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Prevention of Ventilator-associated Pneumonia by Oral Decontamination

A Prospective, Randomized, Double-blind, Placebo-controlled Study

DENNIS C. J. J. BERGMANS, MARC J. M. BONTEN, CARLO A. GAILLARD, JOHAN C. PALING, SIEBE van der GEEST, FRANK H. van TIEL, ANTON J. BEYSENS, PETER W. de LEEUW, and ELLEN E. STOBBERINGH

Departments of Internal Medicine, Medical Microbiology, and Clinical Pharmacy, University Hospital Maastricht, Maastricht, Netherlands; Department of Internal Medicine, University Hospital Utrecht, Utrecht, Netherlands; Department of Internal Medicine, Eemland Hospital, Amersfoort, Netherlands; and Department of Surgery, University Hospital Groningen, Groningen, Netherlands

Colonization of the intestinal tract has been assumed to be important in the pathogenesis of ventilator-associated pneumonia (VAP), but relative impacts of oropharyngeal, gastric, or intestinal colonization have not been elucidated. Our aim was to prevent VAP by modulation of oropharyngeal colonization, without influencing gastric and intestinal colonization and without systemic prophylaxis. In a prospective, randomized, placebo-controlled, double-blind study, 87 patients received topical antimicrobial prophylaxis (gentamicin/ colistin/vancomycin 2% in Orabase, every 6 h) in the oropharynx and 139 patients, divided over two control groups, received placebo (78 patients were studied in the presence of patients receiving topical prophylaxis [control group A] and 61 patients were studied in an intensive care unit where no topical prophylaxis was used [control group B]). Baseline characteristics were comparable in all three groups. Topical prophylaxis eradicated colonization present on admission in oropharynx (75% in study group versus 0% in control group A [p < 0.00001] and 9% in control group B patients [p < 0.00001]) and in trachea (52% versus 22% in A [p = 0.03] and 7% in B [p = 0.004]). Moreover, topical prophylaxis prevented acquired oropharyngeal colonization (10% versus 59% in A [p < 0.00001] and 63% in B [p < 0.00001]). Colonization rates in stomach and intestine were not affected. Incidences of VAP were 10% in study patients, 31% in Group A, and 23% in Group B patients (p = 0.001 and p = 0.04, respectively). This was not associated with shorter durations of ventilation or ICU stay or better survival. Oropharyngeal colonization is of paramount importance in the pathogenesis of VAP, and a targeted approach to prevent colonization at this site is a very effective method of infection prevention.

Keywords: cross infection, prevention and control; respiration, artificial, adverse effects; antibiotics, administration and dosage infection control methods; pneumonia, etiology, prevention and control; intubation, intratracheal, adverse effects

Ventilator-associated pneumonia (VAP) is the most frequently occurring nosocomial infection among mechanically ventilated patients, with reported incidences as high as 78% (1, 2). Usually two types of VAP are distinguished: early-onset VAP, when diagnosed within the first 4 d of mechanical ventilation, and late-onset VAP, occurring thereafter. Because VAP has been associated with increased morbidity, longer hospital stay, increased health care costs, and higher mortality rates (3), prevention of this infection is a major challenge for intensive care medicine.

Early-onset VAP is caused by pathogens presumably colonizing the respiratory tract at the time of intubation, such as *Streptococcus pneumoniae, Staphylococcus aureus, and Haemophilus influenzae*. Late-onset VAP is frequently caused by enteric gram-negative bacteria and *Pseudomonas* species. These bacteria may be transmitted from exogenous sources (e.g., other colonized patients or contaminated common sources) or endogenous sources (e.g., the stomach or intestine). Because of concomitant colonization of the upper respiratory and digestive tract with these bacteria, the gastropulmonary route of colonization has been considered to be important in the pathogenesis of late-onset VAP (4). Based on the presumed relevance of gastric colonization, modulation of gastric colonization has been attempted as a measure to prevent VAP. However, neither the use of sucralfate for stress ulcer prophylaxis (5, 6), nor modulation of enteral feeding (7) have proven unequivocally to reduce the incidence of VAP. In addition, administration of nonabsorbable antibiotics into the stomach and the intestine reduced colonization at these sites, but did not influence the incidence of VAP (8). Finally, sequential analyses of colonization failed to demonstrate an important role of the gastropulmonary route in several recent studies (5, 7, 9).

Selective decontamination of the digestive tract (SDD) decreases incidences of VAP (10-14) by eradicating microorganisms from the intestine, the stomach, and the oropharynx by nonabsorbable antibiotics, in combination with systemic antibiotic prophylaxis during the first days of ICU admission. However, the constant threat of selection and overgrowth of antibiotic-resistant microorganisms, lack of formal cost-benefit analyses, and absence of beneficial effects on mortality rates have limited a widespread use of SDD (15). From a conceptual point of view, it has remained unclear which part of SDD prevents VAP. The importance of gastric and intestinal colonization has been questioned, and systemic antibiotics during the first days of intubation may prevent early-onset but not late-onset VAP (16).

We hypothesized that decontamination of the oropharynx, without modulating gastric and intestinal colonization, and without systemic antibiotic prophylaxis, would reduce the incidence of VAP in critically ill intensive care patients.

METHODS

Setting

The study was conducted in three intensive care units (ICU) from September 1994 to December 1996. ICU 1 and ICU 2 are located in the University Hospital Maastricht; both harbor a mixed population of medical, surgical, trauma and neurologic patients. ICU 3 is located in the University Hospital Groningen and is a surgical and trauma ICU.

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Correspondence and requests for reprints should be addressed to M. J. M. Bonten, M.D., Department of Internal Medicine, Division of Infectious Diseases and AIDS, University Hospital Utrecht, Heidelberglaan 100, 3584 CX Utrecht, Netherlands, E-Mail: m.bonten@wxs.nl

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Patients

Adult patients (≥16 yr) admitted to one of these ICUs who were intubated within 24 h of admission and who needed mechanical ventilation with an expected duration of > 2 d could be included. Patients were randomized to receive either topical antimicrobial prophylaxis (TAP), consisting of an Orabase with 2% gentamicin, 2% colistin, and 2% vancomycin or to placebo Orabase without antibiotics. Active medication and placebo could not be visibly distinguished. Orabase was applied in the buccal cavities on a gloved finger every 6 h. The application of Orabase was started within 24 h of intubation. Patients in whom the application of Orabase was not possible or contraindicated were not eligible for the study. No prophylactic antibiotics were administered through the nasogastric tube or systemically as part of the study regimen. Patients were studied until extubation or death. Because ≥ 95% of the first episodes of VAP occur within the first 3 wk of ventilation (5, 17), application of Orabase was limited to 21 d. Patients were evaluable if they had been included in the study for >2 d.

Sucralfate (Ulcogant Suspension; E. Merck, Germany) was used for stress ulcer prophylaxis, unless patients were receiving H_2-antagonists or H^+K^+ATPase inhibitors on admission. Stress ulcer prophylaxis was discontinued when enteral feeding was started. Enteral feeding was started as soon as possible, usually when peristalsis was present. All patients had a nasogastric tube. In general, all patients were in supine position during controlled mechanical ventilation and if possible in semirecumbent position during weaning. Moreover, all ventilated patients received daily chest physiotherapy, and endotracheal suctioning was performed by the nursing staff if necessary. When mechanical ventilation was expected to be necessary for > 3 wk, patients received a tracheostomy, usually after Day 14 of ventilation.

Normal oropharyngeal care in our ICUs consisted of rinsing the mouth with water and, if possible, tooth cleaning, once daily. To prevent cross-acquisition, dispensers with disinfectants were present at each bedside, and all staff was regulary enforced to comply with infection control procedures.

Study Design

This study was a prospective, randomized, double-blind, placebo-controlled study. Randomization was conducted per hospital and was executed by the Department of Clinical Pharmacy of the University Hospital Maastricht. The inclusion scheme aimed to create two separate control groups in ICU 1 and ICU 2. One control group (Control A) was studied in the presence of patients receiving TAP, and a second control group (Control B) was studied in an ICU where no TAP was used. After 9 mo of study the inclusion scheme was reversed for another 6 mo (Table 1). To secure the double-blind study design, only the study supervisor and the hospital pharmacists were aware of this inclusion scheme. In ICU 3, all patients were randomized to receive either TAP or placebo during the whole study period (Table 1). This inclusion scheme was chosen to assess whether TAP influences infection rates in control patients treated simultaneously in the same ICU (18). The study protocol was approved by the ethical committee of both hospitals. Informed consent was obtained from the patient or, if this was not possible, from a representative of the family.

Data Collection

Demographic data (e.g., age, sex, medical specialty, preexistent diseases, and length of hospital stay before admission to ICU) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores (19) were recorded on admission. Number of days in ICU and on mechanical ventilation, surgical procedures, parameters of infection (temperature, leukocyte counts and differential counts, chest radiograph interpretations, culture results) and antibiotic use were monitored prospectively. Surveillance cultures were taken on admission and subsequently twice weekly (Monday and Thursday) of oropharynx, trachea, stomach, and rectum. The results of surveillance cultures of oropharynx, stomach and rectum were not reported to the ICU attendings.

Microbiologic Analysis and Monitoring of Resistance

Semiquantitative or quantitative microbiologic analysis of culture samples was performed according to standard microbiologic methods (20). Antibiotic susceptibility was determined by means of a microbroth dilution method according to the National Committee of Clinical Laboratory Standards (NCCLS) guidelines. *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922 and ATCC 35218, *S. aureus* ATCC 29213, and *Enterococcus faecalis* ATCC 29212 were used as reference strains. The criteria for susceptibility and resistance, according to the NCCLS guidelines, were used. Colonization was analyzed for Enterobacteriaceae, Pseudomonadaceae and *S. aureus* (i.e., potentially pathogenic microogranisms [PPMO]), enterococci, and *Candida* species. Vancomycin susceptibility was tested for all enterococci.

Definitions

Colonization was defined as the isolation of microorganisms (i.e., bacterial or yeast species) in two or more consecutive specimens of one site, in the absence of infection. Colonization on admission was defined as colonization demonstrated within 24 h after admission to ICU. Eradication of colonization was defined as the disappearance of microorganisms in two or more consecutive cultures from a body site that was colonized on admission, and is expressed as the proportion of colonized patients in whom eradication occurred. Acquired coloniza-

tion was defined as colonization demonstrated >24 h after ICU admission, in patients without colonization on admission.

All patients were examined daily for the presence of VAP. A clinical suspicion of VAP was defined as the presence of a new, persistent or progressive infiltrate on chest X-ray and ≥3 of four criteria; rectal temperature >38.0°C or < 35.5°C; blood leukocytosis (>10.10^3/mm^3) and/or left shift or leukopenia (<3.10^3/mm^3); >10 leukocytes per high-power field in Gram stain of tracheal aspirate; and a positive culture from tracheal aspirate. In case of a clinical suspicion of VAP, bronchoscopy with protected specimen brush (PSB) and bronchoalveolar lavage (BAL) were performed and blood cultures were taken. The diagnosis of VAP was established on the basis of positive quantitative cultures from BAL (cutoff point ≥10^4 colony-forming units [cfu]/ml) or PSB (cutoff point ≥10^3 cfu/ml), or a positive blood culture unrelated to another source of infection, or a positive blood culture unrelated to another source of infection, or a positive culture from pleural fluid in the absence of previous pleural instrumentation. Pneumonia was considered ICU-acquired when diagnosed ≥48 h after admission to ICU. Pneumonia was classified early-onset when diagnosed within the first 4 d of mechanical ventilation, and late-onset when occurring thereafter.

Nosocomial infections other than VAP were diagnosed according to Centers for Disease Control (CDC) definitions (21). Antibiotic use was analyzed in courses. A course was defined as an episode of clinical or suspected infection in which antibiotics, either consecutively or in combination, were prescribed. A change in antibiotics, for example narrowing after availability of antibiotic susceptibility, was not considered a separate course.

Outcome Variables

The incidence of VAP was the primary outcome variable of the study. Colonization of oropharynx, trachea, stomach, and rectum, number of days in ICU and on mechanical ventilation, other nosocomial infections, antibiotic use, and mortality were secondary outcome variables.

Statistics

The power analysis was performed with an expected decrease in the incidence of VAP from 30% to 10%; it predicted the necessary number of patients per group to be 63 (ß 0.80, 0.05). Data are expressed as absolute numbers with or without percentages, as means with standard deviation or as medians with ranges. Chi-square or Fisher exact test were used to compare proportions, *t* test or Wilcoxon-Mann-Whitney test to compare continuous variables. For each patient the time until event (i.e., diagnosis of VAP or end of study) and death was determined to calculate the probability of remaining without VAP and survival using Kaplan-Meier survival analysis. Groups were compared by log-rank test. Incidence rates of pneumonia were compared by using risk ratios with 95% confidence interval (CI). A probability value < 0.05 was considered to denote statistical significance and all reported p values are two-sided. To accommodate for multiple statistical testing, the Bonferroni correction was used for the secondary endpoints. In these cases a p value < 0.0125 was considered statistical significant. Statistical analysis was performed using the SPSS/PC statistical package (SPSS, Inc., Chicago, IL.)

RESULTS

Patients

During the 28-mo study period 213 eligible patients were admitted to ICU 1 and 2. Fifteen patients were not included because of mandibular fixation after facial trauma (n = 2), severe intraoral mucosal hemorrhages due to thrombocytopenia (n = 2), and refusal to give informed consent (n =11). Seventeen of 198 included patients were ventilated or intubated ≤ 2 d or succumbed within 2 d (Table 1). Although 93% of all long-term ventilated patients were included, the number of patients studied simultaneously was lower than expected. Overall, the median daily proportion of all patients being included was 14% (range 0 to 86%), which means that per day on average one patient was included in each seven-bed ICU. The low-inclusion rate was a result of an unexpected high admittance rate of children and short-term ventilated postoperative neurosurgical patients, who were not eligible for our study. In addition, several patients remained in ICU long after the 21 d of study. As a result, we were unable to assess whether TAP influences infection rates in control patients studied in an ICU where no TAP was used (Control B).

In ICU 3, informed consent was refused by 10 eligible patients. In this ICU 47 patients were included, two of whom were not evaluable because they were ventilated < 2 d (Table 1). In all, 226 patients were evaluable; 87 study patients, 78 Control A patients, and 61 Control B patients. Baseline characteristics were comparable for the three groups (Table 2). The baseline characteristics of the patients who were not evaluable (n = 19) were comparable to those of evaluable patients (data not shown).

Colonization

Colonization rates on admission in oropharynx, trachea, stomach, and rectum with PPMO, enterococci, and *Candida* species, were comparable for study and control patients (*see* Table E1 in online data supplement). TAP eradicated oropharyngeal colonization with PPMO present on admission (75% of study patients versus 0% in Control A patients [$p < 0.00001$] and 9% in Control B patients [$p < 0.00001$]) and reduced rates of acquisition of colonization with PPMO at this site (10% of study patients versus 59% in Control A patients [$p < 0.00001$]) and 63% in Control B patients [$p < 0.00001$]). In addition, TAP was associated with eradication (52% of study, 22% of Control A [$p = 0.03$], and 7% of Control B patients [$p = 0.004$]), and with a tendency toward prevention of acquisition.

TABLE 2. BASELINE CHARACTERISTICS OF THE STUDY PATIENTS AND CONTROL SUBJECTS*

Characteristic	Study Patients *(n = 87)*	Control A *(n = 78)*	Control B *(n = 61)*
Male	59(68)	53(68)	47(77)
Mean age, yr± SD	56.6 ± 19.0	58.1 ± 16.4	58.7 ± 16.7
APACHE II score, mean± SD	21.0 ± 6.8	22.0 ± 6.6	21.2 ± 8.4
Days in hospital before ICU, median (range)	2(0-66)	2(0-48)	2(0-21)
Medical specialty			
Medical	34(39)	20(26)	24(39)
Surgery	29(33)	39(50)	20(33)
Trauma	17(20)	15(19)	11(18)
Neurology§	6(17)	3(4)	5(8)
Other‖	1(1)	1(1)	1(2)
Antibiotic use on admission	41(47)	31(40)	27(44)
Underlying diseases¶			
Cardiovascular disease	34(39)	36(46)	32(52)
Gastrointestinal disease	22(25)	15(19)	14(23)
Respiratory disease	25(29)	20(26)	17(28)
Alcoholism or drug abuse	10(12)	11(14)	7(11)
Neoplastic disease	13(15)	7(9)	8(13)
Diabetes mellitus	12(14)	15(19)	9(15)
Neurologic disease	20(23)	14(18)	8(13)
Renal insufficiency	4(5)	3(4)	3(5)
Immunodeficiency	3(3)	2(3)	1(2)
Reason for intubation			
Respiratory failure	32(37)	26(33)	15(25)
Trauma	10(12)	10(13)	9(15)
Stock or hypoxic acidosis	10(12)	22(28)	4(7)
Cardiopulmonary failure	4(5)	3(4)	6(10)
Pneumonia on admission	10(12)	5(6)	9(15)
Neurologic disease	6(7)	4(5)	5(8)
Elective	15(17)	8(10)	13(21)

* Data are presented as numbers of patients (percent), unless stated otherwise.

‖ Including pulmonology and cardiology.

‖ Including cardiopulmonary surgery and urology.

§ Including neurosurgery.

‖ Gynecology and ENT.

¶ More than one condition possible per patient.

TABLE 3. OUTCOME DATA OF THE STUDY PATIENTS AND CONTROL SUBJECTS*

Variable	Study (*n = 87*)	Control A (*n = 78*)	Control B (*n = 61*)	p Value
Days studied, mean± SD	10.1± 5.9	11.3± 6.5	10.5± 6.9	
Days ventilated, median (range)	10 (1-50)	11 (3-77)	9 (1-95)	
Days in ICU, median (range)	13 (4-54)	15 (4-79)	12 (4-108)	
Days in hospital after ICU admission, median (range)	26 (4-185)	26 (4-280)	21 (4-157)	
VAP	9 (10)	24 (31)	14 (23)	0.001/0.04
Polymicrobial	4	10	8	
Pathogens				
Pseudomonas oeruginosa	3	8	5	
Staphylococcus aureus	3	6	5	
Haemophilus influenzae	2	5	1	
Enterobacteriaceae	4	9	7	
Streptococcus species		4	2	
Candida species	1	3	1	
Other		2	4	
Recurrent episode of VAP during study	2 (22)	2 (8)	1 (7)	
Nosocomial infections				
Number of patients	31 (36)	40 (51)	26 (43)	0.04/NS
Total number of nosocomial infections	37	64	47	
Respiratory tract excluding VAP§	11	20	10	
Abdominal	4	7	4	
Other	13	13	19	
Courses of antibiotics, mean± SD				
During study period	0.95± 0.68	1.30± 0.85	1.23± 0.90	0.02/NS
During ICU stay	1.33± 0.76	1.82± 1.23	1.69± 1.31	0.02/NS
Tracheostomy	13 (15)	16 (21)	12 (20)	
Enteral feeding	71 (82)	57 (73)	39 (64)	NS/0.02
Sucralfate	53 (61)	59 (76)	46 (75)	0.04/NS
H_2 -antagonists/H^+K^+ ATPase inhibitors	27 (31)	18 (23)	20 (33)	
Mortality				
ICU	25 (29)	27 (35)	26 (43)	
Hospital	30 (35)	32 (41)	27 (44)	
1 yr after inclusion in the study	43 (49)	39 (50)	30 (49)	
Follow-up until 01-01-98	46 (53)	42 (54)	36 (59)	

* Numbers (percent), unless stated otherwise.
NS denotes not significant, comparison study versus control A/study versus Control B.
Including *E. faecalis, Staphylococcus epidermidis, Hafnia alvei, Pasteurella* species, and *Bacillus* species.
§ Including sinusitis, tracheobronchitis, and lung empyema.
Including infections of urinary tract, central nervous system and tissue, intravenous line-related infections, and sepsis of unknown origin.

with PPMO in the trachea in Control A patients (36% versus 50%; p = 0.06). Importantly, in all three groups colonization rates of the stomach and rectum were not influenced (Table E1).

Acquisition of enterococcal colonization occurred more frequently in control patients in the oropharynx (28% of Control A and 30% of Control B patients versus 3% of study patients; p < 0.00001 for both comparisons), and in the stomach (37% of Control A and 35% of Control B patients versus 18% of study patients; p = 0.01 and p = 0.03 respectively). Acquired enterococcal colonization was comparable in trachea and rectum. Rates of acquired colonization with *Candida* species were comparable in all groups at all body sites (Table E1).

VAP

During the study period VAP was diagnosed in nine (10.3%) study, 24 (30.8%) Control A patients, and 14 (23.0%) Control B patients (study versus Control A, p = 0.001; study versus Control B, p = 0.04; Table 3; Figure 1), after 9 d (range 2 to 18), after 7 d (range 2 to 19), and after 5 d (range 3 to 18) in study, Control A, and Control B patients respectively. Therefore, comparing study and Control A patients, administration of TAP resulted in a relative risk for VAP of 0.33 (95% CI 0.16 to 0.67), a relative risk reduction of 0.67 (95% CI 0.33 to 0.84), and an absolute risk reduction of 0.21 (95% CI 0.09 to 0.33), which implies that five patients needed to be treated to prevent one episode of VAP.

Comparing study and Control B patients, administration of TAP resulted in a relative risk for VAP of 0.45 (95% of CI 0.21 to 0.97), a relative risk reduction of 0.55 (95% CI 0.03 to 0.79), and an absolute risk reduction of 0.13 (95% CI 0.004 to 0.25), which implies that eight patients needed to be treated to prevent one episode of VAP.

Figure 1. Probability of remaining free of VAP during study period in study patients and control subjects (study patients versus Control A, p = 0.0004; study patients versus Control B, p = 0.02).

Approximately 20% of the episodes of VAP were early-onset (2 of 9 study patients, 6 of 24 Control A patients, and 2 of 14 Control B patients). VAP was accompanied by bacteremia in 2 Control A, 1 Control B, and in none of the study patients. A similar distribution of etiologic pathogens was observed (Table 2). The difference in the incidence of VAP persisted after Day 21, demonstrating that ceasing TAP was not associated with a rebound effect on the incidence of VAP (data not shown). Of the patients who were ventilated for more than 21 d, VAP was diagnosed in one study patient, 2 Control A patients, and 2 Control B patients after the application of trial medication was stopped.

A clinical suspicion of VAP with negative or nonsignificant culture results from bronchoscopy occurred with equal frequency in all study groups (24 [28%], 25 [32%], and 15 [25%] in study, Control A, and Control B patients, respectively).

Secondary Outcome Variables

The number of days in study, on mechanical ventilation, in ICU, and in hospital were comparable for study and control patients (Table 3). There were differences in the use of enteral feeding and sucralfate: study patients received enteral feeding more frequently than Control B patients (82% versus 64%; $p = 0.02$), and Control A patients were more likely to receive sucralfate for stress ulcer prophylaxis compared with study patients (76% versus 61%; $p = 0.04$). H_2-antagonists or H^+K^+ATPase inhibitors were administered to comparable numbers of patients in all groups. Mean durations of enteral feeding, use of sucralfate, and H_2-antagonists and/or H^+K^+ATPase inhibitors were also comparable.

Although ICU mortality tended to be lower in study patients (29%) as compared with Control A and Control B patients (35% and 43%, respectively), this difference did not persist during follow-up (Table 3; Figure 2).

Systemic Antibiotic Use and Resistance

On admission, systemic antibiotics were prescribed for 41 (47%) study, 31 (40%) Control A, and 27 (44%) Control B patients. Twenty-one of the 131 surgical/trauma patients received antibiotic prophylaxis during surgery, 15% of study, 15% of Control A, and 19% of Control B patients. Mean numbers of courses of antibiotics per patient were 0.95 ± 0.68 for study patients and 1.30 ± 0.85 for Control A patients during study period ($p = 0.02$) and 1.23 ± 0.90 for Control B patients ($p = 0.10$). During total ICU stay these figures were as follows: 1.33 ± 0.76 for study and 1.82 ± 1.23 for Control A patients ($p = 0.02$) and 1.69 ± 1.31 for Control B patients ($p = 0.34$) (Table 3).

Figure 2. Probability of survival during prolonged follow-up in study patients and control subjects (study patients versus Control A, $p = 0.7$; study patients versus Control B, $p = 0.4$).

No vancomycin-resistant enterococci (VRE) were isolated in either hospital before, during, or after the study. No increase in the number of patients colonized or infected with microorganisms resistant to gentamicin was observed during the study. Separate analysis of the resistance patterns of the pathogens causing VAP did not reveal cases of acquired resistance to the antibiotics used in the oropharyngeal paste.

DISCUSSION

The main feature of this study is that modulation of oropharyngeal colonization, without influencing gastric and intestinal colonization and without systemic antibiotic prophylaxis, resulted in a relative risk reduction of 67% in the incidence of VAP. This finding underscores the pivotal role of oropharyngeal colonization in the pathogenesis of VAP, and strongly suggests that modulation of colonization at this site will effectively prevent VAP.

The present study shows that prevention of colonization of the oropharynx, and not the stomach, reduces the incidence of late-onset VAP. The effects of oropharyngeal decontamination have been studied previously in two smaller studies. Rodríguez-Roldán and coworkers (22) used an oropharyngeal paste containing tobramycin, amphotericin B, and polymyxin E. Decontamination of oropharynx and trachea was established in 10 of 13 patients receiving active medication and none developed pneumonia. Eleven (73%) of 15 patients receiving placebo medication developed pneumonia. In a double-blind study, Pugin and coworkers (2) randomized 52 patients to receive either a solution of polymyxin B, neomycin, and vancomycin or placebo in the retropharynx. Colonization with aerobic gram-negative bacteria was significantly reduced in oropharynx and stomach, resulting in a relative risk reduction of VAP of 0.79. Our findings expand the results of both studies. Incidences of VAP in the control groups of both studies (73% and 78% respectively) were extremely high, and not comparable to incidences found in other ICU studies (3, 5, 6). This is probably due to the use of clinical and microbiologic criteria, instead of bronchoscopic techniques, in the diagnosis of VAP, or due to patient selection. Furthermore, because gastric colonization was significantly decreased in the study by Pugin and coworkers,

their findings do not contribute to the determination of the relative importance of gastric and oropharyngeal colonization (2).

Our findings demonstrate that VAP can be prevented effectively by modulation of oropharyngeal colonization. Importantly, the relative risk reduction of VAP in the present study is similar to the relative risk reductions reported in the meta-analyses of SDD (ranging from 53% to 78%) (10-14). This strongly suggests that oropharyngeal decontamination, indeed, represents the effective part of SDD, and that the majority of antibiotic use in SDD is unlikely to add beneficial effects. A similar preventive effect on the incidence of VAP can be achieved with only a fraction of the antibiotics used in SDD. The data, therefore, question the concept of SDD, a method of infection prevention that is used in some ICUs (1). However, antibiotic use bears the constant threat of induction or selection of resistant microorganisms. Absence of resistance problems and very strict control, as in the present study, are mandatory.

Ideally, modulation of oropharyngeal colonization should be established with nonantibiotic methods. One potential approach might be the use of chlorhexidine for oropharyngeal

decontamination. An oral rinse of 0.12% chlorhexidine reduced the incidence of respiratory tract infections among 353 cardiosurgical patients from 9% in control patients to 3% in patients receiving oropharyngeal decontamination with chlorhexidine (23). The difference was mainly caused by a reduction of infections with gram-negative pathogens. However, how prolonged chlorhexidine use will affect oral, esophageal, and gastric mucosa in critically ill ICU patients is unclear, as is the risk of chlorhexidine resistance after long-term application.

How should our findings be applied together with the results of other studies on prevention of VAP? There is strong evidence that modulation of oropharyngeal colonization will influence the development of late-onset VAP. However, in settings where early-onset VAP represents a bigger problem, other strategies, such as subglottic secretions drainage (24) or targeted systemic prophylaxis during the first 24 h (16) may be more appropriate.

In a previous study in our hospital, topical antimicrobial prophylaxis of the oropharynx and stomach with colistin, tobramycin, and amphotericin B was associated with overgrowth and infections caused by gram-positive species, such as *E.facecalis* and coagulase-negative staphylococci (25), findings that have been reported by others as well (26, 27). Because our aim was to perform a conceptual study to determine the effects of modulation of oropharyngeal colonization on the incidence of VAP and to elucidate the pathogenesis of VAP, we included vancomycin in our prophylactic regimen. We are well aware of the emergence of VRE in many countries and the Hospital Infection Control Practices Advisory Committee recommendations to avoid the prophylactic use of vancomycin (28). However, neither VRE nor methicillin-resistant *S. aureus* (MRSA) had been isolated on a regular basis in the Netherlands or in the ICUs of both hospitals, at the start of the study, and systemic vancomycin was used only sporadically (29). In addition, the duration of topical antibiotic prophylaxis was limited to a maximum of 21 d to minimize the risk of induction of resistant strains. Finally, susceptibilities for vancomycin were determined for all enterococci isolated during the study. A plan of enforced infection control had been developed when vancomycin-resistant strains would have emerged. With all these control measures, we felt assured to use vancomycin as a prophylactic agent in a setting with low vancomycin use, an overall low incidence of antibiotic resistance, and complete absence of VRE and MRSA. Although acquired resistance in gram-negative bacteria is also a potential threat of topical antimicrobial prophylaxis, the susceptibility of gram-negative bacteria to gentamicin was approximately 90% in our ICU and this did not decrease during the study.

Several potential insufficiencies of our study must be addressed. Incidences of VAP may have been influenced by several variables that were not equally distributed in the study groups. For instance, more control patients (Control A as well as Control B) received sucralfate and study patients were more likely to receive enteral feeding. However, because sucralfate has been associated with lower incidences of VAP in some studies (17, 30) and enteral feeding has been assumed to be a risk factor for VAP (31), both of these discrepancies would have favored the control groups rather than the study patients. If so, the true beneficial effects of oropharyngeal decontamination would have been even higher. Another concern is whether aspiration of antibiotics into the lungs influenced the diagnostic yield of bronchoscopic samples. However, negative bronchoscopic results obtained because of a clinical suspicion of VAP occurred with equal frequency in both control groups and study patients, suggesting that leakage of antibiotics in the lower respiratory tract did not occur. Moreover, from a number of study patients, samples of tracheal aspirate were obtained for determination of gentamicin and vancomycin concentrations during the study period (Days 3, 7, 14, and 21). All gentamicin concentrations were below the threshold of detection (i.e., < 0.03 mg/L). Vancomycin concentrations were below the threshold of detection (i.e., < 0.05 mg/L) in most samples and very low concentrations in the remaining (median 0.25 mg/L) (data not shown).

In conclusion, our study demonstrated that modulation of oropharyngeal colonization, without influencing gastric and intestinal colonization, effectively reduces the incidence of late-onset VAP. This finding proves the pivotal role of oropharyngeal colonization in the pathogenesis of this infection. When compared with preventive strategies for VAP which aim to modulate either gastric or intestinal colonization, prevention of oropharyngeal colonization is by far the most effective.

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Science commentary: Why do some children grow out of peanut allergy?

i

One hypothesis which may explain why some children grow out of their peanut allergy lies in the physical structure of the peanut proteins. If the protein is visualised as a string of amino acid beads scrunched up into a 3-dimensional ball there are two ways an antibody can bind to that structure. Firstly, an antibody can bind to a specific antigen by attaching itself to sequential amino acid beads in the protein. These sections of the protein are known as linear epitopes. Alternatively, an antibody binds to a section which is effectively folded up so that it not only binds to a number of amino acid beads in one part of the protein string but also to beads in other sections of the string. These antigenic binding sites are known as conformational epitopes.

Research in other food allergies suggests that children who develop tolerance to peanuts may have peanut specific IgE which binds much more to conformational peanut epitopes (which are generally more labile and easily destroyed by heat) and that children who remain reactive to peanuts have IgE which binds mostly to linear epitopes (which are very stable). As the gut matures with age more linear epitopes than conformational epitopes pass through the gut wall. So if the hypothesis is found to be true this could explain why some people continue to react to peanuts and others seemingly outgrow their allergy.

Such differences in IgE binding have already been observed in children with egg or cows milk allergy. An interesting question is why up to 50% of children with egg or cows milk allergy outgrow the allergy while only about 10% seem to develop tolerance to peanuts.

Abi Berger, *science editor, BMJ*

Editorial
Berger and Smith

Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials

Roberto D Amico, Silvia Pifferi, Cinzia Leonetti, Valter Torri, Angelo Tinazzi, Alessandro Liberati on behalf of the study investigators

Abstract

Objective: To determine whether antibiotic prophylaxis reduces respiratory tract infections and overall mortality in unselected critically ill adult patients.

Design: Meta-analysis of randomised controlled trials from 1984 and 1996 that compared different forms of antibiotic prophylaxis used to reduce respiratory tract infections and mortality with aggregate data and, in a subset of trials, data from individual patients.

Subjects: Unselected critically ill adult patients; 5727 patients for aggregate data meta-analysis, 4343 for confirmatory meta-analysis with data from individual patients.

Main outcome measures: Respiratory tract infections and total mortality.

Results: Two categories of eligible trials were defined: topical plus systemic antibiotics versus no treatment and topical preparation with or without a systemic antibiotic versus a systemic agent or placebo. Estimates from aggregate data meta-analysis of 16 trials (3361 patients) that tested combined treatment indicated a strong significant reduction in infection (odds ratio 0.35; 95% confidence interval 0.29 to 0.41) and total mortality (0.80; 0.69 to 0.93). With this treatment five and 23 patients would need to be treated to prevent one infection and one death, respectively. Similar analysis of 17 trials (2366 patients) that tested only topical antibiotics indicated a clear reduction in infection (0.56; 0.46 to 0.68) without a significant effect on total mortality (1.01; 0.84 to 1.22). Analysis of data from individual patients yielded similar results. No significant differences in treatment effect by major subgroups of patients emerged from the analyses.

Conclusions: This meta-analysis of 15 years of clinical research suggests that antibiotic prophylaxis with a combination of topical and systemic drugs can reduce respiratory tract infections and overall mortality in critically ill patients. This effect is significant and worth while, and it should be considered when practice guidelines are defined.

Mario Negri Institute for Pharmacological Research, 20157 Milan, Italy

Roberto D Amico, *research fellow*

Valter Torri, *chief of biometry unit*

Angelo Tinazzi, *computer scientist*

Alesandro Liberati, *head*

Maggiore Ospedale IRCCS, 20122 Milan

Silvia Pifferi, *research fellow*

Cinzia Leonetti, *research fellow*

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Introduction

Nosocomial infections, especially pneumonia, are an important cause of morbidity and mortality in critically ill patients. The incidence of pneumonia in such patients ranges between 7% and 40%, and the crude mortality from ventilator associated pneumonia (VAP) may exceed 50%. Although not all deaths in patients with this form of pneumonia are directly attributable to infection, it has been shown to contribute to mortality in intensive care units independently of other factors that are also strongly associated with such deaths.[1] In a case-control study of ventilated patients an increase in mortality of 27% was attributable to ventilator associated pneumonia.[2] Considerable efforts have been made to develop and evaluate methods for reducing respiratory infections. One strategy involves the use of selective decontamination of the digestive tract (SDD). Different decontamination protocols have been used in different trials, and investigators often disagree on its most appropriate definition. Traditionally, selective decontamination of the digestive tract indicates a method designed to prevent infection by eradicating and preventing carriage of potentially pathogenic aerobic microorganisms from the oropharynx, stomach, and gut. It consists of antibiotics applied topically to the oropharynx and through a nasogastric tube. In many trials treatment with systemic antibiotics has been added in the first days after patients are admitted to prevent early infections.

A decontamination regimen based on oral non-absorbable antibiotics was first used in 1984 by Stoutenbeek et al in a group of patients with multiple trauma.[3] The incidence of nosocomial infections was reduced from 81% to 16% in a non-randomised comparison with a historical control group. Further studies tested the efficacy of decontamination in patients in intensive care with morbidity related to infection as the main end point. The results showed that decontamination reduced infection, but it was not clear whether there was a reduction in mortality.

Between 1991 and 1995 five different meta-analyses on the effect of antibiotic prophylaxis on infections and mortality were published.[4-8] Their results are summarised in table 1. All confirmed a significant reduction in infections, though the magnitude of the effect varied from one review to another. The estimated impact on overall mortality was less evident and generated considerable controversy on the cost effectiveness of the treatment. Only one among the five available reviews, however, suggested that a weak association between respiratory tract infections and mortality and lack of sufficient statistical power may have accounted for the limited effect on mortality.[5] The authors suggested that, given the baseline risk of death in the populations typically enrolled in existing trials, between 2000 and 3000 patients were probably needed to detect reliably a relative reduction in mortality in the 10%-20% range.[5]

We report here on an updated and refined meta-analysis made possible by the enthusiastic collaboration of most investigators in the topic. Besides updating the results by using data from randomised controlled trials published since the 1993 paper,[5] there are two main differences between this and previously published meta-analyses. The first is the way trials have been grouped to test the effectiveness of the treatment. Contrary to previous practice we have separately analysed trials that tested combinations of topical and systemic antibiotics from trials that tested the effect of topical drugs alone. The second is that information for individual patients was sought from all trials. Results from this more refined type of meta-analysis, which proved feasible in 4343/5727 (76%) patients, are reported and compared with findings from the corresponding aggregate datasets.

Patients and methods

Search strategy

We searched for randomised controlled trials published from January 1984 to December 1996. Studies were identified through Medline (MeSH keywords: Intensive care units, Critical care, Antibiotic combined therapeutic use, Antibiotics combined administration and dosage, Respiratory tract infections prevention and control with the keyword SDD). Other studies were evaluated because they were listed in previous meta-analyses. The organiser of the first European Consensus Conference on Intensive Care Medicine (held in December 1991) also provided a list of all investigators who had ever published on the topic. An additional search focused on proceedings of scientific meetings held on the subject and personal contacts were established with other known investigators. No formal inquiry was made through pharmaceutical companies.

Eligibility criteria for studies

All trials, published and unpublished, which tested the effect of antibiotic prophylaxis for the prevention of respiratory tract infections and deaths in unselected critically ill adult patients were considered. No language restriction was applied. Only randomised trials were accepted to guarantee control of selection bias. Studies that were determined on closer scrutiny not to be properly randomised (see definition below) were not included.

Table 1 Results of five published meta-analyses of randomised controlled trials on antibiotic prophylaxis for mortality and respiratory tract infection in patients in intensive care

End points	Point estimates (95% CI)		
	All trials	Topical plus systemic antibiotics	Topical antibiotics alone
Vandenbroucke-Grauls et al[4] (6 trials, 491 patients)			
Mortality	0.70* (0.45 to 1.09)	NA	NA
Infection	0.12* (0.06 to 0.19)	NA	NA
SDD Trialists Group[5] (22 trials, 4142 patients)			
Mortality	0.90* (0.79 to 1.04)	0.80 (0.67 to 0.97)	1.07 (0.86 to 1.32)
Infection	0.37* (0.31 to 0.43)	0.33 (0.27 to 0.40)	0.43 (0.33 to 0.56)
Heyland et al[6] (24 trials, 3312 patients)			
Mortality	0.87 (0.79 to 0.97)	0.81 (0.71 to 0.95)	1.00 (0.83 to 1.19)
Pneumonia	0.46 (0.39 to 0.56)	0.48 (0.39 to 0.60)	0.43 (0.32 to 0.59)
Kollet et al[6] (16 trials, 2270 patients)			
Mortality	0.02 (-0.02 to 0.05)	NA	NA
Pneumonia	0.14 (0.12 to 0.17)	NA	NA
Tracheobronchitis	0.05 (0.02 to 0.09)	NA	NA
Hurley et al[7] (26 trials, 3768 patients)			
Mortality	0.86* (0.74 to 0.99)	NA	NA
Infection	0.35* (0.30 to 0.42)	NA	NA

NA = data not in published articles. *Odds ratio. Relative risk. Risk difference.

Correspondence to: Dr. A Liberati, Italian Cochrane Centre, Laboratory of Health Services Research, Mario Negri Institute, Via Eritrea 62, 20157 Milan, Italy

Cochrane@irfmn.mnegri.it

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Studies based on specific preselected types of patients (that is, patients undergoing elective oesophageal resection, cardiac or gastric surgery, and liver transplantation or suffering from acute liver failure) were excluded from this meta-analysis. Similarly, we excluded studies in which over half the patients did not undergo mechanical ventilation for more than 48 hours. Details on the reasons for exclusion are reported in the appendix.[9-18]

We grouped eligible trials into two categories according to the type of antibiotic prophylaxis. The first group comprised studies in which a combination of systemic and topical antibiotics was compared with no prophylactic treatment.[19-34] The second comprised studies in which topical antibiotics alone were tested. In this second category two types of trials were considered together those in which topical antibiotics were tested against an untreated group (S Jacobs, M Zuleika, personal communication)[35-44] and those in which the combination of topical plus a systemic drug was compared with a protocol based on a systemic antibiotic agent only.[45-50] Any combination of topical or systemic antibiotic (that is, type of drugs) was accepted.

Data extraction and relevant information sought

The results of the meta-analysis of aggregate data presented in table 2 are based on 33 trials; in the other tables, however, more studies and patients are shown because the two trials with three arms were split into two parts in which two different treatments were compared with the same control group.[33-49]

In a qualitative review of published studies it was recently documented that in many trials some patients had been excluded from the final analysis.[51] We therefore tried to contact all investigators to analyse the whole original population enrolled into the trials. In 25/33 trials information on all randomised patients was retrieved according to the treatment arm to which they were originally allocated, allowing an intention to treat analysis. This, however, proved impossible in the trials of Finch et al,[24] Rocha et al,[29] and Verwaest et al[33] for respiratory tract infections and those of Lenhart et al,[27] Georges et al,[38] Wiener et al,[44] and Laggner et al[48] for infections and mortality.

Data on key variables relevant for this review were available from published reports. For 30 studies published figures were integrated with the following

Table 2. General characteristics of randomised clinical trials included in meta-analysis. Data were aggregate or for individual patients or both. End points were respiratory tract infection or mortality or both.

Study name	Type of Treatment		Mean age (years)	Trauma patients(%)	Surgical patients(%)	Medical patients(%)	Type of data	End points
	Topical	Systemic						
Abele-Horn et al[19]	Polymyxin, tobramycin, amphotericin	Cefotaxime	41.5	84	16	0	Aggregate	Both
Aerdts et al[20]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	46.7	34	26	40	Both	Both
Blair et al[21]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	47.6	40	46	14	Both	Both
Boland et al[22]	Polymyxin, tobramycin, nystatin	Ceftriaxone	33.9	100	0	0	Both	Both
Brun-Buisson et al[35]	Polymyxin, neomycin, nalidixic acid	None	59.0	2	23	75	Both	Both
Cerra et al[36]	Norfloxacin, nystatin	None	63.5	4	96	0	Aggregate	Mortality
Cockerill et al[23]	Nystatin, polymyxin, gentamicin	Ceftriaxone	65.0	34	48	18	Both	Both
Ferrer et al[45]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	61.0	20	14	66	Both	Both
Finch et al[24]	Polymyxin, gentamicin, amphotericin	Ceftriaxone	59.2	4	37	59	Both	Both
Gastinne et al[37]	Tobramycin, amphotericin, polymyxin		55.0	15	13	72	Both	Both
Gaussorgues et al[46]	Polymyxin, gentamicin, vancomycin, amphotericin	Not specified	57.0	17	0	83	Aggregate	Mortality
Georges et al[38]	Polymyxin, netilmicin, amphotericin	None	32.3	100	0	0	Both	Both

Hammond et al[47]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	43.3	31	14	55	Both	Both
Jacobs et al[25]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	51.5	18	57	25	Aggregate	Both
Jacobs and Zuleika*	Polymyxin, gentamicin, amphotericin	None	49.4	21	21	58	Both	Both
Kerver et al[26]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	55.6	28	60	12	Aggregate	Both
Korinek et al[39]	Polymyxin, tobramycin, amphotericin, vancomycin	None	45.0	50	50	0	Both	Both
Laggner et al[48]	Gentamicin, amphotericin	Not specified	53.8	2	10	88	Both	Both
Lenhart et al[27]	Polymyxin, gentamicin	Ciprofloxacin	Information not available				Aggregate	Mortality
Lingnau et al[49]	1: Polymyxin, tobramycin, amphotericin 2: Polymyxin, ciprofloxacin, amphotericin	Ciprofloxacin	38.0	100	0	0	Both	Both
Palomar et al[28]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	45.5	50	10	40	Both	Both
Pugin et al[40]	Polymyxin, vancomycin, neomicin	None	45.5	56	33	11	Both	Both
Quinio et al[41]	Polymyxin, gentamicin, amphotericin	None	34.6	98	0	2	Both	Both
Rocha et al[29]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	43.5	68	4	28	Both	Both
Rodriquez-Roldan et al [42]	Polymyxin, tobramycin/netilmicin, amphotaricin	None	51.3	42	19	39	Both	Both
Sanchez-Garcia et al [30]	Polymyxin, gentamicin, amphotaricin	Ceftriaxone	54.4	18	12	70	Both	Both
Stoutanbeek et al[3]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	40.4	100	0	0	Both	Both
Stoutanbeek et al[31]	Polymyxin, tobramycin, amphotericin	Ceftriaxone	39.8	100	0	0	Both	Both
Ulrich et al[32]	Polymyxin, norfloxacin, amphotericin	Trimethoprim	62.0	16	50	34	Both	Both
Unertl et al[43]	Polymyxin, gentamicin, amphotericin		49.4	33	15	52	Aggregate	Both
Verwaest et al[33]	1: Ofloxacin, amphotericin 2: Polymyxin, tobramycin, amphotericin	1: Ofloxacin 2: Ceftriaxone	55.8	23	67	10	Both	Both
Wiener et al[44]	Polymyxin, gentamicin, nystatin	None	Information not available				Aggregate	Both
Winter et al[34]	Polymyxin, tobramycin, amphotaricin	Ceftazidime	59.2	13	47	40	Both	Both

* Personal communication.

Fig 1 Meta-analysis of aggregate data. Effect of combination of topical and systemic antibiotics as prophylaxis for respiratory tract infections in patients in intensive care units

information that we obtained, in a standardised format, directly through personal contacts with study investigators: number of patients and their treatment allocation; method of randomisation and use of blinding techniques; type of comparison (type and dose of antibiotic); number of patients with at least one respiratory infection by treatment arm; number of deaths by treatment arm; and number of excluded patients, and number of respiratory infections and deaths among them.

To perform a meta-analysis on data from individual patients we sought the following information for each randomised subject: treatment arm; date of birth; sex; date of admission to intensive care unit; date of randomisation; type of diagnostic category (medical, surgical, trauma); severity score (simplified acute physiology score (SAPS)), acute physiological and chronic health evaluation (APACHE), and injury severity score (ISS) for trauma patients; systemic antibiotic treatment in the first 3 days; respiratory infections; vital status at discharge from intensive care; vital status at last follow up; and inclusion or exclusion and reason(s) for exclusion.

To explore whether the trials for which we obtained data on individual patients differed from all the trials we compared the results of pooled estimates of treatment effects on respiratory infections and mortality in the two datasets.

Quality assessment of studies

Study quality was assessed by looking at methods of randomisation (blind versus open) and use of blinding techniques (double blind versus unblind studies). The randomisation procedure was classified as blind when it was done by telephone through a pharmacy or a central office or by using sealed envelopes. It was classified as open when it was done with a computer generated list directly managed by study investigators or when patients were allocated by odd-even number or other types of open lists.

The assignment of a study to a double blind or unblind category was according to what was reported by the authors. No attempt was made to measure the extent to which studies that were defined double blind kept their masked nature during the study.

Outcome measures and statistical analysis

Two main outcome measures were considered: respiratory tract infections and overall mortality. No restriction was made on type of infection considered and on diagnostic criteria for infection chosen by the trialists. Both tracheobronchitis and pneumonia were acceptable. Both primary (diagnosed within 48 hours after admission) and acquired (diagnosed after 48 hours after admission) infections were considered, even if we used data on acquired infections when information on both was available. Mortality was evaluated at hospital discharge, if this information was available, otherwise mortality in the intensive care unit was considered.

All patient records, for both aggregated and individual data, were converted to an agreed format and the following checks (performed by CL and SP) run on each dataset: simple checks of missing values; no duplicate patient records; treatment group assigned and survival status; range of prognostic variables; and checks for random allocation. For trials for which data on individual patients were available we constructed a plot of cumulative proportion of patients per arm versus time of randomisation for each study to check for major unbalances in the sequence of randomisation.

In the analysis of data on individual patients we classified patients into three diagnostic categories: medical, surgical, and trauma. For classification of severity we relied on the APACHE II score in most cases; in seven trials for which the SAPS score was reported,[24 32 35 37 39 41 45] we transformed it into APACHE II using the following algorithm: APACHE II=-1.24+1.484*(SAPS).[52] Patients were grouped into three mutually exclusive classes within groups defined by the main diagnostic categories (medical, surgical, trauma) according to severity of disease. APACHE II cut off points were chosen to define low or medium or high severity with reference to the expected mortality rate (<10%, 10-60%, >60%).[53]

In addition to odds ratios of each outcome in each trial, computed with the fixed effects model (Peto method),[54] we estimated the number of patients in intensive care who would need to be treated to prevent one infection and one death. The calculation was based on the median rates of infections and deaths in untreated controls and the common odds ratio for all trials.

We carried out two prespecified subgroup analyses on the basis of quality criteria within the above mentioned two main groups of trials: quality of randomisation procedures (blind versus open) and blinding of patients and doctors to allocated treatment (double blind versus unblind). For analyses on data on individual patients odds ratios, stratified by prognostic factor, were calculated with the fixed effects model.

Results

Information from 33 trials that between 1984 and 1996 enrolled a total of 5727 patients was the base for the aggregate data meta-analysis (table 2). Data on individual patients were obtained from 25/33 trials including 4343/5727 (76%) patients.

Respiratory tract infections

Evaluation from meta-analysis of aggregate data

Overall, results from 30 trials including 4898 patients were available for the analysis of the effects of different types of antibiotic prophylaxis on respiratory tract infections: 1184 patients developed one or more infections (S Jacobs and M Zuleika, personal communication).[19-26 28-36 37-45 47-50]

The prevalence of respiratory infections was 16% among treated patients and 36% among controls in trials that used a combination of topical plus systemic antibiotics and 18% and 28%, respectively, in trials that tested the effectiveness of topical prophylaxis alone. Overall, the odds ratio was lower than unity in all but two comparisons[44 49] and reached conventional significance (P<0.05) in 21/32 comparisons.

The results indicated a strong protective effect of the combination of topical and systemic treatment (odds ratio 0.35;95% confidence interval 0.29 to 0.41) (fig 1). A clear though less extreme protection was also seen when treatment effect was explored in trials that tested topical antibiotics (0.56; 0.46 to 0.68) (fig 2).

Fig 2 Meta-analysis of aggregate data. Effect of topical antibiotics as prophylaxis for respiratory tract infections in patients in intensive care units

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Table 3 Meta-analysis of data from individual patients. Effect of combination of topical and systemic antibiotics as prophylaxis for respiratory tract infections in patients in intensive care

APACHE II scores	No of studies	No treated	No of controls	Odds ratio (95% CI)
Medical patients				
0-14	10	10/67	23/76	0.37 (0.16 to 0.87)
15-29	10	14/155	53/180	0.28 (0.16 to 0.48)
≥30	10	7/54	12/52	0.57 (0.20 to 1.69)
Total		31/276	88/308	0.33 (0.22 to 0.51)
Surgical patients				
0-14	9	15/166	24/142	0.47 (0.23 to 0.94)
15-29	9	36/299	70/309	0.51 (0.33 to 0.78)
≥30	9	4/22	6/26	0.87 (0.21 to 3.64)
Total		55/487	100/477	0.51 (0.36 to 0.73)
Trauma patients				
0-14	11	54/269	116/294	0.40 (0.28 to 0.58)
15-29	12	59/258	108/249	0.37 (0.25 to 0.54)
≥30	12	5/13	4/10	0.07 (0.01 to 1.63)
Total		118/540	228/553	0.38 (0.29 to 0.50)
Overall		204/1303	476/1338	0.40 (0.33 to 0.49)

Table 4 Meta-analysis of data from individual patients. Effect of topical antibiotics as prophylaxis for respiratory tract infections in patients in intensive care

APACHE II scores	No of studies	No treated	No of controls	Odds ratio (95% CI)
Medical patients				

0-14	8	11/108	17/117	0.75 (0.34 to 1.67)
15-29	8	17/205	43/232	0.44 (0.25 to 0.77)
≥30	9	1/29	4/23	1.03 (0.06 to 16.69)
Total		29/342	64/372	0.54 (0.34 to 0.84)
Surgical patients				
0-14	8	8/48	13/57	0.52 (0.17 to 1.53)
15-29	9	15/64	17/63	0.84 (0.35 to 1.99)
≥30	9	3/6	0/4	12.18 (0.55 to 270.15)
Total		26/118	30/124	0.79 (0.41 to 1.53)
Trauma patients				
0-14	12	52/238	103/303	0.59 (0.40 to 0.88)
15-29	11	77/231	148/312	0.59 (0.41 to 0.85)
≥30	12	4/8	6/12	5.29 (0.31 to 89.62)
Total		133/477	257/627	0.60 (0.46 to 0.79)
Overall		188/937	351/1123	0.61 (0.49 to 0.75)

Table 5 Comparison of results of randomised controlled trials according to availability of data from individual patients for prophylaxis with topical and systemic antibiotics and topical antibiotics only

	Topical plus systemic		Topical alone	
End points and dataset used	**No of trials**	**Odds ratio (95% CI)**	**No of trials**	**Odds ratio (95% CI)**
Mortality				
Aggregate and individual data	12	0.86 (0.72 to 1.02)	13	1.03 (0.84 to 1.26)
Aggregate data only	3	0.61 (0.44 to 0.86)	4	0.93 (0.57 to 1.52)
Respiratory tract infection				
Aggregate and individual data	12	0.39 (0.32 to 0.47)	13	0.57 (0.47 to 0.70)
Aggregate data only	2	0.10 (0.05 to 0.21)	2	0.47 (0.19 to 1.13)

These results suggest that 5 (4 to 5) and 9 (7 to 13) patients would need to be treated to prevent one infection, depending on whether a combination of topical and systemic drugs or a topical antibiotic only is tested. This assumes the median values of 44% and 32% for baseline risk, respectively, as seen among control patients.

The effect of the quality of randomisation could meaningfully be explored only among trials that tested the relative effectiveness of topical antibiotic agents (given that all but two trials of the topical plus systemic group had blind randomisation): trials with blind randomisation showed a greater effect (0.51; 0.40 to 0.66) compared with those in which the procedure was open (0.66; 0.48 to 0.91). Results from double blind trials did not differ from those obtained in unblind studies.

Evaluation from meta-analysis of data from individual patients

The results from the 25 studies for which data were provided by the trialist are reported in tables 3 and 4 (S Jacobs and M Zuleika, personal communication).[20-24 28-35 37-42 45 47-50] Odds ratios and relative confidence intervals are presented within specific groups of diagnostic category and severity score. The effect of the treatment on infections is shown for both types of treatment protocols that is, topical plus systemic (0.40; 0.33 to 0.49) and topical alone (0.61; 0.49 to 0.75). The results seem more pronounced, however, in trials in which the combination was used.

The widespread belief that the treatment is more effective in patients with intermediate severity scores (that is, APACHE II score 15-29) and less effective among medical patients was not supported by the data from trials that tested the topical and systemic combination. The extent of the treatment effect was quite consistent across disease categories and severity groups. Data from trials that tested topical antibiotics are more difficult to interpret because of the small number of patients in the highest APACHE II category that is≥30.

Overall, these results did not differ substantially from those obtained by pooling data from trials for which data on individual patients were not available (table 5), suggesting that no bias was introduced by lack of data provided by study investigators.

Mortality

Evaluation from meta-analysis of aggregate data

A total of 1515 deaths occurred in the 33 trials with 5727 patients available for analysis (S Jacobs and M Zuleika, personal communication).[19-50] The mortality was 24% in treated patients and 30% in controls for trials that tested a combination of topical plus systemic antibiotics and 26% in control and treated patients for trials that tested the effectiveness of topical treatment. The odds ratio was lower than unity in 23/35 comparisons but reached significance in only two trials[27 31]; no trial suggested a significant harmful effect of antibiotic prophylaxis. Results indicate a significant reduction in mortality attributable to the use of a combination of topical and systemic treatment (0.80; 0.69 to 0.93) (fig 3). Twenty three patients (14 to 68) would need to be treated to prevent one death (if we assume a median baseline risk of 29% among control patients). No effect was seen when trials that tested topical antibiotics alone were analysed (1.01; 0.84 to 1.22) (fig 4).

While analyses by quality of randomisation did not affect the results, reduction in mortality among trials that tested a combination of topical and systemic antibiotics was greater in trials that used a double blind design (0.63; 0.48 to 0.83) compared with unblind studies (0.90; 0.74 to 1.08).

Fig 3 Meta-analysis of aggregate data. Effect of combination of topical and systemic antibiotics on mortality in patients in intensive care units

Evaluation from meta-analysis of data from individual patients

Results from 25 studies are reported in table 6 and 7 (S Jacobs and M Zuleika, personal communication).[20-24 28-35 37-42 45 47-50] Odds ratios with their relative confidence intervals are presented within specific groups of diagnostic categories and severity scores. Similarly to the results derived from the corresponding aggregate data analysis, a significant reduction in overall mortality was observed for trials that tested a combination of topical and systemic antibiotics (0.79; 0.65 to 0.9 7) but not from studies that tested topical drugs alone (1.02; 0.81 to 1.30). Treatment effect did not vary substantially by main diagnostic category.

Overall, these results did not differ substantially from those obtained by pooling data from trials for which individual patient data were available (table 5).

Discussion

Effectiveness of antibiotic prophylaxis

Since its introduction as a method designed to prevent infection in critically ill patients the effectiveness of antibiotic prophylaxis has remained controversial.5 The lack of standard protocols and insufficient numbers of patients have made it difficult to derive meaningful conclusions from individual randomised controlled trials. Despite initial enthusiasm after results from early uncontrolled studies and initial trials, antibiotic prophylaxis as tested in available trials is not widely used in intensive care units. The concern about the risk of long term emergence of antibiotic resistance and of increasing costs dominates in recent American documents based on expert opinions on prevention of infections such as the *Guidelines for Prevention* of *Nosocomial Pneumonia* recently published by the Centers for Disease Control and Prevention[55] and the consensus statement of the American Thoracic Society on *Hospital-Acquired Pneumonia in Adults.*[56] A conservative attitude in introducing a new treatment into practice is understandable as long as doubts exist about its efficacy. In fact studies on prevention of ventilator associated pneumonia in patients in intensive care units are complex because patients are heterogeneous, diagnosis of pneumonia is controversial, and outcome depends on many factors, Although the ability of antibiotic prophylaxis to reduce respiratory tract infections emerged with remarkable consistency across individual trials, the effect on mortality was significant in only two. It was never fully realised that this was

Table 6 Meta-analysis of data from individual patients. Effect of combination of prophylactic topical and systemic antibiotics on mortality in patients in intensive care

APACHE II score	No of studies	No treated	No of controls	Odds ratio (95% CI)
Medical patients				
0-14	10	16/67	15/76	1.45 (0.63 to 3.36)
15-29	10	57/155	77/180	0.80 (0.50 to 1.29)
≥30	10	26/54	26/52	0.72 (0.32 to 1.63)
Total		99/276	118/308	0.88 (0.61 to 1.27)
Surgical patients				
0-14	10	12/166	20/142	0.43 (0.21 to 0.92)
15-29	9	67/299	76/309	0.91 (0.61 to 1.34)
≥30	9	12/22	21/26	0.26 (0.06 to 1.20)
Total		91/487	117/477	0.73 (0.52 to 1.03)
Trauma patients				
0-14	11	26/268	35/294	0.81 (0.48 to 1.39)
15-29	12	57/258	65/249	0.76 (0.49 to 1.16)
≥30	12	8/13	5/10	0.95 (0.08 to 10.93)
Total		91/539	105/553	0.78 (0.56 to 1.09)
Overall		281/1302	340/1338	0.79 (0.65 to 0.97)

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Fig 4 Meta-analysis of aggregate data. Effect of topical antibiotics on mortality in patients in intensive care units.

probably because of the small sample sizes of individual studies and, possibly, the weak association between respiratory infections and mortality.

The meta-analysis reported here combines data across studies to estimate treatment effects with more precision than in a single study.[57] Moreover, for a large proportion of trials data on individual patients were available, thus allowing a more refined analysis.

Table 7 Meta-analysis of data from indidual patients. Effect of propylactic topical antibiotics on mortality in patients in intensive care

APACHE II score	No of studies	No treated	No of controls	Odds ratio (95% CI)
Medical patients				
0-14	8	18/108	19/117	0.99 (0.47 to 2.06)
15-29	6	77/205	77/232	1.08 (0.72 to 1.62)
≥30	9	15/29	13/23	1.09 (0.32 to 3.68)
Total		104/342	109/372	1.06 (0.75 to 1.49)
Surgical patients				
0-14	8	10/48	11/57	1.25 (0.44 to 3.53)
15-29	9	18/64	15/63	1.18 (0.52 to 2.70)
≥30	9	2/6	3/4	0.46 (0.04 to 5.27)
Total		30/118	29/124	1.13 (0.61 to 2.12)
Trauma Patients				
0-14	12	17/238	19/303	1.20 (0.59 to 2.46)
15-29	11	36/231	54/312	0.84 (0.52 to 1.34)
≥30	12	4/8	6/12	1.17 (0.10 to 13.26)
Total		57/477	79/627	0.94 (0.64 to 1.39)
Overall		191/937	217/1123	1.02 (0.81 to 1.30)

Compared with the five previously published meta-analyses we decided to analyse separately trials that tested a combination of topical and systemic antibiotics and those that tested topical antibiotics alone. Though there is no consensus on the best way to classify antibiotic prophylaxis regimens,[56] it seemed rational to analyse these two groups of trials separately without combining all trials together. Our results confirm that both of these methods of prophylaxis have a strong protective effect on infections with a more pronounces effect when patients are treated with the combination of topical plus systemic antibiotics. This effect was consistent for all subgroups of patients regardless of study design (blind or open randomisation, double blind or unblind studies). Overall, these results seem convincing even though it is acknowledged

that no diagnostic test or procedure is ideal for diagnosing respiratory infections in patients in intensive care units.

The important new finding from this meta-analysis is that for prophylactic regimens that combine topical and systemic antibiotics there is also a relevant reduction of overall mortality.

Given the enthusiastic collaboration provided by most investigators and the efforts to include unpublished studies, it is unlikely that we have missed any important trials conducted so far. Moreover, as nearly all trials did not show significant reduction in mortality

on their own, there is no good reason to believe that publication bias represents a major problem in this literature.

The inability to obtain data on individual patients from all trials is unlikely to have biased results of the meta-analysis of such data. As table 5 shows, results of trials for which we could not obtain information on individual patients were not substantially different from those with such data available. Further details on patients mix and treatments can be found in the version of this review available in the Cochrane Library.[58]

Insights from meta-analysis on data from individual patients

A methodological strength of this review is the availability of data from individual patients for a large number of trials. Firstly, this allowed a comprehensive quality check of the data, which, by and large, confirmed the validity of the aggregate analysis. Secondly, the availability of data on individual patients permitted the identification of subgroups more likely to benefit from treatment. There is a widespread belief among clinicians that some patients may respond more favourably to the treatment. For example, patients categorised according to their underlying conditions as surgical or trauma patients and those with medium severity of illness scores are expected to respond more favourably to antibiotic prophylaxis than those labelled as medical patients or with low or high severity scores. Our subgroup analyses, however, do not support this view. The data in tables 3, 4, and 6 suggest that when the treatment works there is no difference in the size of treatment effect of the combined prophylaxis regimens among medical, surgical, and trauma patients within corresponding severity of disease.

Even though findings from subgroup analyses should always be treated with great caution these results could be important as they challenge a commonly held view among clinicians and provide useful information to orient the design of future trials. Indeed our failure to detect differences by diagnostic group could be because of lack of statistical power within subgroups. With the studies now available, however, claims suggesting that surgical and trauma patients[59] and patients with high APACHE scores[60 61] have better outcomes do not seem well founded and cannot be accepted.

Implications for practice

This systematic review indicates that a protocol that uses a combination of topical and systemic antibiotics reduces both the occurrence of respiratory tract infections and overall mortality. The effect of this intervention expressed in terms of patients needed to be treated to prevent one infection and one death is substantial five and 23, respectively and compares favourably with several interventions largely used in clinical practice. Though 8/16 trials used an identical regiment, including polymyxin, tobramycin, and amphotericin as the topical combination and cefotaxime as the systemic component[19 21 24-26 28 29 50] this review does not allow a unique regimen to be recommended. The use of topical antibiotics alone, however, is not justified by available data.

Finally, it is important to bear in mind that given the lack of valid data no absolute conclusion can be drawn from this systematic review on the risk of antibiotic resistance. Future studies should look at this problem more carefully.

Implications for research

The number of trials examining antibiotic prophylaxis provides sufficient statistical power to detect a moderate but worthwhile effect of the treatment on mortality.[5] According to this systematic review a protocol of a combination of topical and systemic antibiotics should be the standard against which new treatments are tested.

This meta-analysis could be critised for the way trials have been grouped. We in fact assumed that the different drug combinations categorised as either topical plus systemic or topical only were equivalent. Although this may be inaccurate as it may obscure the fact that the effective digestive decontamination achieved by different regimens can vary[62-64] we did not envision a viable alternative and preferred to be consistent with the other published meta-analyses. On the other hand, even if results of all available trials are combined as has been done in other recent meta-analyses[6-8] the reduction in mortality is still significant (odds ratio 0.88; 95% confidence interval 0.78 to 0.98).

A logical next step for future trials would thus be the comparison of this protocol against a regimen of a systemic antibiotic agent only to see whether the topical component can be dropped. We have already identified six such trials[31 45-49] but the total number of patients so far enrolled (1056) is too small for us to be confident that the two treatments are really equally effective. If the hypothesis is therefore considered worth testing more and larger randomised controlled trials are warranted.

Trials of this kind, however, would not resolve the relevant issue of treatment induced resistance. To produce a satisfactory answer to this, studies with a different design would be necessary. Though a detailed discussion goes beyond the scope of this paper, studies in which the intensive care unit rather than the individual patient is the unit of randomisation and in which the occurrence of antibiotic resistance is monitored over a long period of time should be undertaken. One or more coordinated trials of this sort should be able to enroll a few thousands patients and should be designed in a pragmatic fashion concentrating on outcomes such as mortality, resistance, and costs. On the basis of our results it is not

clear whether enrollment in these trials should be limited to specific categories of patients or should be open to all patients in intensive care. Given the uncertainty on this issue that stems from our analysis, trials with less strict eligibility criteria would be preferable. The growing collaboration among intensivists in the European Union Biomed Programme could provide a framework for designing and carrying out efficient studies aimed at settling this important research question.

The steering committee comprised DJ Cook (McMaster University Faculty of Health Sciences, Ontario), J Carlet (Hospital Saint-Joseph, Paris), M Langer (Ospedale Maggiore Policlinico IRCCS, Milan), P Loirat (CMC FOCH Suresnes, Paris), and HFK Van Saene (University of Liverpool, Liverpool). The investiga-

Key messages

Over 40% of patients who need ventilation in intensive care develop respiratory tract infections and about 30% may die in the units

If the most effective antibiotic prophylaxis (that is, a protocol combining topical and systemic antibiotics) is used the incidence of respiratory tract infections can be reduced by 65% and total mortality by 20%

A regimen of topical antibiotics alone reduces respiratory tract infections but does not influence survival

The concern that widespread antibiotic use may lead to resistance cannot be confirmed or ruled out by this review. Trials with different design are probably warranted to handle this question

This important effect of antibiotic prophylaxis with a combination of topical and systemic antibiotics on survival should be considered by intensivists when treatment policies are designed.

tors who were coauthors of this paper and provided data for meta-analysis of data from individual patients were SJA Aerdts (Sophia Hospital, Zwolle, the Netherlands); P. Blair, BJ Rowlands, H Webb, and K Lowry (Royal Victoria Hospital, Belfast); JP Bowland, D Sadler, A Stewart, and J Pollock (Health Science Center Charlestone, West Virginia University); FR Cockerill and RI Thomson (Mayo Clinic, Rochester, Minnesota); M Ferrer and A Torres (Servei de Peneumologia, Hospital Clinic, Barcelona); RG Finch, P Thomlinson, and G Rocker (Nottingham City Hospital, Nottingham); H Gastinne (on behalf of the French Study Group on Selective Decontamination of the Digestive Tract); B Georges (Hôpital de Rangueil, Toulouse); JMJ Hammond and PD Potgieter (Groote Schuur Hospital, Cape Town); S Jacobs and M Zuleika (Riyadh Armed Forces Hospital, Riyadh); AM Korinek (Hôpital Pitié-Salpêtrière, Paris); AN Laggner (Vienna General Hospital, Vienna); W Lingnau (Leopold-Franzens-Universitat Innsbruck, Innsbruck); A Martinez-Pellus and J Rodriguez-Roldan (General Hospital, Murcia); M Palomar (Hospital Vall d Hebron, Barcelona); J Pugin and P Suter (University Hospital, Geneva); C Martin, B Quinio, and J Albanese (Hôpital Nord, Marseilles); LA Rocha (Hospital Juan Canalejo, La Coruna); M Sanchez-Garcia (Hospital PPE Asturias, Alcala de Henares); CP Stoutenbeek (Academisch Ziekenhuis, Universiteit van Amsterdam, Amsterdam); C Ulrich and JE Harinck-De Weerd (Westeinde Hospital, The Hague); J Verhaegen and C Verwaest (University Hospital, Louvain); R Winter (Queen s Medical Centre University Hospital, Nottingham).

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Contributors: RD A discussed core ideas of the project, participated in the design of the protocol for the meta-analysis of data from individual patients, had the main responsibility for data analysis and interpretation, and participated in writing the paper. SP discussed core ideas of the project, participated in the design of the protocol for the meta-analysis of data from individual patients, organised data collection, maintained contacts with the trialists checking data validity and accuracy, contributed to the interpretation of results, and participated in writing the paper. CL participated in the design of the protocol for the meta-analysis of data from individual patients, organised data collection, maintained contacts with the trialists checking data validity and accuracy, and contributed to the interpretation of results. VT discussed core ideas of the project, participated in the design of the protocol for the meta-analysis of data from individual patients, contributed to data analysis, and provided, useful suggestions to the various drafts of the paper. AT designed and prepared the software for data management and helped with data analysis. AL initiated and

coordinated the earlier phases of this research, discussed core ideas of the project, participated in the design of the protocol for the meta-analysis of data from individual patients, contributed to data analysis and interpretation, and had the main responsibility for writing the paper.

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Conflict of Interest: None.

APPENDIX

Studies excluded from this meta-analysis

Author	Reason for exclusion
Bion et al[9]	Included selected population of patients undergoing liver transplant
Flaherty et al[10]	Included selected population of cardiosurgical patients
Hunefeldt et al[11]	Not properly randomised (that is, enrollment of consecutive patients)
Lipman et al[12]	Not properly randomised (that is, enrollment of consecutive patients)
Luiten et al[13]	Included selected population of patients with pancretitis characterised by low percentage of admissions to intensive care unit randomised (that is, enrollment of consecutive patients)
Martinez-Pellus et al[14]	Included selected population of cardiosurgical patients
Rolando et al[15]	Included selected population of patients with acute hepatic failure
Scharey et al[16]	Included selected population of patients undergoing gastric surgery and characterised by low percentage of admissions to intensive care unit
Smith et al[17]	Included selected population of paediatric liver transplanted patients
Tetteroo et al[18]	Included selected population of patients undergoing oesophageal resection and characterised by short length of stay in intensive care unit

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Endpiece

Alternative definitions

Ambition: An overmastering desire to be villified by enemies while living and made ridiculous by friends when dead.

Amborse Bierce, *The Cynic s Word Book* (1906),

subsequently titled *The Devil s Dictionary*

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A CONTROLLED TRIAL IN INTENSIVE CARE UNITS OF SELECTIVE DECONTAMINATION OF THE DIGESTIVE TRACT WITH NONABSORBABLE ANTIBIOTICS

H. Gastinne, M.D., M. Wolff, M.D., F. Delatour, M.D., F. Faurisson, M.D., and S. Chevret, M.D.,

for the French Study Group on Selective Decontamination of the Digestive Tract*

Abstract *Background.* Selective decontamination of the digestive tract with topical nonabsorbable antibiotics has been reported to prevent nosocomial infections in patients receiving mechanical ventilation, and the procedure is used widely in Europe. However, it is unclear whether selective decontamination improves survival.

Methods. We conducted a randomized, double-blind multicenter study in which 445 patients receiving mechanical ventilation in 15 intensive care units were given either prophylactic nonabsorbable antibiotics (n = 220) or a placebo (n = 225). Topical antibiotics (tobramycin, colistin sulfate, and amphotericin B) or placebo was administered through a nasogastric tube and applied to the oropharynx throughout the period of ventilation. The main end points were the mortality rate in the intensive care unit and the mortality rate within 60 days of randomization.

Results. A total of 142 patients died in the intensive care unit: 75 (34 percent) in the treatment group and 67 (30 percent) in the placebo group (P = 0.37). Mortality within 60 days of randomization was similar in the two groups (P = 0.40), even after adjustment for factors that were either unbalanced or individually predictive of survival in the two groups (P = 0.70). Pneumonia developed in 59 patients (13 percent) in the intensive care unit within 30 days of enrollment in the study (33 in the placebo group and 26 in the treatment group, (P = 0.42). Pneumonia acquired in the intensive care unit and due to gram-negative bacilli was less frequent (P = 0.01) in the treatment group than in the placebo group. The total charges for antibiotics were 2.2 times higher in the treatment group.

Conclusions. Selective decontamination of the digestive tract does not improve survival among patients receiving mechanical ventilation in the intensive care unit, although it substantially increases the cost of their care. (N Engl J Med 1992;326:594-9.)

INFECTIONS acquired in the intensive care unit are a major cause of death in hospitalized patients. Infection is also the main cause of multiple-organ failure, which usually ends in death.[1,2] Recent reports have suggested that selective decontamination of the digestive tract can reduce the incidence of nosocomial infections in patients in the intensive care unit. The rationale for this approach is the well-documented observation that colonization of the gastrointestinal tract by gram-negative bacilli frequently occurs before the onset of infection.[3-5] Decontamination could also help prevent the failure of multiple organ systems by reducing the bacterial load in the gastrointestinal tract and the transfer of endotoxin to the bloodstream.[6] The most impressive results with decontamination have been achieved in patients who received mechanical ventilation after trauma; in these patients a combination of topical antibiotics and a short course of systemic antibiotics significantly reduced the incidence of nosocomial respiratory tract infections.[7] Several other investigators have reported similar beneficial effects with[8-16] and without[17-20] the use of additional systemic antibiotics. The inferences to be drawn from these data are controversial for a number of reasons: the treatment regimens differed from one study to another, and all but two trials[18,19] were not blinded. All were conducted in single centers, and some included only a small number of patients. None of the studies explicitly demonstrated a beneficial effect on a major index of outcome, such as mortality. Despite this, the prophylactic use of nonabsorbable antibiotics has gained wide acceptance in Europe. This trial was undertaken to study the efficacy of selective decontamination of the digestive tract with topical antibiotics in patients receiving mechanical ventilation.

Address reprint requests to Dr. Gastinne at the Service de Réanimation, Hôpital Universitaire Dupuytren, 2 ave. Alexis-Carrel, 87042 Limoges CEDEX, France.

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*The French Study Group on Selective Decontamination of the Digestive Tract included the following: C. Richard, M.D., J. Depret, M.D., A.M. Taburet, Ph.D., J.M. Boles, M.D., B. Garo, M.D., A. Primualt, Ph.D., J.P. Bedos, M.D., A. Certain, Ph.D., D. Dreyfuss, M.D., K. Djedaini, M.D., C. Giraud, Ph.D., R. Boiteau, M.D., A. Tenaillon, M.D., M. Willoquet, Ph.D., B. Clair, M.D., P. Moine, M.D., I. Jolivet, Ph.D., F.P. Savy, M.D., F. Carron, Ph.D., C. Martin, M.D., L. Papazian, M.D., C. Penot-Ragon, Ph.D., P. Damas, M.D., M. Delporte, Ph.D., D. Villers, M.D., C. Bonin, M.D., F. Vincent-Ballereau, Ph.D., C. Camus, M.D., Y. Letulzo, M.D., M. Javaudin, Ph.D., B. Guidet, M.D., G. Offenstadt, M.D., A. Daguenel, Ph.D., F. Fraisse, M.D., G. Moret, M.D., M. Talbert, Ph.D., B. Misset, M.D., J. Carlet, M.D., J. Huchet, Ph.D., G. Nitenberg, M.D., B. Leclercq, M.D., and J. Alarcon, Ph.D.

METHODS

Study Design

This was a prospective, randomized, double-blind, placebo-controlled, multicenter study of topical antibiotics in patients receiving mechanical ventilation. The main end points were the overall survival in the intensive care unit and the overall survival within 60 days of randomization. We also studied the acquisition of pulmonary infections in the intensive care unit by day 30 and the types of pathogens involved, the duration of mechanical ventilation, the length of stay in the intensive care unit, and the charges for antibiotic treatment. Patients with conditions in which the probability of survival and the duration of mechanical ventilation are strongly related to status on admission were excluded.

Study Organization

Fifteen medical intensive care units in 15 referral hospitals participated in the study. All aspects of the protocol were approved by two institutional review committees on human investigation. Written informed consent was obtained from the patients or their closest relatives. The study was monitored by a coordinating center

(Institut National de la Santé et de la Recherche Médicale U13, Paris).

Eligibility Criteria

Patients older than 15 years who required mechanical ventilation were eligible for the trial provided that intubation was performed no more than 48 hours before randomization. Patients were excluded from the study for any of the following reasons: mechanical ventilation was discontinued less than 24 hours after a scheduled operation, mechanical ventilation was begun after an overdose of sedative drugs or alcohol, there was neutropenia (<500 polymorphonuclear cells per cubic millimeter), the simplified acute physiologic score[21] was more than 24 or the Glasgow coma score was less than 4, a decision was made that only palliative treatment was to be used, or there was chronic degenerative central nervous system disease or a spinal-cord injury above the level of C-4. Patients were also excluded if they had chronic or acute severe enteroparhy, were pregnant, were participating in another ongoing clinical trial, or refused to give written informed consent.

Randomization and Treatment Regimens

Within 48 hours of the start of mechanical ventilation, patients were assigned to receive either topical antibiotics or placebo, according to a randomized list of consecutive treatment assignments. Randomization was performed separately in each center. Identical drug and placebo capsules were manufactured by the Pharmacie Centrale des Hôpitaux de Paris and dispensed by each hospital s pharmacist. The oropharyngeal cavity was carefully cleaned with isotonic saline before the antibiotic or placebo was applied, Four times daily, 3 g of a sticky gel containing the placebo (nonabsorbable calcium salt) or a combination of colistin sulfate, tobramycin, and amphotericin B, each at a concentration of 2 percent, was applied to the oropharyngeal cavity. At the same time, the solutions of antibiotics (or placebo) were administered through a nasogastric tube at doses of 100 mg of colistin sulfate, 80 mg of tobramycin, and 100 mg of amphotericin B. One milliliter of the suspension was injected into each nostril. Topical antibiotics and placebo were administered throughout the period of ventilation. Gels and suspensions were made from the powders contained in the capsules. To ensure the blinded nature of the observations, antibiotics and placebo powders were made in a variety of colors. Samples for bacteriologic analysis were taken only when infection was suspected. Serum levels of tobramycin were measured twice a week to avoid renal toxicity; the results were revealed by the laboratory only if levels exceeded 2.5 mmol per liter, in which case the treatment was discontinued. Prophylactic systemic antibiotics were given only if they were required for surgical procedures.

Data Collection and Definitions

The severity of the acute illness on admission to the intensive care unit was assessed by means of the simplified acute physiologic score.[21] Acute organ-system failure was diagnosed according to the definition of Knaus et al. [22] at the time of enrollment in the study and every seven days thereafter. Follow-up continued until patients were sent home from the hospital. Patients who were sent home were considered to be alive on day 60 after enrollment in the study. The type and dosage of antibiotic therapy administered were scrupulously recorded throughout each patient s stay in the intensive care unit, and treatment was subdivided into that for respiratory tract infections acquired in the intensive care unit and that given for other infections. The charges for antibiotics administered to each patient were calculated.

Respiratory tract infection diagnosed within 48 hours of admission to the intensive care unit were classified as primary. All subsequent episodes were classified as having been acquired in the intensive care unit. Pneumonia was defined by the presence of all of the following: purulent tracheal aspirate, fever (temperature, (>38.5°C), and peripheral leukocytosis (>10,000 leukocytes per cubic millimeter) associated with a new and persistent infiltrate on the chest film. A fiberoptic bronchoscopy, with specimens obtained by brushing, was recommended but was not mandatory. Bacteriologic documentation was not required for the diagnosis of nosocomial pneumonia because the presence of antibiotics in the bronchial tree can interfere with the accuracy of culture.[17,23] Tracheobronchitis was defined by the presence of clinical signs and the absence of pulmonary infiltrates on the chest film.

Statistical Analysis

The sample size (600 patients) was calculated to allow the detection of a 25 percent reduction in mortality among the treated patients on day 60, assuming a mortality rate of 40 percent in the placebo group, an alpha error of 0.05, and a beta error of 0.20. An interim analysis was planned after the treatment of 200 patients and after the treatment of 400 patients. These analyses were performed by the coordinating center, and the investigators were unaware of the results. Enrollment was closed after the second interim analysis because the goals of the study had been achieved. The analysis was made on an intention-to-treat basis. Time-censored criteria were estimated with the Kaplan-Meier method and compared with the log-rank test.[24] The comparative terms of overall survival and the length of time to the onset of nosocomial pneumonia were adjusted with the semiparametric Cox model.[25] The duration of mechanical ventilation was analyzed, and the patients who died were censored.

Continuous variables were compared with the nonparametric Mann-Whitney test. Qualitative variables were compared with the chi-square test, with correction for continuity when appropriate. All tests of significance were two-tailed. A P value of 0.05 or less was considered to indicate statistical significance.

RESULTS

Recruitment

Between February 10 and June 30, 1990, 2703 patients were admitted to the 15 participating intensive care units, and 1437 (53 percent) of these patients required mechanical ventilation. Of the 1437 patients, 966 did not meet the entry criteria. The main reasons for exclusion were withdrawal of mechanical ventilation less than 24 hours after a scheduled operation (29 percent), a need for mechanical ventilation because of sedative or alcohol overdose (26 percent), a simplified acute physiologic score of more than 24 or a Glasgow coma score of less than 4 (16 percent), initiation of mechanical ventilation more than 48 hours before enrollment (11 percent), or the presence of neutropenia (4 percent). In addition, 26 eligible patients were not randomized for the following reasons: 7 died before randomization, 7 were unable to receive oropharyngeal or gastric antibiotics, and 12 were not enrolled within 48 hours of the initiation of mechanical ventilation. When recruitment was complete, a total of 445 patients had been randomly assigned to one of the two groups 225 to the placebo group and 220 to the topical-decontamination group (treatment group).

Characteristics of the Patients

The demographic and base-line characteristics of the 445 patients are shown in Table 1. There was a higher proportion of males in the treatment group. The two groups were comparable in terms of the number and types of underlying diseases and diag-

nostic categories on admission. The simplified acute physiologic score was higher in the patients assigned to receive prophylactic nonabsorbable antibiotics, and more patients in this group had failure of more than one organ system at enrollment. Fewer patients in the treatment group than in the placebo group had received one or more systemic antibiotics before randomization. The two groups were similar with respect to adjunctive treatment and prophylaxis for stress ulcers during the stay in the intensive care unit (Table 1).

Discontinuation and Safety of Treatment

Topical treatment had to be discontinued before weaning from mechanical ventilation in 31 patients (15 receiving placebo and 16 receiving nonabsorbable antibiotics). In 28 cases, this was because of discomfort due to the oropharyngeal gel. In the three other patients, all of whom had renal impairment, treatment with antibiotics was interrupted because serum levels of tobramycin exceeded 2.5 mmol per liter. The average (±SD) length of treatment was 11.7±12.2 days in the placebo group and 10.5±8.2 days in the treatment group.

Table 1. Characteristics of the 445 Study Patients in the Two Groups.*

CHARACTERISTIC	PLACEBO (N = 225)	TOPICAL DECONTAMINATION (N = 220)
Base line		
Age	53.9±18.4	55.7±18.6
No. of males	140 (62)	156 (71)
Underlying disease		
COPD	53 (24)	52 (24)
Diabetes	8 (3.5)	11 (5)
Chronic liver disease	5 (2)	10 (4.5)
Cancer	17 (8)	25 (11)
HIV infection	19 (8)	19 (9)
Reason for admission		
Medical	161 (71.5)	159 (72.5)
Sepsis	59 (26)	62 (28)
CRF	36 (16)	28 (13)
Heart failure	10 (4.5)	17 (8)
Neurologic conditions	9 (4)	3 (1.5)
Miscellaneous	47 (21)	49 (22)
Trauma	35 (15.5)	32 (14.5)
Postoperative recovery	29 (13)	28 (13)
SAPS	13±4	14±4
Glasgow coma score	11.8±3.6	11.6±3.7
Organ-system failure		
1 organ	178 (79)	155 (71)§
2 organs	40 (18)	56 (25)
3 organs	7 (3)	9 (4)
Impaired consciousness before intubation	87 (39)	80 (36)
Referral from other wards	98 (44)	98 (45)
Antibiotic treatment	165 (73)	144 (65)
Adjunctive treatment		
Sedatives	110 (49)	120 (54)
Muscle relaxants > 24 hr	29 (13)	34 (15.5)
Steroids	32 (14)	30 (13.5)
Prophylaxis for stress ulcer		
Sucralfate	95 (42)	98 (44.5)
Histamine H_2-blockers	29 (13)	29 (13)
Antacids	4 (2)	6 (3)
None	97 (43)	87 (39.5)

* Plus-minus values are means ±SD. Values in parentheses are percentages. COPD denotes chronic obstructive pulmonary disease. HIV human immunodeficiency virus. CRF chronic respiratory failure, and SAPS simplified acute physiologic score.

P = 0.04.

P = 0.03.

§P = 0.02.

Figure 1. Overall Survival in the Two Groups.

A comparison of overall survival during the 60 days after randomization showed no significant differences in survival between the 225 patients who received placebo and the 220 patients who received prophylactic nonabsorbable antibiotics (P = 0.40 by two-sided log-rank test). After adjustment for factors predictive of mortality (Cox model), the risk of death was 1.06 times higher in the placebo group than in the treatment group (P = 0.70).

Survival

Of the 445 patients, 170 died in the hospital: 88 in the treatment group and 82 in the placebo group. One hundred forty-two of these deaths occurred in the intensive care unit: 75 in the treatment group and 67 in the placebo group (P = 0.37 by the chi-square test). Forty-one patients were discharged from the hospital more than 60 days after entering the study. Two hundred thirty-four patients were discharged within 60 days of entering the study: 104 in the treatment group and 130 in the placebo group. One hundred fifty-eight deaths occurred within 60 days of enrollment: 82 in the treatment group and 76 in the placebo group (P = 0.40 by the log-rank test) (Fig. 1). The 15-day and 30-day survival rates were 80 percent and 74 percent, respectively, in the placebo group and 76 percent and 66 percent in the treatment group. The estimated risk of death was 1.14 times higher in the treatment group (95 percent confidence interval, 0.87 to 1.67). The comparison of survival in the groups was adjusted for 13 base-line variables that were either unbalanced between the two groups or individually predictive of survival (Table 2). The variables at the time of admission that were predictive of survival were age, the number of underlying diseases, admission from other wards, the simplified acute physiologic score, the number of organ-system failures, and the presence of infection with the human immunodeficiency virus, cancer, trauma, chronic respiratory failure, sepsis, and pneumonia. The adjusted comparison gave similar overall survival estimates in the two groups (P = 0.70 by the log-rank test), with a risk of death

Table 2. Prognostic Value of Several Characteristics Determined at Admission.*

Variable	All Patients (N = 445)	Patients Dying within 60 Days of Enrollment (N = 158)	P Value
Age ≥ 50 yr	279	115	0.002
Male sex	296	103	0.69
Referral from other wards	199	52	0.005
Reason for admission			
Recovery from unscheduled surgery	45	19	0.32
Recovery from scheduled surgery	13	3	0.32
Trauma	67	9	0.0002
Medical			
Sepsis	121	56	0.005
CRF	64	16	0.04
Heart failure	27	8	0.66
Neurologic conditions	12	3	0.44
Pneumonia	110	49	0.02
≥1 underlying diseases	208	92	0.0006
HIV infection	38	21	0.01
Cancer	42	21	0.02
SAPS ≥13	215	96	<0.0001
Failure of > 1 organ system	112	69	<0.0001
Impaired consciousness	167	58	0.85
Antibiotic treatment	309	117	0.13
Topical decontamination	220	82	0.40
Placebo	225	76	

* CRF denotes chronic respiratory failure. HIV human immunodeficiency virus, and SAPS simplified acute physiologic score.

The P values refer to the differences in survival between the patients with the relevant characteristic and the rest of the population.

1.06 times higher in the placebo group (95 percent confidence interval, 0.72 to 1.42).

Organ-System Failure

The number of organ-system failures that occurred in the intensive care unit was calculated each week from entry into the study until discharge or death. This number did not change between entry and death for 118 of the 142 patients who died in the intensive care unit (60 in the control group and 58 in the treatment group); it decreased for 2 patients in each group and increased for 5 patients in the placebo group and 15 in the treatment group.

Figure 2. Comparison of the Length of Time to the Occurrence of Pneumonia Acquired in the Intensive Care Unit during the First 30 Days after Randomization in the 225 Patients Who Received Placebo and the 220 Patients Who Received Prophylactic Non-absorbable Antibiotics.

There was no significant difference between groups (P = 0.42 by two-sided log-rank test).

Respiratory Tract Infection

Primary pneumonia occurred in 14 patients (9 in the placebo group and 5 in the treatment group; P = 0.30 by the chi-square test). Pneumonia developed within 30 days of enrollment in 59 of the 445 patients (13 percent; 33 in the placebo group and 26 in the decontamination group; P = 0.42 by the two-sided log-rank test) (Fig. 2). The Kaplan-Meier estimates at 15 days were 8.2 ± 1.97 percent (mean ± SE; the standard error was estimated with Greenwood s formula) in the treatment group as compared with 12.7 ± 2.3 percent in the placebo group. The comparison of the time to the occurrence of pneumonia was also adjusted from seven base-line variables that were unequal in the two groups or predictive at the 10 percent level of the occurrence of pneumonia; the latter included the presence of underlying disease, the need for antibiotic therapy, and admission for trauma. The adjustment for these variables did not change the estimated risk of pneumonia significantly (P = 0.32 by the log-rank test). The causative organisms were isolated from specimens obtained by bronchial brushing during bronchoscopy in 33 of the 59 patients whose first episode of pneumonia occurred in the intensive care unit. In a further 21 cases, the pathogens were isolated from either bronchial secretions obtained with a distally wedged catheter (n = 16) or tracheal aspirates (n = 5). No pathogen was isolated in the remaining five patients. Gram-negative bacilli were significantly less common in patients receiving prophylactic nonabsorbable antibiotics than in those receiving placebo (P = 0.01 by the chi-square test). However, a trend toward an increase in the rate of staphylococcal pneumonia was observed in the treatment group (P = 0.06 by the chi-square test) (Table 3). Five patients in the placebo group had a second episode of pneumonia in the intensive care unit, and all cases were due to gram-negative bacilli. Nine other patients (six in the placebo group and three in the treatment group) received antibiotics for tracheobronchitis.

Duration of Mechanical Ventilation and Stay in the Intensive Care Unit

A Kaplan-Meier estimate of the duration of mechanical ventilation revealed no difference between the two groups (P = 0.70 by the log-rank test). The mean length of stay in the intensive care unit was also similar in the groups: 19±16 days in the placebo group as compared with 18±19 days in the treatment group.

Charges for Antibiotic Treatment

The daily charge for the antibiotics used for selective decontamination of the digestive tract was $66.50

Table 3. Causes of the First Episode of Pneumonia Acquired in the Intensive Care Unit in the Two Groups.

Pathogen	Placebo (N = 225)	Topical Decontamination (N = 220)	P Value
		number (percent)	
Indigenous flora*	4	3	
Gram-negative bacilli	16	5	0.01
Staphylococci			0.06
Methicillin-resistant	2	6	
Methicillin-susceptible	4	9	
Gram-negative bacilli + staphylococci	4	1	
Not isolated	3	2	
Total	33(15)	26(12)	0.50

* **Streptococci, *Streptococcus pneumoniae,* and *Hoemophilus influenzae.***
Excludes *H. influenzae.*
Methicillin-susceptible and methicillin-resistant staphylococci.

per patient (according to information provided by the Pharmacie Centrale des Hôpitaux de Paris, and assuming a conversion rate of 5.5 French francs to the U.S. dollar), and the mean total charge (±SD) per patient was $694 ±544. There was no significant difference between the two groups in the mean total charge for systemic antibiotics during the stay in the intensive care unit ($577 ±1,051 in the placebo group and $593 ±1,015 in the treatment group). The mean charge per patient for the systemic antibiotics used to treat all episodes of respiratory tract infections acquired in the intensive care unit (44 in the placebo group and 29 in the treatment group) was higher in the placebo group ($158 ± 691 vs. $53 ± 202), but the difference was not significant (P = 0.21). The mean total charge for antibiotics (topical and systemic) was 2.2 times higher in the treatment group than in the placebo group ($1,287 ± 1,368 vs. $577 ± 1,051; P<0.001).

DISCUSSION

Selective decontamination of the digestive tract with oral nonabsorbable antibiotics has been widely used to prevent infection in patients with neutropenia.[26] Stoutenbeek et al.[7] reported that the use of such a regimen in patients in the intensive care unit produced a sixfold reduction in the incidence of nosocomial infections in two successive groups of patients with trauma. Numerous investigators have confirmed this beneficial effect on nosocomial infection rates.[8-20] However, the results of controlled trials have been much less consistent with regard to the mortality rate; only one study has shown a significant improvement in survival.[13] Although infection-related deaths were examined separately in three trials and found to be significantly reduced in the group receiving prophylactic nonabsorbable antibiotics, none of these studies were blinded and the authors did not list their selection criteria.[9,13,17] Similarly, in a large study Ledingham et al. reported improved survival among a subgroup of 25 patients with trauma,[8] whereas Godard et al.[18] found that the mortality rate was lower in treated patients with disease-severity scores in the middle range. These results were, however, obtained in groups determined retrospectively, thus precluding any assignment of statistical significance. The results of our study, which were adjusted to avoid the possibility of bias due to differences in prognostic factors, showed similar overall mortality rates in the treatment and placebo groups, with no significant differences in any specific subgroup. In previous studies, a large proportion of patients were referred after trauma or surgical procedures, whereas most (72 percent) of our patients were admitted for preexisting conditions. The presence of underlying disease and the reason for admission to the intensive care unit may have had a great influence on outcome. Thus, our findings do not completely rule out the possible efficacy of decontamination of the gut in patients referred after trauma or surgery.

Prognosis was recently found to be strongly related to the number of organ-system failures.[27] The failure of multiple organs may involve the transfer of intestinal endotoxin to the bloodstream.[6] Selective decontamination of the digestive tract may reduce the production of endotoxin by diminishing gut colonization by gram-negative bacilli. Van Saene et al. reduced the pool of fecal endotoxin in healthy volunteers undergoing decontamination of the gut.[28] However, in our trial, topical decontamination did not reduce the occurrence of multiple-organ failures.

Pneumonia acquired in the intensive care unit is another important cause of death[29-31]; the incidence of pneumonia in our placebo group was low (15 percent), and the mortality rates were similar in the two groups. The rate of nosocomial pneumonia varies depending on the type of hospital unit studied and the presence of underlying disease.[29] Differences in diagnostic criteria for nosocomial pneumonia may also explain why its rate in most decontamination trials was higher (>40 percent) than in our trial.[7,9,11,16,17] Diagnosis was blinded in our study and most often included the results of cultures of specimens obtained by bronchial brushing or catheterization. Two recent studies that also used protected specimens obtained by bronchial brushing[18,30] reported rates of pneumonia in patients receiving mechanical ventilation in the intensive care unit that were similar to the rate that we observed. Pneumonia should not be diagnosed solely on the basis of culture results, since the presence of antibiotics in the bronchial tree after decontamination[17,23] may lead to an underestimation of the actual incidence of disease.

Although the overall incidence of pneumonia acquired in the intensive care unit was similar in the treatment and placebo groups, the number of respiratory tract infections caused by gram-negative bacilli was lower in the treated patients. In contrast, staphylococci were isolated in a higher proportion (60 per-

cent) of patients with pneumonia in the treatment group, a finding that is in keeping with reports of increased oropharyngeal colonization by staphylococci after selective decontamination of the digestive tract.[10-12]

Although selective decontamination of the digestive tract originally included treatment with intravenous cefotaxime to prevent primary pneumonia due to indigenous flora,[7] more recent studies[17-20] have reported beneficial effects with the use of the topical regimen alone. Few cases of primary pneumonia occurred in our trial, and 72 percent of the patients were receiving systemic antibiotics at the time of randomization, so the addition of cefotaxime would probably not have substantially changed our results.

One might expect that lowering the incidence of sepsis would reduce the need for curative systemic antibiotic treatment, but there was no substantial difference between the two groups in terms of the total charges for systemic antibiotics during the stay in the intensive care unit. On the contrary, topical decontamination was substantially more expensive. The antibiotics used to treat respiratory tract infections acquired in the intensive care unit in the patients in the treatment group cost less than those used in the placebo group, but this reduction was not significant. In two nonblinded trials, the same amounts of systemic antibiotics were administered to the treatment and control groups[9,13]; in the trial by Ledingham et al., there was a 20 percent reduction in the use of systemic agents, including cefotaxime, in the treatment group as compared with the placebo group.[8]

We conclude that although selective decontamination of the digestive tract with topical antibiotics can prevent pneumonia due to gram-negative bacilli in the intensive care unit, the overall benefit is limited and is achieved at an increase in cost. The results of this study do not support the routine use of topical antibiotics for selective decontamination in patients in an intensive care unit.

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INFLUENCE OF COMBINED INTRAVENOUS AND TOPICAL ANTIBIOTIC PROPHYLAXIS ON THE INCIDENCE OF INFECTIONS, ORGAN DYSFUNCTIONS, AND MORTALITY IN CRITICALLY ILL SURGICAL PATIENTS

A Prospective, Stratified, Randomized, Double-Blind, Placebo-controlled Clinical Trial

Wolfgang A. Krueger, Franz-Peter Lenhart, Gertraud Neeser, Gotthart Ruckdeschel, Heidi Schreckhase, Hans-Joachim Eissner, Helmuth Forst, Joachim Eckart, Klaus Peter, and Klaus E. Unertl

Department of Anesthesiology and Intensive Care Medicine, Tübingen University Hospital, Tübingen; Institute of Anesthesiology, Klinikum Grosshadern, Munich University Hospital, Munich; Department of Anesthesiology and Intensive Care Medicine, Zentralklinikum, Augsburg; Max-von-Pettenkofer Institute of Hygiene and Medical Microbiology, University of Munich; and Department of Medical Informatics, Biometry, and Epidemiology, University of Munich, Munich, Germany

We prospectively studied the impact of an antibiotic prophylaxis regimen on the incidence of infections, organ dysfunctions, and mortality in a predominantly surgical and trauma intensive care unit (ICU) population. A total of 546 patients were enrolled and stratified according to Acute Physiology and Chronic Health Evaluation (APACHE)-II scores. They were then randomized to receive either 2 × 400 mg of intravenous ciprofloxacin for 4 days, together with a mixture of topical gentamicin and polymyxin applied to the nostrils, mouth, and stomach throughout their ICU stay or to receive intravenous and topical placebo. When receiving prophlaxis, significantly fewer patients acquired infections ($p = 0.001$, risk ratio [RR], 0.477; 95% confidence interval [CI], 0.367-0.620), especially pneumonias (6 versus 29, $p = 0.007$), other lower respiratory tract infections (39 versus 70, $p = 0.007$), bloodstream infections (14 versus 36, $p = 0.007$), or urinary tract infections (36 versus 60, $p = 0.042$). Also, significantly fewer patients acquired severe organ dysfunctions (63 versus 96 patients, $p = 0.0051$; RR, 0.636; 95% CI, 0.463-0.874), especially renal dysfunctions (17 versus 38; $p = 0.018$). Within 5 days after admission, 24 patients died in each group, whereas 28 patients receiving prophylaxis and 51 receiving placebo died in the ICU thereafter ($p = 0.0589$; RR, 0.640; 95% CI, 0.402-1.017). The overall ICU mortality was not statistically different (52 versus 75 fatalities), but the mortality was significantly reduced for 237 patients of the midrange stratum with APACHE-II scores of 20-29 on admission (20 versus 38 fatalities, $p = 0.0147$; RR, 0.508; 95% CI, 0.295-0.875); there was still a favorable trend after 1 year (51 versus 60 fatalities; $p = 0.0844$; RR, 0.720; 95% CI, 0.496-1.046). Surveillance cultures from tracheobronchial, oropharyngeal, and gastric secretoins and from rectal swabs did not show any evidence for the selection of resistant microorganisms in the patients receiving prophylaxis.

Keywords: ICU infection prevention; nosocomial pneumonia; multiple organ failure; mortality; selective digestive decontamination; antibiotic resistance

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Correspondence and requests for reprints should be addressed to Klaus E. Unertl, M.D., Department of Anesthesiology and Intensive Care Medicine, Tübingen University Hospital, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany. E-mail; ksunert1@med.uni-tuebingen.de

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Intensive care unit (ICU) patients are at increased risk for the development of severe and even fatal infections, despite the high level of care, meticulous monitoring, and advanced preventive and therapeutic measures (1,2). Data from a large European survey indicate that approximately 45% of ICU patients are infected, and 21% acquired the infections within the ICU (3). Ventilator-associated pneumonia and bloodstream infections are among the most frequent infections and are associated with an attributable mortality of approximately 30% in certain ICU populations (4-6). Together with other infections, they also significantly contribute to increased morbidity, length of hospital stay, and costs (5, 7-9).

The high risk for infections is the result of multiple factors, and only some of these are amenable to preventive measures. The major determinant is the severity of the underlying illness, which dramatically increases the likelihood of acquiring infections and at the same time decreases the chance of a favorable response to treatment (10-13). Severe underlying diseases are also coupled with more frequent or prolonged

use of invasive devices. These cause a breach of natural barrier functions, and this is typically reflected in the occurrence of device-related infections (14). Finally, there is also an increased exposure to potentially pathogenic microorganisms; these may originate from the hospital environment, but the patients own microflora is considered equally important (15). Increased exposure to such microorganisms can therefore only partially be avoided by strictly adhering to hygienic policies.

Three decades ago, oropharyngeal carriage of Gram-negative bacteria was linked to hospitalization, to the severity of the underlying diseases, and to the development of lower respiratory tract infections (16, 17). The patients intestinal tracts have subsequently been discerned as reservoirs for microorganisms causing endogenous infections and promoting the failure of remote organs (18-20). Consequently, numerous investigators attempted to eliminate potentially pathogenic bacteria from the upper respiratory and intestinal tracts and to prevent abnormal colonization by prophylactic administration of antibiotics; this procedure was coined selective digestive decontamination (21-24). The selective digestive decontamination strategy yielded conflicting results reflecting the complex nature of cofactors in the pathogenesis of infections as previously outlined briefly here. Meta-analyses have shown that regimens comprising a combination of systemic and topical antibiotics are superior to topical antibiotics alone (25, 26). Furthermore, there is no uniform ICU patient population, and a benefit can only be expected when the prophylaxis is applied

in a timely fashion to patients who are at high risk for the development of infections and adverse outcome. A reduction in mortality may be especially expected in surgical patients (26), but a reduced incidence of infections has also been reported in a predominantly medical ICU population with high Acute Physiology and Chronic Health Evaluation (APACHE)-II scores (27). Thus, it becomes clear that the term selective must not only be understood with respect to suppression of certain bacterial species but also with respect to appropriate patient selection; the latter should be based on the kind and severity of underlying diseases at ICU admission. Restriction of such prophylaxis to patients who can expect the most benefit should also essentially contribute to control the development of resistance, which is one of the major concerns associated with the prophylactic use of antibiotics (28).

Many different regimens have been proposed in the past; however, most selective digestive decontamination studies used systemic cefotaxime and a combination of aminoglycosides and polymyxin as the topical component (25). The rationale for the use of cefotaxime is its activity against staphylococci, coliform bacteria, streptococci, and *Haemophilus influenzae*, which are important pathogens of early-onset ICU infections. However, cefotaxime does not reach therapeutically effective levels in the intestinal tract, and it has been questioned whether decolonization of the gut may consistently be achieved in ICU patients by the administration of topical antibiotics(29). Ciprofloxacin is less active against Gram-positive bacteria but has the pharmacokinetic advantage of being secreted by the intestinal mucosa (30). We have previously shown in healthy volunteers and in patients with various disease conditions that intravenously administered ciprofloxacin rapidly and consistently eliminates coliform bacteria from the gut, and recolonization by such bacteria does not occur for several days after cessation of the therapy (31, 32).

Recent meta-analyses suggest that critically ill surgical patients will most likely benefit from a combined topical and systemic antibiotic regimen; this should, however, be confirmed in large prospective and randomized trials (26, 33). We studied the impact of an antibiotic prophylaxis regimen on the incidence of infections, organ dysfunctions, and mortality in a predominantly surgical and trauma ICU population. Organ dysfunctions were chosen as an endpoint in addition to infections, as the diagnoses can be established without interference with the antibiotic prophylaxis. The choice of intravenous ciprofloxacin was based on the consideration that it may be used as systemic prophylaxis for infections occurring early after ICU admission and that it may at the same time prevent endogenous infections by its effect on the intestinal microflora in combination with the topical gentamicin/polymyxin B regimen. To find out whether the assumed reduction in infections may translate into reduced mortality in patients with varying degrees of underlying diseases, we prospectively stratified the patients according to the calculation of APACHE-II scores on admission.

METHODS

Endpoints

The study was conducted to evaluate the impact of a combined systemic and topical antibiotic prophylaxis for the prevention of infections in critically ill adult patients. The primary endpoints were incidence and time of onset of infections, incidence and time of onset of severe organ dysfunctions, and mortality. Secondary endpoints were the length of ICU stay, the duration of intubation, and the evaluation of microbial species colonizing or infecting the patients during the course of the study (especially with respect to the emergence of resistant bacteria). We also documented the frequency and costs of antibiotic therapy and other therapeutic interventions, the side-effects of the antibiotic prophylaxis, and the frequency of stress bleedings and their consequences.

Patients

All patients aged 18 years or older were eligible if a clinical assessment by the attending physician indicated that they had to stay in the ICU for more than 48 hours. Additionally, at least one of the following conditions had to be present: expected intubation period of more than 24 hours, respiratory failure (Pa_{O2} of less than 55 mm Hg on room air), thoracic or abdominal surgery within the preceding 24 hours, severe organ dysfunction on admission, increased risk of aspiration caused by swallowing disorder, chronic obstructive pulmonary disease, immunosuppressive therapy, or advanced age (more than 70 years). Patients were not included if they were expected to die within 48 hours or if randomization was not achieved within 12 hours after admission to the ICU. Further exclusion criteria were intolerance to the study medications, upper gastrointestinal bleeding within the preceding 4 weeks, pregnancy, or withdrawal of consent. Patients were continued on their study medications if they had left the ICU and were readmitted within 24 hours, but they were not eligible for further participation once they had been transferred from the ICU for more than 24 hours. The study was performed in accordance with the Declaration of Helsinki and subsequent amendments and under the regulations of Good Clinical Practice. Ethics committee approval was gained at each participating study center, and informed written consent was obtained by all patients or their close relatives.

Setting

The study was conducted in two ICUs run by the anesthesia departments and located in large tertiary-care centers. ICU-I (22 beds) belonged to a university hospital, and ICU-II (24 beds) belonged to a university-affiliated hospital. The respective annual ICU admission rates were approximately 1,000 and 1,500, and surgical and trauma patients contributed to more than 90% of their admissions.

Design

The study was prospectively stratified and conducted in a randomized, double-blind, placebo-controlled manner. The patients were assigned to one of three strata according to the severity of their disease, as determined by APACHE-II scores (34) calculated within the first 12 hours after admission (stratum I: APACHE-II score below 20; stratum II: 20-29; stratum III: 30 and above). For each stratum, separate randomization lists consisting of randomized blocks of size 6 were applied. A computer-generated randomization scheme and the sealed-envelope technique served for assignment to the treatment or placebo group. The hospital pharmacist was the only person to be informed about the identity of the study medication.

Study Medication

All study medication was started immediately after randomization and after baseline samples for microbiologic cultures had been obtained. The treatment group received 400 mg of intravenous ciprofloxacin (Bayer, Leverkusen, Germany) every 12 hours for 4 days and a mixture of topical antibiotics every 6 hours throughout the ICU stay. The topical regimen consisted of 80 mg of gentamicin (Merck, Darmstadt, Germany) and 50 mg of polymyxin B (Pfizer, Karlsruhe, Germany) dissolved in 10 ml of sterile saline, and additionally contained 125 mg of vancomycin (Lilly, Bad Homburg, Germany) for patients with acute respiratory distress syndrome or immunosuppressive therapy. One milliliter of this solution was applied into each nostril, and 3 and 5 ml were given into the oral cavity and stomach, respectively, after the oropharynx had been thoroughly suctioned. Because only few patients were able to swallow, the administration into the stomach was usually achieved via nasogastric tubes, which were subsequently clamped for 30 minutes. The placebo group received 200 ml of 0.9% NaCl intravenously twice a day and NaCl as placebo for topical administration, which was prepared and administered in the same manner as for the treatment group. The study drugs and corresponding placebos were visibly indistinguishable and were prepared by a study nurse. They were provided by the manufacturers and were labeled with an identification number, which was noted in the patients' charts to allow for unblinding after completion of the study.

Patients who were already being treated for infections with any intravenous antibiotics did not receive intravenous study medications but were continued on the topically administered drugs. The doses of all study drugs were reduced by 50% in case of severe renal impairment (creatinine clearance of less than 15 ml/minute or serum creatinine of more than 4 mg/dl).

Antimycotics were not part of the prophylaxis regimen. In case of repeated culture of fungi from wounds or from digestive, urinary, or respiratory tracts, amphotericin B suspension (Bristol Myers Squibb, Munich, Germany) was applied every 6 hours together with the topical antibiotics into the oropharynx and stomach (250 mg at each location).

Throughout their stay, all patients included in the study received 1.5 g of sucralfate suspension four times a day (Merck, Darmstadt) into the stomach 3 hours after the administration of the topical study drugs: this served as a prophylaxis for stress ulcer.

Data Collection

All data were noted on standardized documentation sheets and were exclusively collected by a study nurse and a medical doctor in each center. None of these persons were involved in patient care or in diagnostic or therapeutic decisions. Data recorded on admission included demographic and diagnostic information on the patients, recent hospitalization periods, surgical procedures, drugs taken within the preceding 48 hours, duration of intubation and ventilatory support, and the calculation of APACHE-II and Mortality Prediction Model scores (34, 35). The patients were monitored daily for the presence of organ failures and infections according to the definitions specified later here, and all physiologic and laboratory parameters were recorded for daily calculation of the following scores: acute physiology score (34), lung injury score, (36) and therapeutic intervention scoring system (37, 38).

Microbiological Sampling and Culture

Quantitative cultures of the oropharynx, trachea, and stomach were obtained from each patient on admission and according to the following schedule: Days 2 or 3, 5 or 6, 8 or 9, 11 or 12, 14 or 15, 20 or 21, and 27 or 28. This was followed by two to three cultures on a weekly basis up to a further 4 weeks. Additional samples were collected on the day of extubation and on the day of discharge or at the end of prophylaxis in case the study drugs had to be discontinued. All specimens were diluted 1:10 in phosphate-buffered saline and were processed microbiologically within 24 hours of sampling. The microorganisms were identified, counted, and tested for resistance using standard laboratory techniques, and the detection threshold was 10^2 colony forming units/ml. For immediate detection of resistant bacteria, all samples were additionally spread onto Mueller-Hinton agar II containing 2 mg/L of ciprofloxacin, 2 mg/L of polymyxin B, or 5 mg/L of gentamicin. Rectal swabs were obtained according to the same schedule and were placed in 1 ml of Mueller-Hinton broth (Oxoid, Wesel, Germany), thereby limiting carryover effects of the study drugs that might inhibit bacterial growth. Enumeration of microorganisms from rectal swabs was performed in a semiquantitative manner (Grades 0-4).

Definitions

Any organ dysfunction or infection prevailing within 24 hours after admission to the ICU was defined as present on admission ; they were classified as acquired if presenting thereafter. The diagnoses of infections were based on clinical criteria to avoid bias, as the study drugs might interfere with the microbiological cultures. Tracheobronchitis was diagnosed by the presence of purulent tracheobronchial secretions (more than 15 granulocytes per high-power field in Gram-stained smear) and at least one of the following clinical symptoms: temperature of more than 38.5° C, leukocytosis (more than $12{,}000 \times 10^9$/L), leukopenia (less than $4{,}000 \times 10^9$/L), or more than 10% of band forms of neutrophil granulocytes. Pneumonia was diagnosed if the following conditions were present in addition to the previously mentioned criteria: chest radiographic examination with indication of a new or progressive infiltrate, of consolidation, of cavitation or of pleural effusion, or if an increase in the inspiratory oxygen fraction of more than 0.15 was necessary to maintain the arterial oxygen tension (Pa_{O2}) at the same level. Microbiologic culture results derived from blood cultures, tracheobronchial secretions, protected specimen brush, bronchoalveolar lavage, pleural fluid, or lung biopsy were attempted but were not a prerequisite for the diagnosis. Alternatively, results of serologic tests, as specified by the Centers for Disease Control, could be used (39). Other infections were diagnosed according to Centers for Disease Control definitions in as far as they were applicable for ICU patients(39).

Severe organ dysfunctions and irreversible organ failures were defined according to the criteria given by other investigators (40-42) with slight modifications (*see* Table E1 in online data supplement). Irreversible organ failures were counted as primary cause of death.

Statistical Analysis

A sample size of 296 patients per group was calculated as being necessary to show a reduction of the infection rate from 20% in the placebo group to 10% in the group receiving antibiotic prophylaxis, assuming an error of 0.05 and a **[B]** error of 0.20. The recruitment of patients had to be achieved within a period of 2.5 years.

The primary endpoints were time-censored criteria (incidence and time of onset of infections, incidence and time of onset of severe organ dysfunctions, and mortality). They were plotted as Kaplan-Meier curves and Cox proportional hazards regression modeling was used for the efficacy analysis, the corresponding risk ratios (RRs), and confidence intervals (CIs). The comparison of baseline variables, of acquired infections, and of acquired organ dysfunctions was performed using the nonparametric Wilcoxon test for continuous variables and the chi-square test or Fisher's exact test for 2 × 2 tables, when appropriate. The multiple testing problem for the categories of infections and severe organ dysfunctions was addressed by applying Bonferroni's correction. All tests of significance were two tailed, and a p value of 0.05 or less was considered statistically significant. Statistical analysis was performed using the SAS software package(43).

RESULTS

Patients

A total of 546 patients were enrolled within 2.5 years. The study patients represented 12.0% and 8.6% of all admissions to ICU-I and ICU-II, respectively. Nineteen patients were excluded after enrollment (8 of the prophylaxis group and 11 of the control group, all survived) because of withdrawal of consent (five patients), violation of entry criteria (nine patients), and other reasons (five patients). Thus, 527 patients were eligible for analysis, 265 of whom received prophylaxis and 262 of whom received placebo. The two groups were similar with respect to age, sex, acute and chronic diseases, infections, organ dysfunctions, severity of illness on admission (calculated by APACHE-II scores), risk of mortality (calculated by Mortality Prediction Model or by APACHE-II), and the extent of treatment classified by therapeutic intervention scoring system (*see* Table E2 in online data supplement).

The study drugs were continuously administered to 228 patients of the antibiotic prophylaxis group and to 226 patients of the placebo group for as long as they stayed in the ICU. They were discontinued for 37 patients receiving prophylaxis and for 36 patients receiving placebo. The reasons for discontinuation were withdrawal of all treatment because of fatal prognosis (13 versus 19 patients), change of stress ulcer prophylaxis caused by gastrointestinal bleeding (13 versus 6 patients), suspected adverse event (four versus four patients), error in drug administration (three versus three patients) or other reasons (four versus four patients). Fifty-six patients (21.1%) of the prophylaxis group and 64 patients (24.4%) of the placebo group were being treated with systemic antibiotics and therefore received only the topical part of the regimen (Table E2). The actual durations of prophylaxis were 1.9 ± 1.8 days of ciprofloxacin versus 2.2 ± 1.8 days of intravenous placebo and 10.6 ± 8.5 days of topical gentamicin and polymyxin versus 12.2 ± 9.5 days of topical placebo. Because of repeated isolation of fungi, 63 patients of the prophylaxis group and 67 patients of the placebo group received topical amphotericin B for 11.1 ± 7.5 days and 10.5 ± 6.9 days, respectively.

Figure 1. Comparison of Kaplan-Meier estimates of probability of remaining free of infections acquired in the ICU during Days 1-28 after randomization in 265 patients receiving antibiotic prophylaxis and in 262 patients receiving placebo (p = 0.001; RR, 0.447; 95% CI, 0.367-0.620 for Cox proportional hazards regression analysis).

Figure 2. Comparison of Kaplan-Meier estimates of probability of remaining free of severe organ system dysfunctions acquired in the ICU during Days 1-28 after randomization in 265 patients receiving antibiotic prophylaxis and in 262 patients receiving placebo (p = 0.0051; RR, 0.636; 95% CI, 0.463-0.874 for Cox proportional hazards regression analysis).

Infections

On admission, a total of 211 patients were infected (101 of the prophylaxis and 110 of the placebo group). In the antibiotic prophylaxis group, significantly fewer patients acquired infections (91 versus 149 patients), and the time of onset of the first acquired infection was significantly delayed compared with the patients receiving placebo (Figure 1; p = 0.001; RR, 0.477; 95% CI, 0.367-0.620). The total number of acquired infections was lower in the prophylaxis group than in the placebo group (141 versus 274). When receiving prophylaxis, significantly fewer patients acquired pneumonias (6 versus 29; p = 0.007, chi-square test with Bonferroni correction), other lower respiratory tract infections (39 versus 70; p = 0.007), bloodstream infections (14 versus 36; p = 0.007) or urinary tract infections (36 versus 60; p = 0.042). Table 1 shows further details.

Organ Dysfunctions

On admission, one or more severe organ dysfunctions were present in 339 patients (64.3%), and they were equally distributed between the two groups (Table E2). Significantly fewer patients acquired severe organ dysfunctions (63 versus 96 patients), and the time of onset of the first acquired organ dysfunction was significantly delayed when receiving antibiotic prophylaxis as compared with the patients receiving placebo (Figure 2; p = 0.0051; RR, 0.636; 95% CI, 0.463-0.874). The total number of severe organ dysfunctions acquired after 24 hours was lower in the prophylaxis group (113 versus 185). A significant decrease in favor of the prophylaxis group was found with respect to renal dysfunction (17 versus 38; p = 0.018, chi-square test with Bonferroni correction). Table 1 shows further details.

Mortality

There were fewer fatalities in the ICU in the prophylaxis group (52 versus 75), but the difference was not statistically significant if all patients were analyzed together (Figure 3; p = 0.1321; RR, 0.761; 95% CI, 0.533-1.086). Whereas 24 patients of each group died within the first 5 days, only 28 patients of the prophylaxis group versus 51 patients receiving placebo died in the ICU thereafter (p = 0.0589; RR, 0.640; 95% CI, 0.402-1.017).

TABLE 1. NUMBER OF PATIENTS WITH ACQUIRED INFECTIONS AND WITH ACQUIRED SEVERE ORGAN DYSFUNCTIONS

	Prophylaxis *(n, %)*	**Placebo** *(n, %)*	**RR**	**95% Confidence Intervals**	**p Value**
Infections					
Pneumonia	6 (2.3)	29 (11.1)	0.205	0.072-0.587	0.007
Lower respiratory tract (not pneumonia)	39 (14.7)	70 (26.7)	0.551	0.344-0.883	0.007
Bloodstream	14 (5.3)	36 (13.7)	0.384	0.176-0.836	0.007
Urinary tract	36 (13.6)	60 (22.9)	0.593	0.357-0.985	0.042
Wound	8 (3.0)	15 (5.7)	0.527	0.169-1.639	NS
Intra-abdominal	4 (1.5)	9 (3.4)	0.439	0.093-2.080	NS
Other	18 (6.8)	27 (10.3)	0.659	0.303-1.435	NS
Severe organ dysfunctions					
Lung	15 (5.7)	27 (10.3)	0.549	0.236-1.279	NS
Circulation	27 (10.2)	45 (17.2)	0.593	0.319-1.104	NS

Kidney	17 (6.4)	38 (14.5)	0.442	0.210-0.932	0.018
Heart	8 (3.0)	8 (3.1)	0.989	0.375-2.608	NS
Central nervous system	3 (1.1)	5 (1.9)	0.593	0.081-4.339	NS
Coagulation	1 (0.4)	5 (1.9)	0.198	0.013-2.985	NS
Hematologic system	5 (1.9)	11 (4.2)	0.449	0.107-1.889	NS
Liver	26 (9.8)	29 (11.1)	0.887	0.438-1.796	NS
Gastrointestinal tract	5 (1.9)	7 (2.7)	0.706	0.143-3.497	NS

Definition of abbreviations: NS = not significant; RR = risk ratio.
Values in parentheses are percentages. Statistics were calculated by chi-square tests with Bonferroni correction.

Figure 3. Comparison of Kaplan-Meier estimates of probability of survival during Days 1-60 after randomization in 265 patients receiving antibiotic prophylaxis and in 262 patients receiving placebo (p = 0.1321;RR, 0.761; 95% CI, 0.533-1.086 for Cox proportional hazards regression analysis).

When analyzed according to the severity of illness on admission, the ICU mortality of patients in stratum II (APACHE-II scores of 20-29) was significantly reduced in the group receiving prophylaxis (20 versus 38 deaths; p = 0.0147; RR, 0.508; 95% CI, 0.295-0.875), whereas there were no significant differences for patients in stratum I or stratum III. The survival rates of patients in stratum II remained significantly different throughout the entire hospital stay (p = 0.0372; RR, 0.604; 95% CI, 0.376-0.971). One year after randomization, there were still fewer deaths in the prophylaxis group (51 versus 60), but the difference was not significant (p = 0.0844; RR, 0.720; 95% CI, 0.496-1.046). Further details on mortality data are given in Table 2.

There were no significant differences for acute physiology scores at the end of the administration of study drugs for survivors (6.9 ± 4.7 in the prophylaxis group versus 7.0 ± 4.5 in the placebo group) nor for patients who died (26.5 ± 7.3 versus 26.9 ± 6.3, respectively). Most deaths were associated with the occurrence of multiple organ failures. Fatal circulatory failure was less frequent in the prophylaxis group (4 versus 17 patients; p = 0.027; RR, 0.233; 95% CI, 0.087-0.619; chi-square test with Bonferroni's correction), whereas the frequencies of other fatal organ failures were similar in both groups (data not shown).

Length of ICU Stay and Duration of Intubation

The median length of ICU stay was 10 days for both groups, and the interquartile ranges between the first and third quartiles were 5 to 19 days (maximum, 120) and 5 to 23 days (maximum, 171) for the prophylaxis and placebo group, respectively. The median duration of intubation was 119 hours for the patients receiving prophylaxis (interquartile range, 46.5-283.0 hours; maximum, 1,838 hours) and 153.5 hours for patients in the placebo group (interquartile range, 48-369; maximum, 3,114 hours). The trends for shorter length of stay and shorter duration of intubation for patients receiving prophylaxis were not statistically significant.

Microbiology

A causative microorganism was found in 97.8% of infections acquired by patients in the prophylaxis group and in 90.8% of the acquired infections in the placebo group. They were polymicrobial in 29.1% and 51.1% of cases. Gram-negative bacilli were found in 48 versus 236 infections and *Staphylococcus aureus* in 15 versus 63 infections in patients receiving prophylaxis or placebo, respectively. Enterococci were isolated in 13 versus 24 cases, coagulase-negative staphylococci in 20 versus 24, and *Candida* spp. in 53 versus 53 cases. Infections caused by resistant microorganisms occurred at similar frequencies in both groups (Table 3).

Surveillance cultures of tracheobronchial secretions yielded similar microflora in both groups at baseline. In the course of the study, colonization by Gram-negative and Gram-positive bacteria became less frequent in patients in the prophylaxis group (*Escherichia coli,* 3 versus 18 patients; *Klebsiella* spp., 4 versus 18 patients; other *Enterobacteriaceae,* 0 versus 22 patients; *Pseudomonas* spp., 3 versus 30 patients; *Acinetobacter* spp., 2 versus 7 patients; *H. influenzae*, 3 versus 28 patients; *S. aureus*, 16 versus 58; and *Streptococcus pneumoniae*, 1 versus 7 patients), whereas yeasts were isolated at high frequencies in both groups (99 versus 96 patients). These routinely performed cultures as well as cultures from oropharyngeal and gastric secretions and from rectal swabs did not show any remarkable differences between the groups with respect to the isolation of resistant bacteria. However, increasing numbers of patients in both groups became colonized by coagulase-negative staphylococci, by enterococci resistant to ciprofloxacin and gentamicin, and by oxacillin-resistant coagulase-negative staphylococci; Methicillin-resistant *Staphylococcus aureus*, on the other hand, were rarely isolated (*see* Table E3 in the online data supplement).

Antibiotic Therapy and Therapeutic Interventions

Antibiotic treatment for suspected or documented infections was given to 181 patients (68.3%) of the prophylaxis group and to 197 patients (75.2%) of the placebo group. Figure 4 shows a comparison of the amount of antibiotics, and Figure

TABLE 2. MORTALITY IN THE ICU AND ONE YEAR AFTER RANDOMIZATION, SPECIFIED ACCORDING TO THE SEVERITY OF THE ILLNESS ON ADMISSION

Stratum According to APACHE-II	Patients *n*	Fatalities in the ICU *(n, %)*	RR (ICU) *(95% CI)*	p Value	Fatalities after one year *(n, %)*	RR (after one year) *(95% CI)*	p Value
All strata*	Prophyl.:265	52 (19.6)	0.761	0.1321	102 (38.5)	0.856	0.2542

Definition of abbreviations: CI = confidence interval; ICU = intensive care unit; Prophyl. = prophylaxis; RR = risk ratio.

* For stratification, APACHE-II scores were calculated within 12 hours after ICU admission. Data were analyzed using Cox proportional hazards modeling using APACHE-II scores, time periods, and treatment variables with outcomes of survival and time.

TABLE 3. NUMBER OF PATIENTS WITH ACQUIRED INFECTIONS, LISTED BY CAUSATIVE MICROORGANISMS

	Prophylaxis Group (*n* = 265)				Placebo Group (*n* = 262)			
		Resistant to				Resistant to		
	Total	Ciprofloxacin	Gentamicin	Polymyxin	Total	Ciprofloxacin	Gentamicin	Polymyxin
Enterobacteriaceae	20	0	0	2	151	2	2	17
Haemophilus spp.	0	0	0	0	20	0	0	0
Pseudomonas spp.	24	4	3	0	46	2	5	1
Other Gram-negative bacteria	4	1	1	0	19	3	3	0
		Ciprofloxacin	Gentamicin	Oxacillin		Ciprofloxacin	Gentamicin	Oxacillin
Staphyloccus aureus	15	3	4	4	63	8	5	7
Coagulase-negative Staphylococci	20	9	11	12	24	2	10	11
Enterococci	13	8	13	Not applicable	24	12	18	Not applicable
Other Gram-positive bacteria	31	1	1	Not applicable	77	5	8	Not applicable
Yeasts	53	Not applicable	Not applicable	Not applicable	53	Not applicable	Not applicable	Not applicable

E1 (online data supplement) shows the percentage of patients treated with specific antibiotics. Seven patients of the prophylaxis group and four of the placebo group were treated with amphotericin B for a total of 224 and 279 days, respectively. The costs for antibiotic treatment amounted to 118,325 Euro and 151,235 Euro, respectively. Because 73,319 Euro were additionally spent for antimicrobial prophylaxis, the total costs for antibiotics were higher in the prophylaxis group (48.21 versus 32.31 Euro per patient per day).

The sum of mean therapeutic intervention scoring system points calculated for Days 0-14 was significantly lower for the prophylaxis group (333.4 ± 217.5 versus 373.6 ± 229.6, p = 0.034), indicating cost reductions in overall patient care.

Gastrointestinal Bleeding

Stress ulcer prophylaxis with sucralfate was changed in 86 patients (45 patients of the antibiotic prophylaxis group and 41 patients of the placebo group), usually because of suspected or overt gastrointestinal bleeding (35 versus 31 patients). Endoscopy was performed in 33 patients and revealed the source of bleeding in 22 cases (9 cases of mucosal erosions, 8 cases of trauma by nasogastric tube, 3 cases of gastric ulcer, and 2 cases of duodenal ulcer). The dose of sucralfate was increased in 67 patients, and 19 patients were switched to H_2 blockers. The bleeding was followed by transfusion of paced red blood cells in 15 patients, and surgical intervention was necessary in 3 cases.

Figure 4. Comparison of the amount of antibiotics that were administered to at least 2% of the patients. Second-generation cephalosporins: cefotiame, cefamandole, cefoxitine; third-generation cephalosporins: cefotaxime, ceftriaxone, cefmenoxime, ceftazidme; aclaminopenicillins: piperacillin, mezlocillin; carbapenem: imipenem-cilastatin; quinolones: ceprofloxacin, ofloxacin; and aminoglycosides: tobramycin, gentamicin, amikacin.

Safety

The frequency of adverse events in the prophylaxis group (66 patients with 85 events) was not statistically different from the frequency in the placebo group (65 patients with 77 events). Most adverse events were minor gastrointestinal or skin reactions. The study drugs were discontinued because of serious adverse events in four patients of the prophylaxis group (four cases of vomiting) and in four patients of the placebo group (single cases of vomiting, diarrhea, nausea, and one patient suffering from pruritus and conjunctivitis). Life-threatening events were recorded in three patients. These were one fatal case of anaphylactic shock in the prophylaxis group and a nonfatal anaphylactic shock in the placebo group. None of the study drugs were considered to be involved in these events by the attending physicians. The nonfatal case was thought to be caused by dextran, and no further patient in the placebo group suffered from focal seizures and renal failure and died 5 days after these adverse events had been recorded. Under double-blind conditions, sucralfate and polymyxin were deemed to be the causes for the observed

events.

DISCUSSION

In this randomized, placebo-controlled, double-blind clinical trial in critically ill patients, the prophylactic administration of intravenous ciprofloxacin in combination with topical nonabsorbable antibiotics significantly reduced the incidence of infections and organ dysfunctions. The overall difference in survival was not statistically different, but were found a significant reduction in death rates throughout the entire hospitalization period for patients receiving antibiotic prophylaxis with APACHE-II scores of 20-29 on admission ($p = 0.0372$). Thus, the prophylactic administration of antibiotics exerted relevant beneficial effects, including an increase in survival in well-defined subsets of our surgical and trauma ICU population.

Infections are related to a worse outcome in critically ill patients (3,5); however, it is difficult to assess the exact contribution to fatalities given the multitude and complexity of interacting prognastic factors. Furthermore, it is notoriously difficult to establish the diagnosis of infections early and with certainty in critically ill patients. It was shown in autopsies that approximately 20% of such patients suffered from infections not diagnosed during their lifetime; these were categorized postmortem as

major errors in diagnosis (44). In contrast to this, nosocomial pneumonia is considered to be the major cause of infection-related death but may be grossly overdiagnosed in mechanically ventilated patients. In fact, pneumonia may be present in only half of the assumed cases if the diagnosis is based on clinical criteria (45, 46), this despite such criteria being well accepted and commonly used (47). Thus, with some infections undetected and others suspected too often, there is considerable uncertainty with respect to their exact frequency. To avoid at least partially the problems related to the diagnoses of infections, we defined the occurrence of organ system dysfunctions as one of the major endpoints in our study. The reduced incidence and delayed onset of organ dysfunctions, especially renal dysfunctions, are thus clear benefits, which were measured in our study by parameters devoid of the previously mentioned diagnostic difficulties. Furthermore, our results illustrate the important contribution of overt or occult infections to organ failures in ICU patients.

The four most common ICU infections are pneumonias and other lower respiratory tract infections and urinary tract and bloodstream infections (3). All of these were significantly reduced in our patients receiving antimicrobial prophylaxis. Such topical and systemic antibiotics may interfere with the retrieval of microorganisms from tracheobronchial secretions and from specimens derived from invasive sampling methods (48, 49). To avoid bias in favor of the treatment group, we used clinical criteria as far as this was appropriate. Thus, it seems unlikely that the lower incidence of pneumonias in the prophylaxis group is an artificial finding, as microbiologic confirmation was not a prerequisite for the diagnosis (39). The incidence of pneumonias in the placebo group (6.5% within 24 hours after admission and 11.1% thereafter) equals the figures described in large surveys in mechanically ventilated patients (50). Therefore, there is also no evidence for systematic overdiagnosis in the placebo group.

The mortalities attributable to nosocomial pneumonias (4, 8, 51) and bloodstream infections (5, 6) range from 24% to 30% and from 28% to 35%, respectively, and even higher numbers have been reported for high-risk organisms such as *Pseudomonas aeruginosa* (8, 11, 13). In the prophylaxis group, 23 and 22 less patients acquired pneumonias and bloodstream infections, respectively, and we conclude that the prevention of these infections mainly contributed to the observed reduction of hospital mortality. It is important to note that our patients were stratified at the beginning and were then randomized. This is different from subgroup analyses, which are performed retrospectively and where the benefits of randomization are lost. The mortality attributable to infections depends also on the severity of the underlying diseases (12, 13). It is therefore not surprising that the prevention of infections did not necessarily increase survival in less severely ill patients with APACHE-II scores below 20 on admission. The mortality was also not reduced in the most severely ill patients. One interpretation is that the fatalities were mainly determined by the underlying diseases rather than by the infections; however, because less than 10% of our patients had scores above 29, no definite conclusions may be drawn.

The trends for shorter duration of intubation and shorter ICU stay for patients receiving antibiotic prophylaxis did not reach statistical significance despite significant reductions in numbers of organ dysfunctions. This discrepancy may possibly be explained by the lower ICU fatality rate after more than 5 days, which was not significant (28 versus 51 patients, $p = 0.0589$), as the surplus of survivors constituted a group with increased needs for ventilatory support and intensive care.

To our knowledge, our study groups were the largest of all prospective clinical trials conducted so far for the investigation of an antibiotic prophylaxis in critically ill patients. However, the design of the study does not allow us to conclude whether the observed effects can be attributed to the systemic or topical component of the regimen. The rationale for the use of topical antibiotics is based on the observation that the oropharynges of critically ill patients are colonized by potentially pathogenic bacteria (16, 17), which together with gastrointestinal overgrowth cause nosocomial pneumonia and multiple organ failure (19, 52, 53). A recently published trial showed that the incidence of pneumonia is considerably lower with oropharyngeal decontamination, and it is unclear whether further benefit may be expected from additional gastric application of antibiotics (54). On the other hand, the use of a systemic component is directed against early or incubating infections (22, 23). The incidence of pneumonia is highest within the first days of mechanical ventilation (50)

and can already be reduced by two doses of antibiotics in certain risk populations (55). In our patients, the incidences of infections and of severe organ dysfunctions were reduced within the first days, followed by a difference in mortality shortly thereafter (Figures 1-3). Although the early effects can most likely be attributed to ciprofloxacin (which was only given for an average of 1.9 days), we can only speculate about its contribution to the sustained reduction of infections occurring at a later time point. In addition to serving as systemic prophylaxis, a short course of intravenous ciprofloxacin rapidly decolonizes the intestines from potentially pathogenic bacteria (31, 32). Because such bacteria usually recolonize the gut within 2 weeks after ciprofloxacin has been stopped (31), a longer lasting effect may only be achieved in combination with topical antibiotics. Another aspect that points to the advantage of the combination is that we did not administer ciprofloxacin or intravenous placebo to patients who were already being treated with antibiotics on admission. This was the case in 21.1% of the prophylaxis group and in 24.4% of the patients receiving placebo (Table E2) and might be seen as a potential bias that would tend to minimize any observed differences between the groups. Despite this partial overlap, the differences were significant, and it may therefore be assumed that the combined approach of systemic and topical antibiotics was responsible for the overall reduction in the incidence of infections; this result is in agreement with the literature (25, 26).

A recent meta-analysis suggests that the incidence of nosocomial pneumonia is significantly decreased when sucralfate is used as stress bleeding prophylaxis in comparison to ranitidine (56); contradictory results can, however, be found in the literature (57). To exclude possibly confounding factors, we standardized the stress bleeding prophylaxis, and all patients received sucralfate. It might be argued that orally administered ciprofloxacin is bound and inactivated by sucralfate (58, 59), but this interaction is clearly not relevant with respect to the elimination of intestinal bacteria by intravenous ciprofloxacin (31, 32).

The benefits of this antibiotic prophylaxis raise the question of whether we could recommend the use of this regimen to other institutions. Apart from the inconvenience and costs associated with the administration, the major argument against such regimens is the fear of the emergence of resistant microorganisms (28). In the case of ciprofloxacin, the selection of multiresistant Gram-negative bacteria or of poorly covered Gram-positive bacteria, such as pneumococci, might be a special concern. Our surveillance cultures, however, did not show any evidence for an increase or selection of resistant bacteria in the prophylaxis group in comparison to the placebo group. This is a very positive result, but it needs to be cautiously interpreted. First, the use of antibiotics in a group of patients may influence the microbial exposure of all patients (60, 61), which means that comparisons between the

groups may not be valid for estimating the risk. It is therefore difficult to assess the contribution of our prophylactic regimen to the increased colonization of all patients by ciprofloxacin- and gentamicin-resistant coagulase-negative staphylococci and enterococci (Table E3); these microorganisms, however, rarely caused infections in our patients (Table 3). Second, the overall occurrence of more virulent organisms such as pneumococci, MRSA, and multiresistant Gram-negatives was low in our hospitals, which also lowers the likelihood of selection.

In contrast, Verwaest and coworkers found a significant increase in ofloxacin-resistant *Enterobacteriacea* and nonfermentors when using the fluoroquinolone ofloxacin together with topical amphotericin B for selective decontamination. Several factors that were different from our situation might have contributed to the failure of their regimen (62). Ofloxacin was the only antibacterial agent in this study group; this agent has limited activity against pseudomonads and was administered at a dose of only 200 mg intravenously daily for 4 days. The investigators also administered a 2% ofloxacin oral paste and 2 × 200 mg ofloxacin over a gastric tube throughout the study, at 2-hour intervals from the administration of sucralfate. It is, however, questionable whether this interval prevents the interaction between ofloxacin and sucralfate in ICU patients (63, 64). Because more than 20% of their patients were colonized by nonfermentors on their mucosal surfaces on admission (15.9% *P. aeruginosa* and 5.5% *Acinetobacter* spp.), the short intravenous course of low-dose ofloxacin followed by (presumably) subtherapeutic levels may very likely have triggered the ecological disaster that they described.

To prevent such selection pressure, we applied strict entry criteria and included only patients likely to benefit from antibiotic prophylaxis (which was the case in approximately 10% of all admissions), and we limited the systemic administration to 4 days. Also, we did not add ciprofloxacin for patients already being treated with other antibiotics, even though ciprofloxacin was our preferred drug because of its previously mentioned pharmacokinetic properties. We certainly do not recommend our regimen to institutions with an existing high prevalence of resistant microorganisms or if resistance statistics are not available, as it may be wise to stop the prophylaxis during outbreaks or change it according to the susceptibility pattern of the emerging pathogen (61). Because increased resistance not only compromises the effectiveness of the prophylaxis but also increases the likelihood of treatment failures, any recommendations about its use must be given very cautiously. Further research should also be directed to nonantibiotic interventions to prevent and interrupt abnormal bacterial colonization of mucosal surfaces in critically ill patients and its serious sequels.

In conclusion, the prophylactic administration of a short course of intravenous antibiotics in combination with topical nonabsorbable antibiotics significantly reduced the incidence of infections and also the progression to severe organ dysfunctions in critically ill surgical and trauma patients. Moreover, the hospital mortality was significantly reduced in patients with APACHE-II scores of 20-29 on admission. Although we found no evidence for an increase in resistance, this possibility cannot be completely ignored. We therefore believe that currently only a restrictive and controlled use of such a regimen in certain institutions and well-defined patient groups appears to be justified, and further controlled studies on the long-term effects on outcome and on resistance are warranted.

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Epidemiology and Outcomes of Ventilator-Associated Pneumonia in a Large US Database*

Jordi Rello, MD; Daniel A. Ollendorf, MPH; Gerry Oster, PhD; Montserrat Vera-Llonch, MD, MPH; Lisa Bellm, MIM; Rebecca Redman, MD; Marin H. Kollef, MD, FCCP; for the VAP Outcomes Scientific Advisory Group

Objectives: **To evaluate risk factors for ventilator-associated pneumonia (VAP), as well as its influence on in-hospital mortality, resource utilization, and hospital charges.**

Design: **Retrospective matched cohort study using data from a large US inpatient database.**

Patients: **Patients admitted to an ICU between January 1998 and June 1999 who received mechanical ventilation for >24 h.**

Measurements: **Risk factors for VAP were examined using crude and adjusted odds ratios (AORs). Cases of VAP were matched on duration of mechanical ventilation, severity of illness on admission (predicted mortality), type of admission (medical, surgical, trauma), and age with up to three control subjects. Mortality, resource utilization, and billed hospital charges were then compared between cases and control subjects.**

Results: **Of the 9,080 patients meeting study entry criteria, VAP developed in 842 patients (9.3%). The mean interval between intubation, admission to the ICU, hospital admission, and the identification of VAP was 3.3 days, 4.5 days, and 5.4 days, respectively. Identified independent risk factors for the development of VAP were male gender, trauma admission, and intermediate deciles of underlying illness severity (on admission)[AOR, 1.58, 1.75, and 1.47 to 1.70, respectively]. Patients with VAP were matched with 2,243 control subjects without VAP. Hospital mortality did not differ significantly between cases and matched control subjects (30.5% vs 30.4%, p = 0.713). Nevertheless, patients with VAP had a significantly longer duration of mechanical ventilation (14.3 ± 15.5 days vs 4.7 ± 7.0 days, p < 0.001), ICU stay (11.7 ± 11.0 days vs 5.6 ± 6.1 days, p < 0.001), and hospital stay (25.5 ± 22.8 days vs 14.0 ± 14.6 days, p < 0.001). Development of VAP was also associated with an increase of >$40,000 in mean hospital charges per patient ($104,983 ± $91,080 vs $63,689 ± $75,030, p < 0.001).**

Conclusions: **This retrospective matched cohort study, the largest of its kind, demonstrates that VAP is a common nosocomial infection that is associated with poor clinical and economic outcomes. While strategies to prevent the occurrence of VAP may not reduce mortality, they may yield other important benefits to patients, their families, and hospital systems.** *(CHEST 2002; 122:2115-2121)*

Key words: critical care; hospital costs; ICU; mechanical ventilation; outcome; ventilator-associated pneumonia

Abbreviations: AOR = adjusted odds ratio; CI = confidence interval; CIC = Cardinal Information Corporation; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; KCF = key clinical finding; VAP = ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) is reported to be the most common hospital-acquired infection among patients requiring mechanical ventilation.[1,2] Risk factors associated with VAP have been identified using multivariate statistical methods.[3,4] These risk factors appear to predispose patients to either colonization of the aerodigestive tract with pathogenic microorganisms and/or aspiration of

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contaminated secretions.[3-5] Several investigators[6-9] have assessed the impact of VAP on patient out-

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Correspondence to: Martin H. Kollef, MD, FCCP, Washington University School of Medicine, Campus Box 8052, 660 South Euclid Ave, St. Louis, MO 63110; e-mail: kollefm@msnotes.wustl.edu

*From the University Hospital Joan XXIII (Dr. Rello), University Rovira and Virgili, Tarragona, Spain; Policy Analysis Inc. (Drs. Oster and Vera-Llonch and Mr. Ollendorf), Boston, MA; IntraBiotics Pharmaceuticals, Inc. (Ms. Bellm and Dr. Redman), Mountain View, CA; and Washington University School of Medicine (Dr. Kollef), St. Louis, MO.

A list of VAP Outcomes Scientific Advisory Group members is located in the Appendix.

comes, including attributable hospital mortality, demonstrating variable results. Most clinical studies evaluating VAP and its clinical importance have analyzed patients from single centers outside of the United States. Vincent et al[2] assessed the prevalence of nosocomial pneumonia among ICU patients in Europe, and Heyland et al[8] examined the attributable mortality of VAP in Canadian hospitals. The largest US study[1] published to date reported the prevalence of hospital-acquired pneumonia from US ICUs without analysis of risk factors or attributable mortality.

We performed a study involving a large US database with two main goals: to identify risk factors associated with the development of VAP among patients admitted to ICUs, and to assess the influence of VAP on patient outcomes, including attributable hospital mortality, inpatient resource utilization, and medical care costs. These study goals were selected to assist in the future design of interventional studies aimed at the prevention of VAP and to help assess the potential impact of such interventions on patient and economic outcomes.

MATERIALS AND METHODS

Study Design

A retrospective matched cohort study was undertaken to examine the incidence of VAP, to identify risk factors associated with its development, and to assess the impact of VAP on clinical and economic outcomes. Data were obtained for all patients admitted to an ICU from January 1998 to June 1999 who received mechanical ventilation for > 24 h. Cases of VAP were defined as patients with hospital-acquired pneumonia diagnoses occurring ≥ 24 h following intubation. Control subjects without VAP consisted of all patients in the study cohort who did not meet the definition for cases.

To identify risk factors for VAP, the entire cohort was evaluated in order to identify risk factors that would be applicable to the entire study population. Demographic and clinical characteristics of cases were compared to control subjects, including age, gender, race, severity of illness on admission, use of cardiopulmonary resuscitation, presence of coma or stupor, and the type of hospital admission (*ie*, medical, surgical, trauma). To evaluate outcomes of VAP, cases were matched with up to three control subjects on four variables: duration of mechanical ventilation (control subjects had to be intubated for at least as long as cases prior to the onset of VAP), severity of illness on admission, type of hospital admission (medical, surgical, trauma), and age in 20-year intervals. A matched analysis was selected to evaluate the impact of VAP on clinical outcomes in order to minimize confounding from the matching variables. Outcomes evaluated included hospital mortality, days on mechanical ventilation, days in the ICU, days in the hospital, and total billed inpatient charges.

Data Source

Data for this study were obtained from the MediQual Profile database, which is maintained by the Cardinal Information Corporation (CIC) [MediQual Division; Marlborough, MA]. CIC manufactures and distributes Atlas software to US acute-care hospitals for the collection and analysis of detailed clinical and administrative data. Each participating hospital submits data to CIC for use in proprietary comparative databases (including the MediQual-Profile database), which are employed primarily by the hospitals for risk-adjusted benchmarking and internal outcome studies. The MediQual-Profile database is the largest of these databases, and contains information on approximately 750,000 inpatient admissions annually to > 100 US acute-care hospitals. These hospitals are similar in bed size and geographic region to American Hospital Association member hospitals. Hospitals participating in the MediQual-Profile database must collect data on all patients admitted to their facility, thus minimizing selection or reporting biases. CIC audits these hospitals periodically to ensure compliance with proper data collection.

Data available for each patient admission in the MediQual-Profile database include patient demographics (*eg*, age, gender, race/ethnicity), admission source, type of ICU (*ie*, medical, surgical, trauma, pediatric, neonatal, and other), all documented procedure and diagnosis codes (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]), admission and discharge dates for each stay in the ICU, total length of stay in the hospital, billed total and ancillary hospital charges, and discharge disposition. Detailed information also is included on specific interventions received during the hospital admission (*eg*, mechanical ventilation) as well as unplanned events (*eg*, medication errors, respiratory events [including hospital-acquired pneumonia]). Importantly, all intervention and unplanned event data are dated to allow for their examination on a temporal basis.

In addition to administrative data elements, information also is available on > 400 key clinical findings (KCFs). Trained abstractors at each participating hospital use a standardized glossary to obtain KCFs through chart review from admission through the fifth hospital day. As with the intervention and event data described above, KCFs are dated to allow for time-dependent examination of the clinical course of each hospital admission. KCFs also are used to calculate clinical severity; severity scores are derived based on the probability of in-hospital mortality, which is calculated using disease-specific logistic regression models.[10,11] The predictive capabilities of these models have been shown to be comparable to those of other severity adjustment methodologies (*eg*, APACHE [acute physiology and chronic health evaluation] II, disease staging).[12,13] For this study, all available clinical and financial data were obtained for all patients in the MediQual-Profile database who were hospitalized between January 1, 1998, and June 30, 1999, meeting the sample-selection criteria set forth below.

Study Sample

The study sample was constructed stepwise. First, we identified all patients who are admitted to an ICU and received mechanical ventilation for > 24 h. For patients with multiple ICU admissions, only the first admission was considered for analysis. Second, we excluded all patients admitted to the ICU with a diagnosis of pneumonia on or before the first day of mechanical ventilation, so that the sample would include only patients who had hospital-acquired pneumonia develop while receiving mechanical ventilation. All remaining patients constituted the study cohort, from which cases and control subjects were selected. VAP cases were identified by a secondary diagnosis of bacterial pneumonia (ICD-9-CM codes 481-483) and the presence of either a KCF or an event code indicative of pneumonia, such as an abnormal chest radiographic finding,

documentation of hospital-acquired pneumonia in physician progress notes, and/or positive respiratory culture finding. VAP, as defined by KCFs, was ascertained using data for days 2 through 5 of the hospital admission (the day of admission was not included because KCFs recorded on this date likely represent cases of community-acquired pneumonia). Hospital-acquired pneumonia, as defined by the presence of a coded respiratory event, was ascertained on the basis of information recorded any time during hospital admission documenting the presence of hospital-acquired pneumonia. Control subjects were defined as all patients in the study cohort who did not meet the criteria for the definition of cases, and also did not have secondary diagnoses of viral, fungal, or unspecified pneumonia (ICD-9-CM codes 480, 484-486).

Statistical Analysis

The first part of the analysis examined the entire cohort of patients. Univariate analysis was used to compare variables for the outcome groups of interest, and all tests of significance were two tailed. Continuous variables were compared using Student *t* test for normally distributed variables and Wilcoxon rank-sum test for nonnormally distributed variables. The X^2 statistic or Fisher exact test were used to compare categorical variables as appropriate. The primary data analysis compared patients with VAP to patients without VAP. We confirmed the results of these tests, while controlling for specific patient characteristics and severity of illness (Table 1), with multiple logistic regression analysis using a commercial statistical package.[14]

Table 1 ***Characteristics of Patients With and Without VAP****

Characteristics	Patients With VAP (n = 842)	Patients Without VAP (n = 8,238)	p Value
Age, yr	61.7 ± 19.2	64.6 ± 17.7	<0.001
Gender			
Male	540 (64.1)	4262 (51.7)	<0.001
Female	302 (35.9)	3976 (48.3)	
Race			
White	655 (77.8)	6207 (75.3)	0.303
African-American	122 (14.5)	1240 (15.1)	
Asian	3 (0.3)	37 (0.4)	
Other	62 (7.4)	754 (9.2)	
Predicted mortality, %			
0-10	399 (47.4)	4305 (52.2)	0.015
11-20	130 (15.4)	1273 (15.5)	
21-30	76 (9.0)	678 (8.2)	
31-40	62 (7.4)	484 (5.9)	
41-50	45 (5.3)	320 (3.9)	
51-60	35 (4.2)	270 (3.3)	
61-70	26 (3.1)	224 (2.7)	
71-80	33 (3.9)	233 (2.8)	
81-90	21 (2.5)	198 (2.4)	
91-100	15 (1.8)	253 (3.1)	
Presence of coma/stupor	344 (40.9)	2981 (36.2)	0.007
Use of CPR	38 (4.5)	412 (5.0)	0.534
Type of admission			
Medical	320 (38.0)	3497 (42.5)	<0.001
Surgical	334 (39.7)	3667 (44.5)	
Trauma	188 (22.3)	1074 (13.0)	

* Data are presented as mean ± SD or No. (%). CPR = cardiopulmonary resuscitation.

Multivariate analysis was performed using variables that were prespecified by the members of the VAP Outcomes Scientific Advisory Group. This approach minimized the number of comparisons and avoided data-derived analyses.[15] We examined model overfitting by evaluating the ratio of outcome events to the total number of independent variables in the final model, and we tested for interactions between the individual variables included in our analysis. Results of the logistic regression analyses are reported as adjusted odds ratios (AORs) with their 95% confidence intervals (CIs). All values are expressed as the mean ± SD (continuous variables), or as a percentage of the group they were derived

from (categorical variables). All p values ≤ 0.05 were considered to indicate statistical significance.

Cases of VAP were matched on duration of mechanical ventilation, severity of illness on admission (predicted mortality), type of admission (medical, surgical, trauma), and age within 20 years with up to three control subjects. Mortality, resource utilization, and billed hospital charges were then compared between cases and control subjects. The McNemar test for correlated proportions was used to compare mortality, and the Wilcoxon signed-ranks test was used to compare resource utilization (*eg,* days) and hospital charges in the case-control analysis.

RESULTS

Patient Characteristics and Risk Factors for VAP

In the database, 9,080 patients met all study entry criteria. Among these patients, VAP developed in 842 patients (9.3%). The mean interval between intubation, ICU admission, hospital admission, and identification of VAP was 3.3 ± 6.6 days, 4.5 ± 7.5 days, and 5.4 ± 7.7 days, respectively. Patients with VAP were significantly younger, more likely to be male, had intermediate deciles of illness severity, had a greater incidence of coma or stupor, and were more frequently admitted for trauma compared to patients without VAP (Table 1). Multiple logistic regression analysis demonstrated that male gender (AOR, 1.58; 95% CI, 1.36 to 1.83), trauma admission (AOR, 1.75; 95% CI, 1.41 to 2.18), and intermediate deciles of underlying illness severity at the time of hospital admission (31 to 40% [AOR, 1.48; 95% CI, 1.10 to 1.99], 41 to 50% [AOR, 1.61; 95% CI, 1.15 to 2.26], 51 to 60% [AOR, 1.47; 95% CI, 1.01 to 2.14], and 71 to 80% [AOR, 1.70; 95% CI, 1.15 to 2.51]) were independently associated with the development of VAP.

The patients with VAP were stratified according to time of onset of VAP from both hospital admission and the start of mechanical ventilation. Three hundred eighty-one episodes (45.2%) of VAP occurred during the first 2 days of hospitalization, compared to 245 episodes (29.1%) occurring between days 3 to 6, and 216 episodes (25.7%) diagnosed after hospital day 6. Similarly, 532 episodes (63.2%) of VAP developed within 48 h of mechanical ventilation, compared to 135 episodes (16.0%) between 48 h and 96 h of mechanical ventilation, and 175 episodes

(20.8%) after 96 h of mechanical ventilation. Among patients with VAP, 603 patients (71.6%) had a microorganism identified in a respiratory culture. *Pseudomonas aeruginosa* was isolated most frequently in patients with VAP occurring > 4 days after the start of mechanical ventilation (19.7)%, while *Staphylococcus aureus* was isolated most frequently in patients whose episode of VAP was diagnosed during the first 4 days of mechanical ventilation (23.7%).

Impact of VAP on Outcomes

Eight hundred sixteen patients (96.9%) with VAP were matched to at least 1 of 2,243 patients without VAP (2.7 control subjects were matched for each case of VAP). Twenty-six cases were excluded from the analysis because no suitable control subjects were identified. Patients with VAP in the case-control population were significantly more likely to be male (Table 2). There was no statistically significant difference in hospital morality among patients with and without VAP (30.5% vs 30.4%, respectively; p = 0.713). Kaplan-Meier curves demonstrated that

Table 2 ***Characteristics of Patients With and Without***

VAP (Matched Sample)*

Characteristics	Patients With VAP (n = 816)	Patients Without VAP (n = 2,243)	p Value
Age, yr	62.3 ± 19.1	63.0 ± 17.7	0.389
Gender			
Male	522(64.0)	1210(53.9)	< 0.001
Female	294(36.0)	1033(46,1)	
Race			
White	639(78.3)	1687(75.2)	0.143
African-American	117(14.3)	332(14.8)	
Asian	3(0.4)	14(0.6)	
Other	57(7.0)	210(9.4)	
Predicted mortality, %			
0-10	399(48.9)	1142(50.9)	0.928
11-20	130(15.9)	389(17.3)	
21-30	75(9.2)	187(8.3)	
31-40	56(6.9)	146(6.5)	
41-50	39(4.8)	91(4.1)	
51-60	32(3.9)	76(3.4)	
61-70	21(2.6)	50(2.2)	
71-80	32(3.9)	81(3.6)	
81-90	18(2.2)	43(1.9)	
91-100	14(1.7)	38(1.7)	
Presence of coma/stupor	329(40.3)	824(36.7)	0.071
Use of CPR	38(4.7)	119(5.3)	0.472
Type of admission			
Medical	320(39.2)	923(41.2)	0.517
Surgical	312(38.2)	851(37.9)	
Trauma	184(22.5)	469(20.9)	

* Data are presented as mean ± SD or No. (%). See Table 1 for expansion of abbreviation.

patients with and without VAP had similar in-hospital survival, although these curves suggest that the morality was higher for patients without VAP during the first 30 hospital days (Fig 1). Patients with VAP had a significantly longer duration of mechanical ventilation (14.3 ± 15.5 days vs 4.7 ± 7.0 days, p < 0.001), a greater number of ICU days (11.7 ± 11.0 days vs 5.6 ± 6.1 days, p < 0.001) and a longer hospital length of stay (25.5 ± 22.8 days vs 14.0 ± 14.6 days, p < 0.001.) compared to patients without VAP (Fig 2). Similarly, mean billed hospital charges were significantly greater for patients with VAP ($104,983 ± $91,080 vs $63,689 ± $75,030, respectively; p < 0.001) compared to patients without

VAP. Outcomes for the 26 patients with VAP who were unmatched were as follows: hospital mortality, 26.9%; duration of mechanical ventilation, 19.8 ± 19.4 days; CU days, 16.2 ± 19.4 days; hospital days, 35.7 ± 34.9 days; and hospital charges, $183,312 ± $222,176.

DISCUSSION

This is the largest US study of patients with VAP performed to date. These data suggest that VAP is a common hospital-acquired infection occurring in 9.3% of patients requiring mechanical ventilation for > 24 h. Male gender, trauma admission, and intermediate predicted risks of morality were identified as independent risk factors associated with VAP. The case-control analysis we performed demonstrated no attributable morality associated with VAP. However, patients with VAP had other statistically significant outcomes that indicate they fare poorly compared to patients without VAP: on average, 9.6 additional days of mechanical ventilation, 6.1 additional days in the ICU, and 11.5 additional days in the hospital. The inpatient billed charges were also significantly higher among patients with VAP, averaging > $40,000 more compared to patients without VAP.

Previous studies[3-5] have identified male gender, trauma, and severity of illness as risk factors for VAP. Cook and Kollef[3] performed a systematic review of risk factors for VAP using multiple logistic regression analysis. In their analysis, most risk factors associated with VAP appeared to either predispose patients to colonization of the aerodigestive tract with pathogenic bacteria (*eg*, prior use of antibiotics, treatment with histamine type 2 receptor antagonists) or aspiration (*eg*, supine positioning, patient transport out of intensive care). Male gender and trauma may be markers for other risk factors, predisposing patients to either colonization with pathogenic bacteria or aspiration. Similarly, intermediate underlying illness

FIGURE 1. In-hospital survival among patients with (solid line) and without (dashed line) VAP from the matched case-control analysis; p = 0.1733 using the log-rank test for analysis of Kaplan-Meier survival curves.

severity suggests that patients with either low or high illness severity are less likely to have VAP develop. Potential explanations for this finding have been reported previously: very low-risk patients may not have sufficient exposure time to mechanical ventilation to acquire VAP, and high-risk patients may receive earlier treatment with antibiotics thus reducing the likelihood of acquiring VAP.[8]

Hospital mortality was not attributable to VAP in our analysis. This finding is consistent with the recent analysis of Bregeon et al,[6] and the results of several interventional studies[6,16-18] examining continuous aspiration of subglottic secretions, selective

FIGURE 2. Health and economic outcomes associated with VAP. Mean values and SDs are shown; *p < 0.001 for all comparisons.

digestive decontamination, and semirecumbent positioning, which showed reduced rates of VAP but no associated survival advantage. However, other investigators[7,19] found hospital mortality to be increased among patients with VAP, particularly among patients with antibiotic-resistant bacteria infection. Furthermore, mortality associated with VAP may differ by population, with attributable mortality higher for medical patients than for surgical patients.[8] This may explain the greater survival for patients with VAP during the first 30 hospital days, as there were more medical patients and fewer trauma patients in the group without VAP. The treatment of VAP may also be an important determinant of patient outcome. Several studied[8,20-22] have shown that inappropriate initial antibiotic treatment of VAP is associated with excessive hospital mortality.

Our study has several potential implications for design of future interventional trials. In terms of patient eligibility, our findings suggest that trauma patients may be a suitable, discrete population to target. A significant drawback of limiting inclusion criteria to this population, however, is the generalizability of the findings to other at-risk populations. Given the lack of association between VAP and mortality, it is unknown whether interventional studies aimed at preventing or reducing VAP will demonstrate a survival benefit. End points that are potentially more achievable to meet, yet are still clinically and economically important, include days of mechanical ventilation, days in the ICU, hospital

days, and perhaps health-care costs. Although not evaluated in this study, end points that capture use of antibiotics (antibiotic-free days) would also be clinically meaningful and important to measure.

Strengths of our study include use of a national multicenter database that contained temporal information to examine clinical and economic variables (eg, mechanical ventilation) as both risk factors for, and outcomes of, VAP. Our sample size was larger than those in previous case-control studies examining attributable mortality from VAP, even though we only considered the first ICU admission. This was done to avoid entering repetitive data on the same patients, although it may have resulted in an underestimation of the VAP incidence. We also identified cases of VAP based on diagnoses made at participating institutions reflecting a spectrum of diagnostic approaches used in current US clinical practice. The availability of financial information also allowed us to quantify the extra costs associated with VAP. However, patients with VAP and control subjects were not matched for the same hospital. Therefore, variability in charges among different hospitals could account for some of the cost differences we observed. Finally, microbiology data were available for most patients and appeared consistent with that reported in the literature.[1,23-26]

The analysis has several important limitations. First, the variables entered into the database did not allow us to ascertain the importance of other potential risk factors for VAP (eg, supine positioning, chronic lung disease, specific surgical procedures, prior antibiotic use). Second, the time cutoff of 24 h following intubation to define the presence of VAP may have included some patients with community-acquired pneumonia that was not diagnosed earlier. Third, the diagnosis of VAP, and other unplanned events, likely varied among hospitals. Fourth, the identification of VAP cases may have biased the study toward early-onset cases, not allowing the identification for some late-onset cases in the control group. This may also have contributed to our inability to identify a difference in mortality between patients with and without VAP. No information was available on antibiotic utilization; therefore, we could not ascertain the role of antibiotics on outcome. Additionally, we may have underestimated the impact of VAP on resource utilization by excluding the 26 unmatched patients with VAP. Finally, as with most retrospective studies, we cannot exclude the possibility that our findings simply reflect the effects of systematic differences between patients with and without VAP, above and beyond those for which the matched study design controlled.

Despite the above-mentioned limitations, this study provides data highlighting the clinical and economic importance of VAP. It suggests that the occurrence of VAP is an important determinant of excessive hospital length of stay and inpatient medical care costs. Moreover, these data support the need to develop effective strategies for the prevention of VAP and other nosocomial infections.[27] Implementation of such interventions should be cost-effective because they should lower the incidence and lessen the sequelae of VAP.

APPENDIX

Members of the VAP Outcomes Scientific Advisory Group include Marc Bonten, MD, PHD, University Medical Center, Utrecht, the Netherlands; Jean Carlet, MD (Co-Chair), Hôpital St. Joseph, Paris, France; Deborah Cook, MD, St. Joseph s Hospital, Hamilton, ON, Canada; Jean-Yves Fagon, MD, Hôpital European Georges Pompidou, Paris, France; Mike Niederman, MD Winthrop, University Hospital, Mineola, NY; and Janet Wittes, PhD, Statistics Collaborative, Washington, DC.

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Effectiveness and Cost of Selective Decontamination of the

Digestive Tract in Critically Ill Intubated Patients

A Randomized, Double-blind, Placebo-controlled, Multicenter Trial

MIGUEL SÁNCHEZ GARCÍA, JOSÉ A. CAMBRONERO GALACHE, JULIA LÓPEZ DIAZ, ENRIQUE CERDÁ CERDÁ, JOSÉ RUBIO BLASCO, MIGUEL A. GÓMEZ AGUINAGA, ANTONIO NÚÑEZ REIZ, SANTIAGO ROGERO MARÍN, JUAN J. OÑORO CAÑAVERAL, and JOSÉ A. SACRISTÁN del CASTILLO

Hospital Universitario Principe de Asturias, Alcalá de Henares; Hospital La Paz; Hospital Central de la Cruz Roja; Hospital Doce de Octubre; and Hospital Severo Ochoa, Leganés, Madrid, Spain

We evaluated the effect of selective decontamination of the digestive tract (SDD) on the incidence of ventilator-associated pneumonia (VAP) and its associated morbidity and cost in a mixed population of intubated patients. Two hundred seventy-one consecutive patients admitted to the intensive care units (ICUs) of five teaching hospitals and who had an expected need for intubation exceeding 48 h were enrolled and received topical antibiotics or placebo. Uninfected patients additionally received ceftriaxone or placebo for 3 d. VAP occurred in 11.4% of SDD-treated and 29.3% of control-group patients ($p < 0.001$; 95% confidence interval [CI]: 7.8 to 27.9). The incidence of nonrespiratory infections in the two groups was 19.1% and 30.7%, respectively ($p = 0.04$; 95% CI: 0.7 to 22.7). Among survivors, the median length of ICU stay was 11 d (interquartile range: 7 to 21.5 d) for the SDD-treated group and 16.5 d (10 to 30 d) for the control group ($p = 0.006$). Mean cost per survivor was $11,926 for treated and $16,296 for control-group patients. Mortality was 38.9% and 47.1%, respectively ($p = 0.57$). In decontaminated patients, the prevalence of gram-negative bacilli fell within 7 d from 47.4% to 13.0% ($p < 0.001$), whereas colonization with resistant gram-positive strains was higher ($p < 0.05$) than in the placebo group. In a mixed population of intubated patients, SDD was associated with a significant reduction of morbidity at a reduced cost. Our findings support the use of SDD in this high-risk group. **Sánchez García M, Cambronero Galache JA, López Diaz J, Cerdá Cerdá E, Rubio Blasco J, Gómez Aguinaga MA, Núñez Reiz A, Rogero Marín S, Oñoro Cañaveral JJ, Sacristán del Castillo JA. Effectiveness and cost of selective decontamination of the digestive tract in critically ill intubated patients: a randomized, double-blind, placebo-controlled, multicenter trial.**

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Ventilator-associated pneumonia (VAP) remains a frequent problem in most intensive care settings, its incidence ranging from 9% to more than 40% (1-5). VAP is thought to increase both length of stay in the intensive care unit (ICU) and mortality (6), and the costs attributed to it are therefore high (7).

Infections occurring in critically ill patients are mainly of endogenous and less frequently of exogenous origin. Infections of the lower respiratory tract are usually preceded by an abnormal carriage pattern, which consists of the presence of potentially pathogenic aerobic organisms in the oropharynx and gut. The importance of oropharyngeal carriage and subsequent entry of oropharyngeal content into the trachea in the pathogenesis of nosocomial pneumonia is well established (8, 9). The stomach and proximal intestine have been suggested to be reservoirs for retrograde colonization of the oropharynx (10). The sequence of events whereby microbes of the gut colonize the upper respiratory tract and are subsequently aspirated, leading to pneumonia, is termed secondary endogenous pneumonia, and constitutes the main target of the nonabsorbable antimicrobial agents used for selective decontamination of the digestive tract (SDD). Locally applied lethal oropharyngeal and gastrointestinal antibiotics are directed at eradicating the carriage of potentially pathogenic aerobic micro-organisms, including *Staphylococcus aureus*, enterobacteria, pseudomonads, and yeast (11).

Different study designs and patient populations in previous trials (12-14) of the efficacy of SDD in patients requiring intensive care yielded mixed results. A high prevalence and incidence rate of gram-negative VAP, with its associated morbidity and costs, prompted us to undertake the present study of whether SDD reduces morbidity and cost for mechanically ventilated, critically ill patients (15).

Methods

We conducted a double-blind, randomized, placebo-controlled trial of SDD in the general ICUs of five teaching hospitals in the Madrid area. Besides the primary end point of pneumonia, we studied the in-

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This study is dedicated to the memory of Dr. Christiaan P. Stoutenbeek.

Correspondence and requests for reprints should be addressed to Dr. M. Sánchez García, Unidad de Cuidados Intensivos, Hospital Universitario Principe de Asturias. 28805 Alcalá de Henares, Madrid, Spain.

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cidence of nonrespiratory infections, length and total cost of ICU stay, ICU mortality, and the two microbiologic end points of carriage and bacterial resistance. The trial protocol was approved by the ethics committee of each institution. Written informed consent was required of each participating patient.

Patient Population

The five ICUs participating in the study treat medical and surgical patients. Patients with trauma and those undergoing emergency surgery comprise 30% of the units admissions.

All patients aged 16 yr or older who were expected to require intubation for a minimum of 48 h, as assessed by the attending intensive-care physician, were considered for inclusion in the study. Severity of the patient s acute disease or underlying condition, infection present on admission, gut surgery, ileus, prior antibiotic therapy, or previous length of stay were not exclusion criteria for the study. Patients not randomized at the time of intubation were enrolled as soon as their clinical course predicted a prolonged duration of intubation. Patients were excluded if they were pregnant, allergic to study antibiotics, received an organ transplantation, or did not require a nasogastric tube.

Study Organization and Design

Baseline samples for microbiology were obtained readily after intubation. The study medications were immediately administered and given until extubation or death. Patients were randomized through a computer-generated random-number table and were stratified by center. Treatment codes were kept in individual sealed envelopes. Treatment and placebo SDD preparations were manufactured by the pharmacy department of the coordinating center, and were indistinguishable from one another in taste, color, and consistency. Severity of illness was assessed by means of the Acute Physiology and Chronic Health Evaluation (APACHE II) score (16) at intubation.

The microbiologists who examined specimens for the study were blinded to the patients groups. Results of surveillance culture were withheld from the attending physician. Results for tracheal aspirates were reported if antibiotic therapy for purulent tracheobronchitis or pneumonia was considered.

The association between SDD and colonization with methicillin-resistant *S.aureus* (MRSA) was evaluated in one unit during an additional 14-mo poststudy period. An identical treatment protocol was followed for all patients. Surveillance cultures were obtained for 100 consecutive patients who met the entry criteria of the study. Generally accepted patient isolation procedures were implemented following the isolation of MRSA in any of the surveillance samples, as was also done during the period of controlled study.

Selective Decontamination Regimen and Study Groups

At 6-h intervals, the oropharyngeal cavity was thoroughly cleansed with 0.1% hexetidine solution and 0.25 g of an adherent methylcellulose paste were applied with a gloved finger. Ten milliliters of active drug or placebo suspension were administered through the patient s nasogastric tube, and aspiration was interrupted for 1 h. An intravenous solution of active drug or placebo was given once daily to noninfected patients during the first three days of the protocol (Figure 1).

The orally applied paste for the SDD-treatment group contained a 2% concentration of gentamicin, polymyxin E, and amphotericin B. The 10-ml suspension included 80 mg of gentamicin, 100 mg of polymyxin E, and 500 mg of amphotericin B. The intravenous solution contained 2 g of ceftriaxone. The control group received placebo paste and placebo suspension, and an intravenous aqueous solution of placebo.

Surveillance samples from the throat and rectum (swabs), stomach (aspirate), and tracheal aspirate (sterile unprotected catheter) were obtained twice weekly. Blood, urine, and other diagnostic samples were taken on clinical indication only. Microorganisms were identified through standard microbiologic techniques. Antibiotic sensitivity patterns were investigated with standardized disk-diffusion methods (17).

Each center followed the local antibiotic policies designed for its respective ecology. Patients were openly randomized to receive either sucralfate or alkalinizing agents to balance gut-protection medication in the different study groups (18). The enteral nutrition protocol consisted of early feeding into the stomach and swift progression to full

nutritional support within 72 h. If severe gastroparesis was documented in three gastric aspirates of more than 150 ml each, taken 6 h apart, parenteral nutrition was started at the discretion of the intensive-care physician.

Infection-control Measures

Routine care, including generally recommended infection-control measures, was applied in all the participating centers (19).

Definitions

Pneumonia was defined by the presence of a compatible, new and persistent infiltrate on chest X-ray, with at least three of the following four criteria: fever (temperature > 38° C), peripheral leukocytosis (> 12,000/mm^3) or leukopenia (< 3,000/mm^3), purulent tracheal aspirate, and growth of a potentially pathogenic microorganism in lower-airway secretions. Because of the expected high level of administration of systemic antibiotics, no protected specimen was required (20).

A time cutoff of 48 h was chosen to distinguish primary from secondary infections. Five days or 120 h was the time criterion for the distinction between early-onset and late-onset pneumonia. Secondary endogenous infection and pneumonia were considered to be present if the bacterium causing an infection had been previously identified in surveillance cultures (21).

Index culture was defined as the first sample, for either diagnostic or surveillance purposes, yielding MRSA during the additional study of MRSA. For calculation of the incidence of MRSA, we considered all patients with one or more MRSA-positive isolates.

Cost

The ICU costs per day were $666 (at a conversion rate of 150 Spanish Pesetas to the U.S. Dollar), including fixed costs, nutrition, and all drugs except systemic and topical antibiotics. The price of the topical antibiotic powder was $4 daily per patient. All episodes of pneumonia not existing at the time of admission were considered in calculating cost. The cost for each bacterial culture of a clinical specimen was $24.30. The cost for processing of endotracheal aspirates was $40. Bronchoscopy with bronchoalveolar lavage (BAL) and a telescoping catheter, including the processing of samples, cost $227. The cost of the abdominal computed tomographic scan used for the diagnosis of abdominal infection was $140. One catheter-related infection included one multilumen intravenous catheter at a cost of $33. In the SDD-treatment group, the cost of weekly surveillance cultures (four samples) was compared with the cost of one weekly culture of endo-

tracheal aspirate in the control group ($24.30 per culture). The ratio of the total cost in the two groups, divided by the number of survivors in each group, was considered to reflect the average cost-effectiveness.

Statistical Analysis

A sample size of 295 was calculated as necessary to demonstrate a reduction in VAP from 30% to 15%, including 10% losses, with a statistical power of 0.80, with a two-sided test at the 0.05 significance level. All data were analyzed according to the intention-to-treat principle.

Categorical variables were compared through use of the chi-square test, with Yates correction for continuity. Fisher s exact test was used whenever required by the smallest value of the contingency (2×2) table. Differences in means of normally distributed variables were analyzed with Student s *t* test. Nonparametric variables were compared with Wilcoxon s rank-sum test.

The probabilities of survival, of remaining intubated, and of remaining free of pneumonia were estimated for each study group with the Kaplan-Meier method, and were compared with the log-rank test.

Prognostic factors for mortality were studied with a Cox proportional hazards model. The model was adjusted for the following covariates: APACHE II score on admission, study group, receiving intravenous component of the protocol (ceftriaxone), age and center.

A value of $\leq$0.05 or less was considered statistically significant. Statistical analyses were performed with SAS, version 6, release 6.08 (SAS Institute, Cary, NC).

RESULTS

Patients

A total of 271 patients were consecutively enrolled in the study, of whom 131 received antibiotic prophylaxis and 140 received placebo. The APACHE II score on admission was 26.6 $\pm$ 10(mean $\pm$ SD) (Table 1); approximately 20% of the patients were in a state of shock, and one third of the patients in each study group had multiple organ failure at the time of ICU admission. Impaired consciousness was more frequent on admission in treated patients. The diagnostic category was medical in 70.5%, surgical in 12.9%, and trauma in 16.6%. Primary infection was present in 31.3% of treated and 36.4% of control patients. In the SDD-treated group, four patients died within 48 h of intubation, and five improved and were extubated. In the control group, eight patients died and eight were extubated within 48 h of intubation. Baseline characteristics (Table 1) were comparable in the two groups, except for a significantly higher percentage of patients with chronic renal failure undergoing SDD.

Infections, Morbidity, and Costs

Of 74 (27.3%) patients who were considered infection-free on admission, 35 received intravenous ceftriaxone and 39 received placebo for 3 d (Table 2). The incidence of early-onset pneumonia was 14.3% (five patients) in the treated group and 51.3% (20 patients) in the control group ($p = 0.002$). The overall incidence of early-onset pneumonia remained significantly lower. (Table 3).

The reduction in the incidence of secondary pneumonia and nonrespiratory infection in the SDD-treated group was highly significant (Table 3). The daily incidence rate of VAP decreased from 17.3 episodes per 1,000 ventilator-days in the placebo group to 8.5 episodes per 1,000 ventilator-days in the SDD-treated group ($p<0.001$). The probability of remaining free of secondary pneumonia was significantly higher in decontaminated patients than in controls (Figure 2). Given a baseline risk of 29.3% and assuming a relative risk reduction of 61%, 5.6 patients had to be treated in order to prevent 1 episode of pneumonia. Two patients in the treatment group and seven in the control group had more than one episode of pneumonia. All patients in whom there was no microbiologic proof for the clinical signs of pneumonia (n = 19), save for one control subject, were receiving systemic antibiotic therapy at the time of sampling (Table 4). The incidence of gram-negative secondary pneumonia (Table 4) was significantly lower in the SDD-treated group, as was the incidence of episodes of secondary pneumonia of endogenous origin. Two of the three cases of gram-negative secondary endogenous pneumonia were diagnosed in patients in the SDD-treated group in whom administration of the study medications had been discontinued.

Nine treated patients and six in the control group did not receive gut-protection medication. In a comparison based on intention-to-treat, the incidence of VAP was 23%, versus 19.2% in patients allocated to sucralfate and an H_2-blocker, respectively ($p>0.05$).

Among survivors, the probability of remaining intubated over the course of the study (Figure 3) as well as during the

TABLE 1

BASELINE CHARACTERISTICS

Characteristic	SDD *(n=131)*	Placebo *(n=140)*
Age	55.0±18.7	55.1±18.3
No. of males	96(73.8)	96(68.1)
Underlying conditions		
COPD	28(21.4)	21(15)
Diabetes	21(16.0)	19(13.6)
Cirrhosis	9(6.9)	9(6.4)
Alcoholism	7(5.3)	9(6.4)
Chronic renal failure	11(8.4)	3(2.1)*
Asthma	1(0.7)	4(2.8)
HIV infection	3(2.8)	2(1.6)
Diagnostic group		
Medical	90(68.7)	101(72.1)
Surgical	18(13.7)	17(12.1)
Elective	5	5
Emergency	13	12
Trauma	22(16.8)	23(16.4)

Definition of abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus; ICU = intensive care unit; MOF = multiple organ failure; SDD = selective decontamination of the digestive tract.

Plus-minus values are means ±SD. Values in parentheses are percentages.

*p = 0.04, and p = 0.1 by chi-square test.

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TABLE 2

MORBIDITY AND MORTALITY IN PATIENTS WITHOUT (INTRAVENOUS CEFTRIAXONE OR INTRAVENOUS PLACEBO) AND WITH PRIMARY INFECTION (INFECTION-SPECIFIC INTRAVENOUS ANTIBIOTICS)

	Randomized *(n = 271)*			
	SDD *(n = 131)*		Placebo *(n = 140)*	
	Intravenous Ceftriaxone (3 d) *(n = 35)*	Infection-specific Intravenous Antibiotics *(n = 39)*	Intravenous Placebo (3 d) *(n = 39)*	Infection-specific Intravenous Antibiotics *(n = 101)*
EOP	5 (14.3)*	18 (18.7)	20 (51.3)	26 (25.7)
VAP	4 (11.4)	11 (11.4)*	13 (33.3)	28 (27.7)
ICU mortality	10 (28.6)	41 (43.6)	19 (48.7)	47 (46.5)
LOS	9 (6-15)	15 (7-23)	11 (5-21)	14 (8-29)

Definition of abbreviations: EPO = early-onset pneumonia; ICU = intensive care unit; LOS = length of ICU stay; SDD = selective decontamination of the digestive tract; VAP = ventilator-associated pneumonia.

Values in parentheses are percentages.

LOS is expressed as median (interquartile range).

Statistical comparisons were performed between intravenous ceftriaxone and intravenous placebo groups and between infection-specific SDD and placebo groups, respectively.

*$p < 0.01$, and [1]$p = 0.05$ by chi-square test.

ICU stay (Table 3) was significantly reduced in patients undergoing SDD. Significantly fewer patients in the SDD-treated group required systemic antibiotic therapy, and the duration of antibiotic therapy was significantly shorter (Table 3). In the SDD-treated group, the mean cost of systemic antibiotics, including prophylactic ceftriaxone, was 37% lower than in the control group (Table 5), and the cost of diagnostic procedures for infection was significantly reduced. The calculations of cost of diagnosis of pneumonia that was not present at the time of admission were based on 38 episodes in the

TABLE 3

INFECTION RATES AND MORBIDITY

	SDD *(n = 131)*		Placebo *(n = 140)*			
	n (%)	95% CI	**n (%)**	**95% CI**	**p Value**	**95% CI**
Infection						
Primary infection	63 (48.1)	(39.3-56.9)	73 (52.1)	(43.6-60.6)	0.58	(-16.7,8.6)
Pneumonia	38 (29.0)	(21.6-37.7)	57 (40.7)	(32.6-49.3)	0.058	(-23.7,4.1)
Early-onset pneumonia	23 (17.5)	(11.7-25.4)	46 (32.8)	(25.3-41.4)	< 0.01	(-26.2,-4.4)
Secondary infection	35 (26.7)	(19.5-35.3)	64 (45.7)	(37.3-54.3)	0.002	(-30.9,-7.0)
Pneumonia	15 (11.4)	(6.8-18.5)	41 (29.3)	(22.1-37.7)	< 0.001	(-27.9,-7.8)
Other infections	25 (19.1)	(12.9-27.1)	43 (30.7)	(23.3-39.2)	0.04	(-22.5,-0.7)
Bloodstream	15 (15.4)	(6.8-18.5)	23 (16.4)	(10.9-23.8)	0.98	(-13.9,3.9)
Wounds	11 (8.4)	(4.5-14.9)	14 (10.0)	(5.8-16.5)	0.56	(-9.2,6.0)
Urinary tract	6 (4.6)	(1.9-10.1)	14 (10.0)	(5.8-16.5)	0.54	(-12.3,1.4)
Abdominal	5 (3.8)	(1.4-9.1)	9 (6.4)	(3.2-12.2)	0.91	(-8.6,3.3)
Sepsis	6 (4.6)	(1.9-10.1)	7 (5.0)	(2.2-10.4)	0.72	(-6.2,5.4)

Catheter-related	3 (2.3)	(0.6-7.1)	9 (6.4)	(3.2-12.2)	0.17	(-9.7,1.4)
Antibiotics						
Patients	108 (82.4)	(74.6-88.3)	128 (91.4)	(85.2-95.3)	0.04	(-17.7,-0.2)
Duration in days	12 (4-34)	(23.1 ± 27.6)	20 (8-44.5)	(31.9 ± 42.0)	0.015	
Aminoglycosides						
Patients	78 (59.5)	(50.6-67.9)	101 (72.1)	(63.8-79.2)	0.039	(-24.1,-6.5)
Duration in days	2 (0-10)	(6.4 ± 8.7)	6 (0-14)	(8.6 ± 11.2)	0.011	
Third-generation cephalosporins						
Patients	46 (35.1)	(27.1-44.0)	57 (40.7)	(32.6-49.3)	0.41	(-17.9,6.7)
Duration in days	0 (0-5)	(3.0 ± 5.4)	0 (0-7.5)	(4.5 ± 7.5)	0.09	
Morbidity (in days)						
All patients						
Intubation	9 (4-18)	(13.4 ± 13.5)	10 (5-20.5)	(16.9 ± 22.8)	0.20	
ICU stay	13 (7-22)	(16.6 ± 15.8)	13 (7-25)	(19.9 ± 23.5)	0.21	
Survivors						
Intubation	8.5 (3-17)	(11.7 ± 11.1)	12 (5-26)	(18.4 ± 20.7)	0.01	
ICU stay	11 (7-21.5)	(16.5 ± 15.6)	16.5 (10-30)	(22.8 ± 21.0)	0.006	
Nonsurvivors						
Intubation	13 (5-22)	(16.0 ± 16.5)	8.5 (4-17)	(15.2 ± 25.0)	0.07	
ICU stay	13 (6-22)	(16.7 ± 16.3)	10.5 (4-17)	(16.6 ± 25.8)	0.07	

Definition of abbreviations: ICU = intensive care unit; SDD = selective decontamination of the digestive tract.

Values in parentheses are percentages.

Plus-minus values are means ± SD.

Duration of antibiotic therapy, intubation, and stay expressed as median (first, third quartile). Antimicrobial therapy included 3 d of ceftriaxone in the treated group.

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Figure 2. Comparison of Kaplan-Meier estimates of probability of remaining free of pneumonia at 3 wk of intubation (p = 0.0002 by two-sided long-rank test). SDD = selective decontamination of the digestive tract.

Figure 3. Comparison of Kaplan-Meier estimates of survivors requiring ventilation at third week of ICU stay (p = 0.006 by two-sided log-rank test). SDD = selective decontamination of the digestive tract.

treated group and 82 episodes in the control group. There was a 21% reduction of the total cost per survivor in the SDD-treated group.

Mortality

ICU mortality was 38.9% (51 patients) in the SDD-treated group and 47.1% (66 patients) in the control group (p = 0.57 by the log-rank test). APACHE II score on admission was the only independent, statistically significant predictor of mortality (p = 0.0001). All other examined covariates were not independent predictors of mortality, with p values above 0.05.

Microbiology

Figure 4 shows the impact of SDD on the prevalence of gram-negative microorganisms. Baseline figures are comparable, at about 50%, and the carriage rate decreased significantly in the treated group, to 23.9% (p = 0.001) and to 13.1% of patients on Days 3 and 7, respectively, and was significantly lower throughout the study than in the placebo-control group. The prevalence of aerobic gram-negative bacilli in the oropharynx and rectum of patients undergoing SDD was significantly reduced during the study, from 30.9% to 11.4% on Day 3 (p = 0.002), and from 34% to 11.5% on Day 7 (p = 0.003), respectively, and always remained significantly lower than in the control group at both of these anatomic sites. Colonization of the lower airway with gram-negative microorganisms was significantly lower in treated patients than in controls (Table 6). A gram-negative bacillus was identified in tracheal aspirate on an average of every 22 d of intubation (45 per 1,000 ventilator-days) in decontaminated patients, and every 8.4 d (119 per 1,000 ventilator days) in the control group (p &#60 0.001).

Baseline levels of gram-positive cocci (Figure 5) were comparable in the treatment and control groups, but in decontaminated patients the prevalence increased significantly over the study period. The level of carriage of MRSA, coagulase-negative staphylococci, and enterococci was significantly higher in the SDD-treated group (p &#60 0.001, individually, for each microorganism), whereas methicillin-sensitive *S. aureus* was carried in a similar proportion in both groups.

The incidence of MRSA was 27.6% during the study itself and 8% during the follow-up period. The median and mean times of index cultures were identical during each of the two periods. The mean number of gram-positive cocci cultured from all four sampling sites decreased from 547 per 1,000 ventilator-days to 73 per 1,000 ventilator-days.

Adverse Effects

No adverse effects were attributed to the study preparations.

DISCUSSION

The principal finding of this randomized double-blind study was that routine SDD reduces both the rate of VAP and the costs of caring for intubated, mechanically ventilated, critically ill patients. Although mortality was not significantly affected by SDD, the sample size of this multicenter trial, performed in a general ICU setting, was not sufficient to permit detection of a significant difference with SDD (12,22).

Infection rates mainly reflect severity of underlying disease (23). For example a randomized French trial of SDD found a 9% infection rate of the lower airways in control patients with a low severity score, of whom less than 60% required ventilation (24). In contrast, the lower-airway infection rate was more than 90% in a Dutch trial of SDD enrolling only ventilated patients with an APACHE II score above 14 (25). The category of ICU (i.e., medical, surgical, trauma) constitutes another factor influencing the risk of infection. Medical patients, who are in general older and more often suffering from

TABLE 4

ETIOLOGY AND MECHANISM OF SECONDARY PNEUMONIA

Microorganism	SDD (*n = 131*)	Placebo (*n = 140*)	p Value
Aerobic gram-negative bacilli	5	19	0.005
Endogenous	3	18	0.001
Staphylococcus aureus	3	5	ns
Methicillin-resistant	3	4	ns
Endogenous	2	2	
Methicillin-sensitive	0	1	ns
Endogenous	0	1	
Mixed	2	2	ns
Enterococcus	1	0	
Endogenous	1	0	
Not isolated	4	15	0.02
Total	15	41	< 0.001

Definition of abbreviation: SDD = selective decontamination of the digestive tract.

Etiology of mixed pneumonia in the selective decontamination group: methicillin-resistant *S. aureus* with *Pseudomonas aeruginosa* and methicillin-resistant *S. aureus* with *Enterobacter cloacae.* Etiology of mixed pneumonia in the placebo group: methicillin-resistant *S. aureus* with *P. aeruginosa* and methicillin-resistant *S. aureus* with *Burkholderia cepacia.*

TABLE 5

COMPARATIVE COSTS

Parameter	Median Cost in U.S. Dollars		p Value
	SDD(n = 131)	Placebo(n = 140)	
Antibiotics			
Total	244(84-1,035)	268(73-1,324)	0.3
Systemic	169(65-927)	268(73-1,324)	0.06
Topical	36(16-76)	0	<0.001
Diagnostic procedures of infection	0(0-48)	40(0-80)	<0.001
Surveillance cultures	247(109-521)	35(23-73)	<0.001
ICU stay	8,666(4,667-15,333)	8,666(4,667-16,666)	0.3
Total	8,840(4,837-16,861)	9,318(5,084-18,470)	0.3
Total per survivor	21,507	27,250	
Total of group	1,720,624	2,016,470	

Definition of abbreviations: ICU = intensive care unit: SDD = selective decontamination of the digestive tract. Conversion rate is 150 Spanish pesetas to the U.S. Dollar. Median (interquartile range).

chronic debilitating diseases, are thought to be at higher risk than surgical and trauma patients (1, 6). Although length of ICU stay and days of mechanical ventilation again reflect the severity of underlying disease, a change in denominator from a patient-based to a device-associated infection rate is thought to facilitate meaningful comparisons among trials of SDD (26, 27). Among all randomized SDD trials so far reported, the mean APACHE II score of 26.6 in our trial is the highest, suggesting that ours were a critically ill subset of ICU patients. Moreover, more than 70% were medical patients. In our control group, the overall infection rate, the percentage of patients developing secondary pneumonia, and the median rate of VAP were 50%, 32%, and 17.3 per 1,000 ventilator-days, respectively. These figures are similar to those reported for comparable patient populations from Spain (1), Europe (3, 4), and the United States (2, 5, 26). The use of SDD, as described in this protocol, was highly effective. The overall infection rate, secondary-pneumonia rate, and number of pneumonias per 1,000 ventilator-days were 25%, 10%, and 8.5 pneumonias per 1,000 ventilator-days ($p < 0.005$). Moreover, our data show that the chance of critically ill ICU patients with mean APACHE II score of 26.6 of remaining free of pneumonia after 3 wk of ventilation is significantly higher with SDD than with the traditional approach. Our data are consistent with four recent metaanalyses (12-14, 22). In addition, a significant reduction in ventilator-days for patients who underwent SDD and survived was observed in this multicenter study.

The substantial impact of SDD on infectious morbidity in critically ill ICU patients in this trial was associated with a lower total treatment cost. Incremental analysis was therefore not applicable (28). A significant 37% reduction of systemic antibiotic cost was observed for decontaminated patients, which is similar to findings in other studies (29-32). However, because more than 90% of the mean total costs in both study groups were fixed, the savings and increased cost-effectiveness associated with SDD in the present study were mainly a function of reduction of length of stay (33). The cost of SDD (32, 34) can be substantially reduced if generic antibiotic powders instead of commercial preparations are used, if preparations for SDD are manufactured in the hospital pharmacy, and if gentamicin is used instead of tobramycin. Although *in vitro* data show a relatively higher degree of inactivation of gentamicin than of tobramycin by feces (35), the combination with polymyxin E proved to be effective *in vivo* in this and previous trials(29, 36).

The combined finding of more survivors at lower cost generates the attractive economic message that it is cheaper to produce a survivor in an ICU by implementing SDD than it is with a traditional approach. There were more survivors in the SDD-treated group in our study (80 of 131; 61%) than in the control group (74 of 140; 53%). Because of the limited sample size, the difference of mortality ($p = 0.57$) was not significant. A recent metaanalysis, including 5,727 patients in 33 randomized trials, found a significant reduction of mortality in the subset of 3,581 patients in 16 trials who were treated with the full protocol (22). In addition, the findings

in the present study support a very recent analysis which found that the more ill the ICU patient (APACHE II score: 26.6), the more effective is SDD in reducing mortality (37). The greater number of survivors, even if not significant, supported the favorable cost-effectiveness findings previously reported by Rocha (30) and Korinek (31). Our findings are also consistent with the findings in other trials(1) that the severity of underlying disease determines outcome. However, our study failed to show that pneumonia independently contributes to ICU mortality (6).

Surveillance samples from the throat and rectum are taken with the purpose of detecting the carrier state. Carriage of aerobic gram-negative bacilli (AGNB) is abnormal and reflects severity of underlying disease. Two recent French studies showed that severity of illness and infection on admission were two independent risk factors for the development of abnormal bacterial carriage (38, 39). Half of our mainly medical population carried AGNB on entering the present trail, sup-

Figure 4. Prevalence of aerobicgram-negative bacilli (AGNB) at all sites (oropharynx, trachea, stomach, and rectum). SDD = selective decontamination of the digestive tract.

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TABLE 6

COLONIZATION OF THE LOWER AIRWAY:

NUMBER OF POSITIVE CULTURES

Microorganism	SDD (*41.3 Sampling Days*)	Placebo (*655 Sampling Days*)
Baseline		
Gram negative		
Total	55	70
Escherichia coli	24	24
Pseudomonas spp.	10	10
Proteus spp.	7	6
Enterobacter spp.	5	8
Haemophilus spp.	7	12
Other	2	10
Gram positive		
Total	48	49
MSSA	13	13
MRSA	16	14
CNS	6	7
Enterococcus spp.	10	13
Streptococcus pneumoniae	5	3
Fungi, total	6	10
Acquired		
Gram negative		
Total	65	272*
Pseudomonas spp.	26	142*
Escherichia coli	21	34
Acinetobacter spp.	6	28§
Enterobacter spp.	7	16
Proteus spp.	2	22
Serratia spp.	1	18
Klebsiella spp.	1	3
Other	1	10
Gram Positive		
Total	260	162*
MSSA	37	42
MRSA	109	43*
CNS	33	21*
Enterococcus spp.	81	54*
Streptococcus pneumoniae	0	2
Fungi		
Total	4	18
Candida albicans	3	16
Mucor	1	0
Other	0	2

Definition of abbreviations: CNS = coagulase-negative staphylococci: MRSA = methicillin-resistant *Staphylococcus aureus:* MSSA = methicillin-sensitive *S. aurius;* SDD = selective decontamination of the digestive tract. All statistical comparisons corrected for differences in number of sampling days between groups.

[*]p <0.001.
p <0.01.
p <0.1.
[§]p <0.05.

porting the observation that our study population belonged to a severely ill subset of patients. Apart from their value for identification of patients at high risk for secondary infection with an abnormal carrier state of AGNB, surveillance cultures are an integral part of the SDD strategy (27) for three reasons: (*1*) to monitor compliance with and efficacy of SDD; (*2*) to distinguish exogenous (without previous carriage) from endogenous infections: and (*3*) to detect antimicrobial resistance in an early stage.

AGNB, methicillin-sensitive *S. aureus*, and yeasts are the target microorganisms of SDD. The effective eradication of AGNB carriage reflects good compliance. By design, SDD will not affect the indigenous flora, including coagulase-negative staphylococci and enterococci, Inevitably, SDD will exert selective pressure on potentially pathogenic microorganisms (PPM) such as MRSA that are intrinsically resistant to polymyxin E, gentamicin, and amphotericin B, and cause the observed associate increased in colonization with coagulase-negative staphylococci, enterococci, and MRSA. The topical antimicrobial agents used in our study were carefully chosen for their propensity to leave largely undisturbed the indigenous flora, which are thought to play a role in the resistance to colonization by PPM (40). However, although coagulase-negative staphylococci and enterococci rarely cause lower airway infections, MRSA is a serious PPM known to be responsible for infections of both endogenous and exogenous origin. Although of no clinical relevance in the present study, MRSA was significantly more prevalent in the SDD-treated group. The 14-mo follow-up period did not show an increase in colonization with MRSA, but this finding requires confirmation after prolonged use of SDD. Some studies of SDD found endemic MRSA during and their prevention phases (41-46). This is a substantial (4) and complex issue, and requires further evaluation (47).

Figure 5. Prevalence of gram-positive cocci (GPC), including methicillin-sensitive and methicillin-resistant *Staphylococcus aureus,* coagulase-negative staphylococci, and enterococci, at all sites (oropharynx, trachea, stomach, and rectum). SDD = selective decontamination of the digestive tract.

The emergence of microorganisms resistant to the antimicrobials used for SDD could reduce the long-term effectiveness of SDD in routine clinical practice. The traditional experience is that the extensive use of antimicrobials inevitably leads to resistance. However, there is a fundamental difference between the conventional use of parenteral agents only (48) and the full SDD protocol, combining short-term systemic antibiotics with long-term nonabsorbable antibiotics. Resistant strains generally emerge first in the gut, following overgrowth. These resistant strains have been successfully abolished by polymyxin E and gentamicin. Resistance developing in a patient who is free of PPM is thought to be unlikely. University hospitals (11,46) that have used SDD for more than 10 yr have not detected an increase in the frequency of such resistant infections. The significant reduction of systemic antibiotic usage found in the present and other studies (29-32) could be a contributory factor in controlling the incidence of resistance among both gram-negative and gram-positive microorganisms. The reduced antibiotic usage may be partly responsible for the absence of resistant gram-negative bacilli in previous trials of SDD and in long-term follow-up studies (46,49), and for the absence of an increase in colonization of infection with MRSA during observational periods by Hammond and colleagues (46) as well as in the present trial.

In conclusion, we found that SDD was highly effective in preventing secondary infections in a mixed population of ven-

tilated patients at high risk for infection. The associated significant reductions in use of systemic antibiotic therapy and length of stay account for a lower cost in the SDD-treated group of patients in the study. We observed no resistant gram-negative bacilli or superinfections following failures of SDD. However, colonization, although not infection, with intrinsically resistant gram-positive cocci was increased in the treated group, and close microbiologic surveillance is therefore mandatory with the use of SDD.

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