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Epidemiological impact of prolonged systematic use of topical SDD on bacterial colonization of the tracheobronchial tree and antibiotic resistance

A three year study

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Abstract. *Objective:* to evaluate the effect of the prolonged systematic use of topical SDD (tobramycin 80 mg, polymyxin E 100 mg, amphotericin B 500 mg) on ICU ecology as expressed by changes in tracheal colonization and bacterial resistances.
Design: Prospective microbiological survey.
Setting: Polyvalent ICU of a 2000 beds general hospital.
Patients: Data concerning bacterial strains isolated from the tracheo-bronchial aspirates of all the patients admitted to a polyvalent ICU over 3 consecutive periods of 12 months ('88, '89, '90) were prospectively entered in a database and subsequently analyzed. During a 3-year period 502 patients required artificial ventilation for more than 72 h and 332 of them ('89 and '90) were treated with SDD. All samples collected within 72 h from ICU admission were excluded as well as duplicate samples from the same patients.
Intervention: All the patients admitted to the ICU in '89 and '90 and submitted to artificial ventilation for at least 24 h were routinely treated with topical SDD without i.v. antibiotic prophylaxis; in '88 SDD was not empoloyed.
Measurements and results: Criteria for collecting sputum samples and microbiological procedures remained unchanged troughout the study-time. Positive sputum were significantly less in '89 (80.8% versus 92.3% $p<0.001$) and this was due to a very sharp decrease in the isolation of Gram-negative strains from 43–28% (−64% $p<0.0001$) involving both: *Enterobacteriaceae* (−45%) and *Pseudomonaceae* (−77%). In 1990; however, a new increase in Gram negative was observed, although the overall amount of Gram-negative was still 49% lower in '90 if compared to '88 ($p<0.0001$). A dramatic increase in *Pseudomonas* isolation was the only factor responsible for the "rebound" observed. An increasing percentage of *Pseudomonas* developed a resistance towards tobramycin and only 45% of *Pseudomonas* strains turned out to be sensible to tobramycin in '90 against 79% in '88. A similar trend was registered for all aminoglycosides with the exception of amikacin. Gram-positive colonizations tended to increase (+63%) ($p<0.0001$) and this was mainly due to Coagulase negative *Staphylococci* (+290% $p<0.0001$) and *S. pneumoniae*, whereas *S. aureus* isolations decreased (−18%) but not significantly.
Conclusions: Our data suggest that the prolonged use of SDD is associated with dramatic changes in ICU ecology: the incidence of Gram negative colonization is significantly diminished by SDD whereas Gram positive tend to increase. *Pseudomonas* developed an increasing resistance towards tobramycin one of the components of the SDD formula we used.

Key words: Selective decontamination of the digestive tract (SDD) – Intensive care unit (ICU) – Bacterial colonization – Tracheobronchial aspirates – Antibiotic resistance

Selective Digestive Decontamination (SDD) was first proposed by Stoutenbeek [1] as a method to decrease colonization and infection rate in critically ill patients submitted to artificial ventilation. In most of the studies [1–7] in addition to oral antibiotics, cefotaxime was given systematically during the first days of ICU stay, with the aim of treating either infections already present on admission or as a prophylaxis of infections acquired on the ICU during the early days of admission [8]. Several reports confirmed the effectiveness of SDD in the prevention of nosocomial pneumonia, although its superiority over conventional prophylactic measures in terms of reduction in mortality, antibiotics consumption and length of hospital stay has not been proved [9]. Ledingham [5], however, reported a reduction in mortality and hospital stay in a selected group of trauma patients while a similar trend lacking statistical significance was reported by others [9].

Recently the rationale of the association of SDD with systemic prophylaxis has been criticized [10] and a few reports demonstrate a reduction in the incidence of pulmo-

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nary infections related to the use of the sole topical SDD [11–13]. When no systemic antibiotics are used prophylactically, the overall antibiotics consumption appears to be significantly lower in the SDD groups [13, 14]. In a recent large multicenter study, Gastinne [15] observed no improvement in survival and no reduction in the mean total charge for systemic antibiotics among patients receiving SDD, in spite of an increase in the cost of their care; in his study, however, over 70% of the patients were admitted to the ICU for medical reasons and 72% were receiving systemic antibiotics at the time of randomization.

One of the major obstacles for a better assessment of the role of SDD in the prevention of lung infections in the critically ill lies in the lack of a clear definition of pneumonia. The clinical criteria proposed by Johanson [16] have been used by most authors, but the predictability of these criteria in ICU patients is controversial [17–19]. As far as we know, no controlled study has been published to investigate the effect of SDD, while pneumonia was strictly diagnosed on the basis of quantitative cultures of samples obtained by means of a protected double lumen catheter [20] or with a brush catheter [19].

Recently Pugin and Suter employed a score index based on clinical findings to demonstrate a reduction in the incidence of pneumonia, related to the use of modified oropharingeal decontamination in surgical and trauma patients [13].

In a previous comparative study [12] we reported a sharp reduction in the incidence of nosocomial pneumonia and in antibiotics consumption when topical SDD was administered to patients who had no evidence of infections and were not on antibiotics on admission. On that basis we decided to treat all the patients admitted to our ICU and submitted to artificial ventilation systematically with topic-only SDD. The aim of this report is to monitor the impact of prolonged systematic use of topical SDD and ICU ecology expressed by changes in the microbiology of tracheo-bronchial secretions and in bacterial resistances.

Methods

Data concerning bacterial strains isolated from the tracheobronchial aspirates of all the patients admitted to our ICU over 3 consecutive periods of 12 months ('88 – '89 – '90) were prospectively entered into a database. All the patients admitted to the ICU in '89 and '90 and submitted to artificial ventilation for at least 24 h were routinely treated with topical SDD throughout their ICU stay and until extubation or death. The SDD regimen we employed was: tobramycin 80 mg, Polymixin E 100 mg, Amphotericin B 500 mg every 6 h administered through the gastric tube and applied to the oral mucosa with a prefilled disposable syringe as a 2% paste. Systemic antibiotic prophylaxis was not used. Antibiotic treatment of pre-existing and hospital acquired infections was prescribed, when required, according to a statistically oriented protocol or to the results of cultures. Criteria for collecting sputum samples remained unchanged throughout the study-time: a first sample was collected within the first 24–36 h with the only exception of patients admitted after 9.00 a.m. on Saturday or on days preceding holiday. Subsequent samples were taken according to clinical findings (changes in sputum characteristics, pulmonary infiltrate on X-ray) or routinely twice a week. In most cases a tracheo-bronchial aspirate was collected immediately before extubation.

Data of samples collected on admission and within the first 72 h were excluded from our analysis, since SDD is unlikely to influence samples taken during this period.

Microbiological procedures were as follows: all the samples were submitted to Gram stain in order to assess their suitability. The prepared specimens consisted of the most purulent parts of the samples and were first examined at a low magnification in order to assess the presence of leukocytes and of squamous epithelial cells. The samples were classified on the basis of the ratio between the two cell-components. Samples with more than 25 squamous cells per field were considered highly contaminated and unsuitable for culture-examination [21, 22]. Therefore they were excluded. Each suitable sample was observed at magnification 1000 for a preliminary ethiological diagnosis and subsequently cultivated.

As culture examinations often show the growth of various bacterial species, only the prevailing species were isolated and identified. The prevailing charge was assessed by a semiquantitative method. We defined as "predominant" those microorganisms that showed a growth rate higher or equal to +++. When two germs of the same sample had both a growth rate equal or over +++, they were both entered into the database, otherwise the germ with the lower charge was excluded.

The material was inoculated into free-growth culture media (5% blood agar and enriched chocolate agar) and into selective differential media for the isolation of Gram-negative (Mac Conkey agar), Gram-positive micro-organisms (5% blood agar with colystin and nalidixic acid) and for fungi (Sabouraud). Cultures were incubated at 35 °C in an atmosphere containing 5–10% CO_2 (with the exception of the media used for fungi that require an aerobe atmosphere) and examined after 18–24 h.

Significant colonization was defined as the presence of microorganisms with a growth rate equal or over +++ unreguarding to the presence of clinical signs of infection. Bacteria strains with a significant charge (+++ or more) were isolated, identified and tested for sensitivity to antibiotics. Identification was carried out according to the Manual of Clinical Microbiology [23]. Sensitivity to antibiotics was assessed according to the MIC method. The break points for resistance are listed in Table 4 [24, 25]. Duplicate isolates obtained from the same patient and within 7 days from their first isolation were excluded from the analysis when the isolated germs showed the same sensitivity to antibiotics.

The protocol of antimicrobial treatment, which is statistically oriented on the basis of a 6-monthly epidemiological survey, remained unchanged in '88 and '89. But in '90 the first line anti-Pseudomonas association we employed was changed from ceftazidime+amikacin to piperacillin+amikacin, as piperacillin resulted to be statistically the most effective antibiotic in vitro. Moreover in Jan. '90 sulcralfate was introduced as the standard stress-ulcer prophylaxis for all the patients admitted to the ICU.

Data relating to '88 (no SDD prophylaxis) were compared with those of '89 and '90 (SDD with different antibiotic protocol) to understand whether or not SDD was effective in reducing tracheobronchial colonizations and whether a prolonged use of topical SDD was associated with the emergence of resistant strains. Changes in bacterial resistances to antibiotics before and after the introduction of SDD were also analyzed.

Frequency comparisons were analyzed by χ^2 or Fisher's exact test as appropriate. A level of $p<0.05$ was considered significant.

Results

During a 3-year period 1232 patients were admitted to our ICU as reported in Table 1.

No significant differences were recorded over the 3 periods as for number of admitted patients, number of patients submitted to artificial ventilation, average age, percentage of trauma patients (35% of the admitted patients but 60% of those ventilated over 24 h) and F/M ratio. The percentage of patients ventilated over 24 h having been previously admitted to other departments or other hospitals ranged between 21 and 24% without significant

Table 1. Patients admitted to a polyvalent ICU over 3 consecutive periods of 12 months ('88 – '89 – '90)

	1988	1989	1990
Total admissions	428	415	389
Ventilated less than 24 h (no SDD)	194	186	147
Ventilated over 24 and less than 72 h (excluded)	64	61	78
Ventilated 72 h or more (included)	170	168	164
Ventilated over 30 days	12	10	11
Mean ICU stay	6.96	6.17	6.35
Mean time of ventilation (for patients ventilated over 72 h)	11 +12.7	9.6 +13.4	10.3 +10.8

differences over the 3 periods. The number of patients submitted to artificial ventilation for 72 h or more was roughly the same over the 3 periods as well as the number of patients who required artificial ventilation for more than 30 days (Table 1). The mean ICU stay for all the patients admitted to the ICU, as well as the mean ventilation time for patients ventilated over 72 h was higher, although not significantly, in '88.

527 patients were submitted to artificial ventilation for less than 24 h and were therefore excluded from this study. There were 471 patients ventilated for over 24 h and treated with SDD in '89 (229 patients) and '90 (242 patients). In '88 (234 patients) SDD was not employed.

Data relating to the 203 patients ventilated for less than 72 h were also excluded. There were 502 patients artificial ventilated for 72 h or more in the 3 periods examined. Data relating to samples collected within the first 72 h and excluded from subsequent analysis are reported in Table 2. About 80% of the tracheo-bronchial aspirates sampled over this period of time proved negative. Among the positive samples, Gram-positive bacterial isolates accounted for the highest percentage (62%), whereas Gram-negative other than *Haemophilus* as well as fungi were isolated mainly from patients admitted to the ICU after a prolonged hospital stay. No statistically significant differences among the three groups were observed as far as the percentage of positive samples and the predominance of the different bacterial strains are concerned. Data relating to the samples obtained 72 h or more after admission are reported in Table 3. Once samples taken within the first 72 h were excluded, the results of an overall 1049 samples were analyzed. A certain percentage of samples showed more than one isolate, but as isolates with low charge were not considered, the isolate/samples ratio was 1.1/1 and remained unchanged over the three periods. The percentage of positive samples as well as the number of isolates was significantly lower in '89 (256; 80.8%) than in '88 (368; 92.3%) ($p<0.001$) and this was due to a very sharp decrease in the isolation of Gram-negative strains (99 vs. 272) ($p<0.0001$) involving both *Enterobacteriaceae* and *Pseudomonaceae*. In 1990 however, a new increase in Gram-negative was observed (n.s; $p = 0.64$), although the overall amount of Gram-negative strains remained still 49% lower in '90 if compared to '88 ($p<0.0001$). A dramatic increase in *Pseudomonas* isolations was the main factor responsible for the "rebound" we observed, whereas isolations of all the other Gram-negative remained as low as in '89. Among the Gram-negative strains Klebsiella resulted to be probably the most affected. Isolations of *Klebsiella spp.* dropped by 6 times in '89 ($p<0.0001$) and in '90 remained 4 times lower than in '88 ($p<0.0001$).

Gram-positive showed a progressive trend towards augmentation and this was mainly due to Coagulase negative *Staphylococci* (4 times; $p<0.0001$), *S. pneumoniae*

Table 2. Isolates obtained within 72 h from intubation. Isolates with a low charge (lower than + + +) are not included

	1988	1989	1990
Gram-positive	20 (57%)	26 (66%)	20 (54%)
S. aureus	8	9	3
S. epidermidis	0	3	0
S. pneumoniae	6	8	10
S. group D	0	0	4
Other *Streptococci*	6	6	3
Gram-negative	15 (43%)	11 (28%)	15 (41%)
Pseudomonas	5	3	8
Acinetobacter	1	0	0
Klebsiella	3	0	0
Morganella	0	0	1
Serratia	0	0	1
E. coli	1	1	2
Other AGNB	0	2	1
Haemophilus	5	5	2
Fungi	0	3 (6%)	2 (5%)

Table 3. Samples and isolates obtained 72 h or more after admission. Isolates with a low charge (lower than + + +) are not included. Unsuitable samples have also been excluded

	1988		1989		1990	
Total samples	397		317		335	
Positive samples	368	(92.3%)	256	(80.8%)	291	(86.9%)
Isolates	390		278		318	
Isolates/pts. ratio	2.3		1.7*		1.9	
Gram-negative	272	(70%)	99*	(36%)	138*	(43%)
Pseudomonas	164	(42%)	38*	(14%)	86*	(27%)
Acinetobacter	11	(3%)	9	(3%)	2	(1%)
Enterobacter spp.	4	(1%)	3	(1%)	2	(1%)
Proteus	8	(2%)	8	(3%)	4	(1%)
Morganella	8	(2%)	1		4	(1%)
Serratia	10	(3%)	10	(4%)	15	(5%)
E. coli	11	(3%)	13	(5%)	9	(3%)
Klebsiella spp.	41	(11%)	7*	(3%)	11*	(3%)
Other AGNB	2		1		2	
Haemophilus	13	(3%)	10	(3%)	3 ns	(1%)
Gram-positive	94	(24%)	153*	(55%)	159*	(50%)
S. aureus	68	(17%)	56 ns	(20%)	45 ns	(14%)
S. Coag. neg.	13	(3%)	51*	(18%)	41*	(13%)
S. pneumoniae	6	(2%)	20*	(7%)	22*	(7%)
Group D *Strep.*	0		12*	(4%)	38*	(12%)
Enterococci	6	(2%)	14	(5%)	13*	(4%)
Other *Strep.*	1		0		0	
Fungi	24	(6%)	25 ns	(9%)	21 ns	(7%)

*$p<0.0001$

Table 4. Changes in Gram-negative resistance to different antibiotics over the three periods. Data are expressed as percentage of resistant strains. Data for "Other AGNB" concern the overall isolates of: *Klebsiella spp., Serratia, Proteus spp., Morganella, Acinetobacter, Enterobacter* and *E. coli*

Amikacin			Tobramycin			Netil.			Piperacill.			Cefotaxime			Ceftazidime			Pefloxacine		
88	89	90	88	89	90	88	89	90	88	89	90	88	89	90	88	89	90	88	89	90
Pseudomonas																				
13	7	20	21	44	55	33	42	57	20	2	2	86	73	62	29	12	25	N.T.	50	36
Other AGNB																				
21	17	9	24	26	29	20	25	29	45	28	6	49	33	6	11	10	6	N.T.	9	9
Total Gram-negative																				
17	11	18	23	47	48	26	35	50	32	16	6	67	60	50	20	11	22	N.T.	36	32

N.T. = not tested
Breakpoints for resistance: Amikacin 16 μg/ml, tobramycin 4 μg/ml, netilmicin 8 μg/ml, piperacillin 16 μg/ml, cefotaxime 8 μg/ml, ceftazidime 8 μg/ml, pefloxacin 2 μg/ml

and *Streptococci* goup D-non *Enterococci*, whereas *S. aureus* decreased (18%) although not significantly.

Gram-negative resistance to tobramycin, one of SDD components, showed a progressive increase, which was dramatic for *Pseudomonas*. Only 45% of *Pseudomonas* strains turned out to be sensitive to tobramycin in '90, against 79% in '88. A similar trend was registered for all aminoglycosides with the exception of amikacin. No significant modifications in *Pseudomonas* resistances towards other antibiotics (i. e. cephalosporins, ureidopenicillins and quinolones) were recorded (Table 4).

Among the Gram-positives, *S. aureus* showed no trend towards an increase in resistance to tobramycin. The percentage of resistant strains dropped slightly over the three periods and resulted as high as in the other Departments of our hospital (Table 5), while *S. aureus* strains isolated from outpatients showed a very low resistance to tobramycin (6%). Nearly all group D *Streptococci* isolated over the three periods resulted resistant to tobramycin as well as coagulase negative *Staphylococci.*

Discussion

In the early seventies Johanson [16] demonstrated that colonization of stomach, oropharynx and trachea with aerobic Gram-negative bacilli increases throughout the hospital and ICU stay, and is associated with a higher risk of developing pneumonia.

Many authors reported a reduction in AGNB identification on tracheo-bronchial aspirates in patients treated with SDD, which was parallel to the decrease in the incidence of nosocomial pneumonia they observed [3, 11, 26].

Although bacterial colonization of the tracheo-bronchial tree is not necessarily predictive of subsequent pneumonia, its reduction in mechanically ventilated patients in intensive care units could be an important target.

The overall number of suitable samples resulted in '88 higher than in '89 and in '90, although the positive rate was lower in '89 and in '90 suggesting that an oversampling bias in '88 is not probable. More probably, clinical conditions requiring cultures to be performed (as purulent sputum) occurred more frequently when patients were not treated with SDD ('88). A similar trend was reported by Stoutenbeek [1] who observed a 35% reduction in the overall number of samples in the SDD group, while Pugin [13] reported a sharp reduction in purulent tracheobronchial secretions.

In our study one or more sputum samples were collected from every patient, so that the overall amount of positive samples could be influenced by the efficacy of antibiotic treatment. From that point of view, data relating to '88 and '89 are probably better comparable, as the antibiotic protocol was the same during the two periods, hence the differences in Gram-negative identifications that we observed are most probably due to the introduction of SDD. In '90 the number of positive samples increased due to a higher rate of Pseudomonas identifications. Several explanations are possible: in 1990 the antibiotic protocol was modified on the basis of statistical "in vitro" results. Piperacillin "in vivo"could result less effective on *Pseudomonas* strains than ceftazidime or it could simply have been used in lower dosages than re-

Table 5. Changes in Gram-positive resistance to tobramycin. Data from all other departments concern all the suitable samples obtained from patients admitted to medical and surgical departments of the same hospital and from ICUs where SDD was not employed

	1988		1989		1990		
	ICU	All other depts.	ICU	All other depts.	ICU	All other depts.	Outpts.
S. aureus	41%	35%	47%	43%	29%	26%	6%
S. coag. neg.	52%	NA	75%	54%	92%	58%	
Group D *Streptococci*	90%	NA	100%	NA	92%	NA	

NA = not available

quired, demanding a longer time to achive negativization of the sputum cultures. However, as duplicate samples collected within one week have been excluded from the analysis, bias due to the use of different antibiotics should not alter our result significantly. The aspiration of SDD solution in the trachea of intubated patients could contribute to negaive cultures and lead to major bias. The importance of this phenomenon is unclear as well as its clinical consequences. The phenomenon of inhibition of bacterial growth that can occur in cultures can also arise in "vivo", thus contributing to the reduction of colonization in the respiratory tract and falling within the clinical effects of SDD. The results of cultures relating to the tracheo-bronchial aspirates collected within the first 72 h and excluded from our analysis (Table 2) have however proved to be the same over the three periods. These data suggest that the impact of the "carry over" is not of such importance, at least within a short time of exposition to the SDD regimen.

Many authors did investigate bacterial resistance in patients treated with SDD and the majority of them failed to demonstrate an emergence of resistance [5, 27–30]. All these reports, however, considered short periods of time; moreover in all cases a systemic antibiotic was associated with SDD.

Eastway [31] reported a higher rate of tobramycin resistant strains in the treated group, while the appearence of ribosomal resistance to Tobramicine in Pseudomanas has been reported by Botha [32].

Detectable tobramycin levels in the blood as a result of intestinal absorption have been reported [33] and this could enhance the development of resistances suggesting cause for concern. We observed a progressive decrease in *Pseudomonas* sensitivity to tobramycin since the introduction of SDD and at the end of our microbiological monitoring as much as 55% of *Pseudomonas* strains resulted resistant. Our data are not consistent with a previous report by Stoutenbeek who observed no increase in bacterial resistance to tobramycin over a 30-month period [25, 34]. In Stoutenbeek's study, however, the patterns of bacterial resistance both before and after the introduction of SDD were extremely low if compared with our data. Stoutenbeek employed the Kirby method to define sensitivity, while we used the MIC, but as the break point we considered for tobramycin (4 μg/ml) correlates well with an inhibition zone of less than 24 mm according to the Agar diffusion method (Kirby-Bauer) [24, 25], the two methods are comparable and this discrepancy may therefore not be due to technical reasons.

In Jan 1990 we introduced sulcralfate for routinely stress ulcer prophylaxis and the large majority of the ventilated patients received sulcralfate Q.I.D. It has recently been suggested [35] that sulcralfate could bind and inactivate the SDD agents within the stomach. Even though this observation need to be confirmed, in June '91 we decided to discontinue sulcralfate maintaining the same antibiotic regimen. Since then, *Pseudomonas* resistance to tobramycin dropped from 55–27%.

A diametrically opposite trend was observed in Gram-positive identifications on tracheo-bronchial aspirates. Many Authors have reported an increase in tracheo-bronchial colonizations by Gram-positive (mostly coagulase negative *Staphylococci*) in patients treated with SDD [4, 11, 27], but it has never been proved that this can be associated with an increasing number of Gram-positive pneumonia [27] even when SDD was used without systemic prophylaxis [12]. Our data suggest that SDD is associated with a sharp increase in tracheo-bronchial colonization by Gram-positive bacteria generally resistant to tobramycin (coagulase negative *Staphylococci* and group D *Streptococci*), whose pathogenicity at lung level has not been clearly demonstrated although there are a few reports of autoptically-defined pneumonia associated with pure cultures of *S. epidermidis* [36].

S. aureus colonizations, on the contrary, decreased in '89 and '90 although not significantly. These data are probably related to the degree of activity of tobramycin against *S. aureus* itself. Although coagulase negative *Staphylococci* showed an increasing resistance to tobramycin, this was not the case for *S. aureus.*

To reduce the incidence of Gram-positive colonizations and the risks of infections related to the use of the "classic" SDD, Pugin included topical vancomycin in the SDD regimen [13]. In his treated group he observed a significant reduction in tracheobronchial colonization by *S. aureus.* The high cost of vancomycin and the risk of the appearance of resistant strains could however lead to limitations in the use of vancomycin as one of the components of a standard SDD regimen.

We failed to observe any reduction in tracheo-bronchial colonizations by yeasts. Stoutenbeek [1] reported a sharp reduction in *C. albicans* isolations in tracheal aspirates and urine in the group treated with SDD, but its correlation with clinical infections was not recorded. In Ledingham's study [5] the incidence of infections by yeasts was not affected by SDD. Pugin [13] didn' t employ amphotericin in his SDD regimen, and although the colonization rates by yeasts were higher in the treated group, no clinically significant infection was recorded. The need to include amphotericin B in the SDD regimen is probably questionable and should be further investigated.

Conclusions

Our data suggest that the prolonged use of SDD in all ICU patients submitted to artificial ventilation for more than 24 h brings about a sharp change in the ICU ecology expressed by bacterial isolations on tracheo-bronchial aspirates.

The incidence of Gram-negative colonizations is significantly reduced by SDD, but other factors such as antibiotic regimen and stress ulcer prophylaxis also can modulate the impact of SDD. During our survey an increasing percentage of *Pseudomonas* strains developed a resistance towards tobramycin. This trend was reversed when stress ulcer prophylaxis with sulcralfate was discontinued. This observation needs further investigation.

Gram-positive colonizations tend to increase when SDD is used, but this is mostly related to bacterial strains that rarely cause lung infections.

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