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Tract

The effect of selective decontamination of the digestive tract on mortality in multiple trauma patients: a multicenter randomized controlled trial

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Abstract *Objective:* Evaluation of selective decontamination of the digestive tract (SDD) on late mortality in ventilated trauma patients in an intensive care unit (ICU). *Methods:* A multicenter, randomized controlled trial was undertaken in 401 trauma patients with Hospital Trauma Index-Injury Severity Score of 16 or higher. Patients were randomized to control ($n = 200$) or SDD ($n = 201$), using polymyxin E, tobramycin, and amphotericin B in throat and gut throughout ICU treatment combined with cefotaxime for 4 days. Primary endpoint was late mortality excluding early death from hemorrhage or craniocerebral injury. Secondary endpoints were infection and organ dysfunction. *Results:* Mortality was 20.9% with SDD and 22.0% in controls. Overall late mortality was 15.3% (57/372) as 29 patients died from cerebral injury, 16 SDD and 13 control. The odds ratio (95% confidence intervals) of late mortality for SDD relative to control was 0.75 (0.40–1.37), corresponding to estimates of 13.4% SDD and 17.2% control. The overall infection rate was reduced in the test group (48.8% vs. 61.0%). SDD reduced lower airway infections (30.9% vs. 50.0%) and bloodstream infections due to aerobic Gram-negative bacilli (2.5% vs. 7.5%). No difference in organ dysfunction was found. *Conclusion:* This study demonstrates that SDD significantly reduces infection in multiple trauma, although this RCT in 401 patients was underpowered to detect a mortality benefit.

Introduction

Selective decontamination of the digestive tract (SDD) has been assessed in 54 randomized controlled trials (RCTs) and ten meta-analyses of RCTs only [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. The most recent meta-analysis includes 36 RCTs in 6,922 unselected patients and shows that SDD using enteral and parenteral antimicrobials reduces the odds ratio (OR) for pneumonia to 0.35 (95% confidence interval, CI, 0.29–0.41) and mortality to 0.78 (0.68–0.89) [9, 11]. The absolute mortality reduction was 4.8%. This indicates that five ICU patients need to be treated with SDD to prevent one case of pneumonia, and 21 ICU patients need to be treated to prevent one death [9, 11]. Two recent large RCTs [12, 13] report an absolute mortality reduction of 8%, corresponding to the treatment of 12 patients with SDD to save one life. The discrepancy between the 65% reduction in ICU-acquired respiratory tract infections and

the 22% reduction in mortality in the most recent meta-analysis [9, 11] may be explained by the inclusion of patients with incurable underlying conditions, who may die of other causes even when kept infection free.

This RCT was undertaken to study the effect of SDD on mortality in multiple trauma patients. Trauma patients are thought to respond more favorably to the SDD prophylaxis [6] for three reasons: (a) they are admitted without infection, (b) they have in general a curable underlying condition once they have survived the first 5 days following trauma, and (c) late mortality in this group is mainly related to infection [14, 15]. Our experience with SDD in trauma patients [16] and the data from six other RCTs [17, 18, 19, 20, 21, 22] suggest that trauma patients are a prime subset of ICU patients to benefit more from SDD in terms of both infectious morbidity and mortality. An RCT with a group-sequential design using the triangular test [23] was chosen for the present study. This design ensures early stopping when a large treatment difference is apparent, or when no treatment difference seems to be present. Blinded outcome adjudication was chosen, and because of the inherent large sample size of a mortality study a multicenter design was required.

Patients and methods

Detailed information on definitions, study design, study organization, randomization procedure, and statistical methods are available in the Electronic Supplementary Material [24, 25, 26].

Patients

All patients admitted to the ICU within 24 h after nonpenetrating blunt trauma were eligible for the study. Inclusion criteria were a Hospital Trauma Index-Injury Severity Score (HTI-ISS) of 16 or higher and mechanical ventilation. Patients who previously received antibiotics for more than 3 days or patients known to be allergic to β-lactam antibiotics were excluded as were referrals from other hospitals. The lower stopping boundary of the triangular test was crossed at the 12th interim analysis (Fig. 1). At this point a total of 405 patients from the 17 participating ICUs had been randomized. Four patients were excluded from the final analysis after randomization (two because they did not fulfill the inclusion criteria, the data from one patient were not available, and one patient was lost to follow-up after the 7th day). The demographic and baseline characteristics are shown in Table 1. Patients receiving standard treatment were slightly older than those on SDD but had a lower HTI-ISS score. As age and injury severity are associated with increased mortality, the mortality analysis included adjustment for these two variables. The two groups were comparable with regard to other baseline characteristics.
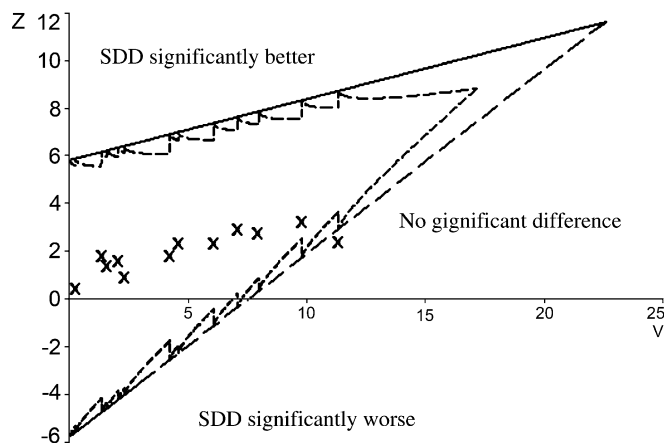
Fig. 1 Sample path and stopping boundaries for the group-sequential design using the triangular test. The statistics Z and V are the efficient score and Fisher's information for the log-odds ratio of late mortality for SDD relative to control, after stratification for age and HTI-ISS severity score

Table 1 Demographic data (*APACHE* Acute Physiology and Chronic Health Evaluation)

	SDD ($n = 201$)	Control ($n = 200$)
Age, mean (years)	38.1 ± 17.0	40.6 ± 17.9
Gender: M/F	155/46	154/46
Height, mean (cm)	175.3 ± 8.1	174.7 ± 8.1
Weight, mean (kg)	77.1 ± 14.4	76.5 ± 13.7
HTI-ISS, median (IQR)	34 (17)	29 (20)
APACHE II, median (IQR)	15 (11)	14 (11)

Treatment regimens

The SDD regimen consisted of a 10 ml suspension of polymyxin E 100 mg, tobramycin 80 mg, and amphotericin B 500 mg administered through the nasogastric tube four times a day. The nasogastric tube was then clamped, and gastric suction was discontinued for 1 h. A dose of 0.5 g carboxymethylcellulose paste (Orabase, Bristol-Myers Squibb) containing 2% polymyxin E, 2% tobramycin, and 2% amphotericin B was applied to the buccal mucosa four times a day [27]. SDD was given throughout the treatment on ICU. All SDD patients received 1 g cefotaxime intravenously every 6 h for 4 days. In patients in whom stress-ulcer prophylaxis was indicated H_2 blockers or omeprazol were used instead of sucralfate, claimed to inactivate the enteral antibiotics [28]. The control group was treated according to the standard antibiotic protocol used in each participating center. No attempt was made to standardize the standard antibiotic prophylaxis and treatment protocols between centers. Fluoroquinolones were not allowed for prophylaxis due to their decontaminating side effect [29]. Stress ulcer prophylaxis could be used freely with the exception of sucralfate. Diagnostic samples were taken on clinical indi-

cation only and analyzed using standard methods [30]. In the case of an infection parenteral antibiotic treatment was commenced according to standard antibiotic guidelines.

Data collection

On admission the severity of injury and illness were assessed using the HTI-ISS and the Acute Physiology and Chronic Health Evaluation II, respectively. All patients were monitored daily for signs of infection throughout the treatment on ICU. The type and dose of prescribed antibiotics for prophylaxis and treatment were recorded daily. From day 5 the organ dysfunction score was calculated since organ dysfunction in the first 4 days was considered not to be infection related.

Results

All-cause mortality was 21.4% (86/401) in the overall study population: 20.9% (42/201) in the SDD group and 22.0% (44/200) in the control group. A total of 29 patients died from cerebral injury, 16 in the SDD group and 13 in the control group. The overall late mortality excluding brain death was 15.3% (57/372). Patients dying from cerebral injury had a significantly higher HTI for the central nervous system ($p < 0.01$) but a significantly lower total HTI-ISS score ($p < 0.01$) than patients dying from other causes. The median time to death was 4 days (interquartile range, IQR, 4) after admission to the ICU in patients dying from cerebral injury and 12 days (IQR 9) in patients dying from other causes. The OR of late mortality for SDD relative to control was 0.75 (95% CI 0.40–1.37, $p = 0.35$). The overall estimate of late mortality for SDD was 13.4% and for control 17.2%. There was no difference in the median length of ICU stay between the two groups: 13 days (IQR 13.5) in the SDD group and 12 (IQR 14) in the control group ($p = 0.56$). The median duration of mechanical ventilation was 9 days (IQR 12) in the SDD group and 8 (IQR 12) in the control group ($p = 0.82$). The overall infection rate, with or without microbiological confirmation, was significantly reduced from 61.0% in controls to 48.8% in the SDD group ($p = 0.01$; Table 2).

Respiratory tract infections were significantly reduced by SDD (50.0% to 30.9%, ($p < 0.01$; Tables 2, 3].

Table 2 Number of patients with clinically recorded infections with or without causative agent

	SDD ($n = 201$)		Control ($n = 200$)		χ^2(df = 1)	p
	n	%	n	%		
Lower airway infection	62	30.9	100	50.0	15.3	< 0.01
Pneumonia	19	9.5	46	23.0	13.5	< 0.01
Tracheobronchitis	52	25.9	80	40.0	9.1	< 0.01
Urinary tract infection	26	12.9	33	16.5	1.0	0.31
Blood stream infection	31	15.4	31	15.5	< 0.1	0.98
Wound infection	22	11.0	20	10.0	0.1	0.76
Any other infection	11	5.5	26	13.0	6.8	< 0.01
Total infected patients[a]	98	48.8	122	161.0	6.1	0.01

[a] The total number of infections exceeds the total number of infected patients as some patients had more than one infection

Table 3 Number of patients with microbiologically confirmed pneumonia or tracheobronchitis (*MRSA* methicillin-resistant *S. aureus*)
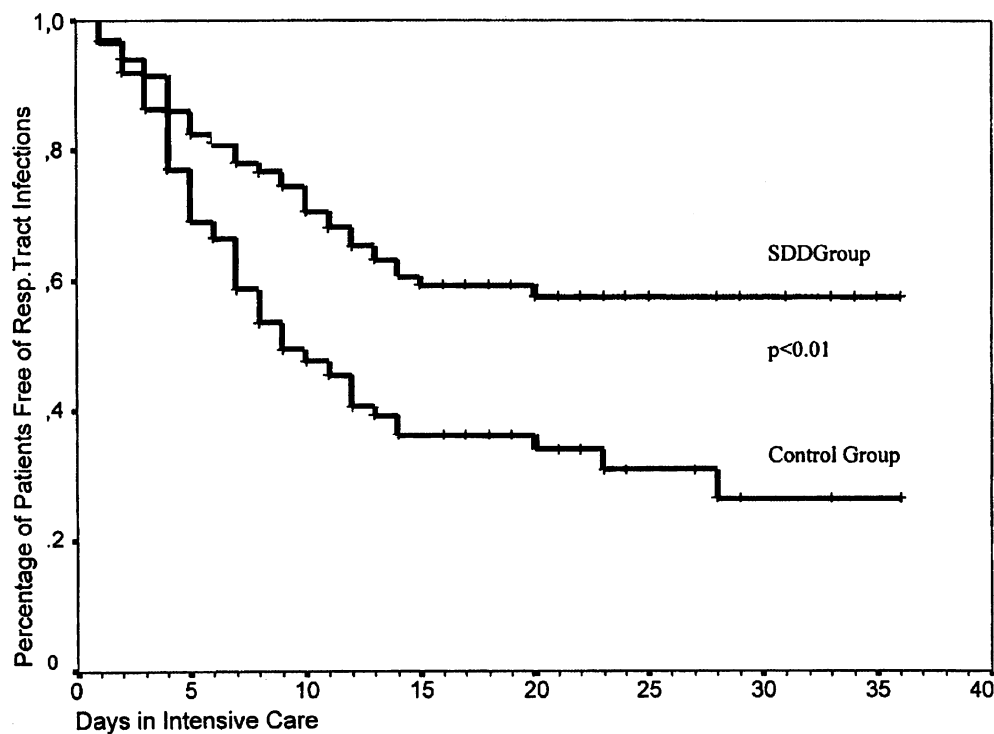
	SDD ($n = 201$)		Control ($n = 200$)		χ^2(df = 1)	p
	n	%	n	%		
Gram positive cocci	17	8.5	10	5.0	1.9	0.17
S. aureus	16	8.9	36	18.0	9.9[a]	< 0.01
MRSA	2	1.0	4	2.0	–	–
Enterobacteriaceae	3	1.5	72	36.0	78.5	< 0.01
Acinetobacter spp.	15	7.5	23	11.5	–	–
Pseudomonas spp.	11	5.5	28	14.0	11.1[b]	< 0.01
Serratia spp.	7	3.5	3	1.5	–	–
Xanthomonas maltophilia	0	0.0	7	3.5	–	–
H. influenzae	2	1.0	28	14.0	24.5	< 0.01
Other	2	1.0	4	2.0	–	–
Yeasts	6	3.0	21	10.5	9.0	< 0.01
Total infected patients[c]	47	23.4	81	40.5	13.5	< 0.01

[a] For total of *S. aureus* and MRSA
[b] For total of *Pseudomonas*, *Acinetobacter*, *Serratia*, and *Xanthomonas* spp.
[c] The total number of infected patients with microbiologically confirmed respiratory tract infections is smaller than the number of patients with the clinical diagnosis of respiratory tract infection (Table 2)

Fig. 2 Kaplan-Meier curve demonstrating a significantly longer period free of lower airway infections in the test group than in controls: a median of 9 days vs. 7 days ($p < 0.01$)

Table 4 Number of patients with periods of sepsis confirmed by positive blood culture (*CNS* coagulase-negative staphylococci, *MRSA* methicillin-resistant *S. aureus*)

	SDD ($n = 201$)		Control ($n = 200$)		$\chi^2 (\text{df} = 1)$	p
	n	%	n	%		
Gram-positive cocci	20	10.0	21	10.5	<0.1	0.86
CNS	9	4.5	12	6.0	0.5	0.49
Enterococci	3	1.5	14	7.0	7.5	<0.01
MRSA	2	1.0	2	1.0	–	–
S. aureus	6	3.0	3	1.5	0.7[a]	0.40
S. pneumoniae	0	0.0	2	1.0	–	–
Other Gram-positive cocci	3	1.5	3	1.5	–	–
Gram-negative bacteria	5	2.5	15	7.5	5.3	0.02
Enterobacteriaceae	3	1.5	11	5.5	4.8	0.03
Pseudomonas sp.	3	1.5	2	1.0	1.7[b]	0.20
Acinetobacter sp.	0	0.0	3	1.5	–	–
Serratia sp.	0	0.0	2	1.0	–	–
Other	1	0.5	2	1.0	–	–
Candida sp.	1	0.5	0	0.0	–	–
Total infected patients	24	12	29	14.5	0.6	0.45

[a] For total of *S. aureus* and MRSA
[b] For total of *Pseudomonas*, *Acinetobacter*, and Serratia spp.

The pneumonia rate was reduced from 23.0% to 9.5% ($p < 0.01$) and the tracheobronchitis rate from 40.0% to 25.9% ($p < 0.01$). Figure 2 shows the infection-free period for lower airway infections. The infection-free period was significantly longer in the SDD group (median 9 days, IQR 9.5) than in controls (median 7 days, IQR 6; $p < 0.01$). Once a patient developed a respiratory tract infection, the median duration of the infection did not differ between the two groups: 5 days (IQR 7) in the SDD group and 6 (IQR 7) in controls ($p = 0.70$).

Table 3 shows the micro-organisms causing pneumonia and tracheobronchitis. The number of patients infected by *Staphylococcus aureus*, *Haemophilus influenzae*, Enterobacteriaceae, or *Pseudomonas* spp. was significantly lower in the SDD group than in controls ($p < 0.01$), but there was no significant increase in lower airway infections due to Gram-positive micro-organisms. In both groups the incidence of early onset infections (i.e., within 4 days) was low: 4.5% in the SDD group and 7.0% in controls. Clinically diagnosed sepsis, wound, and urinary tract

Table 5 Number of patients receiving therapeutic antibiotics during ICU stay

	SDD (n = 201)		Control (n = 200)		χ^2 (df = 1)	p
	n	%	n	%		
Aminoglycosides	52	25.9	65	32.5	2.1	0.14
Broad-spectrum β-lactams	118	158.7	141	70.5	6.1	0.01
Cephalosporins 1st/2nd generation	24	11.9	45	22.5	7.8	<0.01
Antistaphylococcal drugs	35	17.4	50	25	3.5	0.06
Antianaerobic drugs	1	5	29	14.5	10.4	<0.01
Glycopeptides	43	21.4	28	14.0	3.8	0.05
Amoxicillin	1	8	38	19.0	10.5	<0.01
Quinolones	15	17.5	17	8.5	0.1	0.70
Miscellaneous antimicrobials	11	5.5	9	4.5	0.2	0.66
Fungicidal agents	4	2.0	8	4.0	1.4	0.24
Antiviral agents	0	0.0	1	0.5	–	–
No antibiotic therapy	72	35.8	51	25.5	5.0	0.03

Fig. 3 The total number of days during which systemic antibiotics were administered to treat infections was 2,165 days in the prophylaxis group and 3,189 in the control group. Cephalorins I, II, and III denote the generations; penicillin III includes piperacillin, ticarcillin, mezlocillin, and temocillin; and antistaphylococcal agents used in the RCT were clindamycin, cloxacillins, fosfomycin, and fusidic acid
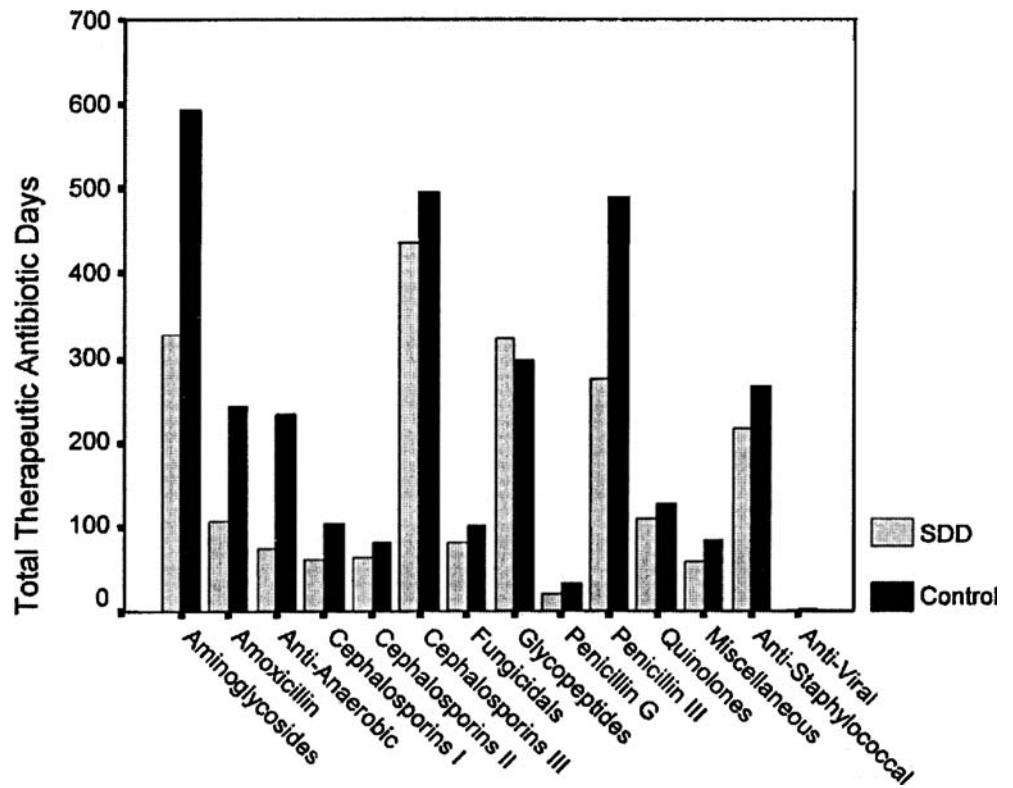
infections did not differ between SDD and controls. There were significantly fewer patients with "other infections", including peritonitis, pleuritis, meningitis, sinusitis, and laryngitis: 5.5% in the SDD group vs. 13.0% in the control group (p < 0.01). In addition, the proportion of patients with septic periods with positive blood cultures did not differ significantly between the two groups (Table 4). However, there was a significant reduction in bloodstream infections due to aerobic Gram-negative bacilli (AGNB; p = 0.02). Gram-positive bloodstream infections were similar in test and control. Of note, there were fewer patients with enterococcal sepsis in the SDD group (1.5%) than in controls (7.0%, p < 0.01).

In the SDD group all 201 patients (100%) received 4 days of systemic antibiotic prophylaxis with cefotaxime (804 days). Additionally, there were 339 antibiotic days, due mainly to the use of aminoglycosides, antistaphylococcal, or antianaerobic agents. A total of 1,143 antibiotic days were prophylactic in the test group. In the control group 175 patients (88%) received systemic antibiotic prophylaxis during the first 4 days, mostly for perioperative prophylaxis of open fractures, totalling 1,139 antibiotic days.

Table 5 shows the use of parenteral antibiotics for the treatment of infections. Significantly fewer patients in the SDD group (64.2%) received any antibiotic treatment than

in controls (74.5%, $p = 0.03$). The SDD group received fewer therapeutic antibiotics than the control group with the exception of glycopeptides. Figure 3 presents the number of antibiotic days per antibiotic group. The total number of systemic antibiotic days, excluding the first 4 days, was 2,165 days in the SDD group and 3,189 days in controls. Three patients in the control group developed antibiotic-associated enterocolitis with diarrhea positive for *Clostridium difficile* toxin and were treated with oral vancomycin. No enterocolitis was observed in the SDD group. Severe organ dysfunction after 5 days was observed with the same frequency in both groups. Gut dysfunction (59.9%) was most frequent, followed by dysfunction of the clotting system (49.1%), circulatory (42.9%), respiratory (26.2%), liver dysfunction (15.9%), and renal failure (11.0%).

Discussion

This multicenter RCT in 401 trauma patients failed to reach statistical significance on the primary endpoint of late mortality due to infection and/or multiple organ failure. The study was designed to detect a 50% reduction in late mortality from a baseline value of 25%. However, the late mortality in the control group was much lower than assumed and lower than expected on the basis of the mean HTI-ISS. The reduction in late mortality from 17.2% to 13.4% (OR 0.75) found in this study is in agreement with the meta-analyses that found an OR of 0.80 in the subgroup of studies in which SDD using parenteral and enteral antimicrobials was implemented [2, 4, 5, 6, 9, 11]. Assuming that a 20% reduction in late mortality is realistic and clinically relevant, and that the mean late mortality with an HTI-ISS greater than 16 is about 18% than a study with a few thousand patients in each arm is required to prove this hypothesis. This calculation is in line with the meta-analysis of the subset of trauma patients ($n = 1,092$) showing that SDD using parenteral and enteral antimicrobials reduces the OR for mortality to 0.78 (0.56–1.09) [5]. Furthermore, the meta-analyses and recent RCTs do not provide evidence that trauma patients do better than surgical and medical patients as the size of treatment effect of 20% is similar for the three diagnostic groups.

The overall infection rate in this study was high in both groups (48.8% vs. 61.0%). However, this RCT included severely injured patients with prolonged mechanical ventilation and treatment on ICU and at a particularly high risk of infection. Major differences were observed between infection rates among centers and in the reduction in infection rates achieved in the different centers. Factors such as outbreaks and exogenous infections were found to increase the infection rate in both SDD and control group in particular centers.

This study confirms the finding of the meta-analysis of the data from individual trauma patients ($n = 1,092$) that SDD using parenteral and enteral antimicrobials reduces the OR for respiratory tract infections to 0.38 (0.29–0.50) [5]. Protected specimen brush and bronchoalveolar lavage were not routinely used in this study to diagnose pneumonia because these techniques have a relatively low sensitivity of 40% in patients treated with systemic antibiotics, and in this study the great majority of patients received prophylactic antibiotics [31, 32]. No difference in early onset pneumonia was observed, due to the fact that 88% of the patients in the control group also received perioperative antibiotics in the first few days for surgical prophylaxis. However, the incidence of secondary pneumonia by AGNB was higher and the infection-free period was shorter in the control group than in the treatment group [33]. Since both groups used systemic antibiotic prophylaxis this reduction in late onset pneumonia must be due to the administration of polymyxin and tobramycin in throat and gut. This RCT is in line with the most recent meta-analysis of RCTs with endpoint of bloodstream infections demonstrating that SDD using parenteral and enteral antimicrobials reduces the OR for bloodstream infections due to AGNB to 0.38 (0.19–0.73) [11]. Additionally, infections including peritonitis, pleuritis, meningitis, and sinusitis, being mostly secondary endogenous infections, were effectively lowered by SDD. Multiple organ failure was common in this group of severely injured patients and did not differ between the two groups.

This multicenter RCT was conducted without regular surveillance samples of throat and rectum. Among the 54 RCTs on SDD, this trial is the eighth study without surveillance cultures [18, 34, 35, 36, 37, 38, 39]. Surveillance cultures are an integral part of the SDD philosophy [27] for three reasons: (a) to monitor efficacy and compliance of the enteral antimicrobials, (b) to detect abnormal carriage of resistant bacteria in particular (multiresistant) AGNB and methicillin-resistant *S. aureus* [40, 41], and (c) to distinguish endogenous from exogenous infections. However, SDD can still be used in their absence, as the treatment effect on infection and mortality is independent of the use of surveillance cultures. If the microbiology department is unable to provide a service based on surveillance cultures, SDD prophylaxis is still feasible and well supported by evidence.

The significantly higher number of patients receiving systemic antibiotic therapy in the control group reflects the higher infection rate. The combination of broad-spectrum β-lactams, aminoglycosides, and/or antistaphylococcal agents was frequently used for blind therapy in the control group and accounts for the high number of antibiotic days. These data are in line with those froim previous RCTs [16, 17, 22]. The high antibiotic use is also reflected in the incidence of three cases of antibiotic-associated enterocolitis in the control group.

A recent clinical practice guideline for the prevention of ventilator-associated pneumonia suggests a link between antimicrobial resistance and SDD [42]. A resistance analysis requires the distinction of the number of patients with infections due to resistant AGNB from patients with infections due to MRSA and vancomycin-resistant enterococci (VRE). The ten meta-analyses and the 54 RCTs do not provide data for a link between SDD and resistance. The parenteral and enteral antimicrobials of the SDD protocol target mainly AGNB. Two RCTs evaluated the impact of SDD among AGNB as primary endpoint [13, 43]. The Dutch study [13] demonstrated that carriage of AGNB resistant to imipenem, ceftazidime, ciprofloxacin, tobramycin, and polymyxins occurred in 16% of SDD patients vs. 26% in control patients, with a relative risk of 0.6 (95% CI 0.5–0.8). This is in line with an earlier French RCT [43] showing that the addition of enteral to the parenteral antimicrobials controls carriage and infection due to extended spectrum β-lactamase producing *Klebsiella* spp. SDD is not designed to control MRSA and VRE [27]. VRE carriage and infection were the primary endpoints of SDD-RCTs in two ICUs in the United States [44, 45]. There was no difference between test and control. There are seven RCTs conducted in ICUs where MRSA was endemic at the time of the trial, and therefore they report a trend towards higher MRSA infection rates in patients receiving SDD [20, 36, 46, 47, 48, 49, 50]. The addition of enteral vancomycin to the classical SDD agents is required in ICUs with endemic MRSA [51, 52, 53, 54, 54]. VRE did not emerge in any of the eight RCTs using enteral vancomycin added to the enteral polymyxin, tobramycin, and amphotericin B [12, 37, 51, 52, 55, 56, 57, 58]. The assertion that there is strong contravening evidence that SDD promotes infection due to Gram-positive bacteria is unsupported by the facts including this RCT [59, 60]. Antimicrobial resistance, being a long-term issue, has been evaluated in ten studies monitoring antimicrobial resistance between 2 and 9 years, and bacterial resistance associated with SDD has not been a clinical problem [40, 54, 61, 62, 63, 64, 65, 66, 67, 68, 69].

The same guideline [42] implies a higher cost to implement SDD on ICU. This statement contrasts with the conclusion of the recent report of the Agency for Health Research and Quality of the United States Department for Health and Human Services that SDD is cheap and easy to implement [70]. Indeed, the cost-effectiveness of SDD has not yet been properly assessed, but costs can hardly be a major concern for a maneuver of 6 euro's per day [22] that reduces pneumonia by 65% and mortality by 22% without antimicrobial resistance emerging in unselected patients.

In conclusion, although this RCT had a rigorous sequential multicenter design with blinded outcome adjudication, it was insufficiently powered to detect a mortality difference of 25% given a baseline late mortality rate of 17%. However, this RCT of small sample size is in line with the meta-analyses of SDD-trials in unselected and selected trauma patients, showing a significant 20% survival benefit in both subsets once the appropriate sample size is obtained. Importantly, trauma patients do not respond to SDD to a higher extent than surgical and medical patients.

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