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Originals

Prevention of nosocomial infection in critically ill patients by selective decontamination of the digestive tract

A randomized, double blind, placebo-controlled study

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Abstract. *Objective:* To evaluate the effect of a method of Selective Decontamination of the Digestive Tract (SDD) on colonization, nosocomial infection (NI), bacterial resistance, mortality and economic costs. *Design:* Randomized, double blind, placebo controlled study. *Setting:* Polyvalent intensive care unit (ICU) of a tertiary care hospital with 27 beds. *Patients:* 101 patients with >3 days of mechanical ventilation and >5 days of stay, without infection at the start of the study. 47 belonged to the Treated Group (TG) and 54 to the Placebo Group (PG). *Interventions:* The TG was given Cefotaxime i.v. (6 g/day) for the first four days and an association of Polymyxin E, Tobramycin and Amphothericin B at the oropharyngeal and gastrointestinal level throughout the whole stay. *Results:* In the TG, colonization by gram-negative agents at oropharyngeal, tracheal and gastrointestinal level fell significantly. There was a significant drop in the overall, respiratory and urinary NI (26% vs 63%, $p<0.001$; 15% vs 46%, $p<0.001$; 9% vs 31%, $p<0.01$). The overall mortality and NI related mortality was less in the TG (21% vs 44%, $p<0.05$; 2% vs 20%, $p<0.01$). The economic costs, mechanical ventilation time and length of stay were similar. The percentage of bacterial isolations resistant to Cefotaxime and Tobramycin was greater in the TG (38% vs 15% and 38% vs 9%, $p<0.001$). *Conclusions:* colonization by gram-negative bacilli, NI and the mortality related to it can be modified by SDD. Continuous bacteriological surveillance is necessary.

Key words: Selective decontamination of the digestive tract – Infection prevention – Nosocomial – Intensive care unit – Artificial ventilation

Nosocomial infection (NI) continues to be a major medical problem in ICUs where, due to the severity of the illness, the poor defences and the handling of patients [1, 2], its incidence stands at 23%–28%, in some cases exceeding 80% [3–5]. Even with careful hygienic measures and a restrictive antibiotic policy its rate is high [6–8]. Mortality, length of stay and other hospital costs can be altered by the development of a NI [8–12]. Some 70%–90% are of endogenous origin, caused by organisms that had previously colonized the patient, especially at the oropharyngeal and gastrointestinal level [3, 13–17]. Digestive decontamination with non-absorbable antibiotics is an old technique for preventing NI, used basically in hematological neoplasias with varying results [18]. In 1984 Stoutenbeek et al. [5] published the results of the use in ICU patients of a method of Selective Decontamination of the Digestive Tract (SDD) whose spectrum aimed to respect the habitual anaerobic microflora participating in resistance to colonization [19]; they cut down the rate of NI from 81% to 16%. Other authors later confirmed the use of SDD in ICUs [20–29], though important points remain unclarified [29–33] (kinds of patients benefiting, development of resistance, effect on hospital mortality and stay). We therefore began a prospective, randomized, double blind, placebo controlled study with the aim of evaluating its efficiency in the prevention of NI in ICUs and the influence on colonization and the other aforementioned variables.

Material and methods

Study design

We included only those patients with mechanical ventilation (MV)>3 days and stay in ICU>5 days. Causes for exclusion were: infection or strong suspicion of this at the start of the MV, antibiotic treatment in the previous seven days, neutropenia (<500 pmn/ml) and fever, pregnancy, and a history of hypersensitivity to the agents used in SDD.

Those patients that we expected to meet the criteria for inclusion were initially assiged in the center's Pharmacy Service to the placebo group (PG) or the treated group (TG), according to a table of random distribution numbers generated by computer. The necessary medication was sent daily in an individualized manner. All were carriers of a nasogastric tube, a bladder catheter connected to a closed drainage system and central venous catheters. We conducted stress ulcer prophylaxis solely with antacids and H2 blockers. The ventilator tubings were changed every 48 h. Every day, patients underwent physical examination and chest radiograph for signs of infection, and biochemical and hematological data were gathered. Problems related to the infections

were discussed in clinical sessions. If these were life threatening they were treated initially with an association of cephthazidim or piperacilin and tobramycin, using metronidazole or clindamycin if anaerobics were suspected; later we used the antibiotics that were indicated. We only used cefotaxime in SDD or in infections with bacteriological documentation that made this necessary. The severity of their illness was tabulated by APACHE II [34], the Glasgow coma score (GCS) and number of organ-system failures [35].

Decontamination regimen

The TG was given cefotaxime i.v. (6 g/day) for the first four days; throughout the whole stay in the unit a paste of carboxymethylcellulose (0.5 g/q.i.d.) with 2% of polymyxin E, tobramycin and amphothericin B was applied to the oropharynx, and a solution containing 100 mg of polymyxin E, 80 mg of tobramycin and 500 mg of amphothericin B was given via a nasogastric tube four times a day. The PG was given the same quantity of paste/solutions containing just an inert colorant substance.

Bacteriological surveillance

Randomly and up to a maximum of four patients simultaneously, in the 24 h following their inclusion and then twice a week samples of oropharynx, tracheal aspirate, gastric aspirate, and feces were cultured. When there was a suspicion of infection all the necessary bacteriological samples were taken. They were cultured aerobically using standard microbiological techniques and anaerobically when there was a clinical indication. Sensitivity to cefotaxime and tobramycin was studied by means of disk diffusion techniques. The surveillance samples were taken by Dr M J Martín without any of the other investigators or doctors in charge having access to them.

Definitions

(i) Lower respiratory tract infection: Presence of purulent pulmonary secretions, new infiltrates in the chest X-rays and one of the following findings: fever/hypothermia, leukocytosis/leukopenia, positive physical examination and drop in arterial partial oxygen pressure. Non-essential bacteriological diagnosis was carried out by means of identification of the agent in two positive samples of tracheal aspirate, associated blood culture, pleural liquid or, in the latest patients, in protected bronchial brushing.

(ii) Urinary tract infection: Urine culture with >100000 cfu/ml and >3 leukocytes/high-power field.

(iii) Wound infection: Data on inflammation and purulent secretion from the wounds, with positive culture.

(iv) Bacteriemia-sepsis: Positive blood culture associated with fever, leukocytosis and/or hypotension. Coagulase-negative *Staphylococcus* had to be confirmed in two different extractions.

(v) Catheter-associated septicemia: Isolation of the same agent in blood culture and semiquantitative culture of the intravascular segment without other sources of infection.

(vi) Superinfection: That developed during antibiotic treatment, caused by germs resistant to it.

(vii) Colonization: Presence of a potentially pathogenic agent in an organ or system without signs of infection during more than three days (isolated in at least two consecutive samples).

(viii) Exitus associated with infection: That occurring as part of an infection that causes shock and severe respiratory failure ($PaO_2/FiO_2<150$).

(ix) NI index: percentage of infected patients.

(x) NI rate: Number of infections developed among all the patients, expressed as a percentage.

Statistical analysis

The Fisher's exact test was used to compare categories. The averages were compared by means of the Student's *t*-test. Survival was estimated with the Kaplan-Meier method compared with the log-rank test and adjusted according to the Cox semiparametric model. A value of $p<0.05$ was considered significant.

Results

During the 14 months of the study, 1600 patients entered the unit. Initially, 151 received medication (SDD or placebo), but only 101 met the requirements demanded. The remainder were excluded because of: development of infection in the first 48 h [4], extubation before the third day [15], discharge before the fifth day [31]. Fifty-four belonged to the PG and 47 to the TG. They were comparable in terms of age, sex and scoring on illness severity scales. The diagnostic grouping was similar, with traumatic patients dominating both groups, head trauma being the most frequent. Within medical patients complicated ischemic cardiopathy and acute cerebrovascular accident in young people predominated (Table 1).

Colonization

The percentage of colonized patients in each group at the oropharyngeal, tracheal, gastric and rectal level followed a similar profile (Fig. 1). While colonization by Gram-negative agents in the TG stayed steady or dropped compared with the first sample, except in the trachea, in the PG it progressively rose, becoming significant from the fourth day on. At the rectal level, the differentiation was slower, becoming significant from day 13. In the PG the

Table 1. Patient distribution and diagnostics

	Placebo group ($n=54$)	Treated group ($n=47$)
Age	44.1 (SD: 21)	42.8 (SD: 19)*
(range)	(16–62)	(15–79)
Male/female	47/7	38/9*
APACHE II score	16 (SD: 5)	14.9 (SD: 5)*
(range)	(7–31)	(7–27)
Glasgow coma score (GCS)	9.1 (SD: 3)	9 (SD: 3.5)*
(range)	(5–15)	(5–15)
No. of patients with GCS<8	19 (35%)	22 (47%)*
Organ-system failure (OSF)		
1 organ	20 (37%)	18 (38%)*
2 organs	11 (20%)	14 (30%)*
3 organs	0	1 (2%)
Medical	12 (22%)	9 (19%)*
Cardiac disease	5	4
Neurologic disease	7	5
Traumatic	42 (78%)	38 (81%)*
Thoracic trauma	2	2
Spinal cord injury	3	4
Head trauma and associated	37	32

* Not significant; OSF, number of patients with organ-system failure

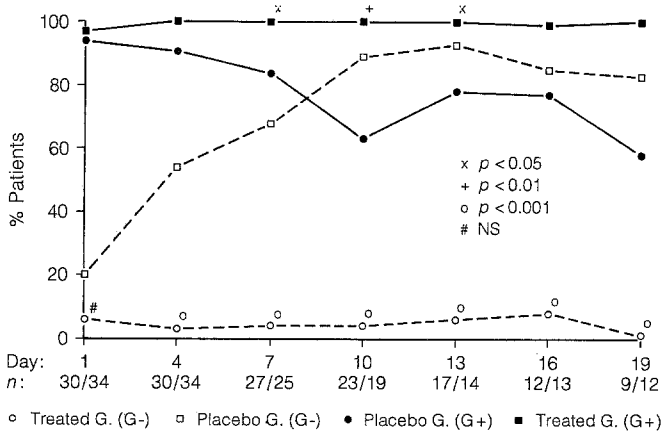

Fig. 1. Oropharyngeal colonization. Evolution of the percentage of patients colonized by Gram-positives ($G+$) and Gram-negatives ($G-$) in each group. *n*: Number of patients sampled in each group (TG/PG)

presence of Gram-positive organisms gradually dropped, but in the TG it remained the same or increased, becoming significant starting from days 7–10. After days 4–7 *Staphylococcus*, mainly *S. aureus*, and *Enterococcus* predominated in both groups, with a higher percentage in the TG.

Oropharynx: In the first sample 20% of PG patients showed Gram-negative organisms and 7% of the TG (NS). After the fourth day (54% vs 3%, $p<0.001$) > 80% and < 8%, respectively, did so. The initial isolation of Gram-positive agents was 94% and 97% (NS); from day 7 (84% vs 100%, $p<0.05$) this was < 80% in the PG and 100% in the TG.

Tracheal aspirate: Gram-negative bacteria colonized 35% in the PG and 6% in the TG ($p<0.01$) on day one. From the tenth day (92% vs 32%, $p<0.001$) colonization occurred in more than 90% of the PG and between 30%–40% in the TG. Gram-positives were initially isolated in 70% and 75% of patients (NS); in the PG they dropped, staying steady from day ten (35% vs 91%, $p<0.001$) at around 30% and in the TG they continued at above 85%.

Gastric aspirate: The presence of Gram-negatives started at 31% and 6% ($p<0.05$). In the PG they rose, from day seven (61% vs 3%, $p<0.001$) remaining at around 60% and in the TG they continued below 6%. After day one (23% vs 6%, NS) Gram-positive agents stayed below 34% in the PG and in the TG rose to 69% on day 16 (8% vs 69%, $p<0.01$).

Feces: From 11% in the PG and 3% in the TG (NS), Gram-negative bacteria (no *E. coli*) rose up to day 16 (58% vs 7%, $p<0.01$) in the first group, while in the second they fell starting from day ten (39% vs 19%, NS). Colonization by *Escherichia coli* (89% vs 91%, NS on day one) continued above 70% in the PG, and in the TG, after the seventh day (75% vs 37%, $p<0.01$), was less than 14%.

Infections

The NI index fell from 63% (34/54) in the PG to 26% (12/47) in the TG ($p<0.001$). 49% (28/57) of NIs in the PG, and 13% (2/15) in the TG ($p<0.05$), were early (< 5 days).

Respiratory infection (Table 2): 46% of patients in the PG and 15% of the TG had pneumonia ($p<0.001$). This

Table 2. Summary of organisms causing infection

	Placebo group	Treated group	
Respiratory infection	25/54 (46%)	7/47 (15%)	$p<0.001$
Staphylococcus aureus	15	5	
Streptococcus pneumoniae	2	0	
Enterococcus	0	1	
Haemophilus influenzae	9	0	
Pseudomonas spp.	4+4	1	
Acinetobacter spp.	4+8	1	
Klebsiella spp.	1	0	
Proteus spp.	1+1	0	
Pasteurella spp.	1	0	
Aeromonas spp.	0+1	0	
Urinary tract infection	17/54 (31%)	4/47 (9%)	$p<0.01$
Staphylococcus aureus	1	1	
Coagulase-negative staphylococcus	2	0	
Enterococcus	5	1	
Escherichia coli	4+1	1	
Klebsiella spp.	4	0	
Enterobacter spp.	3	0	
Proteus spp.	2	0	
Pseudomonas spp.	0	1+1	
Acinetobacter spp.	0	1	
Bacteriemia	10/54 (19%)	3/47 (6%)	N.S.
Catheter-associated	(episodes: 3)	(episodes: 3)	
Staphylococcus aureus	0	2	
Coagulase-negative staphylococcus	2	1	
Klebsiella spp.	1	0	
Pulmonary source	(episodes: 5)		
Staphylococcus aureus	1	0	
Streptococcus pneumoniae	1	0	
Acinetobacter spp.	2	0	
Pseudomonas spp.	1	0	
Urinary source	(episodes: 2)		
Staphylococcus aureus	1	0	
Klebsiella spp.	1	0	
Other sources	(episodes: 3)		
Staphylococcus aureus	1	0	
Acinetobacter spp.	1	0	
Proteus spp.	1	0	
Wound infection	1/54 (2%)	2/47 (4%)	N.S.
Staphylococcus aureus	1	1	
Enterococcus	0	1	
Escherichia coli	0	1	
Pseudomonas spp.	0	1	
Bacteroides spp.	1	0	
Overall Gram-positive agents	32/88 (36%)	13/21 (62%)	
Overall Gram-negative agents	56/88 (64%)	8/21 (38%)	$p<0.05$

NS, not significant; n/n, index of each infection type; the rate of bacteriemias drops from 24% (13/54) to 6% (3/37), $p<0.001$; +n, number of agents isolated in respiratory superinfections and urinary reinfections

started at 4.8 days (SD: 2.8) in the PG and at 16.8 days (SD: 22) in the TG, with 72% and 14% respectively ($p<0.05$) being early. The etiology was Gram-positive, mainly *Staphylococcus aureus*, in 68% of episodes in the PG and in 71% in the TG. Apart from *Haemophilus influenzae* in the PG, *Pseudomonas* and *Acinetobacter* were the most frequent Gram-negatives. In the TG 86% were cured and in the PG 64% were cured or initially improved since 32% (9/25) showed superinfection caused exclusively by Gram-negative agents. The TG had no superinfections.

Urinary infection (Table 2): 31% of individuals in the PG showed this, and 9% in the TG ($p<0.01$). In the first group this started at 9.8 days (SD: 13) and in the second at 13.2 days (SD: 8.5), 35% and 25% (NS) being early. 47% of cases in the PG and 50% in the TG were caused by Gram-positives. 82% and 100%, respectively, were cured. In both groups there was one reinfection.

Bacteriemia (Table 2): The index fell from 19% in the PG to 6% in the TG (NS) and the rate went from 24% (13/54) to 6% (3/47) ($p<0.001$). It appeared sooner in the PG (6.2 days; SD: 3) than in the TG (10.6 days; SD: 3), being early in 31% and 0% of episodes in each group. The focus was exclusively the vascular catheter in the TG, and in the PG the lung was the main source [5]. In the TG we only identified *Staphylococcus*. In 46% of bacteriemias in the PG we isolated Gram-positive bacteria.

Wound infection (Table 2): One patient (2%) in the PG showed this and two (4%) in the TG. Both infections were late. One individual in the TG was not cured.

Resistances

In the PG 15% (144/964) of bacterial isolations were resistant to cefotaxime and 38% (175/462) in the TG ($p<0.001$). Resistance to tobramycin was 9% and 38%, respectively ($p<0.001$). The percentage of resistances to cefotaxime and tobramycin in each of the organisms was usually greater in the TG. Significance was reached in *Staphylococcus aureus* with $p<0.001$ (cefotaxime: 14% (19/136) in the PG and 52% (144/277) in the TG; tobramycin: 10% (13/136) in the PG and 52% (144/277) in the TG) and in *Acinetobacter* with $p<0.05$ for tobramycin (33% (47/143) in the PG and 61% (14/23) in the TG). The resistance patterns of agents responsible for infections were similar in both groups (Table 3).

Mortality

During the study the general mortality in our unit was 20.5%. Overall mortality in the PG was 44% (24/54) and 21% (10/47) in the TG ($p<0.05$). Mortality due to the underlying disease was 24% and 19% (NS), respectively; that related to NI was 20% (11/54) in the PG and 2% (1/47) in the TG ($p<0.01$). A difference existed on comparing the survival curves (Fig. 2) by means of the log-rank test ($p<0.05$). After adjusting with those variables that could have influenced survival at the beginning (age, APACHE II, GCS and presence of organ-system failure) the risk of death was 2.3 times higher in the PG (Cox model: 95% confidence interval, 1.08 to 4.98; $p<0.05$).

Costs

We used therapeutic antibiotics (TA) in 56% of patients in the PG and in 34% in the TG ($p<0.05$). The cost of TA/patient/day was 2736 pesetas in the PG and 1334 pesetas in the TG ($p<0.05$). The cost of SDD/patient/day was 2785 pesetas. The overall cost of antibiot-

Table 3. Resistance patterns of organisms isolated from infected patients

	Cefotaxime		Tobramycin	
	Placebo	Treated	Placebo	Treated
Staphylococcus aureus	4/20 (20%)*	4/9 (44%)	4/20 (20%)*	4/9 (44%)
Coagulase-negative staphylococcus	2/4 (50%)*	1/1 (100%)	2/4 (50%)*	1/1 (100%)
Streptococcus pneumoniae	0/3	0	nd/3	0
Enterococcus	5/5 (100%)*	3/3 (100%)	5/5 (100%)*	3/3 (100%)
Haemophilus influenzae	0/9	0	nd/9	0
Escherichia coli	0/4	0/2	0/4	0/2
Proteus spp.	0/5	0	0/5	0
Klebsiella spp.	0/7	0	0/7	0
Enterobacter spp.	1/3 (33%)	0	0/3	0
Pasteurella spp.	0/1	0	0/1	0
Aeromonas spp.	0/1	0	1/1	0
Acinetobacter spp.	8/15 (53%)*	1/2 (50%)	6/15 (40%)*	1/2 (50%)
Pseudomonas spp.	7/9 (78%)*	2/3 (67%)	4/9 (44%)*	1/3 (33%)
Bacteroides spp.	nd/1	0	nd/1	0
Overall Gram-positive agents	11/32 (34%)*	8/13 (62%)	11/29 (38%)*	8/13 (62%)
Overall Gram-negative agents	16/54 (30%)*	3/7 (43%)	11/45 (24%)*	2/7 (29%)

* Not significant; nd, not done

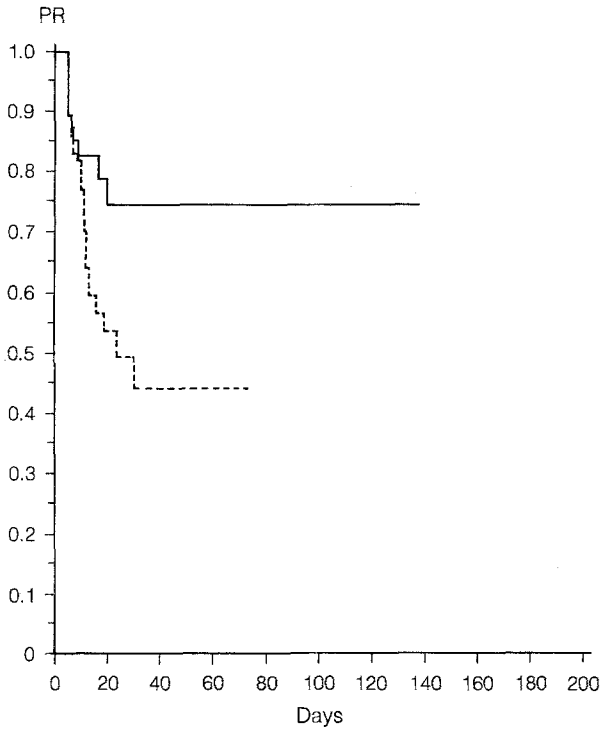

Fig. 2. Survival in both groups is significantly different (log-rank test, $p<0.05$). Adjusting with variables that on arrival could modify survival, the risk of death was 2.3 times higher in the PG (Cox model, $p<0.05$). Treated G: _____ ; Placebo G: ....

ics/patient/day was 2736 in the PG and 4045 pesetas in the TG ($p<0.05$). There was no difference in other antibiotic costs (Table 4).

The average time of MV was 13 days in both groups. In non-infected survivors the time was 7.7 days (SD: 5) in the PG and 11.8 days (SD: 9) in the TG (NS), (Table 4).

The average stay in the PG was 17.8 days (SD: 15) and 18.8 days (SD: 20) in the TG (NS). In non-infected survivors this was 11 days (SD: 5) and 17 days (SD: 10), respectively ($p<0.05$). The cost of stay/patient was similar in both groups. The cost/survivor was 3477246 pesetas in the PG and 2582980 pesetas in the TG (Table 4).

Discussion

The first studies on SDD used a historic control group [5] or a consecutive control and treatment group in order to prevent the use of the two different antibiotic regimens interfering with the colonization/infection profiles of the individuals [23]. Later randomized studies demonstrated the possibility of carrying out simultaneous designs that would ensure that the patients were handled equally [22, 32]. We selected patients subjected to MV and with a stay in ICU of >5 days in order to constitute a high risk group for developing NI and one which could benefit most from SDD [3, 5, 8, 23]. In order to prevent interferences in the results we excluded previously infected patients, the use of sucralfate and we conducted a double blind, placebo controlled study [3, 5, 19, 20, 27].

As with other groups [5, 20–28, 31, 32], we found a significant reduction in colonization by Gram-negative bacteria at all levels. This occurred early (days 4–7) except at the rectal level (days 7–13), probably due to intestinal paresis that these patients can show [5]. Unlike in the PG, in the TG the presence of Gram-positive agents, basically *Staphylococcus* and *Enterococcus* after day 4, remained steady and even increased. These germs can be regarded as forming part of the usual flora [36, 37] and perhaps because of this they are not normally described, though other groups also observed this fact [24]. The difference in the percentage of patients in each group colonized at the beginning was due to the fact that the sample was not always taken prior to administering SDD and the germs isolated in the PG (*Haemophilus, E. coli, Klebsiella, Enterobacter*) are inhibited by it. Related to the changes produced in the colonization profiles, a significant drop in the NI index (63% vs 26%) was achieved, with a marked reduction in Gram-negative agents as being responsible for this. As with the majority of SDD works [28, 31, 32] this was related to a drop in respiratory infection; but as with other authors we also found a fall in urinary infections [3, 25, 28] and in bacteriemias [3], though, unlike the Utrecht and The Hague groups [22, 25], catheter related infections, caused exclusively by Staphylococcus in the TG, did not fall. As with Gastinne et al. [29], we only observed respiratory superinfections in the PG, caused solely by Gram-negative organisms. Though some authors [21, 26, 27, 40] reduced NIs without parenteral prophylaxis, in our study it probably played a major role due to the high percentage of early infections, mainly at the respiratory level.

The risk of a multi-resistant bacterial strain appearing during the use of an antibiotic prophylaxis always exists. But so far no clinically important resistances have been found [31, 32], even in prolonged follow-ups [38, 39]. Though, as with the University of Ulm group [24], we did record a rise in resistances in the bacterial population of the TG, this had no clinical relevance since not only did the resistance patterns of the agents responsible for infections not differ, NIs also decreased and their curing percentage was greater in the TG, with a lower mortality. Nevertheless, this, along with the selection of a Gram-positve flora potentially responsible for serious infections, means that the need must be emphasized for long-term surveillance.

The relation between the development of NI and the rise in mortality is well known but is not easy to demonstrate since a patient may die with an infection before this becomes the cause [9]. The reduction in the incidence of NI with SDD did not cause a uniform drop in mortality [31–33], though some found a decrease in selected groups of patients [23, 40] or in the mortality associated with infection [22]. Not even in an extensive double blind study with a greater number of medical patients was an improvement in survival achieved [29]. Only one randomized study [25] observed, as did we, a drop in the overall mortality with a simultaneous decrease in that associated with NI. This is probably due to our population being mainly traumatic, with midrange APACHE II score and prolonged stay, something that has already been pointed out by Ledingham et al. [23], as well as with a non-terminal situation on admission, as Gross et al. established [9].

Table 4. Costs

	Placebo group ($n = 54$)	Treated group ($n = 47$)	
Antibiotics			
Therapeutical antibiotics (TA)			
Number of patients	30 (56%)	16 (34%)	$p<0.05$
Days/patient	8 (SD: 10)	4.9 (SD: 10)	NS
Days/infected patient	14.4 (SD: 9)	14.4 (SD: 13)	NS
No. of TA/patient	1.7 (SD: 1.9)	0.8 (SD: 1.5)	$p<0.05$
No. of TA/infected patient	3 (SD: 1.5)	2.3 (SD: 1.8)	NS
Overall cost	3589803	1733241	
Cost/patient	66478	36878	NS
Cost/infected patient	119660	108328	NS
Cost/patient/day	2736	1334	$p<0.05$
Cost/infected patient/day of therapy	7804	6966	NS
SDD			
Overall cost	0	1846178	
Cost of parenteral SDD	0	763656	
Cost of topical SDD	0	1082522	
Cost/patient	0	39280	
Cost/patient/day	0	2785	
All the antibiotics			
Overall cost	3589803	3579419	
Cost/patient	66478	76157	NS
Cost/patient/day	2736	4045	$p<0.05$
Cost/day	3716	4045	NS
Length of artificial ventilation			
Days/patient	13.2 (SD: 9)	13.1 (SD: 15)	NS
Days/survivor	15.2 (SD: 11)	14.5 (SD: 17)	NS
Days/infected survivor	19 (SD: 11)	22 (SD: 28)	NS
Days/non-infected survivor	7.7 (SD: 5)	11.8 (SD: 9)	NS
Length of stay			
Days/patient	17.8 (SD: 15)	18.8 (SD: 20)	NS
Days/survivor	23.5 (SD: 17)	21.7 (SD: 21)	NS
Days/infected survivor	29.8 (SD: 18)	33.4 (SD: 37)	NS
Days/non-infected survivor	11 (SD: 5)	17 (SD: 10)	$p<0.05$
Cost of stay/patient	1931803	2033410	NS
Cost of stay/survivor	3477246	2582980	

Costs are expressed in pesetas (1 US$ = 107.11 pesetas). The average cost/bed/day in our ICU is 107989 pesetas

As with other studies [22, 23], the use of therapeutic antibiotics decreased with a significantly lower cost/patient/day in the TG. This saving was canceled out by the higher price represented by SDD, which meant that the average cost of the total antibiotics/patient/day was greater in the TG, though the final cost was similar in both groups. We did not observe the possibility of raising the cost of the treatment of infections in the TG due to the appearance of resistant organisms [12] since the cost/infected patient was not different.

Unlike other authors [5, 20–22, 40], who noted a reduction in the stay of TG patients, we, as with Ulrich et al. [25], did not find any differences in the MV time nor in the stay of both groups. This is probably related to the decrease in the mortality and the appearance later on of infections in the TG. This delay, which has already been noted previously [40], along with a more prolonged MV and stay time among survivors in the TG, allows us to speak of having achieved a greater "infection-free interval" in this group. Finally, it must be pointed out from the cost-effectiveness viewpoint that the overall price/survivor was less in the TG.

To summarize, in selected patients in an ICU, SDD can modify colonization by Gram-negative bacilli, the incidence of NI and associated mortality without increasing costs. During the study period, no resistance of clinical importance has been noted.

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