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Mechanisms of Failure to Decontaminate the Gut with Polymixin E, Gentamicin and Amphotericin B in Patients in Intensive Care

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The objective of the present work was to assess the possible mechanisms of the poor efficiency of selective decontamination of the digestive tract (SDD) in medical and surgical intensive care unit (ICU) patients. Sixty-four consecutive mechanically ventilated patients received gut decontamination with polymixin E, gentamicin and amphotericin B via a nasogastric tube and were assessed for oropharyngeal, gastric and fecal colonization and for the presence of each antibiotic in the stomach and feces. A decrease in fecal colonization with *Escherichia coli* was observed over 20 days but not with other gram-negative bacteria or gram-positive cocci. Fifteen and 26 % of the fecal colonizing gram-negative bacteria were resistant to polymixin E and gentamicin, respectively, at admission. These proportions increased to up to 50 % after 16 days of treatment. Although 50 % of staphylococci were initially sensitive to gentamicin, all strains were resistant to this drug after four days of SDD. Both antibiotics were found in concentrations of less than 20 μg/g in 11 of 38 stools. Of these 38 stools, nine were not contaminated, 20 were colonized with resistant bacteria and 16 with strains sensitive to one antibiotic present in the stool. Therefore, the poor efficiency of gut decontamination observed was probably due to the great proportion of resistant strains on admission of the patients, to the selection of such resistant strains with SDD, to poor intestinal transit of the antibiotics, and to inactivation of the drugs by the feces. These results support stringent monitoring of fecal colonization in patients undergoing SDD in order to detect the fecal carriage of gram-positive and multiresistant gram-negative bacteria.

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Selective decontamination of the digestive tract (SDD) has been advocated by several European authors since 1984 in order to reduce the incidence of nosocomial infections in intensive care unit (ICU) patients (1–7). In most studies SDD was achieved by the application of antibiotics to the oropharynx and the gastrointestinal tract in association with intravenous cefotaxime. The incidence of nosocomial pneumonia was decreased by SDD, but in most studies mortality remained unchanged, leading to several controversies about the use of SDD (8). Recently, the occurrence of secondary infections with multiresistant gram-positive bacteria has been attributed to SDD (7–9). The first European Consensus Conference in Intensive Care Medicine on Selective Decontamination of the Digestive Tract in ICU Patients, held in Paris in December 1991, concluded that the effects of SDD on antimicrobial resistance needed to be evaluated more extensively (8). After employing gastric decontamination in a general ICU, we recently reported that only colonization of the stools with *Escherichia coli* could be eradicated whereas other aerobic gram-negative bacilli (AGNB) or gram-positive cocci remained present in almost all patients (10).

The aim of the present study was to determine the mechanisms of the failure of SDD in ICU patients, especially regarding alterations in the intraluminal kinetics of the antibiotics and resistance of the fecal bacteria to the antibiotics used.

Patients and Methods. Sixty-four consecutive mechanically ventilated patients received SDD in our ICU over a four-month study period. Sucralfate was used for prophylaxis of stress hemorrhage (11) and heparin for prevention of thromboembolic disease. Therapeutic drugs such as sedatives or systemic antibiotics were administered as indicated by the patient's clinical and biological status. Patients received polymixin E (100 mg), gentamicin (80 mg) and amphotericin B (500 mg) every 6 h via a nasogastric tube from the onset of mechanical ventilation until extubation. If gastric suctioning was necessary, the tube was occluded for 60 min following the administration of the antibiotics. No oropharyngeal or prophylactic systemic antibiotics were used.

Oropharyngeal secretions, gastric aspirates and stools (or rectal swabs) were cultured every four days. Colonization was assessed using a semiquantitative method for stool samples (threshold = 10,000 bacteria/g of stool) and a qualitative method for rectal swabs, oropharyngeal and gastric samples. An antibiogram was determined by disk diffusion testing for all bacteria. When an AGNB was recovered from a stool that contained at east one of the two antibiotics used (see below), the MIC of the antibiotic was determined using a broth diffusion technique, and the inhibitory quotient (IQ) was calculated by dividing the antibiotic level by the MIC for that strain. Strains were considered sensitive to gentamicin and polymixin E if the MIC was < 4 μg/ml. After day 4, when the volume of the stool was sufficient, the fecal concentrations of polymixin E and gentamicin were assessed. In patients undergoing continuous gastric suction, concentrations of polymixin E and gentamicin were measured in the gastric aspirate of the 12 previous hours. The concentration of polymixin E was determined by bioassay using *Bordetella bronchiseptica* ATCC 4617 as the test strain, while that of gentamicin was determined by a polarization fluoroimmunoassay. The duration of the evaluation was limited to 28 days for each patient. Quantitative results are expressed as the mean ± SEM.

Results and Discussion. Thirty-nine of the 64 patients (61 %) were assessable, having undergone mechanical ventilation for more than four days. Their age, sex, simplified acute physiologic score (SAPS) (12), mortality, diagnostic category on admission, length of ICU stay, duration of treatment and place of origin are shown in Table 1. Five patients were already hospitalized in the ICU (for 5 to 31 days) at the onset of the study. Seven patients received no parenteral antibiotics during the first week of decontamination, two received penicillin G, four amoxicillin, two oxacillin, 12 amoxicillin plus clavulanate, four piperacillin, four cefotaxime and six imipenem. Oropharyngeal and gastric samples were available

Table 1: Characteristics of the 39 ICU patients assessable in the study.

Age in years (mean ± SEM)	61 ± 18
Sex (no. of males/females)	24/15
Simplified acute physiologic score (mean ± SEM)	14 ± 4
Mortality	30 %
No. in each diagnostic category	
Medical	23
Elective surgery	4
Non-elective surgery	12
Length of ICU stay in days (mean ± SEM)	22.4 ± 24.4 (median 10; range 4 to 125)
Duration of treatment in days (mean ± SEM)	14.6 ± 9.0 (median 10; range 4 to 28)
No. of patients admitted from:	
Home	11
Other unit of hospital	23
Other hospital	5

from 20 patients during the first month of the study and were not taken from the subsequent patients because the stomach was almost always sterile (see below).

Fecal colonization was assessed in 61 stools and 77 rectal swabs. One hundred twenty-two samples (88 %) remained colonized with either AGNB or gram-positive cocci during the entire course of the study. Of the 263 colonizing bacteria, 47 % were gram-positive cocci, 24 % were *Escherichia coli* and 29 % were other AGNB. Overall colonization with AGNB and gram-positive cocci was poorly affected by SDD: initial colonization with *Escherichia coli* (65 %) was eradicated after 20 days of treatment, whereas colonization with other AGNB remained stable at about 40 %. Colonization fluctuated between 33 and 75 % for streptococci and between 25 and 61 % for staphylococci. Nine stools were colonized with *Candida* spp. Fifty-eight percent of the oropharyngeal samples contained AGNB. Thirty-eight percent of the fecal samples collected on day 4 after a positive oropharyngeal swab were colonized with the same bacteria recovered from the oropharyngeal swab. Only 9 % of the gastric samples obtained on the same day were colonized with AGNB also present in the oropharynx.

The proportion of fecal AGNB resistant to the antibiotics was initially 15 % for polymixin E and 26 % for gentamicin, and increased progressively to more than 50 % by the end of the treatment (Figure 1). Fifty percent of the staphylococci were sensitive to gentamicin on day 1, whereas all the strains became resistant during the treatment. In seven patients who underwent continuous gastric suctioning during the first month of the study, gastric levels of both polymixin E and gentamicin was obtained in 17 instances. The mean volume of aspirate for a 12 h period was 433 ml ± 249. The proportion of antibiotics that were then suctioned through the nasogastric tube was 20 % (median 13 %, range 0 to 69 %) for polymixin E and 28 % (median 15 %, range 0 to 83 %) for gentamicin. On six occasions fecal and gastric antibiotic levels were obtained simultaneously. The level of polymixin E in the feces was 81 µg/ml ± 98 (median 43 µg/ml, range 2 to 213 µg/ml) and that of gentamicin 211 µg/ml ± 321(median 81 µg/ml, range 18 to 855 µg/ml). These wide variations in fecal values were independent of the amount of drug suctioned via the gastric tube on the same day.

Fecal antibiotic levels were measurable in 38 stools from 15 patients. The concentration of polymixin E was 94 µg/ml ± 174 (median 42 µg/ml, range 0 to 1055 µg/ml) and of gentamicin 466 µg/ml ± 545 (median 196 µg/ml, range 0 to 2098 µg/ml). Levels of both antibiotics were < 20 µg/ml in ten stools. Nine of the 38 stools (24 %) were not contaminated. In 20 of 29 colonized stools, 26 bacteria were resistant to both polymixin E and gentamicin (15 streptococci, 6 staphylococci, 4 *Serratia marcescens* and 1 *Enterobacter aerogenes*, while in 16 of 29 stools (55 %), 17 bacteria were sensitive to at least one of the two antibiotics present in the stool. MICs and inhibitory quotients (IQ) are shown in Table 2. In five cases (*Pseudomonas aeruginosa* = 4, Escherichia coli = 1), the IQ was < 10 for both antibiotics. For the 12 other strains, the MIC of at least one antibiotic was low and the IQ was more than 10:

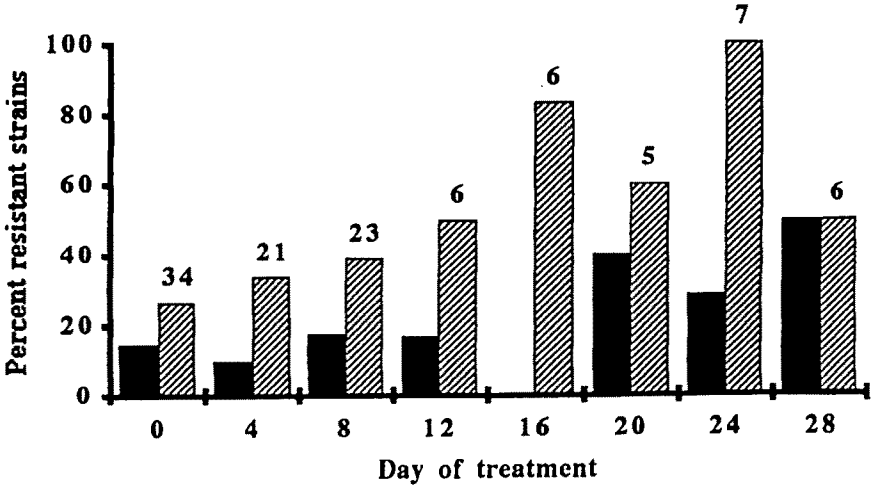

Figure 1: Proportion of fecal gram-negative bacteria resistant to gentamicin (hatched columns) and polymixin E (black columns) during decontamination.

this applied to polymixin E in 9 cases (*Pseudomonas aeruginosa* = 4, *Escherichia coli* = 3, *Enterobacter aerogenes* = 1, *Klebsiella pneumoniae* = 1) and to gentamicin in 7 cases (*Escherichia coli* = 3, *Proteus morganii* = 2, *Pseudomonas aeruginosa* = 1, *Enterobacter aerogenes* = 1) (Figure 2).

The incidence of nosocomial infections in adult ICU patients varies from 10 % to more than 45 % (13). The incidence of nosocomial pneumonia is 7 to 45 % (2, 14), with associated mortality ranging from 20 to 50 % (15). Selective decontamination of the digestive tract has been proposed because nosocomial infections are usually due to microorganisms found in the digestive flora of the patients. In the present study we assessed the impact on the digestive flora of a selective decontamination regimen for the lower digestive tract without oropharyngeal paste or parenteral systemic antibiotics. The choice of polymixin E, gentamicin and amphotericin B is based on the results obtained in previous studies (1–4, 6, 7). The aminoglycoside gentamicin was chosen because it is cheaper than tobramycin in France and it had been successfully used by Unertl et al. (2). Our patients had a prolonged ICU stay and a high risk of developing nosocomial infections, particularly with resistant strains, and should be appropriate subjects for such a preventive treatment. When a topical treatment is not used, the digestive flora remains predominantly colonized with *Escherichia coli*, and other AGNB appear progressively during the ICU stay (1–3). We found that the topical regimen was accompanied by a decrease in *Escherichia coli* but not in other AGNB. This decrease in *Escherichia coli* is in accordance with the findings of other studies on SDD (1–3), but the persistence of AGNB has not been reported previously.

One explanation for this could be that the topical and systemic antibiotics used by other authors (1–4, 6) contributed to fecal decontamination. However, we found colonization in only 9 % of the gastric samples, due to either the local acidity or the antibiotics administered in the stomach. In addition, only 38 % of the fecal samples were colonized with the same bacteria recovered in the oropharynx in the four preceding days. Parenteral antibiotics were not used systematically in our study but most patients received a beta-lactam during the first week of their ICU stay. Moreover, the kinetics of the two antibiotics administered in most of the previous clinical studies (cefotaxime and tobramycin) does not support an important role for these agents in decreasing fecal colonization: biliary concentrations of cefotaxime are usually < 2 µg/ml after intravenous injections of 1 g every 6 h (16), and the increase in fecal levels obtained with intravenous tobramycin should be negligible compared to those obtained with enteral tobramycin.

The efficacy of SDD in this population might have been diminished by the high proportion of

Table 2: Minimal inhibitory concentrations and inhibitory quotients for 17 sensitive strains present in the stools.

Strain	MIC (µg/ml)		Inhibitory quotient	
	Polymixin E	Gentamicin	Polymixin E	Gentamicin
Escherichia coli	1	0.5	6	0
Pseudomonas aeruginosa	4	8	2	0
Pseudomonas aeruginosa	4	64	7	5
Pseudomonas aeruginosa	4	64	3	0
Pseudomonas aeruginosa	4	64	5	4
Escherichia coli	0.5	0.25	300	44
Escherichia coli	1	0.5	1,055	216
Escherichia coli	1	0.25	29	416
Enterobacter aerogenes	0.5	0.5	56	614
Klebsiella pneumoniae	1	8	43	2
Proteus morganii	> 64	1		1,248
Proteus morganii	> 64	1		1,757
Pseudomonas aeruginosa	4	16	38	1
Pseudomonas aeruginosa	8	4	4	26
Pseudomonas aeruginosa	4	32	15	55
Pseudomonas aeruginosa	4	> 64	41	
Pseudomonas aeruginosa	4	> 64	15	

patients already colonized with resistant bacteria before starting SDD. The initial bacterial distributions were similar in patients present in a hospital ward before their ICU stay and in patients directly admitted from home. Another main concern is the acquired resistance of the colonizing bacteria to the antibiotics we used. Even though streptococci and enterococci can produce nosocomial infections, their presence should not be considered a failure of SDD, as these strains are not within the spectrum of this regimen. The decontamination, however, may induce an overgrowth of such strains: 50 % of the staphylococci were initially susceptible to gentamicin, but all of the strains were resistant to this antibiotic as early as day 4 of SDD. This result, as well as the progressive increase in resistance of AGNB to polymixin E and gentamicin, was probably due to a selection of resistant strains by the antibiotics, as many cultured bacteria are naturally (*Serratia marcescens*, *Proteus morganii*, gram-positive cocci) or frequently (*Pseudomonas aeruginosa*, *Acinetobacter calcoaceticus*) resistant to at least one of these antibiotics. The possibility of exogenous colonization of the gut during SDD is unprobable in this study, as the gastric samples were almost always sterile.

Among the patients in whom fecal antibiotic levels could be assessed, levels of both polymixin E and gentamicin were < 20 μg/g in 24 % of the stools, explaining the inefficacy of SDD in some of the patients. Regarding the possibility that antibiotics were removed from patients submitted to gastric suctioning, we found that great amounts of antibiotics in the gastric juice were rarely observed, indicating that the method of drug administration was adequate.

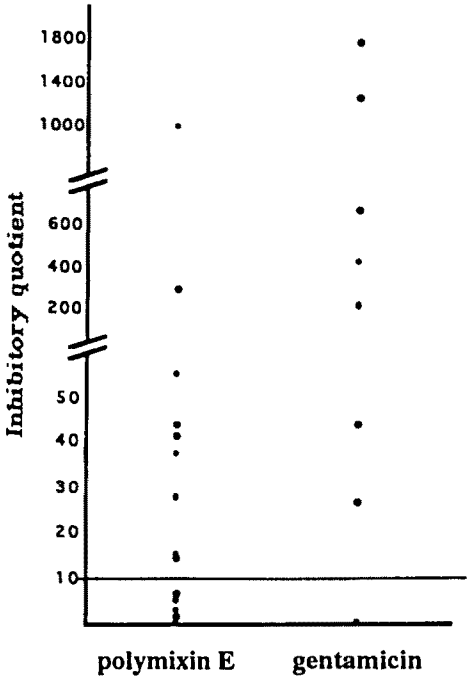

Figure 2: Inhibitory quotients of polymixin E and gentamicin for the fecal gram-negative bacteria sensitive to polymixin E or gentamicin (MIC < 4 μg/ml).

Finally, the antibacterial activity of polymixin E and/or gentamicin might have been altered by drugs present in the stools or by the stools themselves. Of the 38 samples from 15 patients who had a volume of stools sufficient to assess the antibiotic level, only 24 % were sterile, whereas 55 % were colonized with strains sensitive to at least one of the antibiotics used, the presence of such antibiotic being demonstrated in the same sample. Moreover, the inhibitory quotient for at least one antibiotic was > 10 for 12 of 17 strains. This could reflect the increase in MICs and MBBs of polymixin E and aminoglycosides for most species, possibly due to the presence of human feces, as was observed in an in vitro study by Van Saene et al. (17). In aminoglycosides this increase may be due to their capacity to bind to nucleic acids or to inactivation caused by acidity, by an anaerobic environment (18), or by the presence of calcium, which impairs the membrane potential of the bacteria (19).

The antibacterial properties of polymixin E are reduced in the presence of calcium and of normal stools (20). In addition, aminoglycosides could have been inactivated by sucralfate, a non absorbed drug used in most of our patients to decrease the risk of stress hemorrhage (11). This interaction in vivo remains hypothetic, as no clinical study about it has yet been published and this point was not addressed by our study.

The decrease in activity of antibiotics due to feces observed in vitro by Van Saene et al. (17) was lower for tobramycin than for gentamicin regarding *Pseudomonas aeruginosa* and *Acinetobacter calcoaceticus*, but not regarding *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes* or *Proteus morganii*. In the present study these last four species were found more frequently in the feces in the presence of gentamicin (11 cases) than *Pseudomonas aeruginosa* and *Acinetobacter calcoaceticus* (5 cases), indicating that the use of gentamicin is not likely to have influenced the results.

In conclusion, we obtained a slow eradication of *Escherichia coli* and no decrease in colonization with other more resistant gram-negative or gram-

positive strains in the feces using gastric decontamination. These results can be attributed to the presence of strains resistant to the antibiotics used before starting the treatment, to overgrowth of such resistant strains during SDD, or to the absence of antibiotics in the feces due to poor gastroinstestinal transit. Finally, the simultaneous presence of antibiotics and sensitive bacteria in the stools may reflect an inactivation of the antibiotics by the feces. On the basis of these findings we recommend that fecal colonization of patients undergoing SDD be carefully monitored in order to detect the fecal carriage of gram-positive and multiresistant gram-negative bacteria.

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