Review

Bacterial Resistance and Overgrowth due to Selective Decontamination of the Digestive Tract

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Abstract Infection of the lower airways is a major problem in ventilated patients and contributes substantially to morbidity and mortality in the intensive care unit. The selective decontamination of the digestive tract and its effect on the reduction of the gram-negative colonisation rate in patients has been studied widely. However, the findings are inconsistent. Most studies describe an increase in resistant gram-negative bacterial strains and/or an increase in the occurrence of gram-positive strains following selective decontamination of the digestive tract. In light of the unresolved questions concerning the efficacy of selective decontamination of the digestive tract, it would seem that the resultant effect of this treatment on the bacterial flora should be an important consideration when assessing the value of such treatment. To date, none of the studies available for examination have been designed to adequately assess the effect of selective decontamination of the digestive tract on the bacterial flora.

Introduction

Nosocomial infections contribute substantially to morbidity and mortality in the intensive care unit. The most common site of infection is the lower respiratory tract, with multiresistant gram-negative bacteria and *Staphylococcus aureus* being the most common causative organisms. Most of these infections are thought to be endogenous and secondary to the aspiration of oropharyngeal secretions that have become colonised by resistant organisms from the hospital environment. Selective decontamination of the digestive tract (SDD), whereby the anaerobic bacteria are preserved and potentially pathogenic aerobic bacteria are eliminated from the oropharynx and the gastrointestinal tract by means of enterally administered nonabsorbable antibiotics, has been studied widely. However, because of flaws in the design of the studies, including the use of

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historical control groups and small numbers of patients for analysis, the results are inconclusive [1].

Nevertheless, SDD has been implemented in many institutions, and although the procedure reduces secondary infections, especially ventilator-associated pneumonia, there is no conclusive evidence that it reduces mortality or the overall cost of intensive care. A recent meta-analysis of the effectiveness of antibiotic prophylaxis in critically ill adult patients suggests that SDD, administered as a combination of topical and systemic drugs, can reduce the overall mortality in ventilated patients [2]. However, the study that carries the most weight in this meta-analysis (F.P. Lenart et al., 17th International Congress of Chemotherapy, 1994, Abstract no. K101) is to date unpublished. Even the studies by the principal advocates of SDD have not established a reduction in mortality [2].

Although most authors investigating the efficacy of SDD have not found antimicrobial resistance to be a major problem, the emergence of resistant pathogens is a concern for infectious disease specialists. It is worth differentiating between the emergence of resistant bacterial strains and an overgrowth of gram-positive bacteria that are not affected by the antimicrobial

agents used in an SDD regimen. Sometimes both scenarios coincide, as demonstrated by the overgrowth of resistant bacterial strains (in particular, oxacillin-resistant staphylococci).

Emergence of Resistance

The emergence of resistant microorganisms is always a potential risk when antibiotics are administered. Hammond and Potgieter [3] summarise the main problems of SDD with regard to resistance as the induction of beta-lactamase resistance associated with the use of third-generation cephalosporins (if the SDD regimen is a combination of topical and systemically administered antimicrobial agents) and the increase in aminoglycoside resistance. However, in their own 4-year study, they did not find any change in resistance patterns. SDD, however, failed to prevent infections caused by *Acinetobacter* spp., which were already resistant to most antibiotics before the study began [3].

Several studies report the emergence of resistant bacteria during or shortly after the administration of antibiotics for SDD. Lingnau et al. [4] observed increasing resistance to ciprofloxacin among coagulase-negative staphylococci as well as among *Enterococcus faecalis* in SDD patients. In the case of staphylococci, the increase was significant ($P<0.001$). The overall resistance patterns among members of the *Enterobacteriaceae* remained the same during the study period, but single strains of polymyxin-resistant *Klebsiella pneumoniae* and *Escherichia coli* and multiresistant *Serratia marcescens* (susceptible only to polymyxin, fosfomycin and imipenem) were found.

Tobramycin-resistant strains of *Proteus*, *Morganella* and *Providencia* spp. were isolated from three of 114 SDD patients in the surveillance study of Saunders et al. [5]. Nevertheless, the use of SDD did not lead to an overall increase in antibiotic resistance among aerobic gram-negative bacilli. Tobramycin-resistant strains of *Enterobacteriaceae* were even more frequent in the placebo group than in the SDD group. In contrast to these findings, a study carried out by Verwaest et al. [6] showed a significant increase ($P<0.01$) in the emergence of tobramycin-resistant *Enterobacteriaceae*. This finding was observed in a group treated with polymyxin E, tobramycin and amphotericin B. In the other SDD group (ofloxacin plus amphotericin B), the ofloxacin decontamination caused an "ecological disaster". Ofloxacin-resistant *Enterobacteriaceae* and nonfermenters were detected more frequently in the treatment group than in the control group (48% vs. 14%, $P<0.01$; 50% vs. 11%, $P<0.02$). These results were statistically significant. Both study regimens were considered to promote gram-positive overgrowth and selective pressure toward resistance and to create a

clinical problem, even with pathogens exhibiting low-level resistance. Moreover, Verwaest et al. [6] were not able to confirm the favourable results obtained in other SDD studies with regard to a significant reduction in the incidence of respiratory tract infections.

Nardi et al. [7] described an overall increase in the resistance of gram-negative organisms to tobramycin and all other aminoglycosides (with the exception of amikacin), which was dramatic for *Pseudomonas* (79% sensitive pre-SDD, 45% sensitive post-SDD). Another interesting but alarming finding was made by Armstrong et al. [8], who considered the relative effect of the SDD regimen on the occurrence of *Pseudomonas aeruginosa* in an intensive care unit where SDD and control patients were nursed together. One strain of aminoglycoside-resistant *Pseudomonas aeruginosa* was first detected in a patient after admission and was subsequently transferred to SDD patients and then became endemic in the unit. Three other aminoglycoside-resistant strains, which were not transferred to SDD patients, disappeared without becoming endemic. The authors suggest that SDD patients, acting as a reservoir, may have served to promote the spread of the resistant strain in the unit. There was no significant increase in the incidence of infection caused by antibiotic-resistant gram-negative organisms in the study of Wiener et al. [9], but a trend toward increased rectal colonisation of SDD patients with gentamicin- or polymyxin-resistant gram-negative bacilli was observed. Gorman et al. [10] examined the incidence of microbial biofilm formation on endotracheal tubes in patients with or without SDD. They found that three of six *Staphylococcus aureus* strains isolated from SDD patients exhibited resistance to tobramycin. Other tobramycin and polymyxin resistance patterns appeared in patients not treated with SDD, but comparability of the two treatment groups in this study is limited because the groups were recruited from two different hospitals.

Overgrowth of Gram-Positive Organisms

Most of the studies indicate that SDD significantly reduces infection caused by intestinal aerobic gram-negative bacteria; however, they also indicate a shift toward increased colonisation and/or infection by gram-positive organisms. Neither Hammond and Potgieter [3] nor Korinek et al. [11] observed an increase in the rates of microorganisms isolated, yet both groups reported a higher frequency of infection caused by *Staphylococcus aureus* as well as a failure to eradicate *Staphylococcus aureus* from the trachea and lower airways. Furthermore, there was a significant increase in the occurrence of infections caused by *Acinetobacter* spp. [3].

Table 1 Emergence of resistance and overgrowth of/increased incidence of infection caused by gram-negative/gram-positive bacteria

Study	Resistance present	Overgrowth present	Study type	No. of patients	Duration	SDD regimen
Hammond and Potgieter [3]	no	n.m.[a]	surveillance and intervention (double-blind, randomised, controlled)	year preceding: 406 2-yr. study: 719[b] year following: 403 total: 1528	4 yrs.	topical PTA + systemic cefotaxime
Korinek et al. [11]	no	n.m.[c]	prospective, random-ised, double-blind, placebo-controlled	63 with SDD 60 with placebo	19 mos	topical PTA + topical vancomycin[d]
Lingnau et al. [4]	yes gram-neg. (n.s.) gram-pos. (s)	yes gram-pos. (s)	prospective, random-ised, placebo-controlled	preceding year: 357 80 with PTA; 82 with PCA 148 with placebo	66 mos.	topical PCA + systemic ciprofloxacin; topical PTA + systemic ciprofloxacin
Saunders et al. [5]	yes gram-neg. (n.s.) gram-pos. (s)	yes gram-pos. (s)	randomised, placebo-controlled, double-blind	114 with SDD 125 with placebo	2 yrs.	topical PTA + systemic cefotaxime
Verwaest et al. [6]	yes gram-neg. (s) gram-pos. (s)	yes gram-pos. (s)	prospective, random-ised, controlled	185 in the control group 200 with PTA 193 with OA	19 mos.	topical PTA + systemic cefotaxime; topical OA + systemic ofloxacin
Nardi et al. [7]	yes gram-neg. (s)	yes gram-pos. (s)	prospective, microbio-logical survey	year preceding: 234 without SDD 2 years: 471 with SDD	3 yrs.	topical PTA
Wiener et al. [9]	yes gram-pos.[f]	no	randomised, double-blind, placebo-controlled	30 with SDD 31 with placebo	8 mos.	topical PGN
Gorman et al. [10]	yes gram-pos.[f]	yes[f] gram-pos.	prospective	15 with SDD 15 without SDD[e]	n.m.	topical PTA + systemic cefotaxime
Gastinne et al. [12]	n.m.	yes gram-pos. (s)	randomised, double-blind, placebo-controlled, multi-centre	220 with SDD 225 with placebo	4.5 mos.	topical CTA
Hammond et al. [13]	n.m.	yes gram-pos. (s)	prospective, double-blind, placebo-controlled	114 with SDD 125 with placebo	2 yrs.	topical CTA + systemic cefotaxime

[a] SDD failed to prevent infections caused by *Acinetobacter* spp.
[b] It is unclear how many patients received SDD
[c] *S. aureus* remained the main potential pathogen causing infec- tion
[d] Vancomycin was given in addition to cover *S. aureus*
[e] Patients with or without SDD were recruited from two different hospitals
[f] Significance not calculated

n.m., not mentioned; s, significant; n.s., not significant; gram-pos., gram-positive; gram-neg., gram-negative; CTA, colistin, tobra-mycin, amphotericin B; PTA, polymyxin, tobramycin, amphoter-icin B; PCA, polymyxin, ciprofloxacin, amphotericin B; PGN, polymyxin, gentamicin, nystatin; OA, ofloxacin, amphotericin B; VGCA, vancomycin, gentamicin, colimycin, amphotericin B; mos., months; yrs., years

The increasing emergence of gram-positive organisms does not necessarily coincide with a higher frequency of infection by these bacteria. In the study by Gorman et al. [10], organisms of low pathogenic potential, i.e. coagulase-negative staphylococci, streptococci, diphthe-roids and group F streptococci, were isolated more frequently from the endotracheal tubes of SDD patients. Although a reduction in the incidence of gram-negative microorganisms was observed, the anti-biotic regimen did not inhibit biofilm formation by pathogens associated with pneumonia in ventilated patients. An impact on the infection rate was not observed. The same applied to the findings made by Nardi et al. [7]: gram-positive colonisation tended to increase (+63%), mainly due to coagulase-negative staphylococci (+290%) and *Streptococcus pneumoniae* (+230%). The authors also emphasise that it has never been proved that an increase in tracheal-bronchial colonisation by gram-positive organisms can be asso-ciated with an increase in the incidence of gram-posi-tive pneumonia.

Saunders et al. [5] observed that the incidence of colon-isation of the alimentary tract with strains of coagulase-

negative staphylococci and methicillin-resistant *Staphylococcus aureus* (MRSA) and the incidence of infection caused by these organisms increased in the SDD group. Several other authors [6, 12, 13] have also pointed out the relationship between colonisation and infection with gram-positive organisms selected by SDD. In particular, the prevalence of oxacillin-resistant staphylococci poses a threat. Korinek et al. [11] unsuccessfully included the topical application of vancomycin to prevent staphylococci growth. However, the risk of the emergence of vancomycin-resistant organisms after topical use of this antibiotic precludes this practice.

For a synopsis of the results of the studies reported in references 3–7 and 9–13, see Table 1.

Case Reports

Several authors have reported cases in which SDD may have modified the bacterial flora of intensive care patients, resulting in increased colonisation with gram-positive organisms and subsequent infection. Sijpkens et al. [14] suspected colonisation with and endocarditis caused by *Enterococcus faecalis* in five patients to be late sequelae of SDD (consisting of local polymyxin, norfloxacin, amphotericin B and i.v. cefotaxime). Bonten et al. [15] attributed eight cases of pneumonia due to *Enterococcus faecalis* strains intrinsically resistant to tobramycin and colistin to SDD treatment consisting of topical tobramycin, colistin and amphotericin B [15]. Kaufhold et al. [16] reported an outbreak due to MRSA in an intensive care unit where MRSA strains were very uncommon before the introduction of SDD. Nearly all patients who remained in the unit longer than 2 weeks became colonised shortly after admission and subsequently had at least one episode of microbiologically proven MRSA septicaemia. SDD was then discontinued as a final measure, and rates of MRSA infection began to decline within a few weeks.

Conclusion

In 1992 Daschner [17] pointed out the danger of resistance developing within the scope of SDD. At the time, there were few data available that clearly showed levels of significance. Since then, many studies have not only investigated the impact of SDD on the incidence of nosocomial pneumonia and on overall mortality among intensive care patients but have also addressed the question of how topical and systemic administration of antibiotics for eradication of gram-negative pathogens influences the development of resistance and overgrowth of organisms, mainly gram-positive pathogens. These studies provide statistically significant data. Thus, there is no doubt that the use of SDD favours the emergence of bacterial resistance equally among gram-positive and gram-negative pathogens and promotes the selection of gram-positive organisms.

A weak point of all SDD study designs is that, essentially, they focus on the effect of SDD on the individual patient and not on the patient's environment. To gain more insight into this, studies with a different design are necessary, i.e. studies that (i) view the intensive care unit as the unit of randomisation, (ii) monitor the emergence of antibiotic resistance over a long period of time and (iii) concentrate on outcomes such as mortality, resistance and costs [2].

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