Articles

Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial

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Summary

Background Selective decontamination of the digestive tract (SDD) is an infection-prevention regimen used in critically ill patients. We assessed the effects of SDD on intensive-care-unit (ICU) and hospital mortality, and on the acquisition of resistant bacteria in adult patients admitted to intensive care

Methods We did a prospective, controlled, randomised, unblinded clinical trial. 934 patients admitted to a surgical and medical ICU were randomly assigned oral and enteral polymyxin E, tobramycin, and amphotericin B combined with an initial 4-day course of intravenous cefotaxime (SDD group n=466), or standard treatment (controls n=468). Primary endpoints were ICU and hospital mortality and the acquisition of resistant bacteria.

Findings In the SDD group 69 (15%) patients died in the ICU compared with 107 (23%) in the control group (p=0·002). Hospital mortality was lower in the SDD groups than in the control group (113 [24%] *vs* 146 [31%], p=0·02). During their stay in intensive care, colonisation with gram-negative bacteria resistant to ceftazidime, ciprofloxacin, imipenem, polymyxin E, or tobramycin occurred in 61 (16%) of 378 SDD patients and in 104 (26%) of 395 patients in the control group (p=0·001). Colonisation with vancomycin-resistant enterococcus occurred in five (1%) SDD patients and in four (1%) controls (p=1·0). No patient in either group was colonised with meticillin-resistant *Staphylococcus aureus*.

Interpretation In a setting with low prevalence of vancomycin-resistant enterococcus and meticillin-resistant *S aureus*, SDD can decrease ICU and hospital mortality and colonisation with resistant gram-negative aerobic bacteria.

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Introduction

Selective decontamination of the digestive tract (SDD) is an infection-prophylaxis regimen that was introduced into intensive-care medicine in 1984.[1] Nosocomial infections contribute substantially to morbidity and mortality of patients treated in intensive-care units (ICUs).[2] Most of these infections are thought to be preceded by oropharyngeal and intestinal colonisation with pathogenic micro-organisms. SDD is based on the concept of colonisation resistance, according to which the indigenous intestinal flora has a protective effect against secondary colonisation with gram-negative aerobic bacteria. The approach aims to eradicate colonisation of aerobic potentially pathogenic micro-organisms from the oropharynx, stomach, and gut, while leaving the indigenous anaerobic flora largely undisturbed. The classic SDD regimen consists of two components. Topical non-absorbed antibiotics, generally polymyxin E, tobramycin, and amphotericin B, are applied orally and through a nasogastric tube, and treatment with parenteral antibiotics, most frequently cefotaxime, is added for the first 4 days to prevent early infections.

The belief that SDD reduces mortality in ICU patients was fostered by three meta-analyses, each reporting decreased mortality among patients who were treated with combined topical and systemic antibiotics.[3–5] Yet, the meta-analyses on SDD were based partly on unpublished studies[6] and the quality of methods in the published studies has been challenged.[7] Controversy exists about the effect of SDD on mortality and on antibiotic resistance. Studies with antibiotic resistance as an endpoint would ideally focus on the effect of SDD on the ICU environment as well as on individual patients.[5,8] We, therefore, did a controlled randomised study with mortality and the acquisition of resistant bacteria as primary endpoints.

Patients and methods

Patients

From September, 1999, to December, 2001, we enrolled consecutive patients admitted to the ICU at the Academic Medical Centre, Amsterdam, who were older than 18 years, and had expected duration of mechanical ventilation of at least 48 h, expected length of ICU stay of at least 72 h, or both. Exclusion criteria were previous admission to the ICU within 3 months, known hypersensitivity to study medication, pregnancy, perceived imminent death, and participation in another investigational study. Written informed consent was given by the participating patients or their representatives and the study was approved by the institutional scientific and ethics committees.

Methods

We used a randomised controlled trial design. The ICU consisted of two separate units with a similar case mix of

medical and surgical patients. Standard care was administered in the same way in the two units. The same medical staff always administered care but did not mix between units. One unit was designated the SDD unit, and one the control unit to prevent cross-colonisation between SDD patients and controls. In the 2 years before the study, severity of illness, as measured by the acute physiology and chronic health evaluation (APACHE II) score (18·7 [SD 6·6] in the SDD and 19·2 [6·7] in the control units, respectively) and hospital mortality (relative risk in the SDD unit 0·9, 95% CI 0·7–1·1) did not differ between the units. The separation of units meant that the study had to be unblinded. Which unit would be the SDD unit and which the control unit was randomly decided before the study. Patients were assigned to treatment groups by nursing staff not involved in the study. Unless beds were available in one unit only, on admission, patients were allocated to one of the two units, according to computer-generated random-number codes kept in sealed envelopes. If we did not obtain consent to participate, patients were treated with or without SDD dependent on the unit they were admitted to but were not included in the analysis and no cultures for colonisation with resistant bacteria were taken.

Participating patients in the SDD unit were treated four times daily with around 0·5 g of an oral paste, applied to the buccal cavity, containing 2% polymyxin E, 2% tobramycin, and 2% amphotericin B. They also received 100 mg polymyxin E, 80 mg tobramycin, and 500 mg amphotericin B administered through gastric tubes. Among patients who had had tracheostomies, the polymyxin E, tobramycin, and amphotericin B paste was also applied four times daily on the skin surrounding the tracheostomy. Patients with blind bowel loops (eg, after colostomy) were additionally treated two to four times daily with suppositories containing amphotericin B 42 mg, polymyxin E 42 mg, and tobramycin 64 mg. Cefotaxime 1000 mg four times daily was given intravenously throughout the first 4 days. As part of the SDD strategy, surveillance cultures from rectal swabs, throat swabs, and sputum were taken at admission and twice weekly during the stay on the ICU. If aerobic gram-negative bacteria or yeasts were cultured from the sputum on more than one occasion, we gave patients nebulised polymyxin E 80 mg four times daily or amphotericin B 5 mg four times daily until cultures became negative. A separate set of cultures was taken from the two study groups to investigate colonisation with resistant bacteria. SDD treatment was continued until discharge from the ICU. In all patients additional samples for culture (eg, from blood or urine) were taken if infection was clinically suspected.

Standard oropharyngeal care consisted of rinsing the mouth with water four times daily and tooth brushing twice daily. Prophylaxis for stress ulcers was not given routinely. If necessary histamine-2-receptor antagonists or H^+K^+ATPase inhibitors were given to reduce gastric acidity. Enteral feeding was started as early as possible, generally on the first or second day. Systemic antibiotics for proven or suspected infections were given as clinically indicated. Nosocomial pneumonia was diagnosed according to clinical criteria without use of protected sample brush or bronchoalveolar lavage, but was not an endpoint of our study.

We followed up patients until hospital discharge. We obtained baseline information on pre-existing disorders and markers of disease severity according to the guidelines of the Dutch national intensive care database.[9] These assessments included the APACHE II, the simplified acute physiology score II, the mortality prediction model$_0$ II, and mortality prediction model$_{24}$ II.

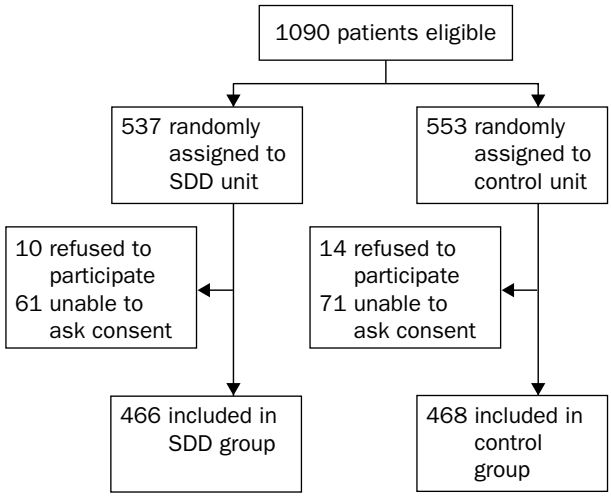


Figure 1: **Trial profile**

Colonisation with resistant bacteria from sputum, throat, rectum, axilla, and wounds was assessed at the time of ICU admission, once weekly during the stay, at discharge from the ICU, and, if possible, at 7 days after ICU discharge. Colonisation of the ICU environment with resistant bacteria was also assessed by culturing once every 14 days four different sinks on each unit. Samples were inoculated on a series of selective culture media to detect *Pseudomonas aeruginosa* and other gram-negative aerobic bacteria that were resistant to tobramycin, polymyxin E, imipenem, ciprofloxacin, or ceftazidime, *Enterococcus* sp resistant to vancomycin or meticillin-resistant *Staphylococcus aureus*. Cultures were done on Columbia agar containing tobramycin 4 mg/L or imipenem 4 mg/L, blood agar containing ceftazidime 8 mg/L or ciprofloxacin 2 mg/L, cysteine-deficient,

	SDD group (n=466)	Control group (n=468)
Characteristic		
Mean (SD) age (years)	60·4 (17·1)	59·5 (17·8)
Male	280 (60·0%)	272 (58·1%)
Admission type		
Urgent surgery	112 (24·0%)	118 (25·2%)
Elective surgery	166 (35·6%)	149 (31·8%)
Medical	185 (39·7%)	196 (41·9%)
Mean APACHE II score (SD)	18·7 (7·4)	18·7 (7·4)
Mean (SD) APACHE II predicted mortality (%)	30·1 (25·0)	29·9 (24·2)
Mean SAPS II score (SD)	41·0 (17·9)	41·5 (17·1)
Mean (SD) SAPS II predicted mortality (%)	32·1 (27·2)	32·7 (26·9)
Mean (SD) MPM$_0$ predicted mortality (%)	25·6 (23·0)	26·7 (22·9)
Mean (SD) MPM$_{24}$ predicted mortality (%)	29·7 (23·7)	31·8 (24·4)
Other indicators of disease severity		
Mechanical ventilation at admission	390 (83·7%)	407 (86·9%)
Use of any inotropic drug or vasopressor	322 (69·1%)	307 (65·6%)
Previous or pre-existent disorders		
Cardiopulmonary resuscitation	50 (10·7%)	42 (9·0%)
Chronic renal failure	29 (6·2%)	30 (6·4%)
Chronic renal replacement therapy	12 (2·6%)	13 (2·8%)
Metastasised neoplasm	12 (2·6%)	15 (3·2%)
AIDS	6 (1·3%)	2 (0·4%)
Leukaemia or malignant lymphoma	9 (1·9%)	7 (1·5%)
Cirrhosis	4 (0·9%)	3 (0·6%)
Heart failure (NYHA class III–IV/IV)	4 (0·9%)	3 (0·6%)
Chronic respiratory failure (class III–IV/IV)	24 (5·2%)	28 (6·0)
Immunodepression	11 (2·4%)	8 (1·7%)

Values are n (%) unless marked otherwise. SAPS=simplified acute physiology score. MPM=mortality prediction model. NYHA=New York Heart Association.

Table 1: **Baseline characteristics**

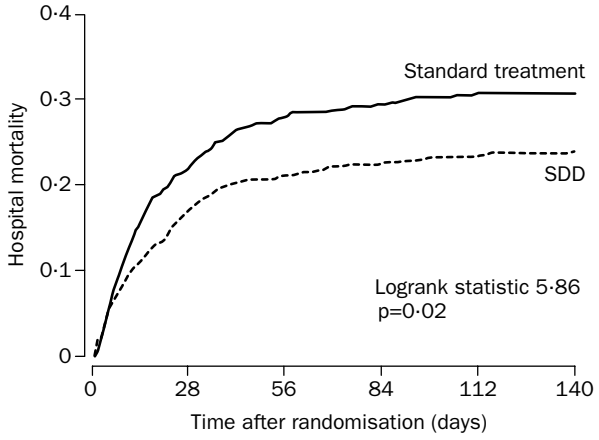
lactose-deficient, and electrolyte-deficient agar containing polymyxin E 50 IE/mL, enterococcosal agar with vancomycin 6 mg/L, and mannitol-salt agar, containing oxacillin 2 mg/L. After incubation at 37°C for 48 h, identification of micro-organisms was done by standard microbiological techniques. We confirmed resistance of bacteria growing on selective media with the E test (AB Biodisk, Solna, Sweden). Growth of bacteria on a medium containing an antibiotic to which the bacterial species is intrinsically resistant was not registered. These species include *Proteus*, *Morganella*, and *Serratia* sp when growing on a medium containing polymyxin E, species possessing chromosomally mediated β lactamases such as *Acinetobacter* sp, *Enterobacter* sp, and *Serratia* sp when growing on the medium with ceftazidime, and the chromosomal carbapenemase-positive species *Stenotrophomonas maltophilia* when growing on the medium with imipenem.[10,11] Colonisation was defined as the presence of a micro-organism (ie, bacteria or yeast species) in at least one of the surveillance cultures, with or without signs of infection. We defined colonisation at inclusion as colonisation demonstrated within 48 h of inclusion in the study, and acquired colonisation as that demonstrated more than 48 h after inclusion. Information on the aggregate use of all antibiotics was obtained from the hospital management information system and is reported as defined daily doses, according to the definitions of the WHO Centre for Drug Statistics Methodology (http://www.whocc.no), and in costs in Euros per 1000 patients.

Statistical analysis

Primary effectiveness measures were the acquired colonisation by any resistant strain, and ICU and hospital mortality. For these two measures we calculated relative risks and 95% CI. We based the sample-size considerations of this study on the anticipated incidence of colonisation with tobramycin-resistant enterobacteriaceae, tobramycin-resistant *P aeruginosa*, vancomycin-resistant enterococcus and meticillin-resistant *S aureus* in the control group of 5%, 5%, 2%, and 0·5%, respectively. We expected around 88% of patients in the control group to be free from colonisation by any resistant strain. To exclude a 50% increase in colonisation by any resistant strain in the SDD group, with use of a one-sided α of 0·05 and requiring a power of 90%, at least 503 patients had to be included in each group. With this sample size, a 95% CI for the effect on mortality would extend from 0·60 to 1·07 around an anticipated odds ratio of 0·80, assuming 25% mortality in the control group. Homogeneity of odds betwen subgroups was tested by Breslow-Day statistics.

	SDD (n/total [%])	Control (n/total [%])	Relative risk (95% CI)	p
Variable				
Death during intensive care				
All patients	69/466 (14·8)	107/468 (22·9)	0·65 (0·49–0·85)	0·002
Reason for intensive care				
Elective surgery	16/167 (9·6)	22/151 (14·6)	0·66 (0·36–1·20)	0·22
Urgent surgery	13/113 (11·5)	29/120 (24·2)	0·48 (0·26–0·87)	0·02
Medical	40/186 (21·5)	56/197 (28·4)	0·76 (0·53–1·08)	0·12
In-hospital death				
All patients	113/466 (24·2)	146/468 (31·2)	0·78 (0·63–0·96)	0·02
Reason for intensive care				
Elective surgery	26/167 (15·6)	28/151 (18·5)	0·84 (0·52–1·37)	0·55
Urgent surgery	30/113 (26·5)	40/120 (33·3)	0·80 (0·54–1·19)	0·31
Medical	57/186 (30·6)	78/197 (39·6)	0·77 (0·54–1·02)	0·07

Table 2: **Mortality**



Numbers of patients at risk

SDD	457	383	360	354	350	348
Non-SDD	460	363	331	324	318	318

Figure 2: **Cumulative hospital mortality for SDD treatment and standard treatment**

Results

Enrolment was stopped on Dec 31, 2001, just before the ICUs were moved to another location in the hospital. Of 1090 patients who fulfilled the inclusion criteria, 24 declined participation. In another 132 cases it was impossible to ask for informed consent from the patients or their representatives. Therefore, 934 patients entered the study, of whom 466 were randomly assigned SDD treatment (figure 1).

The demographic characteristics, baseline severity of disease and coexisting disorders were similar in the SDD group and the control group (table 1). Around 60% of patients were admitted to the ICU after a surgical procedure. The risk of hospital mortality, assessed with APACHE II, the simplified acute physiology score II, the mortality prediction $model_0$ II, and mortality prediction $model_{24}$ II, was 26–32%.

69 (15%) patients in the SDD group died during their stay in the ICU, compared with 107 (23%) in the control group, representing a relative risk of 0·65 (95% CI 0·49–0·85, p=0·002). In-hospital mortality was 24% in

	Number of patients colonised*	
	SDD group (n=432)	Control group (n=436)
Micro-organism and drug to which resistant		
P aeruginosa		
Ceftazidime	2 (0·5%)	0
Ciprofloxacin	0	1 (0·2%)
Imipenem	0	0
Tobramycin	0	2 (0·4%)
Other gram-negative bacteria		
Ceftazidime	1 (0·2%)	4 (0·9%)
Ciprofloxacin	13 (3·0%)	15 (3·4%)
Imipenem	0	2 (0·4%)
Tobramycin	23 (5·3%)	22 (5·0%)
Enterococcus sp		
Vancomycin	6 (1·4%)	4 (0·9%)
S aureus		
Meticillin	0	0

*Patients could be colonised by bacteria resistant to more than one antibiotic.

Table 3: **Patients with resistant bacteria at inclusion**

	Number of patients colonised*		Relative risk (95% CI)
	SDD group (n=378)	Control group (n=395)	
Micro-organism and drug to which resistant			
P aeruginosa			
Ceftazidime	2 (0·5%)	12 (3·0%)	0·2 (0·04–0·8)
Ciprofloxacin	1 (0·3%)	13 (3·3%)	0·1 (0·01–0·6)
Imipenem	1 (0·3%)	16 (4·1%)	0·1 (0·01–0·5)
Polymyxin	1 (0·3%)	0	
Tobramycin	13 (3·4%)	13 (3·3%)	1·0 (0·5–2·2)
Other gram-negative bacteria			
Ceftazidime	7 (1·9%)	9 (2·3%)	0·8 (0·3–2·2)
Ciprofloxacin	9 (2·4%)	31 (7·8%)	0·3 (0·1–0·6)
Imipenem	1 (0·3%)	10 (2·5%)	0·1 (0·01–0·8)
Polymyxin	3 (0·8%)	2 (0·5%)	1·5 (0·3–9·3)
Tobramycin	20 (5·3%)	47 (11·9%)	0·4 (0·3–0·7)
Enterococcus sp			
Vancomycin	4 (1·1%)	5 (1·3%)	0·8 (0·2–3·1)
S aureus			
Meticillin	0	0	

*Patients could be colonised by bacteria resistant to more than one antibiotic.

Table 4: **Acquisition of resistant bacteria**

the SDD group compared with 31% in the control group (0·78, 0·63–0·96, p=0·02; table 2, figure 2). Similar effects of SDD on ICU mortality and hospital mortality were seen in subgroups of medical patients and patients after urgent or elective surgery (p=0·50 and p=0·87, respectively). Median ICU length of stay was 6·8 days (IQR 3·7–12·8) in the SDD group compared with 8·5 days (4·8–15·7) in the control group (p<0·0001).

Selective cultures for resistant micro-organisms were done at baseline in 868 patients. The number of patients who were colonised with one or more resistant bacteria at inclusion did not differ between groups (39 SDD *vs* 35 control, p=0·6). Table 3 shows the number of different resistant bacteria at inclusion in the two groups.

Follow-up cultures were available from 773 patients. Acquired colonisation with one or more resistant strains of *P aeruginosa* or other gram-negative aerobic bacteria was reported in 26% of controls and in 16% of SDD-treated patients (relative risk 0·61, 95% CI 0·46–0·81). In the SDD group less *P aeruginosa* was found that was resistant to ceftazidime, ciprofloxacin, or imipenem, and also fewer other gram-negative bacteria that were resistant to ciprofloxacin, imipenem or tobramycin (table 4). The acquisition of vancomycin-resistant enterococcus was 1·1% and 1·3% in the SDD and control groups, respectively (p=1·0). No meticillin-resistant *S aureus* was isolated during the study in either group. Resistant bacteria were also cultured from the ICU environment (table 5). During the study, 201 cultures were taken from the SDD unit and 194 from the control unit. From the

	Number of patients colonised*		Relative risk (95% CI)
	SDD unit (n=201)	Control unit (n=194)	
Micro-organism and drug to which resistant			
P aeruginosa			
Ceftazidime	2 (1·0)	1 (0·5)	1·9 (0·2–21·1)
Ciprofloxacin	0	4 (2·1)	
Imipenem	0	2 (1·0)	
Tobramycin	16 (8·0)	7 (3·6)	2·2 (0·9–5·2)
Other gram-negative bacteria			
Ceftazidime	3 (1·5)	32 (16·5)	0·1 (0·03–0·3)
Ciprofloxacin	5 (2·5)	12 (6·2)	0·4 (0·1–1·1)
Imipenem	1 (0·5)	2 (1·0)	0·5 (0·04–5·3)
Tobramycin	35 (17·4)	45 (23·2)	0·8 (0·5–1·1)

*Cultures taken once every 14 days from four different sinks in each unit.

Table 5: **Resistant bacteria in the ICU environment**

	Defined daily dose	SDD		Control	
		Defined daily dose*	Cost (€)	Defined daily dose*	Cost (€)
Antibiotics					
SDD suspension	20 mL†	3469	15 741	0	0
SDD orabase	2 g†	1978	3888	0	0
SDD suppositories	2 g†	161	453	0	0
Amphotericin-B suspension	2 g†	3209	6113	6	11
Cefotaxime	4 g	974	18 913	472	9165
Cefamandol	4 g	279	2662	296	2815
Ceftazidime	4 g	170	6024	397	14 144
Ciprofloxacin	0·5 g	720	26284	1259	46 248
Meropenem	2 g	8	457	26	1675
Imipenem	2 g	44	2259	204	10 450
Piperacillin or tazobactam	14 g	32	1266	37	1472
Polymyxin E intravenous or aerosol	0·32 g	123	1799	64	932
Amoxycillin	1 g	1748	1837	1480	1556
Flucloxacillin	2 g	402	1011	484	1221
Vancomycin	2 g	276	3837	296	4123
Amphotericin-B intravenous or aerosol	0·05 g†	296	2311	252	1976
5-flucytosine	10 g	25	4998	81	16 732
Fluconazole	0·2 g	500	13 938	872	24 648
Amphotericin-B lipid complex	0·2 g†	82	21 262	49	12 579
All other antibiotics			11 265		11 557

Antibiotics for intravenous administration unless otherwise stated. *Units as in first defined daily dose column. †Normal daily doses used for some antibiotic formulas if defined daily doses not available.

Table 6: **Prescribed antibiotics per 1000 patients**

control unit more ceftazidim-resistant enterobacteriaceae were isolated (p<0·0001), and more ciprofloxacin-resistant *P aeruginosa* and enterobacteriaceae, although these differences were not significant (p=0·06 and p=0·09, respectively). However, more tobramycin-resistant *P aeruginosa* was found in the SDD unit (p=0·09).

Table 6 shows all antibiotics administered during the study period. Total costs of antibiotics were 11% lower in the SDD unit than in the control unit. This difference was primarily due to a decrease in the administration of antifungal treatment and antibiotics against gram-negative bacteria, such as ciprofloxacin, ceftazidime, and imipenem. Vancomycin administration was similar in the SDD and control units.

Discussion

The administration of SDD reduced ICU and in-hospital mortality, the length-of-stay in the ICU, the frequency of colonisation with resistant bacteria, and the total costs of antibiotic treatment. However, this study does have potential limitations. Because of its design, the study could not be blinded. Surveillance cultures would have shown clearly in which unit SDD was used and which unit it was not. Masking the results of the surveillance cultures and providing sham culture results was not possible because, as part of the SDD strategy, additional treatment with nebulised antibiotics had to be based on these culture results. To keep bias to a minimum, we selected study endpoints that could be objectively assessed, avoiding subjective endpoints such as the frequency of infections. We cannot entirely exclude that the lower mortality in the SDD group was due partly to differences in care other than SDD between units. Since we used the same treatment protocols in the two units, the same members of the medical staff were treating all patients, and the results of treatment were identical in the 2 years preceding the study, we believe that these factors cannot account for the major difference in mortality between the

two treatment strategies. To correct for differences between units we have considered performing a crossover design. However a major limitation of this design is the possibility that the changes in the colonising flora by SDD or control would be present for many months after stopping this treatment, thereby making it mandatory to have long-term washout periods before studying the alternative treatment on the same unit (carry-over effect). Furthermore, since resistance may develop slowly over long periods of time, doing a crossover study would lessen the power of the study to detect differences in resistance during SDD treatment.

So far, 12 studies have been reported on the effects of SDD with oral and intestinal antibiotics combined with systemic prophylaxis.[12–23] The number of patients enrolled in these studies varied between 28 and 265 per treatment group, and no study in itself showed a significant improvement in survival among SDD-treated patients. Decreased ICU mortality has, however, been reported in a subgroup of patients in the mid-range stratum of the APACHE II score.[13] Our results are in agreement with those from a meta-analysis of prospective, randomised, controlled studies on SDD combining topical and systemic antibiotics in ICU patients.[5] The meta-analysis included published and unpublished studies, and reported lower mortality in SDD-treated ICU patients, with an odds ratio of 0·80 (95% CI 0·69–0·93). In our trial, the odds ratios for ICU mortality and hospital mortality were 0·59 and 0·71. There are several possible explanations why the magnitude of improvement in survival is higher in our study than in the meta-analysis. By contrast with most other studies, we included some additional measures in the SDD regimen to prevent colonisation with pathogenic bacteria. First, we treated SDD and control patients in separate units to prevent cross colonisation. Second, SDD patients with persistent tracheal colonisation with gram-negative bacteria were treated with aerosolised polymyxin E. Likewise, patients with blind bowel loops (eg, after colostomy) were given additional SDD by suppository. Although not proven, these measures may have added to the beneficial effects of SDD.

In the past, serious concerns have been expressed that SDD might lead to increased antibiotic resistance of colonising bacteria.[6,24] We noted decreased colonisation with *P aeruginosa* resistant to ceftazidime, imipenem, and ciprofloxacin, and with other aerobic gram-negative bacteria resistant to tobramycin, imipenem, and ciprofloxacin. The decrease in colonisation may be due to the eradication of these strains by the combination of polymyxin E and tobramycin, for which combination virtually all gram-negative aerobic bacteria are sensitive. Other investigators have shown that the administration of broad-spectrum antibiotics predisposes to the development of infections with antibiotic-resistant pathogens.[25,26] Thus, the fact that we administered fewer systemic antibiotics to SDD patients is another factor potentially contributing to decreased resistance in the SDD group. We noted lowered development of resistance among SDD-treated patients over a 27-month period. We cannot rule out the possibility that resistance would increase over a longer period of time, but to date this pattern has not been seen. The costs of SDD medication were more than compensated for by decreased prescription of systemic antibiotics. These findings are in agreement with an earlier report on the effect of SDD on antibiotic prescription.[20] Although we did not do a formal economic assessment, the lower total expenditure on antibiotics and the reduced length of stay on the ICU among SDD-treated patients suggest that costs of treatment may be lower among these patients than among control patients.

In our study no patient was colonised with meticillin-resistant *S aureus*. The frequency of colonisation with vancomycin-resistant enterococcus was very low (<2%) and was not affected by the administration of SDD. Clearly, different effects could have been seen in ICUs with high prevalence of these micro-organisms. Indeed, increased colonisation with meticillin-resistant *S aureus* among SDD treated patients has been reported in ICUs in which this micro-organism is endemic.[22,27] Although no increased colonisation or infection with vancomycin-resistant enterococcus has been reported, it cannot be excluded that SDD has a harmful effect on this micro-organism where it is endemic. We therefore judge surveillance on the frequency of infection with meticillin-resistant *S aureus* and vancomycin-resistant enterococcus mandatory in ICUs that apply SDD to their patients.

Others workers have used SDD, including vancomycin, in situations in which meticillin-resistant *S aureus* is endemic. Although earlier studies show no effect of vancomycin-containing SDD on the incidence of vancomycin-resistant enterococcus, all these studies have been done in ICUs with low rates of vancomycin-resistant enterococcus.[28–30] Since the widespread use of vancomycin will exert selection pressure on vancomycin-resistant enterococcus, more studies are needed, especially where vancomycin-resistant enterococcus is endemic, to assess the effect of vancomycin-containing SDD on the emergence of vancomycin-resistant enterococcus before this treatment can be advocated.

We conclude that SDD may improve survival of ICU patients and lowers the acquisition of resistant gram-negative aerobic bacteria. In ICUs that have low prevalence of vancomycin-resistant enterococcus and meticillin-resistant *S aureus*, we advocate the use of SDD in all patients expected to be on mechanical ventilation for at least 2 days or to be in the ICU for at least 3 days.

Contributors

E de Jonge, J Kesecioglu, and C Stoutenbeek initiated the study. E de Jonge, L Spanjaard, P Bossuyt, J Dankert, J Kesecioglu, and C Stoutenbeek designed the study. E de Jonge wrote the first draft of the report, to which the other investigators added their comments. E de Jonge and M Schultz were responsible for inclusion of patients in the study, assisted by M Vroom and J Kesecioglu. L Spanjaard and J Dankert were responsible for the microbiological analyses. P Bossuyt supervised the statistical analysis.

Conflict of interest statement

None declared.

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