. It is true that some meta-analyses have found a survival benefit with SDD, however, results of meta-analyses must be interpreted with caution when there is extreme heterogeneity in the included studies, as has been the case with SDD. Studies of SDD have been carried out in very diverse patient populations, using a variety of antimicrobial regimens, many with a systemic parenteral broad-spectrum antimicrobial in addition to the multiple topical agents. Only a randomized multicenter trial of sufficient size, with adequate power to detect a mortality difference, can allow us to answer this key question with a high level of confidence.

Clearly, the greatest deterrent to widespread acceptance of SDD is the fear that it will promote the emergence and spread of antimicrobial-resistant microorganisms. Antibiotic pressure is without question the single most powerful force driving the selection of resistant microorganisms, and any strategy for prevention of infection in the ICU that has the potential to increase infections caused by multidrug-resistant microorganisms must be approached very cautiously. We know of no compelling reason why antimicrobials used for SDD should not be associated with increased resistance. The 4 possible explanations that Silvestri et al offer are conjectural, and, until proven to be true, cannot be considered as evidence that SDD is not associated with emergence of resistant microorganisms.

We stand by our statement that a number of studies support the concern of promoting antimicrobial resistance with widespread use of SDD. Numerous studies have documented major shifts in the microbial ecology of the ICU with the use of SDD. In a study by Lingnau et al, 4.5 years of SDD with ciprofloxacin led to a marked increase in methicillin-resistant S. aureus (MRSA) infections, from 17% to 81%, and of ciprofloxacin-resistant S. aureus, from 33% to 80%21. The number of infections caused by other multiresistant bacteria, such as Acinetobacter, was also increased by SDD. While it is true that some of the limited randomized trials that strived to address this issue did not find an increased risk of infection with resistant organisms, it must be emphasized that the duration of these studies and the follow-up surveillance in randomized controlled trials has not been adequate to reliably assess changes in ICU ecology at the population level.

A distinction must be made between the risk to an individual receiving SDD of infection caused by a resistant pathogen and the institutional risk of an increased prevalence of antimicrobial-resistant organisms related to the use of SDD. While both consequences are undesirable, given the skyrocketing rates of endemic nosocomial MRSA and vancomycin-resistant enterococci (VRE) infection in many institutions in the United States, and most of the rest of the world, any—however small—potential for increased antimicrobial resistance must be taken very seriously. Moreover, drawing inferences on the effect of SDD on antimicrobial resistance from randomized trials or observational case-control/cohort studies, where data are typically collected only on individuals, runs the risk of committing an atomistic fallacy—drawing conclusions at the group level based on individual-level data.

Whereas some of the studies cited by Silvestri et al collected data on antimicrobial resistance at a group level, most of the studies were done in single institutions, nearly all were restricted to single units within the study facilities, many relied on passive microbial surveillance, and most focused on the effect of SDD on resistance to a single class of drugs or a single class of organisms (ie, Gram-negative or Gram-positive organisms). These limitations aside, the studies that found no adverse effects on antimicrobial resistance are counterbalanced by studies that clearly documented increasing rates of antimicrobial resistance after the introduction of SDD. These data raise more questions than they answer about the effects of SDD on antimicrobial resistance, which is why wider acceptance of SDD, especially in the United States, has been so slow in coming. In order to address this issue better, well-designed time series or, better yet, cluster-randomized studies that employ multi-level modeling, that specifically address the effects of SDD on antimicrobial resistance across the entire spectrum of microbial pathogens at the institutional level, are needed. Until such data are available, we believe that continued concerns about the effects of SDD on antimicrobial resistance are justified, particularly in institutions where MRSA and VRE are endemic (which, unfortunately, encompasses most larger hospitals and virtually all tertiary university teaching centers).

Preemptive barrier isolation precautions, using nonsterile gowns and gloves for all contacts with the patient or the apparatus, have been shown to be an effective nonpharmacologic approach for reducing nosocomial spread of multi-resistant bacteria. SDD using a fluoroquinolone together with routine barrier contact precautions was highly effective in terminating an outbreak of infections caused by an extended-spectrum beta-lactamase-producing Escherichia coli in a liver-transplant unit. Research is needed on combining SDD with barrier precautions for reducing nosocomial spread of endemic resistant microorganisms. Since asymptomatic colonization greatly exceeds clinical infection, barrier precautions would be expected to be most effective if applied to colonized and infected patients, rather than only to patients who are found to be clinically infected. Detection of colonization requires periodic frequent microbiologic cultures of multiple body sites, an expensive and labor-intensive strategy. We have proposed using barrier precautions preemptively, in all high-risk patients, regardless of known colonization status, as a much simpler method for preventing nosocomial...
transmission of *all* resistant microorganisms. 34,36,39,43

SDD must further be scrutinized in the context of other nonpharmacologic measures that have been shown to reduce VAP: viz, semirecumbent positioning and subglottic suctioning greatly reduce the incidence of VAP without posing a risk of promoting antimicrobial resistance. Does the incremental benefit achieved with the use of SDD for prevention of VAP over such nonpharmacologic preventive measures justify the risk of increasing the already huge problem of antimicrobial resistance? This is the fundamental and as yet unanswered question. The cost-effectiveness of SDD from a societal perspective, compared with simpler, far less expensive, nonpharmacologic alternatives for preventing nosocomial pneumonia, to our knowledge has never been formally assessed.

Finally, we believe that it is critical to determine which of the various components of SDD—the topical agents or the systemic antibiotic(s) usually given—confers the greatest benefit. We strongly suspect the latter, since some of the largest and best-controlled studies of SDD that did not employ a systemic agent found no material benefit.

In sum, SDD clearly reduces the incidence of nosocomial pneumonia; however, better, more sophisticated research on these important questions may provide the needed answers as to how best SDD might be utilized in the ICU population to maximize its benefit but mitigate potentially undesirable consequences, especially the overarching threat of iatrogenic antimicrobial resistance.

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**Selective Decontamination of the Digestive Tract and Ventilator-Associated Pneumonia (Part 2)**

We read with interest the article “The Gastrointestinal Tract and Ventilator-Associated Pneumonia,” by Kallet and Quinn. We are delighted that for the first time since the introduction of SDD in Europe over 20 years ago, American respiratory and infectious-disease physicians acknowledge that SDD is an evidence-based-medicine manoeuvre. SDD using parenteral and enteral antimicrobials, a prophylactic method that costs $7 a day, reduces pneumonia by 65% when compared to gloves without antimicrobial resistance issue into 3 subheadings that amount to 4 major reasons why American colleagues prefer to behave in an “abnormal” way. Their conclusion against the use of SDD is not based on evidence from RCTs and meta-analyses, but on the opinion of the experts (ie, the lowest level of evidence). Although a trend toward improved survival in SDD-treated patients was found in most studies, the majority were too small to show a significant effect. In a recent German study by Krueger and co-authors, mortality was lower in a subgroup of 237 surgical patients who had Acute Physiology and Chronic Health Evaluation (APACHE II) scores in the mid-range stratum (ICU-admission score of 20–29). In those patients ICU mortality was 33% in the placebo group versus 16.4% in the SDD group (p = 0.01). Interestingly, they had analyzed their data on a strict intention-to-treat basis, the reduction in mortality would have been significant, with a relative risk of 0.69 (95% CI 0.51–0.95). In that study, the incidence of both Gram-negative and Gram-positive infections was lower in SDD-treated patients. Strikingly, the authors dismiss the mortality data of that German trial, but refer to it only for secondary end points, such as antibiotic use. Recently, the results of the largest SDD study to date were published. This Dutch study included 934 medical and surgical ICU patients. A significant reduction in hospital mortality, from 31% in the control group to 24% in the SDD group, was found. The reduction in mortality in SDD-treated patients was found in medical as well as in surgical patients. The evidence of the effectiveness of SDD in reducing mortality has been “consistently” confirmed in all 6 meta-analyses of RCTs so far conducted (ie, when the analysis had adequate statistical power). For example, the most recent Cochrane Library meta-analysis, published in 2004, reports reduced mortality in SDD-treated patients, with an odds ratio of 0.78 (95% CI 0.68–0.89).
The parenteral and enteral antimicrobials of the SDD protocol mainly target AGNB. Two RCTs evaluated the impact of SDD on resistance among AGNB as the primary end point. The Dutch study\(^9\) demonstrated that carriage of AGNB resistant to imipenem, cefazidime, ciprofloxacin, tobramycin, and polymyxins occurred in 16% of the SDD patients, compared with 26% of the control patients, with a relative risk of 0.6 (95% CI 0.5–0.8). This is in line with another French RCT, which showed that the addition of enteral to the parenteral antimicrobials controlled carriage and infection due to extended-spectrum \(\beta\)-lactamase-producing *Klebsiella*.\(^6\) Kallet and Quinn write in their summary that SDD reduced morbidity, mortality, and resistance only in RCTs from countries where drug-resistant Gram-positive bacteria such as VRE and MRSA are not endemic. Fair enough; the SDD prophylaxis, being not active against VRE and MRSA, may promote gut overgrowth of these intrinsically resistant Gram-positive bacteria.

VRE carriage and infection were the primary end points of SDD RCTs in 2 American ICUs with endemic VRE.\(^7^,^8\) There were no differences between the test and control groups. Seven RCTs have been conducted in ICUs where MRSA was endemic at the time of the trial, so they report a trend towards higher MRSA carriage and infection rates in patients receiving SDD.\(^9^–^15\) The addition of enteral vancomycin to the classical SDD is required to control MRSA in ICUs with endemic MRSA.\(^16^,^17\) VRE did not emerge in any of the studies that used enteral vancomycin.\(^3^1^–^22^\) The authors’ assertion that there is strong contravening evidence that SDD promotes infection due to Gram-positive bacteria is expert opinion and is unsupported by facts. This makes their claim about resistance during SDD a poor Grade-E recommendation in evidence-based-medicine terms. Kallet and Quinn maintain that the efficacy of SDD depends on the country, but that does not make sense, as all RCTs that have used the patient as the denominator invariably demonstrated control of (multi-resistant) AGNB, regardless of the global position. There are 4 possible explanations why SDD reduces resistance amongst the target bacteria: (1) in eradicating overgrowth, SDD prevents spontaneous mutation, (2) very high topical bactericidal levels in throat and gut eradicate resistant mutants already present, (3) polymyxin E and tobramycin are a synergistic mixture, and (4) the administration of parenteral antimicrobials is lower in successfully decontaminated patients.\(^1\)

Antimicrobial resistance, being a long-term issue, has been evaluated in 10 SDD studies, which monitored it between 2 and 9 years, and bacterial resistance associated with SDD has not been a clinical problem.\(^23^–^32\) The authors have serious concerns about the long-term use of SDD; however, to answer their concerns they should endorse the use of SDD, not reject it.

The emerging public health crisis from the steady rise in drug-resistant Gram-positive bacteria prohibits the recommendation of SDD. We hope that Kallet and Quinn appreciate that the public health crisis in America, where SDD is discouraged, developed during a policy of parenteral antimicrobials only. We assume that the continuation of only systemic antibiotics is one of the less radical alternatives proposed by the authors. Can we respectfully suggest that surveillance cultures of throat and gut are the unique method to fully evaluate the disastrous impact of systemic agents such as piperacillin/tazobactam?\(^33^,^34\)

Kallet and Quinn’s summary and recommendations are expert opinion, but, sadly, are based on a fundamental misunderstanding of the SDD philosophy. SDD is based on the realization that the abnormal carrier state, only detectable by surveillance cultures of throat and rectum, harms the critically ill. Disease influences carriage; that is, illness severity is the major risk factor for abnormal carriage of AGNB, and drugs, including antimicrobials, that disregard “colonization resistance” may promote subsequent overgrowth of these abnormal bacteria.\(^35\) The conversion of “abnormal” into “normal” carriage (ie, a critically ill patient who is successfully decontaminated should be free from AGNB in throat and gut) is pivotal in the management of the critically ill, as this type of patient is unable to clear abnormal flora because of the underlying disease. Surveillance cultures are also required to classify pneumonia into primary and secondary endogenous, and exogenous.\(^36\) The immediate administration of adequate parenteral antimicrobials aims to control primary endogenous pneumonia, secondary endogenous pneumonia is prevented by the enteral decontaminating agents, and a high level of hygiene prevents exogenous pneumonia. This full SDD regimen is required to significantly reduce pneumonia and mortality without antimicrobial resistance emerging. Surveillance cultures supported by molecular techniques have shown that oropharyngeal rather than gastric carriage promotes pneumonia in the critically ill, making the “gastropulmonary hypothesis” expert opinion, the lowest level of evidence.\(^37^,^38\) Nevertheless, the gut component of SDD is crucial in the control of secondary carriage and infection, of translocation, lowering of gut endotoxin to restore the immunosuppression, and minimizing of antimicrobial resistance, resulting in overall mortality reduction.\(^39\)

Finally, can we remind Kallet and Quinn and their followers that, on average, for every 5 patients who do not receive SDD, one extra patient develops a pneumonia, and that there is one extra death every 21 patients in units that do not administer SDD?\(^40\) Twenty years of clinical research into SDD show that the addition of enteral to parenteral antimicrobials prevents mutation and eradicates mutants; therefore, it is not surprising that the pre-1980s antibiotics are still active, as long as they are combined with the eradication of AGNB from the gut.\(^23^–^32\) Furthermore, it can be anticipated that in SDD units the antibiotic era will be prolonged.\(^40\)

We believe that the answer lies not in the development of single, new, more potent and expensive systemic antimicrobials, but in a radical rethinking of the philosophy by which antimicrobials are used.\(^39\)

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The authors reply:

Perhaps the most telling aspect of van Saene and colleagues’ letter is the passage, “To impress the reader, Kallet and Quinn make a mountain out of the second argument” (increased microbial resistance). Of course, the complete expression is “making a mountain out of a mole hill.”—clearly, a statement meant to dismiss valid concerns over what the established medical and scientific communities consider an impending crisis.1–3 SDD is based upon the theories that impaired colonization resistance and the gastropulmonary route are important factors in the development of VAP. Contrary to the impression conveyed by van Saene and colleagues (and as we pointed-out in our paper), neither theory has been proven beyond question, and in fact plausible alternative explanations exist.4

It is particularly noteworthy that other participants in the conference on VAP elucidated several problems and concerns regarding SDD, such as (1) the important role of oral decontamination; (2) that some of the efficacy of SDD is predicated upon the concomitant use of parental antibiotics; (3) the effectiveness of concomitant, stringent, ancillary infection-control practices on microbial resistance at Dutch hospitals that routinely use SDD; (4) SDD requires prolonged antibiotic therapy, and increased microbial resistance is intimately related to the duration of antibiotic use; and (5) a small subgroup of severely debilitated patients may benefit from SDD, but the overall medical value of the therapy is diminished by misapplying antibiotic prophylaxis to patients who do not need it.4

The relationship between SDD and the selection for resistant Gram-positive microorganisms is unclear and requires extensive research. van Saene suggests that we should endorse SDD because of our concerns about antimicrobial resistance, not in spite of these concerns. We respectfully point out that none of the randomized trials used the emergence of antimicrobial resistance as a primary outcome measure. To date, no sufficiently large, temporally-appropriate, prospective, randomized clinical trials clarifying this issue exist. Just because currently there is a higher level of evidence supporting SDD (compared to that which links SDD to promoting drug-resistant microorganisms) does not, by itself, constitute an unambiguous recommendation for general clinical use. Evidence-based medicine is not an epistemological game whereby a particular viewpoint is argued regardless of the larger context in which that evidence exists. Increased microbial resistance has profound ecological consequences, not all of which can be predicted.5 The very real specter of a post-antibiotic world is hardly a “mole hill,” and our recommendations for widespread prophylactic antibiotic use should reflect that concern.

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