Selective Decontamination of the Digestive Tract in Surgical Patients

A Systematic Review of the Evidence

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Objective: To determine the comparative efficacy of selective decontamination of the digestive tract in critically ill surgical and medical patients, and in selected subgroups of surgical patients with pancreatitis, major burn injury, and those undergoing major elective surgery and transplantation.

Data Sources: The MEDLINE database was searched from January 1966 to December 1996 using the terms “decontamination or prophylaxis,” “intensive care units,” and “antibiotics.” The search was limited to English-language studies evaluating the efficacy of selective decontamination of the digestive tract in human subjects.

Study Selection: The primary review was restricted to prospective randomized trials.

Data Extraction: End points of interest included rates of nosocomial pneumonia, bacteremia, urinary tract infection, wound infection, mortality, and length of intensive care unit stay. Methodologic quality of individual studies was assessed using a previously described model.

Data Synthesis: Odds ratios (ORs) together with their (95% confidence interval [CIs]) were reported and determined using the Mantel-Haenszel method. Mortality was significantly reduced with the use of selective decontamination of the digestive tract in critically ill surgical patients (OR, 0.7; 95% CI, 0.52-0.93), while no such effect was demonstrated in critically ill medical patients (OR, 0.91; 95% CI, 0.71-1.18). The greatest effect was demonstrated in studies where both the topical and systemic components of the regimen were used. Rates of pneumonia were reduced in both subsets of patients, while those of bacteremia were significantly reduced only in surgical patients.

Conclusions: Selective decontamination of the digestive tract notably reduces mortality in critically ill surgical patients, while critically ill medical patients derive no such benefit. These data suggest that the use of selective decontamination of the digestive tract should be limited to those populations in whom rates of nosocomial infection are high and in whom infection contributes notably to adverse outcome.


SELECTIVE decontamination of the digestive tract (SDD) is an infection prophylaxis regimen that employs topical and oral nonabsorbable antibiotics to eradicate pathogenic organisms from the gastrointestinal (GI) tract. The regimen was first used in patients with neutropenic leukemia undergoing induction therapy with promising results. In 1983, Stoutenbeek et al adapted the technique of SDD to patients in an intensive care unit (ICU) setting; the first clinical trial in a homogeneous group of multiple trauma patients was described the following year. Since then, at least 25 controlled clinical trials and 4 meta-analyses evaluating the technique have been reported; however, although SDD is widely used in European ICUs, it has not found favor in North America.

The microbiologic rationale for SDD derives from clinical and experimental studies on the normal GI tract flora and its changes in critical illness. The indigenous flora of the oropharynx and GI tract is remarkably constant over time. Mechanisms preventing overgrowth with potentially pathogenic organisms include salivary flow, gastric acidity, bile acids, secretory IgA, and peristalsis. In addition, obligate anaerobic bacteria contribute to the prevention of colonization of the digestive tract by facultative anaerobic and potentially pathogenic bacteria and yeasts, a phenomenon referred to as colonization resistance.

In the critically ill patient, the mechanisms limiting overgrowth of potentially pathogenic organisms are compromised by the underlying disease processes, instrumentation, and medication that result in...
MATERIALS AND METHODS

The MEDLINE database from January 1966 to December 1996 was searched using the search terms “decontamination or prophylaxis,” “intensive care units,” and “antibiotics.” Titles and abstracts were also searched during this period for the term “decontamination.” Additional citations were obtained from several recent meta-analyses and through personal communications from other investigators involved in primary studies. The primary review was restricted to prospective, randomized, or consecutive trials. Studies using historic controls were reviewed only in patient populations where limited data exist. Studies were considered to have enrolled surgical patients if at least 75% of the subjects evaluated had been admitted following trauma or major surgery. Studies were considered to have enrolled medical patients when fewer than 25% of patients met this criterion.

Methodologic quality of the studies selected for this systematic review was evaluated using a model previously described by Heyland et al

Table 1:

| Odds ratios (ORs) and pooled ORs together with their 95% confidence intervals (CIs) were reported and determined using the Mantel-Haenszel method. An OR of less than 1.0 suggests that SDD results in a reduction in the relative odds of dying or developing a nosocomial infection. |

impairment of salivary flow, gastric alkalization, chol- lestasis, and intestinal ileus. In addition, the use of broad-spectrum antibiotics eradicates the anaerobic flora, leading to a loss of colonization resistance. The net result is that within days of admission to an ICU, the relatively avirulent indigenous flora is replaced by a variety of potentially pathogenic species. Abnormal gastric colonization develops within days in more than two thirds of patients admitted to an ICU; the most common isolates include Candida albicans, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus, and coagulase-negative Staphylococcus, the predominant infecting species of nosocomial ICU-acquired infection.

Many descriptive studies have shown an association between pathologic, oropharyngeal, and gastric colonization and the development of nosocomial infection. Interventional studies in which normal gastric acidity is maintained by the use of cytoprotective agents support, but do not confirm, a role for altered gastric flora in the pathogenesis of ventilator-associated pneumonia. Aspiration of contaminated upper GI tract fluid is the most plausible and readily demonstrable mechanism of infection with proximal gut organisms. Alternatively, proximal GI tract colonization may lead to translocation of viable organisms through an intact gut wall. Although a well-established phenomenon in animal models, translocation has not been conclusively demonstrated in humans.

The standard SDD regimen consists of 2 components. Topical, nonabsorbed polymyxin E, tobramycin, and amphotericin B, a combination active against essentially all aerobic gram-negative bacteria and fungi. These antibiotics have limited activity against the normal anaerobic flora and maintain normal colonization resistance. In addition, intravenous cefotaxime sodium is administered until surveillance cultures demonstrate adequate decontamination of the GI tract, generally 4 days following the initiation of SDD. Cefotaxime treats early established infection by community-acquired pathogens, particularly Streptococcus pneumoniae or Haemophilus influenzae, that may be aspirated during intubation, and temporizes until the enterally administered antibiotics have adequately decontaminated the GI tract. Selective decontamination of the digestive tract is initiated as soon as possible following admission and is continued until cessation of mechanical ventilation or discharge from the ICU.

The disparate results of clinical trials in different patient populations suggest that the practice may benefit select groups of patients. Its role in surgical patients has not been explicitly evaluated, although surgical patients might be anticipated to show particular benefit. Rates of nosocomial pneumonia seem to be higher in critically ill surgical patients than in patients admitted to a medical ICU, and the mortality attributable to nosocomial pneumonia is notably greater in the surgical subpopulation. On the other hand, concerns have been voiced that a reduction in rates of pneumonia in SDD studies does not seem to result in improved outcome and that widespread adoption of the technique may contribute to the emergence of antibiotic resistance.

To evaluate the utility of SDD in surgical patients, we conducted a formal, systematic, English-literature review using an evidence-based methodology that generates recommendations based on the strength of positive evidence provided by clinical studies. Grade A recommendations are supported by level I evidence that reflects statistically significant conclusions from randomized, controlled trials and provides a strong argument for adopting the therapy evaluated. Grade B recommendations are supported by level II evidence; and grade C recommendations, by level III, IV, or V evidence. Grade B and C recommendations provide less convincing evidence of therapeutic efficacy and justify either adoption or withholding of the therapy in question. Notable differences in the response to SDD in surgical, as compared with medical, ICU patients are evident, justifying a grade A recommendation in support of the use of routine SDD prophylaxis in critically ill surgical patients. Selective decontamination of the digestive tract shows evidence of clinical benefit in subpopulations of surgical patients as well, although the limited sample sizes of published studies preclude definitive conclusions regarding its use in specific subgroups.

RESULTS

SDD IN CRITICALLY ILL SURGICAL PATIENTS

Eleven randomized prospective studies have been published on the use of SDD in surgical ICU patients. All of the available studies are limited in their sample size, and thus have insufficient power to detect even
modest reductions in mortality. The OR for mortality in patients treated with SDD was less than 1 in 8 of the 11 trials, with 1 demonstrating a significant reduction in mortality34 (Figure 1). The pooled OR for these 11 trials is 0.70, with CIs indicating at worst a 7% and at best a 48% reduction in the odds of death in surgical ICU patients treated with SDD (Table 2). Separate analysis of studies in which systemic antimicrobial therapy was administered32,34,35,38,40 compared with those with only the topical components of the regimen30,31,33,36,37,39 demonstrated the greatest survival benefit in the former group. The effect of SDD on rates of nosocomial infection in surgical patients is similarly evident. Nine of 10 assessable trials demonstrated a statistically significant reduction in the rate of nosocomial pneumonia, with a pooled OR of 0.19. There is a significant reduction in bacteremic episodes and urinary tract infections in patients treated with SDD while wound infection rates are unaffected (Table 2). Only 1 of 8 assessable studies demonstrated a clear reduction in length of ICU stay,37 although there is a significant reduction in the pooled length of stay in these 8 studies (for control patients, 16.9 ± 13 days vs 15.2 ± 12.5 days for SDD patients; P < .05, t test). All values are expressed as mean ± SD.

SDD IN CRITICALLY ILL MEDICAL PATIENTS

Ten prospective, randomized, controlled clinical trials of SDD have been carried out in critically ill medical patients.41-50 Similar to the trials in critically ill surgical patients, almost all of the studies lack sufficient power to detect a clinically significant reduction in mortality. Only 1 study (445 evaluable patients) had adequate power to detect a 25% reduction in mortality. This trial failed to demonstrate any notable survival benefit in patients receiving SDD.43 In contrast to most of the other studies, systemic antimicrobial therapy was not administered. The pooled OR for a reduction in mortality using SDD prophylaxis in medical patients is 0.91 with the upper limit of the CI being more than 1.0 (Figure 2). Even if the analysis is limited to studies in which systemic antimicrobials are administered,41,42,44,46,47,49 the effect on survival fails to reach statistical significance (Table 2). Selective decontamination of the digestive tract had a

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**Table 1. Criteria Used to Assess Methodologic Quality**

<table>
<thead>
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<th>Score</th>
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<td>Methods</td>
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<td>Not randomized</td>
<td>Truly randomized</td>
</tr>
<tr>
<td></td>
<td>Blinding</td>
<td>Not blinded</td>
<td>Double blinded</td>
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<tr>
<td>Analysis</td>
<td>Other</td>
<td>Intention to treat</td>
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</tr>
<tr>
<td>Population</td>
<td>Patient selection</td>
<td>Selected patients or cannot tell</td>
<td>Consecutive eligible patients</td>
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<tr>
<td></td>
<td>Comparability of groups of baseline</td>
<td>No or not sure</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Extent of follow-up, %</td>
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<td>Intervention</td>
<td>Treatment protocol</td>
<td>Poorly described</td>
<td>Reproducibly described</td>
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<tr>
<td></td>
<td>Cointerventions†</td>
<td>Not described</td>
<td>Described but not equal or not sure</td>
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<tr>
<td></td>
<td>Crossovers, %</td>
<td>Not described</td>
<td>&gt;10</td>
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*Variables were dichotomous variables scored on a 3-point scale with no middle value. Ellipses indicate no middle value.
†From Heyland et al.29

**Table 2. Efficacy on Mortality and Nosocomial Infection Rates**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Surgical</th>
<th>Medical</th>
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<tr>
<td>Mortality</td>
<td>Overall 0.70 (0.52-0.93)</td>
<td>0.91 (0.71-1.18)</td>
</tr>
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<td>Topical and systemic 0.60 (0.41-0.88)</td>
<td>0.75 (0.53-1.06)</td>
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<tr>
<td></td>
<td>Topical only 0.86 (0.51-1.45)</td>
<td>1.14 (0.77-1.68)</td>
</tr>
<tr>
<td>Nosocomial Infection</td>
<td>Pneumonia 0.19 (0.15-0.26)</td>
<td>0.45 (0.33-0.62)</td>
</tr>
<tr>
<td></td>
<td>Bacteremia 0.51 (0.34-0.75)</td>
<td>0.77 (0.43-1.36)</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection 0.51 (0.34-0.76)</td>
<td>0.51 (0.32-0.82)</td>
</tr>
<tr>
<td></td>
<td>Wound infection 0.56 (0.23-1.37)</td>
<td>. . .</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; ellipses, no analysis performed.
significant effect in reducing episodes of nosocomial pneumonia and urinary tract infections in medical patients (Table 2); however, there was no reduction in the risk of bacteremia (OR, 0.77) or length of ICU stay (for controls patients, 16.7 ± 16 days vs 16.8 ± 13 days for SDD patients).

To rule out the possibility that differences in the methodologic quality of the clinical trials evaluating medical and surgical patients accounted for the differential benefit seen in surgical patients, a formalized assessment of the quality of the individual trials was performed as described in the "Materials and Methods" section. Methodologic quality scores were similar in medical (7.6 ± 1.9) and surgical trials (7.9 ± 2.3), suggesting that the conduct of the study did not account for the differential results observed.

Data from meta-analyses and from subset analysis of critically ill medical and surgical patients provide sufficient level I and II evidence for a grade A recommendation for the use of SDD in critically ill surgical patients as a prophylactic measure to reduce mortality. Topical antimicrobial therapy should be used in conjunction with a short course of systemic antibiotics.

**SDD IN TRANSPLANTATION**

Infection contributes to mortality in patients undergoing solid-organ transplantation. Selective decontamination of the digestive tract has only been formally evaluated in patients undergoing orthotopic liver transplantation. Case series and retrospective studies suggest a reduction in rates of infection when compared with historic controls. There are 3 randomized prospective studies of SDD in liver transplantation that show a reduction in rates of nosocomial infection and a modest improvement in survival. Support for the use of SDD in liver transplantation is based on level II evidence and is given a grade B recommendation. Further studies are required in both liver transplant and other solid-organ recipients to provide adequate power to determine whether a true survival benefit exists.

**SDD IN MAJOR ELECTIVE SURGERY**

Selective decontamination of the digestive tract has been most extensively studied in cardiac surgical patients, a homogeneous group of patients undergoing major elective surgery. Randomized trials show a reduction in rates of infection, but not mortality, in a group of patients with a low baseline mortality rate (Table 3), and reduced levels of endotoxin and interleukin 6 in the postoperative period.

The role of SDD vs standard perioperative antibiotic prophylaxis in patients undergoing elective esophageal resection for carcinoma has been examined in a prospective, randomized study. Selective decontamination of the digestive tract resulted in a significant reduction in rates of pneumonia (14% vs 2%) and wound infections (35% vs 11%) without a reduction in the length of hospital stay or mortality (2% vs 3%). The effectiveness of SDD in patients undergoing total gastrectomy and esophagojejunal anastomosis has been evaluated in a designed prospective multicenter study. Selective decontamination of the digestive tract initiated the evening prior to the procedure resulted in a significant reduction in the rate of anastomotic leaks (10.9% vs 2.9%), pneumonia (22.3% vs 8.8%), and mortality (10.6% vs 4.9%).

Although SDD can reduce the incidence of postoperative infection in patients undergoing cardiac surgery, its routine use is probably unnecessary. Risk factors for
In a prospective randomized trial of SDD in acute pancreatitis, Luiten et al. described a 50% reduction in the incidence of infected pancreatic necrosis (38% vs 18%). Patients receiving SDD required fewer laparotomies and had a significant reduction in mortality when stratified by Imrie score, with Imrie scores of 3 or higher obtaining the greatest survival benefit. A small, retrospective study of critically ill patients receiving mechanical ventilation examined the effects of SDD on patients with pancreatitis compared with historic controls. This study demonstrated a reduction in the incidence of bacteraemia and nosocomial pneumonia in patients poorly matched for both Acute Physiology and Chronic Health Evaluation score and Ranson criteria. It is recommended that SDD be considered in patients with severe acute pancreatitis. This grade B recommendation is based on a single level I study.

The results of this meta-analysis show that the technique of SDD can benefit surgical patients. Selective decontamination of the digestive tract reduces rates of nosocomial pneumonia and bacteremia and nosocomial infections at remote sites. More importantly, it has a statistically significant effect on mortality. The best estimate for this effect is a 30% reduction in ICU mortality with CIs narrow enough to all but exclude the possibility of a type I error. This mortality effect is larger than that seen with other prophylactic modalities that have become standard care in surgical practice, including those that prevent deep venous thrombosis and pulmonary embolism or surgical wound infections.

Nonetheless, SDD has not been widely adopted as a prophylactic measure. There are several possible explanations for this. Pharmaceutical-grade preparations of polymyxin E and amphotericin B for topical use are not readily available. As a result, centers that have adopted the SDD technique have had to use intravenous preparations at substantially greater cost and local hospital pharmacies must prepare the SDD paste and suspension. The cost of SDD in the ICU setting has received only passing attention. In the 21 studies evaluating the efficacy of SDD in the ICU, 6 make no reference to overall antibiotic use, 35,36,41,45,48,49 In 4 studies, overall antibiotic costs were higher in patients receiving SDD, 34,42,43,50 In only 1 study was total antibiotic cost lower in the treatment group. 50 Further, no attempt has been made to estimate costs related to microbiologic surveillance. With currently available data, it is not possible to conclude that SDD is a cost-effective, infection prevention strategy.

Although available data show no increase in the prevalence of resistant gram-negative organisms in patients managed with SDD (and indeed SDD has been promoted as a potential method of decontaminating patients with resistant gram-negative organisms40), its safety in centers where resistant gram-positive organisms are common has not been established. Several studies have documented an increase in rates of isolation of gram-positive organisms, particularly Staphylococcus aureus, 37,42,43 coagulase-negative Staphylococcus, and Enterococcus 34,37,38 when SDD is implemented. The spectrum of resistance is poorly reported. Gentamicin sulfate-resistant enterococci were prevalent in one study; however, surveillance cultures were not performed on the control group. 38 In another study, a notable increase in methicillin-resistant S aureus colonization in patients receiving SDD compared with controls was documented. 42 Resistant gram-negative organisms seem to be less of a concern; however, tobramycin-resistant, aerobic, gram-negative bacilli have been reported in 2 studies. 34,35 Although notably overt infection with resistant organisms has not been reported with the use of SDD, this potential exists, and routine surveillance cultures may be necessary to allow for the early detection of antimicrobial resistance.

Meta-analyses show that SDD has a favorable effect on both nosocomial infection and ICU mortality when it is used as standard prophylactic therapy for critically ill surgical patients. Yet the technique is not widely employed.
in North America but rather viewed with suspicion and skepticism by many. The appropriate resolution of such a state of clinical equipoise is a randomized, double-blind, placebo-controlled, clinical trial, and we believe it is important that such a trial be undertaken. This trial should evaluate a homogeneous group of patients at high risk for infection-related morbidity and mortality; for example, victims of multiple trauma or patients undergoing solid-organ transplantation. It must have an objective primary end point, namely, ICU mortality, and be adequately powered to include or exclude a clinically important mortality effect. It must also incorporate the microbiologic surveillance that will permit definitive conclusions regarding the effect of SDD on the microbial ecology and resistance patterns in patients undergoing cardiac surgery. Finally, the study should incorporate a control group of patients receiving systemic but not topical prophylaxis. A prospective, randomized trial of SDD in trauma patients showed comparable outcomes in a control group receiving systemic antimicrobial prophylaxis alone.

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REFERENCES


