The Gastrointestinal Tract and Ventilator-Associated Pneumonia

Richard H Kallet MSc RRT FAARC and Thomas E Quinn MD

Introduction
The Role of Gastric pH on the Incidence of VAP
Enteral Feeding and Nosocomial Pneumonia
   Gastric Residual Volumes
   Gastric Versus Post-Pyloric Feeding
   Acidification of Enteral Feedings
Selective Decontamination of the Digestive Tract
   Microbiologic Ecology of the GI Tract
   Rationale for SDD
   Technique
Clinical Evidence: Efficacy of SDD
   SDD and the Incidence of VAP
   SDD and Mortality
   SDD in Specific Sub-Groups
   SDD and ICU Length of Stay, Hospital Costs, and Antibiotic Usage/Costs
Unresolved Aspects of SDD Therapy
   Uncertainties Regarding the Gastropulmonary Hypothesis
   Uncertainties Regarding Colonization Resistance
   SDD and Selection for Drug-Resistant Microorganisms
Summary and Recommendations

The gastrointestinal tract is believed to play an important role in ventilator-associated pneumonia (VAP), because during critical illness the stomach often is colonized with enteric Gram-negative bacteria. These are the same bacteria that frequently are isolated from the sputum of patients with VAP. Interventions such as selective decontamination of the digestive tract (SDD), use of sucralfate for stress ulcer prophylaxis, and enteral feeding strategies that preserve gastric pH, or lessen the likelihood of pulmonary aspiration, are used to decrease the incidence of VAP. A review of both meta-analyses and large randomized controlled trials providing Level I evidence on these topics has led to the following conclusions. First, SDD substantially decreases the incidence of VAP and may have a modest positive effect on mortality. However, there is strong contravening evidence that SDD promotes infections by Gram-positive bacteria. In the context of an emerging public health crisis from the steady rise in drug-resistant Gram-positive bacteria, we cannot endorse the general use of SDD to prevent VAP. Rather, therapy should be focused on strategies other than antibiotic prophylaxis. Second, in patients who are at risk for clinically important gastrointestinal bleeding, a histamine-2 receptor antagonist should be used for stress ulcer prophylaxis, rather than sucralfate, because histamine-2 receptor antagonist provides substantially better protection without substantially increasing the risk of VAP. Third, post-pyloric enteral feeding may reduce the incidence of VAP. Key words: ventilator-associated pneumonia, nosocomial pneumonia, selective decontamination of the digestive tract, stress ulcer prophylaxis.  [Respir Care 2005;50(7):910–921. © 2005 Daedalus Enterprises]
Introduction

Ventilator-associated pneumonia (VAP) is pneumonia acquired in the intensive care unit (ICU) among patients who are mechanically ventilated through an artificial airway. Because the stomach often becomes colonized with Gram-negative bacteria during critical illness, and enteric Gram-negative bacteria are the most frequent microorganisms isolated from sputum cultures of patients with VAP, the gastrointestinal (GI) tract is believed to play an important role. This is known as the "gastropulmonary hypothesis," and it postulates the following sequence. First, the stomach is colonized by potentially pathogenic microorganisms, either from an exogenous source (contaminated liquid injected into a nasogastric tube), or from an endogenous source (duodenogastric reflux). This is followed by retrograde colonization of the oropharynx. Finally, the lower respiratory tract is colonized from sustained microaspiration of contaminated oropharyngeal (or gastric) secretions around the endotracheal tube cuff (Fig. 1).

Recognition of the GI tract as an important source of VAP has lead to several preventive measures, such as the use of sucralfate for stress ulcer prophylaxis and a regimen of antibiotic prophylaxis known as selective decontamination of the digestive tract (SDD). In this article we will examine how GI tract dysfunction during critical illness facilitates the development of VAP and review the evidence of how these therapies impact the incidence of VAP. We will also review the evidence regarding enteral feeding strategies and the risk of VAP. This narrative review will primarily rely upon Level I evidence such as large randomized clinical trials (RCTs) and meta-analyses of RCTs. Level II evidence from smaller RCTs will be used when higher levels of evidence are not available. Lower levels of evidence, such as observational studies, will be used primarily to provide a historical or conceptual context.

The Role of Gastric pH on the Incidence of VAP

Under fasting conditions, gastric sterility is maintained by an acidic pH. Clinical evidence suggests that a gastric pH of 3.5 prevents bacterial colonization, whereas a pH > 4.0 is associated with clinically important bacterial colonization and a higher incidence of nosocomial pneumonia. Critically-ill patients with either respiratory failure requiring mechanical ventilation or coagulopathy are at increased risk for clinically important, stress-related GI bleeding. This has been associated with a significantly higher mortality rate, compared to patients without evidence of bleeding (48.5 vs 9.1%, p < 0.001).

Stress ulcer prophylaxis therapy with antacids or histamine 2-receptor antagonists (H2-RA) increases gastric pH, either by neutralizing gastric acid or suppressing acid pro-
duction. Both therapies are believed to be effective in reducing clinically important GI bleeding. However, an increase in gastric pH may promote bacterial colonization and increase the likelihood of VAP. Therefore, it is recommended that stress ulcer prophylaxis should be achieved with an agent that does not increase gastric pH. Sucralfate provides stress ulcer prophylaxis without raising gastric pH and has both cytoprotective and antibacterial properties that may prevent bacterial colonization of the stomach. Meta-analyses of RCTs concluded that sucralfate, antacids, and H2-RA agents reduced clinically important bleeding equally, but the incidence of VAP and mortality were lower in patients treated with sucralfate.

However, a subsequent large, multi-center RCT found a significantly higher incidence of clinically important bleeding with sucralfate, compared to the H2-RA agent ranitidine (3.8% vs 1.7%, respectively, p = 0.02). There was a 15% relative increase in VAP among patients treated with ranitidine (19.1%), compared to sucralfate (16.2%), but this was not significant; mortality was not different (23.5% vs 22.9%, respectively). Therefore, stress ulcer prophylaxis with an H2-RA agent does not appear to significantly increase the risk for VAP. However, critically ill patients at risk for clinically important GI bleeding should receive stress ulcer prophylaxis with an H2-RA agent such as ranitidine rather than sucralfate.

It has been postulated that stress ulcer prophylaxis may not affect the incidence of VAP because approximately 40–60% of critically ill patients have a gastric pH > 4, so that a further increase in gastric pH may not impact gastric colonization and VAP. Most critically ill patients are not at serious risk for GI bleeding and typically receive early nutritional support in the form of continuous enteral feedings. Continuous enteral feedings cause an increase in gastric pH that tends to negate any differences in stress ulcer prophylaxis upon gastric pH.

**Enteral Feeding and Nosocomial Pneumonia**

**Gastric Residual Volumes**

Another aspect of enteral feeding is the risk of pulmonary aspiration and nosocomial pneumonia when gastric residual volumes are elevated. In a recent prospective observational study of 153 critically ill patients receiving early enteral nutrition, 46% showed evidence of upper digestive feeding intolerance (gastric residual volumes > 150 mL or vomiting). Despite being managed in the semirecumbent position, these patients had a significantly higher rate of nosocomial pneumonia (43%), compared to those whose gastric residual volumes were < 150 mL (24%, p = 0.01).

In a recent RCT, 40 mechanically ventilated, critically ill patients had their enteral feeding withheld when their gastric residual volumes crossed a threshold of either > 200 mL or > 400 mL. Patients were monitored closely for evidence of aspiration. The incidence of pulmonary aspiration among all study patients was high (75%), as was the incidence of pneumonia (50%). However, the average incidence of aspiration per patient in either threshold group (200 mL and 400 mL) was not different (21.6% vs 22.6%, respectively, p = 0.903). Of particular interest, in 93% of all evaluations, the gastric residual volume was below a common cut-off value of 150 mL. This suggests that the presence of relatively low gastric residual volumes does not translate into a lower risk for pulmonary aspiration.

The poor sensitivity of gastric residual volume monitoring to predict pulmonary aspiration risk is explained by the observation that the amount of fluid suctioned from the stomach depends upon several factors, including the type of tube, its position, the number of openings at the distal end of the tube, the type of syringe used for aspiration, and the individual performing the measurement. Therefore, the amount of fluid aspirated may not represent the total residual volume present in the stomach.

**Gastric Versus Post-Pyloric Feeding**

Delivery of enteral feedings directly into the small bowel may decrease the incidence of gastroesophageal reflux and the risk of pulmonary aspiration, when compared to gastric feeding. Three RCTs comparing gastric to post-pyloric enteral feeding found an 8–15% absolute reduction in VAP with post-pyloric feeding. However, these findings were not statistically significant, and an RCT of at least 400 patients would be needed for verification. Two recent meta-analyses reviewed the evidence from RCTs comparing gastric with post-pyloric feedings. Hayland et al found a significant reduction in VAP with post-pyloric feeding, with an odds ratio (OR) of 0.76 (95% confidence interval of 0.59–0.99), while Marik and Zaloga found a nonsignificant trend favoring a reduction in VAP with post-pyloric feeding. Thus post-pyloric enteral feeding may reduce the incidence of VAP.

**Acidification of Enteral Feedings**

As mentioned above, a gastric pH > 4.0 is associated with clinically important bacterial colonization and a higher incidence of nosocomial pneumonia. The pH of commercially available enteral feedings is between 6.0 and 7.0. Therefore, continuous enteral feeding may potentiate colonization of the stomach with pathogenic microorganisms, because there is never a period of time when gastric pH can return to bactericidal levels. In a small RCT, Heyland et al investigated whether acidifying enteral feedings with hydrochloric acid to a pH of 3.5 af-
fected bacterial colonization, compared to a commercial enteral feed (pH of 6.5). They found that 88% of the patients treated with the acidified enteral feedings had a sterile stomach, while only 20% of the control subjects’ stomachs remained sterile (p = 0.02). Unfortunately, no clinical studies have been published demonstrating a reduction in VAP with the use of acidified enteral feedings.

Selective Decontamination of the Digestive Tract

SDD uses prophylactic antibiotic therapy to reduce VAP and sepsis in critically ill patients. Initially SDD was developed for patients with acute leukemia, in whom mortality attributable to infection was as high as 79%. Investigators from the University of Groningen were the first to use SDD in critically-ill patients with multiple trauma. In an uncontrolled study using historical controls (Level IV evidence), the overall infection rate decreased from 80% to 16%. Known as the “Groningen technique,” this method of SDD uses multiple, topical, nonabsorbent antibiotics (supplemented by parenteral antibiotics) to sterilize the oropharynx and GI tract of aerobic Gram-negative bacteria (AGNB), the primary microorganisms that cause VAP. The theoretical foundation behind SDD is the concept of “colonization resistance.”

Microbiologic Ecology of the GI Tract

In a healthy host, potentially pathogenic microorganisms such as AGNB are prevented from colonizing the GI tract because normal GI functioning routinely clears them from the intestines (Table 1). Shortly after the introduction of antibiotics it appeared that maintaining the normal anaerobic flora also was important in preventing overpopulation of the GI tract with AGNB. “Colonization resistance” by enteric anaerobic flora may play an important role in host defense and is believed to prevent colonization of the GI tract by 4 mechanisms (Fig. 2).

During critical illness GI function is impaired so that AGNB are not cleared from the intestines. Stasis of intestinal contents resulting from paralytic ileus often causes duodenogastric reflux and colonization of the stomach with AGNB, particularly because bilirubin in the reflux fluid increases gastric pH. Colonization resistance is compromised further by the deleterious effects of antibiotics (typically penicillins and cephalosporins) on the normal enteric flora. Yeast overgrowth can occur in the GI tract with the use of fluoroquinolones. Abnormal carriage with AGNB in the GI tract also is found in patients with chronic diseases such as diabetes, cirrhosis, and chronic obstructive pulmonary disease, and appears to be independent of antibiotic usage. Among ICU patients, abnormal carriage with AGNB is related to illness severity that may represent immunodepression. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of > 15 are associated with a 33% incidence of abnormal carriage with AGNB, which increase to 50% with a score ≥ 27. Abnormal carriage with AGNB typically develops within a week of ICU admission.

Table 1. Gastrointestinal Tract Host-Defense Mechanisms for Preventing Colonization and Overgrowth by Potentially Pathogenic Microorganisms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Host-Defense Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact mucosal cell lining</td>
<td>Prevents adherence by potentially pathogenic microorganisms</td>
</tr>
<tr>
<td>pH of saliva and gastric secretions</td>
<td>Kills off potentially pathogenic microorganisms</td>
</tr>
<tr>
<td>Quantity/quality of saliva, gastric secretions, bile, and mucus</td>
<td>Washing of potentially pathogenic microorganisms from gastrointestinal lining and statis-prevention</td>
</tr>
<tr>
<td>Persistent acts of chewing, swallowing, and peristalsis</td>
<td>Normal motility prevents stasis, promotes clearance of potentially pathogenic microorganisms from gastrointestinal tract</td>
</tr>
<tr>
<td>Mucosal cell-lining turnover</td>
<td>Sloughing of cell lining eliminates adhering potentially pathogenic microorganisms</td>
</tr>
<tr>
<td>Secretion of immunoglobulin A</td>
<td>Coats potentially pathogenic microorganisms and prevents adherence to cell lining</td>
</tr>
<tr>
<td>Normal anaerobic flora</td>
<td>Colonization resistance</td>
</tr>
</tbody>
</table>
Rationale for SDD

In the early stages of critical illness, the patient’s normal host-defense mechanisms are depressed so that colonizing AGNB cannot be cleared from the GI tract.7 Moreover, systemic antibiotics may not reach sufficiently lethal concentrations in the GI tract to eliminate AGNB, so that topical therapy may be more effective.32 Clearing the GI tract of AGNB with topical antibiotic therapy may decrease the incidence of VAP and bacteremia so that total antibiotic usage also may be reduced.32

Technique

SDD consists of a decontamination regimen for both the oropharynx and the GI tract. The most common regimen uses a combination of 3 topical, nonabsorbent antibiotics: polymyxin E, tobramycin (or gentamicin), and amphotericin B.41–43 In the Groningen technique,7 SDD is augmented with a 3–4 day course of intravenous antibiotics, using a third-generation cephalosporin.41,42 SDD is done at 6-hour intervals each day, although the duration of therapy depends upon the patient population being treated.41 Typically, SDD prophylaxis commences upon admission to the ICU and is discontinued either when the patient has been removed from mechanical ventilation or upon discharge from the ICU.41 Among liver-transplant patients, SDD often begins several months prior to transplantation and continues for 30 days post-transplantation.44

The oral component of SDD starts by cleansing the oropharynx with 0.1% hexetidine solution and is followed by application of the topical triple-antibiotic paste containing 2% concentrations of polymyxin E, tobramycin (or gentamicin), and amphotericin B. A quarter-gram of methylcellulose is used as an adherent, which substantially increases the contact time between antibiotics and microorganisms. Effective decontamination is achieved within 3 days.32

Decontamination of the GI tract is achieved by instilling a 10-mL solution containing 100 mg of polymyxin E, 80 mg of tobramycin (or gentamicin), and 500 mg of amphotericin B into the stomach through an orogastric or nasogastric tube. Gastric suction is discontinued for 1 hour following administration.7 This combination of antibiotics is active against virtually all AGNB.41 Clearance of AGNB from the GI tract occurs within a few days but may take up to a week in patients with impaired gut motility.32 When SDD is supplemented by administration of intravenous antibiotics, it is typically a 3–4 day course of either cefotaxime or ceftriaxone, using a standard dosing regimen. This is done to provide adequate coverage for any potential early infections with community-acquired pathogens such as Streptococcus pneumoniae or Haemophilus influenzae.41

Clinical Evidence: Efficacy of SDD

The reported benefits of SDD include decreased incidence of VAP and other respiratory tract infections,7,38,39,45–47 decreased mortality,39,47,48 decreased ICU length of stay (LOS),48 decreased overall antibiotic usage,38,39,46–48 and decreased hospital costs.38,46–48 Assessment of these findings is difficult because over the past 20 years there have been at least 53 trials of SDD49 in which substantial differences exist both in the patient populations studied and in research design. For example, many studies were done in highly selected populations, such as liver-transplant patients,50–52 severe pancreatitis,53,54 or severe burns,55 and therefore are not applicable to the general ICU population.

SDD regimens have varied substantially, with some trials including a short course of parenteral antibiotics in the treatment group,38,48,56–59 others using topical antibiotics alone,46,50,54,60–63 some using only an oropharyngeal decontamination regimen,55,57,58 while others gave parenteral antibiotics to both the intervention and control groups.54–66 Finally, interpretation of SDD trials is limited by the substantial variations in the criteria used to diagnosis pneumonia.67 Because most of the SDD trials have been relatively small, and thus underpowered, this review will rely on both the meta-analyses41–44,49,68–72 and some of the large RCTs38,45,47,57,58 to assess whether SDD affects clinically important outcomes such as the incidence of VAP, mortality, LOS, and hospital costs.

SDD and the Incidence of VAP

Results of meta-analyses41–44,49,68–70,72 consistently have shown that SDD is associated with a marked reduction in the incidence of VAP, as the aggregate OR were between 0.12 and 0.56 (Table 2). Furthermore, the benefit of SDD is greater when studies using both topical and systemic prophylaxis (OR = 0.35) are compared to those using topical prophylaxis alone (OR = 0.52–0.56).43,49 Despite nonuniformity in the methods used to diagnosis pneumonia, when only studies using rigorous diagnostic criteria were analyzed, a substantial benefit with SDD was still evident (OR = 0.49, 0.41–0.60).69 While one meta-analysis41 reported a greater effect of SDD in reducing VAP in surgical compared to medical patients (OR of 0.19 vs 0.45, respectively), another meta-analysis40 found that trauma patients (OR = 0.38, 0.29–0.50) and medical patients (OR = 0.33, 0.22–0.51) benefited more from SDD than surgical patients (OR = 0.51, 0.36–0.73). Although there is no consistent evidence that SDD is more effective in any particular group of patients, SDD is effective in reducing VAP in the general ICU population of medical, surgical, and trauma patients.
Results of meta-analyses\textsuperscript{41–44,49,68–70} have found both less consistent and less impressive effects of SDD in reducing mortality, as the aggregate ORs were between 0.70 and 1.14 (Table 3). Yet, the largest and most recent meta-analysis\textsuperscript{49} found a distinct mortality benefit. SDD regimens that combined topical with parenteral antibiotic prophylaxis produced a consistent mortality reduction (OR range 0.60–0.81) compared to regimens that used topical prophylaxis alone (OR range 0.86–1.14). When assessed by patient category, a significant mortality benefit with SDD was found only in surgical patients receiving the combination of topical and parental therapy.\textsuperscript{41} Another meta-analysis\textsuperscript{43} found only a trend toward mortality benefit in each group, which was greater in surgical (OR = 0.73, 0.52–1.03) and trauma patients (OR = 0.78, 0.56–1.03) compared to medical patients (OR = 0.88, 0.61–1.27).

### Table 2. Relative Risk of Ventilator-Associated Pneumonia With Selective Decontamination of the Digestive Tract Versus No Treatment/Placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Number of Studies</th>
<th>Aggregate Number of Patients</th>
<th>Trial Interventions Analyzed</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberati et al (2004)\textsuperscript{49}</td>
<td>RCT</td>
<td>32</td>
<td>5,185</td>
<td>T+P</td>
<td>0.35</td>
<td>0.29–0.41</td>
</tr>
<tr>
<td>van Nieuwenhoven et al (2001)\textsuperscript{72}</td>
<td>RCT + SCC</td>
<td>32</td>
<td>4,804</td>
<td>Pooled T+P and T</td>
<td>0.41*</td>
<td>0.37–0.47</td>
</tr>
<tr>
<td>D'Amico et al (1998)\textsuperscript{43}</td>
<td>RCT</td>
<td>16</td>
<td>3,836</td>
<td>T+P</td>
<td>0.35</td>
<td>0.29–0.41</td>
</tr>
<tr>
<td>Nathens et al (1999)\textsuperscript{41}</td>
<td>RCT</td>
<td>11</td>
<td>3,395</td>
<td>Pooled T+P and T</td>
<td>0.19</td>
<td>0.15–0.26</td>
</tr>
<tr>
<td>Kollef (1994)\textsuperscript{70}</td>
<td>RCT</td>
<td>16</td>
<td>2,128</td>
<td>Pooled T+P and T</td>
<td>0.34*</td>
<td>0.26–0.43</td>
</tr>
<tr>
<td>Heyland et al (1994)\textsuperscript{69}</td>
<td>RCT</td>
<td>25</td>
<td>4,142</td>
<td>Pooled T+P and T</td>
<td>0.46</td>
<td>0.39–0.56</td>
</tr>
<tr>
<td>SDD Trialists’ Collaborative Group (1993)\textsuperscript{42}</td>
<td>RCT</td>
<td>22</td>
<td>5,185</td>
<td>T+P</td>
<td>0.37</td>
<td>0.31–0.43</td>
</tr>
<tr>
<td>Vandenbroucke-Grauls et al (1991)\textsuperscript{68}</td>
<td>RCT</td>
<td>5</td>
<td>491</td>
<td>Pooled T+P and T</td>
<td>0.12</td>
<td>0.08–0.19</td>
</tr>
</tbody>
</table>

*Odds ratio calculated by authors from the reported data
RCT = randomized controlled trial
SCC = studies with contemporaneous control groups
T+P = topical + parenteral antibiotic therapy
T = topical antibiotic therapy only
SDD = selective digestive decontamination
NR = not reported

### SDD and Mortality

### SDD in Specific Sub-Groups

Some trials have examined if SDD is beneficial to particular sub-groups of patients, such as those with multiple trauma, those undergoing liver transplantation or cardiac surgery, or those with necrotizing pancreatitis. In patients with multiple trauma, 2 RCTs\textsuperscript{66,73} showed no difference in the incidence of infections, including VAP, but both trial designs gave intravenous antibiotics to both control and treatment patients. In the other large RCT,\textsuperscript{46} no parenteral antibiotics were used, and SDD reduced the incidence of VAP by almost 50%.

Patients undergoing liver transplantation are at very high risk for postoperative infection, making SDD a very compelling therapeutic option. A meta-analysis\textsuperscript{44} of RCTs found a lower incidence of VAP and a marked reduction in Gram-negative infections in patients receiving SDD (OR = 0.16, 0.07–0.37). However, the overall infection rate was not significantly reduced (OR = 0.88, 0.71–1.09).\textsuperscript{36} This im-

---

\textsuperscript{41}SDD and Mortality

Results of meta-analyses\textsuperscript{41–44,49,68–70} have found both less consistent and less impressive effects of SDD in reducing mortality, as the aggregate ORs were between 0.70 and 1.14 (Table 3). Yet, the largest and most recent meta-analysis\textsuperscript{49} found a distinct mortality benefit. SDD regimens that combined topical with parenteral antibiotic prophylaxis produced a consistent mortality reduction (OR range 0.60–0.81) compared to regimens that used topical prophylaxis alone (OR range 0.86–1.14). When assessed by patient category, a significant mortality benefit with SDD was found only in surgical patients receiving the combination of topical and parental therapy.\textsuperscript{41} Another meta-analysis\textsuperscript{43} found only a trend toward mortality benefit in each group, which was greater in surgical (OR = 0.73, 0.52–1.03) and trauma patients (OR = 0.78, 0.56–1.03) compared to medical patients (OR = 0.88, 0.61–1.27).

### Table 2. Relative Risk of Ventilator-Associated Pneumonia With Selective Decontamination of the Digestive Tract Versus No Treatment/Placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Number of Studies</th>
<th>Aggregate Number of Patients</th>
<th>Trial Interventions Analyzed</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberati et al (2004)\textsuperscript{49}</td>
<td>RCT</td>
<td>32</td>
<td>5,185</td>
<td>T+P</td>
<td>0.35</td>
<td>0.29–0.41</td>
</tr>
<tr>
<td>van Nieuwenhoven et al (2001)\textsuperscript{72}</td>
<td>RCT + SCC</td>
<td>32</td>
<td>4,804</td>
<td>Pooled T+P and T</td>
<td>0.41*</td>
<td>0.37–0.47</td>
</tr>
<tr>
<td>D'Amico et al (1998)\textsuperscript{43}</td>
<td>RCT</td>
<td>16</td>
<td>3,836</td>
<td>T+P</td>
<td>0.35</td>
<td>0.29–0.41</td>
</tr>
<tr>
<td>Nathens et al (1999)\textsuperscript{41}</td>
<td>RCT</td>
<td>11</td>
<td>3,395</td>
<td>Pooled T+P and T</td>
<td>0.19</td>
<td>0.15–0.26</td>
</tr>
<tr>
<td>Kollef (1994)\textsuperscript{70}</td>
<td>RCT</td>
<td>16</td>
<td>2,128</td>
<td>Pooled T+P and T</td>
<td>0.34*</td>
<td>0.26–0.43</td>
</tr>
<tr>
<td>Heyland et al (1994)\textsuperscript{69}</td>
<td>RCT</td>
<td>25</td>
<td>4,142</td>
<td>Pooled T+P and T</td>
<td>0.46</td>
<td>0.39–0.56</td>
</tr>
<tr>
<td>SDD Trialists’ Collaborative Group (1993)\textsuperscript{42}</td>
<td>RCT</td>
<td>22</td>
<td>5,185</td>
<td>T+P</td>
<td>0.37</td>
<td>0.31–0.43</td>
</tr>
<tr>
<td>Vandenbroucke-Grauls et al (1991)\textsuperscript{68}</td>
<td>RCT</td>
<td>5</td>
<td>491</td>
<td>Pooled T+P and T</td>
<td>0.12</td>
<td>0.08–0.19</td>
</tr>
</tbody>
</table>

*Odds ratio calculated by authors from the reported data
RCT = randomized controlled trial
SCC = studies with contemporaneous control groups
T+P = topical + parenteral antibiotic therapy
T = topical antibiotic therapy only
SDD = selective digestive decontamination
NR = not reported

### SDD and Mortality

Results of meta-analyses\textsuperscript{41–44,49,68–70} have found both less consistent and less impressive effects of SDD in reducing mortality, as the aggregate ORs were between 0.70 and 1.14 (Table 3). Yet, the largest and most recent meta-analysis\textsuperscript{49} found a distinct mortality benefit. SDD regimens that combined topical with parenteral antibiotic prophylaxis produced a consistent mortality reduction (OR range 0.60–0.81) compared to regimens that used topical prophylaxis alone (OR range 0.86–1.14). When assessed by patient category, a significant mortality benefit with SDD was found only in surgical patients receiving the combination of topical and parental therapy.\textsuperscript{41} Another meta-analysis\textsuperscript{43} found only a trend toward mortality benefit in each group, which was greater in surgical (OR = 0.73, 0.52–1.03) and trauma patients (OR = 0.78, 0.56–1.03) compared to medical patients (OR = 0.88, 0.61–1.27).

### SDD in Specific Sub-Groups

Some trials have examined if SDD is beneficial to particular sub-groups of patients, such as those with multiple trauma, those undergoing liver transplantation or cardiac surgery, or those with necrotizing pancreatitis. In patients with multiple trauma, 2 RCTs\textsuperscript{66,73} showed no difference in the incidence of infections, including VAP, but both trial designs gave intravenous antibiotics to both control and treatment patients. In the other large RCT,\textsuperscript{46} no parenteral antibiotics were used, and SDD reduced the incidence of VAP by almost 50%.

Patients undergoing liver transplantation are at very high risk for postoperative infection, making SDD a very compelling therapeutic option. A meta-analysis\textsuperscript{44} of RCTs found a lower incidence of VAP and a marked reduction in Gram-negative infections in patients receiving SDD (OR = 0.16, 0.07–0.37). However, the overall infection rate was not significantly reduced (OR = 0.88, 0.71–1.09).\textsuperscript{36} This im-
plies that Gram-positive infections increased to counterbalance the improvement in Gram-negative infections. Mortality was not affected (OR 0.82, 0.22–2.45).44 Neither of the 2 RCTs74,75 using SDD in patients undergoing cardiac surgery has found any difference in clinically important outcome measures.

A serious complication of acute pancreatitis is infection of the necrotic tissue in the pancreatic bed. There is strong evidence that these infections are caused by organisms that first colonized the GI tract.53 In the only RCT54 of SDD in patients with acute pancreatitis, Gram-negative infections were significantly reduced, but this did not translate into a reduction in mortality.

SDD and ICU Length of Stay, Hospital Costs, and Antibiotic Usage/Costs

In a large multicenter RCT, Sanchez-Garcia et al38 reported that, compared to controls, SDD reduced both the incidence of VAP (29.3% vs 11.4%, respectively, p < 0.001) and the median LOS among survivors (16.5 d vs 11 d, respectively, p = 0.006). This translated into a reduced cost per survivor, from $16,296 for the control group to $11,926 for the SDD group. Furthermore, when patients receiving SDD were compared to controls, there was a reduction in both the use (82.4% vs 91.4%, respectively, p = 0.04) and duration of parenteral antibiotics (12 d vs 20 d, respectively, p = 0.015). In a large single-center RCT, de Jonge et al48 found that SDD reduced the median LOS from 8.5 days in controls to 6.8 days in the treatment group (p < 0.0001). This coincided with an 11% decrease in total antibiotic costs, which was attributed to decreased use of both antifungal agents and antibiotics for Gram-negative infections. The incidence of VAP was not reported. However, in another large RCT of SDD, Krueger et al57 reported that overall antibiotic usage was lower in the SDD group, compared to the control group (68.3% vs 75.2%), but total antibiotic costs were higher in the SDD

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Number of Studies</th>
<th>Aggregate Number of Patients</th>
<th>Interventions</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberati et al (2004)49</td>
<td>RCT</td>
<td>32</td>
<td>5,185</td>
<td>T+P</td>
<td>0.75</td>
<td>0.65–0.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T</td>
<td>0.97</td>
<td>0.81–1.16</td>
</tr>
<tr>
<td>D’Amico et al (1998)43</td>
<td>RCT</td>
<td>17</td>
<td>3,581</td>
<td>T+P</td>
<td>0.80</td>
<td>0.69–0.93</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>11</td>
<td>2,543</td>
<td>T</td>
<td>1.01</td>
<td>0.84–1.22</td>
</tr>
<tr>
<td>Nathens et al (1999)41</td>
<td>RCT</td>
<td>11</td>
<td>NR (surgical)</td>
<td>Pooled T+P and T</td>
<td>0.70</td>
<td>0.52–0.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T</td>
<td>0.86</td>
<td>0.51–1.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T+P</td>
<td>0.60</td>
<td>0.41–0.88</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>11</td>
<td>NR (medical)</td>
<td>Pooled T+P and T</td>
<td>0.91</td>
<td>0.71–1.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T</td>
<td>1.14</td>
<td>0.77–1.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T+P</td>
<td>0.75</td>
<td>0.53–1.06</td>
</tr>
<tr>
<td>Kollef (1994)70</td>
<td>RCT</td>
<td>16</td>
<td>2,270</td>
<td>Pooled T+P and T</td>
<td>0.92*</td>
<td>0.80–1.07</td>
</tr>
<tr>
<td>Heyland et al (1994)69</td>
<td>RCT</td>
<td>25</td>
<td>3,395</td>
<td>Pooled T+P and T</td>
<td>0.87</td>
<td>0.79–0.97</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>10</td>
<td></td>
<td>T</td>
<td>1.00</td>
<td>0.83–1.19</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>14</td>
<td></td>
<td>T+P</td>
<td>0.81</td>
<td>0.71–0.95</td>
</tr>
<tr>
<td>SDD Trialists Collaborative Group (1993)42</td>
<td>RCT</td>
<td>23</td>
<td>4,142</td>
<td>Pooled T+P and T</td>
<td>0.90</td>
<td>0.79–1.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T</td>
<td>1.07</td>
<td>0.86–1.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T+P</td>
<td>0.80</td>
<td>0.67–0.97</td>
</tr>
<tr>
<td>Vandenbroucke-Grauls et al (1991)68</td>
<td>RCT</td>
<td>5</td>
<td>491</td>
<td>Pooled T+P and T</td>
<td>0.70</td>
<td>0.45–1.09</td>
</tr>
</tbody>
</table>

*Odds ratio calculated by authors from the reported data
RCT = randomized controlled trial
SCC = studies with contemporaneous control groups
T+P = topical + parenteral antibiotic therapy
T = topical antibiotic therapy only
SDD = selective digestive decontamination
NR = not reported
group (48.2 vs 32.3 Euros/d). In addition, the lower incidences of VAP and acquired severe organ dysfunctions found in the SDD group did not translate into a decreased LOS in the ICU.

Unresolved Aspects of SDD Therapy

Although the clinical evidence from large RCTs and related meta-analyses demonstrate the efficacy of SDD prophylaxis to reduce the incidence of VAP and other clinically important outcomes, an unambiguous endorsement for the general use of SDD in critically ill patients cannot be made. In part, this is because of lingering uncertainty regarding the justifications for SDD. But more importantly, prophylactic antibiotic use must be weighed against the emerging crisis posed by multi-resistant microorganisms and concern that SDD contributes to the selection of these microorganisms, particularly Gram-positive bacteria.

Uncertainties Regarding Colonization Resistance

Critics have pointed out that evidence supporting GI tract colonization with AGNB as an important source for VAP is based primarily on clinical trials of SDD, or has been inferred from observational studies (often with suboptimal microbiological surveillance monitoring) in which prior or simultaneous colonization of the GI tract bears a correlation to the incidence of VAP. However, the GI tract is not the only etiologic source of VAP. Early-onset VAP, which occurs within the 4 days of mechanical ventilation, is caused primarily by Gram-positive bacteria that colonize the respiratory tract, whereas VAP associated with AGNB from colonization of the GI tract typically occurs after 5 days of mechanical ventilation. In addition, the role of dental hygiene in VAP has not been appreciated fully. The etiology of nosocomial pneumonia in some ICU patients has been linked to colonization of dental plaques by Staphylococcus aureus and enteric Gram-negative bacilli.

A large observational study of abnormal bacterial carriage in the GI tract reported that the median time from ICU admission to the first positive surveillance cultures (throat or rectal) with AGNB was 9 days, and in patients who developed secondary endogenous infections (the classification of gastropulmonary sources), the median time from ICU admission to onset of infection was 14 days. This suggests that SDD may not be indicated in patients whose LOS in the ICU is less than 2 weeks.

A review of 9 clinical studies examining the sequence of colonization from the stomach to the respiratory tract in critically-ill patients found that the GI tract was unimportant in 5 studies (56%), with respect to lower-respiratory-tract colonization. From the 9 studies that were reviewed, the proportion of patients in whom it could be established that GI colonization preceded pulmonary colonization varied from 9% to 32%. Furthermore, the proportion of patients who developed VAP caused by pathogens first isolated from the GI tract varied between 0% in 2 studies to 55% in 1 study. An alternative explanation for the apparent association between GI tract colonization and VAP is the possibility of a “rectopulmonary route,” whereby contamination of a patient’s skin or bed linen with AGNB from the large intestine could be transferred to medical devices or the hands of health care workers. In our clinical experience, it is not uncommon for medical equipment such as a tonsil suction, a manual resuscitator, or ventilator hosing to inadvertently come in contact with the bed linen, which may be contaminated. This manner of oropharyngeal colonization with enteric bacteria appears to be a plausible alternative explanation to the gastropulmonary hypothesis.

Uncertainties Regarding the Gastropulmonary Hypothesis

SDD was proposed as a method to selectively eliminate AGNB and thereby restore colonization resistance. However, the theory of colonization resistance has never been proven conclusively, and the complex relationship between anaerobic flora, antibiotic therapy, and overgrowth by AGNB in the GI tract has not been fully elucidated. The relevance of colonization resistance was first questioned by the emergence of resistant microorganisms in leukemia patients in prophylaxis studies of cotrimoxazole. Alternatively, these critics proposed that the suppression of AGNB by antibiotic therapy may have been more important than preservation of anaerobic flora. Vollaard and Clasener claim that antibiotic “selectivity” has been greatly overstated by proponents of SDD; they observed that the concept of SDD is only one possible explanation for the elimination of potentially pathogenic microorganisms from the GI tract. A plausible alternative is that of “unselective decontamination,” whereby very high antibiotic concentrations are achieved in the GI tract so that both AGNB and anaerobic flora are eradicated. In this scenario, impairment of colonization resistance may go unrecognized unless resistant AGNB subsequently colonize the GI tract. It is particularly noteworthy that the greatest efficacy of SDD therapy occurs with the supplemental use of parenteral cephalosporins such as cefotaxime, which impairs the anaerobic flora of the GI tract. Thus, the rationale for SDD may be based upon a misinterpretation of the effects of antibiotic therapy on colonization resistance.
SDD and Selection for Drug-Resistant Microorganisms

The use of antibiotics may induce resistance by microorganisms, so that subsequent infections with resistant microorganisms will result in substantial secondary morbidity. All SDD regimens have gaps in the spectrum of coverage, usually in relation to Gram-positive bacteria. Over a prolonged time period both AGNB and pseudomonads may develop intrinsic or acquired resistance as well. Although antibiotic resistance from SDD therapy at first may be restricted to the agents used, over time it is possible that broad-spectrum resistance may develop. Just as evidence of drug-resistance emerged during antibiotic prophylaxis in leukemia patients, by the early 1990s several reports from centers where SDD therapy was used found an ominous increase in microorganisms resistant to tobramycin, polymyxin, and cefotaxime.

Most of the large, more recent clinical trials of SDD have attempted to address this concern by incorporating surveillance monitoring for colonization by resistant organisms and changes in the mix of bacteria isolated. The results of these analyses are mixed, and unfortunately many lack adequate follow-up to address long-term concerns. Yet a relatively consistent finding was increased colonization by Gram-positive organisms when SDD was used without vancomycin. This finding also is consistent with the overgrowth and translocation of Gram-positive bacteria reported in animal models of SDD. Although the study by de Jonge et al was an important exception to this finding, isolation of Gram-positive organisms was infrequent in both arms of that trial. A more recent study by Camus et al, using an SDD regimen of oral and enteral tobramycin/polymerxyn supplemented with nasal mupiricin and chlorhexidine body wash, avoided a shift toward Gram-positive organisms and had a significant beneficial effect on total nosocomial infections. Further study with this regimen is warranted.

The results of some observational studies should be mentioned as well. Hammond et al performed surveillance of isolated organisms in the year before, the 2 years during, and the year after a large clinical trial of SDD. They found no long-term effects on antimicrobial resistance, however, the rates of methicillin-resistant S. aureus colonization were very low in all years. Another study, by van der Voort et al, found a decrease in multi-resistant aerobic Gram-negative bacilli during the year after institution of an SDD policy. However, Lingnau et al examined patients before and during a randomized trial of SDD, using 2 topical regimens plus parenteral ciprofloxacin, and reported a significant increase in resistance of S. aureus isolated in the study to oxacillin and ciprofloxacin. Moreover, there was a rapid increase in the resistance of Enterococcus faecalis to ciprofloxacin. Leone et al found a general increase in Gram-positive colonization, but no increase in methicillin-resistant S. aureus. Finally, Hurley et al reported that use of SDD in the ICU may impact the pattern of organisms isolated in other patients not receiving the regimen.

Although the vast majority of patients who received SDD in clinical trials have tolerated the regimen well, the assessment of whether or not to use SDD as prophylaxis for VAP in critically ill patients must be made in light of concerns that there is substantial long-term risk, namely acceleration of the development of resistant strains of bacteria. This is a concern that may present an ethical dilemma to the medical community, because the risk is not necessarily important to an individual patient being treated with SDD today. Rather, the potential risk would be a long-term risk to public health.

Summary and Recommendations

Based upon our review, there is strong inferential evidence that the GI tract is an important factor in VAP. Whether or not the GI tract is the primary source of VAP is less certain. And it is this uncertainty that affects judgments about the appropriateness of SDD, particularly in the context of the emerging crisis of drug-resistant Gram-positive bacteria. There is consistent Level I evidence that SDD significantly decreases the incidence of VAP, and the largest, most recent meta-analysis provides evidence that SDD reduces mortality as well. There is also Level I evidence, albeit less consistent, that SDD reduces LOS in the ICU, antibiotic usage, and hospital costs.

By the customs of evidence-based medicine, these findings normally would warrant a recommendation favoring SDD. Yet we are not prepared to endorse SDD to reduce the risk of VAP. We believe this is prudent for the following reasons. First, Level I evidence does not consistently suggest a clear mortality benefit. Second, Level I evidence suggesting that SDD does not appreciably impact microbiological resistance comes from countries where drug-resistant Gram-positive bacteria are not endemic, as they are in the United States and much of Europe. Third, surveillance studies on the emergence of drug-resistant bacteria in hospitals using SDD are not of sufficient duration to judge the long-term impact. Fourth, the trajectory for microbial antibiotic resistance appears to be worsening, so that the impact of any contemporary errors in judgment regarding prophylactic antibiotic therapy for medical care in the not-to-distant future will be both profound and irreversible. Viewed within this context, we believe other, less radical alternatives to SDD need to be fully evaluated for efficacy in preventing VAP before antibiotic prophylaxis is considered. In countries where drug-resistant mi-
croorganisms are not a major concern, use of SDD may be an appropriate therapy option if VAP is a major problem.

Stress ulcer prophylaxis with an H2-RA agent does not appear to significantly increase the risk for VAP, but does substantially reduce the risk of clinically important GI bleeding, compared to sucralfate. Therefore, critically ill patients at risk for clinically important GI bleeding should receive stress ulcer prophylaxis with an H2-RA agent rather than sucralfate. The current evidence suggests that there is no practical level of gastric residual volume that can be maintained whereby there is a decreased risk for aspiration and VAP. In this context, the use post-pyloric feeding may reduce the risk of aspiration and VAP.

REFERENCES


Discussion

Maki: I think it’s important to point out that clinicians in the Netherlands, who’ve been very strong proponents of SDD, have very little VRE [vancomycin-resistant enterococci] or MRSA [methicillin-resistant S. aureus]. But they’re absolutely fanatic about many critical issues, I think, that cast a cloud over it. If you took away the oral decontamination alone, I think you’d lose a great deal of the benefit, because the studies of selective oral decontamination show as good a VAP reduction as full-blown SDD. So why fill the entire GI tract with antimicrobials if you don’t really need to?

Almost all the SDD studies also gave systemic third-generation cephalosporins with nonabsorbable topical antibiotics, and that clouds drawing

Respiratory Care • July 2005 Vol 50 No 7 921
conclusions that SDD is making the difference. Some of the best controlled studies that didn’t find much benefit used no third-generation cephalosporins. So I think that it’s probably most accurate to state that if you blitz the patient with anti-infectives topically and systemically, you will reduce VAP.

What’s not addressed adequately, which is a really important question, is the long term. If SDD is used very widely, I think it’s inevitable that it would promote resistance on a major scale. The question is, do we want to make that step?

REFERENCES


Pierson:* Why hasn’t SDD caught on in the United States? We surely do a lot of things for which there are no good outcome data. Is it because it’s just too much hassle for clinicians? Is it because we’re skeptical about the database? Is it because there’s no very expensive reimbursed package available that can simply be ordered?

Kallet: I think, in looking at it, 2 things that jump out are the cost of having these things prepared versus clinicians having to make up the cocktails themselves. I think it is a hassle. My take from reading the editorials and the discussions in many of these papers is I think that people really are scared about microbial resistance. I think some of the questions that Dr Kollef talked about in terms of the methodological problems make people skeptical.

Dr van Saene had an editorial in Intensive Care Medicine last year that basically blasted practitioners, partic-

Kollef: Yesterday Dennis Maki mentioned the chlorhexidine issue, which has also been looked at, and although those studies have methodological problems, the other issue is that when you look at SDD and at those meta-analyses by Nathens and Marshall1 and D’Amico et al,2 they show that the mortality advantage is in the group of patients who got intravenous antibiotic therapy. It really isn’t in the group of patients who got oral decontamination alone.

The problem that I have with those studies—there are data out there that just 24 hours of parenteral antibiotics in a critically ill patient may be enough to reduce the occurrence of early-onset pneumonia, which is what they focus on with the SDD regimen. They don’t really show data that the late-onset pneumonias are prevented. It’s pretty clear that the main driver for resistance in ICUs is the duration of antibiotic exposure. There have been very good studies, such as that by Dennesen et al,3 although they looked at parenteral antibiotics and made the point that once you’re beyond 7 days of antibiotic therapy, the likelihood of seeing multi-resistant organisms in the respiratory tract increases. So for that reason I think that there were flaws in the way those studies have been done, and the way they have used comparators. It would be very interesting to see a study doing the SDD regimen simply compared against 24 hours of prophylactic antibiotics to see if indeed there is any benefit in that particular setting.

REFERENCES

ularly in the United States, for not using this. I think the man is incredibly frustrated, which is understandable; it's a therapy that works and no one's using it. But I just think it's unconvincing. I think we do have a major crisis, and people are, thank God, alert to that, and are not ready to jump on the bandwagon with this. I think there are other ways to treat this.

**REFERENCE**


**Maki:** There's one thing that a lot of people don't know; the hematological community actually used SDD in the 1970s and early 1980s. There's a modest literature out there, and it's very unimpressive. And granulocytopenic patients who would receive oral vancomycin and gentamicin for 4, 5, or 6 days and didn't tolerate it—there were a lot of adverse effects—had an almost frightening increased risk of infection once they stopped it. SDD here was pretty soundly rejected when some of these studies were published.

**REFERENCES**


**Kallet:** Thank you. I haven't had time to go back and look at the really early studies with the leukemia patients, but that's really important information.

**Niederman:** I do think that, as Marin Kollef alluded to, we don't really understand which of the components of SDD is absolutely necessary, and I don't know that it was developed in a logical fashion. They just sort of had a hypothesis, where multiple components were put together. Some studies have suggested that it's only the oral decontamination; some have suggested it's only the systemic antibiotics; and some say it's the whole package. So I think that part of the reluctance is that you don't want—in the context of antibiotic resistance—the applying of antibiotics in every site in the body if it's not absolutely necessary. The other part is that, as with most of these clinical protocols, you don't get a full flavor for what really happens.

About 10 years ago I made rounds with one of the proponents of SDD in his ICU, and they went way beyond what's even in the protocol. If they isolate any pathogens from cultures, they immediately treat colonization. I don't even know that you can conclude that you reduce the incidence of pneumonia, because you're culturing everything in a sea of antibiotics, and there are antibiotics everywhere. If you're using a culture to diagnose pneumonia, I think all you can say is that you're not able to recover organisms when everybody has antibiotics pouring through them. But I don't know if that means they don't have pneumonia, and that's why I think the mortality end point is so important.

**Kollef:** Jean Chastre was involved in this. We recently finished a multicenter, multinational trial looking at an oral protegrin peptide, essentially, and it had reasonably good activity in vivo in phase 1 and 2 trials for preventing colonization of the orodigestive tract. It was probably the most rigorous study to date in terms of design and power, and it looked at VAP in survivors, so it accounted for the mortality issues that complicate a lot of these studies. Basically, we found no effect at all. And there was an effect in reducing colonization.

Now, one could argue that maybe it wasn't as potent as antibiotics, but at least in that setting it did not have any effect on VAP in survivors. The numbers were identical. The only group that showed any signal was the trauma population. And those data have been submitted and hopefully will be published. But there are a lot of methodological problems with the SDD literature, and that makes it even more complicated.

**Solomkin:** My take on it is that the difficulty with this and most other prophylaxis studies is that they encompass multiple groups of patients, most of whom are at low risk of the disease. There really are patients who we periodically will put on SDD. These are critically ill people with very severe respiratory distress who have been on ventilators for weeks, if not more, and who are beginning to get into a pattern of repetitive infection, where we simply can't get them off of systemic antibiotics.

The point is that, as with all technology, there are groups who will probably benefit from it, but its value is being diluted by giving it to others. For example, a lot of the people in these studies using parenteral therapy for several days are actually off SDD before the parenteral therapy is stopped. So it really is very unclear what's happened to them. But I think there is a small group of patients who this may be beneficial for. And I go back to the candida experience as an example of prophylaxis, which—at least for some organisms—does work.