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

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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 prophylaxis, 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 secretions 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

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

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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_{O_2} 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 12.000×10^9/L), leukopenia (less than 4.000×10^9/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_{O_2}) 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 α error of 0.05 and a β 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.

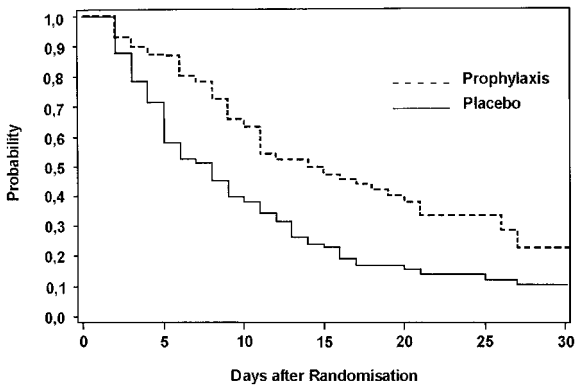

Figure 1. Comparison of Kaplan-Meier estimates of probability of remaining free of infections acquired in the ICU during Days 1–28 after randomization in 265 patients receiving antibiotic prophylaxis and in 262 patients receiving placebo (p = 0.001; RR, 0.477; 95% CI, 0.367–0.620 for Cox proportional hazards regression analysis).

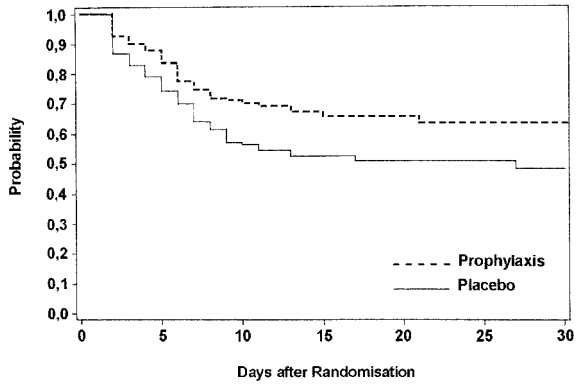

Figure 2. Comparison of Kaplan-Meier estimates of probability of remaining free of severe organ system dysfunctions acquired in the ICU during Days 1–28 after randomization in 265 patients receiving antibiotic prophylaxis and in 262 patients receiving placebo (p = 0.0051; RR, 0.636; 95% CI, 0.463–0.874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

Infections

On admission, a total of 211 patients were infected (101 of the prophylaxis group 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.

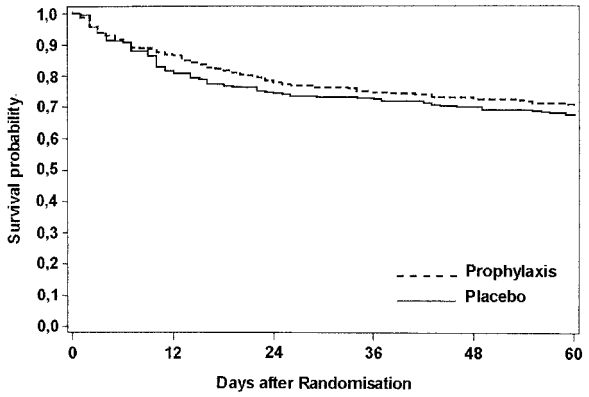

Figure 3. Comparison of Kaplan-Meier estimates of probability of survival during Days 1–60 after randomization in 265 patients receiving antibiotic prophylaxis and in 262 patients receiving placebo (p = 0.1321; RR, 0.761; 95% CI, 0.533–1.086 for Cox proportional hazards regression analysis).

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
	Placebo: 262	75 (28.6)	0.533–1.086		113 (43.1)	0.655–1.118	
Stratum I: scores ⩽ 19	Prophyl.: 120	17 (14.2)	0.885	0.7022	33 (27.5)	0.969	0.8961
	Placebo: 121	23 (19.0)	0.472–1.659		34 (28.1)	0.600–1.564	
Stratum II: scores 20–29	Prophyl.: 122	20 (16.4)	0.508	0.0147	51 (41.8)	0.720	0.0844
	Placebo: 115	38 (33.0)	0.295–0.875		60 (52.2)	0.496–1.046	
Stratum III: scores ⩾ 30	Prophyl.: 23	15 (65.2)	1.593	0.2118	18 (78.3)	1.316	0.4046
	Placebo: 26	14 (53.8)	0.767–3.306		19 (73.1)	0.690–2.508	

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
Staphylococcus 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 packed red blood cells in 15 patients, and surgical intervention was necessary in 3 cases.

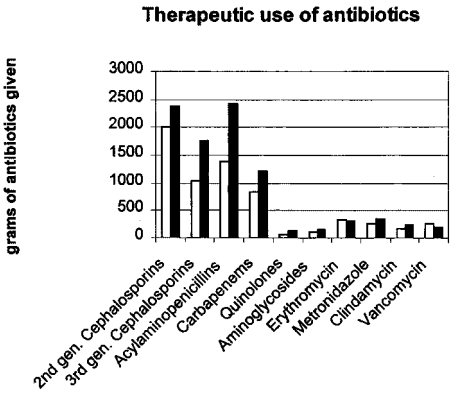

Figure 4. Comparison of the amount of antibiotics that were administered to at least 2% of the patients. Second-generation cephalosporins: cefotiame, cefamandole, cefoxitine; third-generation cephalosporins: cefotaxime, ceftriaxone, cefmenoxime, ceftazidime; acylaminopenicillins: piperacillin, mezlocillin; carbapenem: imipenem-cilastatin; quinolones: ciprofloxacin, 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 specification was given for the fatality. One 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 we 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 prognostic 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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