

Commentary

Opinion: The clinical use of selective digestive decontamination

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Abstract

Several recent meta-analyses have shown that the use of SDD can reduce the occurrence of nosocomial pneumonia among ventilated patients in the intensive care unit (ICU) setting. However, the use of SDD has also been demonstrated to increase subsequent patient colonization and infection with antibiotic-resistant bacteria, particularly Gram-positive cocci. Therefore, the routine use of SDD cannot be advocated at the present time. The mortality benefit of SDD appears to occur in surgical/trauma patients, and to be associated primarily with the administration of parenteral antibiotics. This is already an accepted practice in most patients during the perioperative period (eg prophylactic parenteral antibiotics for 24 h). Prolonged decontamination of the aerodigestive tract with topical antimicrobials does not appear to influence outcome, and should not be routinely employed.

Keywords: intensive care, nosocomial infection, pneumonia, selective digestive decontamination

Introduction

The most important factor influencing the emergence of antibiotic-resistant bacterial infections is the extensive use of antimicrobial agents both within hospitals and in the community. Recently, Levy [1] formulated five underlying principles of antimicrobial resistance that highlight the importance of antibiotic use as a risk factor. First, given sufficient time and drug use, antibiotic resistance will emerge. Second, antibiotic resistance is progressive, evolving from low levels through intermediate to high levels. Third, organisms that are resistant to one drug are likely to become resistant to other antibiotics. Fourth, once

resistance appears, it is likely to decline slowly, if at all. Finally, the use of antibiotics by any one person affects others in the extended and in the immediate environment. These principles apply to all antibiotic administration, including the use of SDD. Therefore, the clinical benefits of SDD must be balanced against the potential for the greater emergence of antibiotic-resistant infections as a result of its use.

ICUs, along with other specialty areas within hospitals (eg organ transplant wards, oncology units), frequently have high levels of antimicrobial usage among patients who are

maintained in close proximity. This type of environment may explain the high levels of antimicrobial resistance that are observed within such areas of the hospital.

A recent multicenter European survey [2] examined a total of 9166 Gram-negative bacterial strains from 7308 patients in ICUs from 118 hospitals. The most frequently isolated organisms were *Enterobacteriaceae* (59%) followed by *Pseudomonas aeruginosa* (24%), with the main sources being respiratory tract (42%), urine (26%), blood (14%), abdomen (11%), and skin and soft tissue (7%). Decreased antibiotic susceptibility was most common for *P aeruginosa*, *Acinetobacter* spp, and *Enterobacter* spp. Resistance to ceftazidime was greater than 70% in some countries for *Acinetobacter* spp, whereas *P aeruginosa* was associated with the highest overall incidence of resistance in all the countries surveyed (37% resistant to ciprofloxacin in Portugal, 24% resistant to imipenem in France). Similar findings were demonstrated in the USA [3], where 33 869 nonduplicate Gram-negative isolates were examined from 396 ICUs from 45 states. Resistance to third-generation cephalosporins was found to be an emerging problem, with increasing resistance to ceftazidime between 1990 and 1993 for *Klebsiella pneumoniae* (3.6–14.4%; $P < 0.01$) and *Enterobacter* spp (30.8–38.3%; $P = 0.0004$). Additionally, ceftazidime resistant Gram-negative bacteria were also frequently resistant to aminoglycosides and ciprofloxacin. These data highlight the presence of important antibiotic resistance among clinically important bacterial species within ICUs in Europe and the USA.

A number of investigators have demonstrated a close association between the use of antibiotics and the emergence of antibiotic resistance in both Gram-negative and Gram-positive bacteria [4–8]. The recent experience with antibiotic cycling or scheduled antibiotic class changes also demonstrates how rapidly antibiotic-resistant bacteria can emerge within the hospital setting as antibiotic use patterns change [9–11]. Trouillet *et al* [12] examined 135 consecutive episodes of ventilator-associated pneumonia, of which 77 (57%) were caused by potentially antibiotic-resistant bacteria (methicillin-resistant *Staphylococcus aureus*, *P aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*). According to logistic regression analysis, duration of mechanical ventilation for 7 days or more, prior antibiotic use, and prior use of broad-spectrum antibiotics (third-generation cephalosporins, fluoroquinolones, and/or imipenem) were associated with the development of ventilator-associated pneumonia due to antibiotic-resistant pathogens. This investigation confirmed the importance of previous antibiotic exposure as a risk factor for the development of nosocomial infections due to antibiotic-resistant bacteria [13–15]. Additionally, the identification of specific risk factors for the occurrence of antibiotic-resistant infections,

such as prior antimicrobial exposure, provides guidance for the development of potential interventions that are aimed at reducing these rates of infection and at providing better antimicrobial treatment when they occur [16,17].

In addition to prior antibiotic exposure, other risk factors have been associated with the emergence of antibiotic-resistant infections. Prolonged duration of stay in the hospital appears to predispose to infection with antibiotic-resistant bacteria [12]. This may be partly due to the greater likelihood of becoming colonized with such bacteria, from either horizontal nosocomial transmission or endogenous emergence of resistance, the longer a patient remains in hospital. Similarly, the presence of invasive devices such as endotracheal tubes, intravascular catheters, and urinary catheters also predisposes to infection with antibiotic-resistant and antibiotic-sensitive bacteria [18]. Patients who are treated with SDD typically require intensive care. Therefore, the risk factors noted above that predispose to the emergence of antibiotic resistance should be applicable to patients receiving SDD. Unfortunately, large, long-term investigations of the use of SDD, examining the influence of SDD on antibiotic susceptibility patterns for clinically important microorganisms in the ICU setting, have not been performed.

Recent meta-analyses of selective digestive decontamination

Two recent meta-analyses have been conducted that review the use of SDD. The first is a European review published in the *British Medical Journal* [19]. That review concluded that 15 years of clinical research suggests that antibiotic prophylaxis with a combination of topical and systemic antibiotics can reduce respiratory tract infections and overall mortality in critically ill patients. The authors stated that “This effect is significant and worthwhile, and it should be considered when practice guidelines are defined.” However, that study observed a reduction in mortality only when the use of topical and systemic antibiotic prophylaxis was compared with no use of prophylaxis (16 studies reviewed). There was no difference in mortality when topical and systemic antibiotic prophylaxis was compared with systemic antibiotic prophylaxis alone (seven studies) and when topical antibiotic prophylaxis was compared with no antibiotic prophylaxis (11 studies). These findings suggest that it is the administration of systemic antibiotic prophylaxis, and not the administration of topical antibiotic prophylaxis, that is responsible for the observed reduction in mortality. Another important element of this analysis is that the majority of patients evaluated who had a survival advantage were surgical and trauma patients (>70%). Trauma and surgical patients have previously been shown to derive benefits from the use of systemic antibiotic prophylaxis, including reduced rates of nosocomial infection and improved hospital survival [20,21].

The second, more recent meta-analysis was conducted by Nathens and Marshall from Canada [22]. Those investigators found that there was no survival advantage with SDD in 10 studies in which postoperative and trauma patients constituted no more than 25% of the overall study population. A survival advantage was found in 11 studies in which postoperative and trauma patients constituted more than 75% of the study population. That meta-analysis also showed that the survival advantage was greatest in studies in which both topical and systemic antibiotic prophylaxes were used. The main conclusion of the investigation was that "SDD notably reduces mortality in critically ill surgical patients, while critically ill medical patients derive no such benefit. These data suggest that the use of SDD should be limited to those populations in whom rates of nosocomial infection are high and in whom infection contributes notably to adverse outcomes."

Interestingly, both of those analyses reported similar results. A common flaw of those studies is a lack of a clear definition for SDD. It should be viewed as the use of antimicrobial agents to reduce oropharyngeal and gastrointestinal colonization by pathogenic micro-organisms, primarily Gram-negative bacilli and *Candida* spp. Nathens and Marshall [22] defined SDD as being made up of two components. The first component consists of topical, non-absorbed antimicrobials, including polymyxin E, tobramycin, and amphotericin B, a combination that is active against aerobic Gram-negative bacteria and fungi. The second component is intravenous cefotaxime sodium, or an equivalent parenteral antibiotic, which is generally administered for 4 days after the initiation of SDD. However, the European meta-analysis demonstrated that there is considerable variation in how SDD is employed (topical antibiotics alone, topical and systemic antibiotics, variations in duration of antibiotic administration, variability in individual antimicrobials employed). Additionally, an important objective of the SDD strategy is to preserve the normal anaerobic flora within the intestinal lumen in order to prevent overgrowth with pathogenic organisms. Unfortunately, this has not been demonstrated to occur. The available clinical data suggest that SDD alters the host's bacterial flora, predisposing to the emergence of colonization and infection with antibiotic-resistant pathogens; these data are reviewed below.

Selective digestive decontamination and antibiotic resistance

In one of the largest trials of SDD, Gastinne *et al* [23] found that pneumonia due to staphylococci was more common among SDD-treated patients. The emergence of pneumonia due to Gram-positive bacteria in association with the use of SDD has also been reported by other investigators [24]. Hammond and Potgieter [25] found a statistically significant increase in the occurrence rate of infections caused by *Acinetobacter* spp in the year after

beginning a trial of SDD in their ICU compared with the year preceding the trial (8.9% versus 5.2%; $P=0.05$). Additionally, *Acinetobacter* spp became the most common pathogens to colonize patients in their unit during this time period, although this could not be specifically linked to the use of SDD. Sanchez-Garcia *et al* [26] demonstrated reductions in the overall occurrence of nosocomial pneumonia with the use of SDD. However, the level of carriage of methicillin-resistant *S aureus*, coagulase-negative staphylococci, and enterococci was significantly higher in the SDD-treated patients. In a large study performed in Belgium [27], significantly more bacteremias due to Gram-positive bacteria were observed among SDD-treated patients. Increased antimicrobial resistance was also detected among the SDD-treated patients, including tobramycin-resistant Enterobacteriaceae, ofloxacin-resistant nonfermenters, ofloxacin-resistant Enterobacteriaceae, and methicillin-resistant *S aureus*. Finally, patient colonization with pathogenic bacteria including *Acinetobacter* spp, in areas such as the skin and pharynx, which may not be decontaminated by SDD, cast doubt on the overall value of SDD as a useful clinical practice [28].

As a result of this controversy, the use of SDD has not been commonplace in the USA. Similarly, clinical use of SDD has not gained a strong foothold in Europe, the continent in which it has been most extensively investigated [29]. In large part, it appears that fears over emerging antimicrobial resistance have limited the general use of SDD in Europe. A recent European consensus conference [29] surveyed 279 ICU physicians on their use of SDD. It was used to treat all ventilated patients by 18%, 50% 'never' employed SDD, and 32% used SDD for selected diagnoses and during epidemic outbreaks of infection. Interestingly, among the respondents surveyed 2 years earlier about their practices, 92% had not changed their practices. Cefotaxime or a second-generation cephalosporin was found to be the most common antibiotic employed (73%) for systemic administration, along with topical antibiotic prophylaxis. A concerning finding of this survey was the absence of any influence of rising antimicrobial resistance rates in Europe on clinical practices [2]. Most respondents using SDD employed the same antibiotics during the years between the survey, and did not have epidemiologic data concerning predominant microbial pathogens and their antibiotic susceptibilities to help guide the use of SDD in their ICUs.

Implications of increasing bacterial antibiotic resistance

In general, infections with antibiotic-resistant bacteria are associated with greater hospital mortality and longer duration of hospital stay [30]. Colonization and infection with antibiotic-resistant bacteria increase the likelihood that patients will receive inadequate antimicrobial therapy (ie antimicrobial therapy for which the identified causative

micro-organisms are resistant). Several investigations have demonstrated a strong association between the administration of inadequate antibiotic treatment and increased hospital mortality rates for patients with ventilator-associated pneumonia [31–33]. Those studies independently demonstrated that patients who receive inadequate empiric antimicrobial treatment, initiated before obtaining the results of cultures from respiratory secretions, blood, and pleural fluid, had greater hospital mortality rates than did patients who received empiric antimicrobial regimens that provided full coverage of all identified bacterial pathogens. More importantly, for patients receiving initially inadequate treatment, it appears that changing antimicrobial therapy on the basis of available culture results may not reduce the excess risk of hospital mortality associated with inadequate antibiotic treatment [32]. Therefore, the timing of the administration of adequate antimicrobial therapy is an important determinant of outcome for patients with ventilator-associated pneumonia.

Most inadequate antimicrobial treatment of nosocomial infections appears to be due to infection with antibiotic-resistant Gram-negative and antibiotic-resistant Gram-positive bacteria [17]. Although inadequate antibiotic therapy may explain, in part, the greater mortality rates associated with antibiotic-resistant bacterial infections, other factors may also contribute to this excess mortality. Gram-positive bacterial pathogens such as *S aureus* can express a number of virulence factors that potentially contribute to the high rates of mortality associated with infections with these pathogens [34]. The presence of methicillin resistance in *S aureus* appears to enhance further its virulence and likelihood of infection-related mortality [35]. However, not all investigators have demonstrated greater mortality rates with infections due to methicillin-resistant *S aureus* compared with methicillin-sensitive *S aureus* [36]. Some antibiotic-resistant Gram-negative bacteria are also associated with increased virulence factors as compared with antibiotic-susceptible pathogens [37]. This may explain some of the excess attributable mortality observed in clinical studies that examined infections due to antibiotic-resistant Gram-negative bacteria [38].

Nosocomial blood-stream infections are among the most serious infections acquired by hospitalized patients. The coexistence of a pathogen population with an ever-increasing resistance to many antibiotics and a patient population that is characterized by increasingly complex clinical problems has contributed to an increase in blood-stream infections, particularly due to antibiotic-resistant Gram-positive bacteria [39]. Antibiotic resistance appears to have contributed to increasing administration of inadequate antimicrobial therapy for nosocomial blood-stream infections, which is associated with greater hospital mortality rates [40,41]. The problem of antibiotic-resistant

bacteremia appears to be increasing both in the hospital setting and in the community [42]. Given the current trend of greater severity of illness for hospitalized patients, it can be expected that infections due to antibiotic-resistant bacterial strains will be associated with greater morbidity and mortality, particularly when inadequate empiric antimicrobial therapy is administered [17].

In addition to higher patient mortality rates, antibiotic-resistant bacterial infections are associated with prolonged hospitalization and increased health care costs relative to antibiotic-sensitive bacterial infections [43]. Recently, a study from Beth Israel Deaconess Medical Center [44] examined 489 inpatients with positive clinical cultures for *P aeruginosa*. The emergence of antibiotic resistance in infections with *P aeruginosa* was independently associated with greater hospital mortality and longer duration of hospital stay. Those investigators estimated that the emergence of antibiotic resistance increased hospital charges by US\$11981. Other authors have also reported increased medical care costs associated with antibiotic-resistant infections [45]. The overall national costs of antimicrobial resistance in the USA have been estimated to be between US\$100 million and US\$30 billion annually for the control and treatment of infections caused by antibiotic-resistant bacteria [43,46]. The increased costs of infection due to antibiotic-resistant bacteria have been attributed to prolonged hospitalizations and greater antibiotic costs [47]. Additionally, the emergence of antibiotic resistance results in the need to develop new antimicrobial agents [48,49]. The costs required for the development of new antimicrobial agents, including the necessary clinical research to demonstrate their effectiveness and safety, has also increased during the past decade [50]. This possibly explains, in part, the relatively slow development of new antibiotics.

Conclusion

Antibiotic resistance has become a major concern for both community-acquired and nosocomial infections. The development and use of SDD has occurred during the recent explosion in infections due to antibiotic-resistant micro-organisms. Unfortunately, the overall impact of SDD on the development of antibiotic resistance cannot be fully determined on the basis of the existing medical literature. However, several factors suggest that the use of SDD should be carefully monitored as a potential stimulus for further antimicrobial resistance [1,51]. First, low-level antimicrobial resistance usually precedes high-level resistance. Second, antibiotic resistance may require prolonged periods before clinical consequences are observed. Third, resistance often starts with selection of microbes from the normal flora that possess plasmids with transferable resistances. This has resulted in important outbreaks of nosocomial infections due to *Escherichia coli* and *Klebsiella pneumoniae*, which possess plasmids for

type-1 β -lactamase production due to selective pressures from the use of cephalosporins and aminoglycosides. Finally, we have experienced difficulty in predicting the emergence of resistance. The recent experience with *Streptococcus pneumoniae* resistant to fluoroquinolones and *S aureus* with intermediate resistance to vancomycin highlight this fact. On the basis of this experience, and the likelihood that antimicrobial resistance will continue to be a major problem for the future, the routine or indiscriminate clinical use of SDD cannot be recommended.

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