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Inadequate Antimicrobial Treatment of Infections

A Risk Factor for Hospital Mortality Among Critically Ill Patients

Marin H. Kollef, MD, FCCP; Glenda Sherman, RN; Suzanne Ward, RN; and Victoria J. Fraser, MD

Study objective: **To evaluate the relationship between inadequate antimicrobial treatment of infections (both community-acquired and nosocomial infections) and hospital mortality for patients requiring ICU admission.**
Design: **Prospective cohort study.**
Setting: **Barnes-Jewish Hospital, a university-affiliated urban teaching hospital.**
Patients: **Two thousand consecutive patients requiring admission to the medical or surgical ICU.**
Interventions: **Prospective patient surveillance and data collection.**
Measurements and results: **One hundred sixty-nine (8.5%) infected patients received inadequate antimicrobial treatment of their infections. This represented 25.8% of the 655 patients assessed to have either community-acquired or nosocomial infections. The occurrence of inadequate antimicrobial treatment of infection was most common among patients with nosocomial infections, which developed after treatment of a community-acquired infection (45.2%), followed by patients with nosocomial infections alone (34.3%) and patients with community-acquired infections alone (17.1%) ($p < 0.001$). Multiple logistic regression analysis, using only the cohort of infected patients ($n = 655$), demonstrated that the prior administration of antibiotics (adjusted odds ratio [OR], 3.39; 95% confidence interval [CI], 2.88 to 4.23; $p < 0.001$), presence of a bloodstream infection (adjusted OR, 1.88; 95% CI, 1.52 to 2.32; $p = 0.003$), increasing acute physiology and chronic health evaluation (APACHE) II scores (adjusted OR, 1.04; 95% CI, 1.03 to 1.05; $p = 0.002$), and decreasing patient age (adjusted OR, 1.01; 95% CI, 1.01 to 1.02; $p = 0.012$) were independently associated with the administration of inadequate antimicrobial treatment. The hospital mortality rate of infected patients receiving inadequate antimicrobial treatment (52.1%) was statistically greater than the hospital mortality rate of the remaining patients in the cohort ($n = 1,831$) without this risk factor (12.2%) (relative risk [RR], 4.26; 95% CI, 3.52 to 5.15; $p < 0.001$). Similarly, the infection-related mortality rate for infected patients receiving inadequate antimicrobial treatment (42.0%) was significantly greater than the infection-related mortality rate of infected patients receiving adequate antimicrobial treatment (17.7%) (RR, 2.37; 95% CI, 1.83 to 3.08; $p < 0.001$). Using a logistic regression model, inadequate antimicrobial treatment of infection was found to be the most important independent determinant of hospital mortality for the entire patient cohort (adjusted OR, 4.27; 95% CI, 3.35 to 5.44; $p < 0.001$). The other identified independent determinants of hospital mortality included the number of acquired organ system derangements, use of vasopressor agents, the presence of an underlying malignancy, increasing APACHE II scores, increasing age, and having a nonsurgical diagnosis at the time of ICU admission.**
Conclusions: **Inadequate treatment of infections among patients requiring ICU admission appears to be an important determinant of hospital mortality. These data suggest that clinical efforts aimed at reducing the occurrence of inadequate antimicrobial treatment could improve the outcomes of critically ill patients. Additionally, prior antimicrobial therapy should be recognized as an important risk factor for the administration of inadequate antimicrobial treatment among ICU patients with clinically suspected infections.**

(CHEST 1999; 115:462–474)

Key words: antibiotics; bacteremia; community-acquired infection; critical care; infection; nosocomial infection; outcomes; pneumonia

Abbreviations: APACHE = acute physiology and chronic health evaluation; CI = confidence interval; OR = odds ratio; ORSA = oxacillin-resistant *Staphylococcus aureus*; RR = relative risk; VAP = ventilator-associated pneumonia; VRE = vancomycin-resistant enterococci

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The presence of infection is recognized as an important determinant of outcome for patients requiring ICU admission. This is especially true in the current era of increasing antimicrobial resistance among common bacterial pathogens.[1,2] Both community-acquired infections necessitating ICU admission and nosocomial infections acquired in the ICU appear to influence the likelihood of mortality as well as the duration of hospitalizations.[3–6] Antimicrobial therapy is recognized as the cornerstone of treatment for acquired infections along with drainage of infected fluid collections and the debridement or removal of infected tissues or prostheses.[7] Once antimicrobial therapy is initiated, it should ideally be directed at the likely pathogens responsible for the clinically suspected infection. Additionally, the selection of antimicrobial agents should take into account the local antibiotic susceptibility patterns of those pathogens. The importance of providing early antimicrobial therapy, which is effective against the microorganisms responsible for infection in hospitalized patients (*ie*, adequate antimicrobial therapy), has been highlighted by several recent clinical investigations. These studies have demonstrated that the absence of adequate antimicrobial therapy in patients with pneumonia, peritonitis, bacteremia, or meningitis is associated with adverse patient outcomes, including increased rates of hospital mortality.[8–16] Failure to treat infections with antimicrobial agents, delays in the administration of adequate antimicrobial treatment, or the initial use of antimicrobial agents to which the identified pathogens are resistant (*ie*, inadequate antimicrobial treatment) all appear to increase the risk for hospital mortality.[8–16]

The overall incidence and clinical importance of inadequate antimicrobial treatment of microbiologically documented infections, as a risk factor for hospital mortality and other adverse clinical outcomes, has not been systematically evaluated in the ICU setting. Therefore, we performed a prospective cohort study with two main goals. First, we wanted to determine the magnitude of the problem of inadequate antimicrobial treatment among critically ill adult patients. Second, we sought to identify the reasons for the administration of inadequate antimicrobial treatment. We selected a cohort of critically ill patients for examination since they are the most likely to be adversely affected by the presence of infection.[3,5] We also purposefully evaluated both community-acquired infections necessitating ICU admission and nosocomial infections that were acquired in the ICU. This was done to assess the relative importance of these infections on patient outcomes and to determine the occurrence of inadequate antimicrobial treatment for each of these classes of infection. It was our hope that such data would provide useful information for the improvement of existing algorithms outlining strategies for the empiric treatment of suspected infection among critically ill patients.[17–19]

*From the Department of Internal Medicine, Pulmonary and Critical Care Division (Drs. Kollef and Ward), Division of Infectious Diseases (Dr. Fraser), Washington University School of Medicine, St. Louis, MO; and the Center for Quality Management (Dr. Sherman), Barnes-Jewish-Christian Health System, St. Louis, MO.

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Correspondence to: Marin H. Kollef, MD, FCCP, Pulmonary and Critical Care Division, 660 S. Euclid Avenue, Campus Box 8052, St. Louis, MO 63110; e-mail: mkollef@pulmonary.wustl.edu

Materials and Methods

Study Location and Patients

The study was conducted at a university-affiliated urban teaching hospital: Barnes-Jewish Hospital (1,400 beds) in St. Louis. During an 8-month period (July 1997 to March 1998), all patients admitted to the medical ICU (19 beds) and surgical ICU (18 beds) were potentially eligible for this investigation. Patients were excluded if they were transferred to the medical or surgical ICU temporarily due to a lack of available beds in one of the other hospital ICUs. The study was approved by the Washington University School of Medicine Human Studies Committee.

Study Design and Data Collection

A prospective cohort study design was employed segregating infected patients according to the presence or absence of inadequate antimicrobial treatment of infection. Hospital mortality was the main outcome variable compared between the two study groups. Additionally, the entire study cohort was segregated according to the presence or absence of hospital mortality. This was done to identify risk factors for hospital mortality for this patient cohort. We also assessed secondary outcomes, including the durations of hospitalization, intensive care, and mechanical ventilation, and the occurrence of acquired organ system derangements. For purposes of this investigation, inadequate antimicrobial treatment of infection was defined as the microbiologic documentation of an infection (*ie*, a positive culture result) which was not being effectively treated at the time of its identification. Inadequate antimicrobial treatment included the absence of antimicrobial agents directed at a specific class of microorganisms (*eg*, absence of therapy for fungemia due to *Candida albicans*) and the administration of an antimicrobial agent to which the microorganism responsible for the infection was resistant (*eg*, empiric treatment with oxacillin for pneumonia subsequently attributed to oxacillin-resistant *Staphylococcus aureus* [ORSA] based on lower airway culture results).

For all study patients, the following characteristics were prospectively recorded: age; gender; race; serum albumin (g/dL); the ratio of arterial blood oxygen tension to the concentration of inspired oxygen (PaO_2/FIO_2) at the time of ICU admission; severity of illness based on acute physiology and chronic health evaluation (APACHE) II scores[20]; the presence of congestive heart failure requiring medical therapy with diuretics, inotropes, and/or vasodilators; COPD requiring medical therapy with in-

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haled bronchodilators or corticosteroids; underlying malignancy; positive serology for the HIV; and the need for surgical intervention. Specific processes of medical care examined included the administration of corticosteroids, antacids, sucralfate, vasopressors, or histamine type-2 receptor antagonists; dialysis; reintubation; presence of a tracheostomy; urinary tract catheterization and its duration; central vein catheterization and its duration; and the need for mechanical ventilation and its duration.

One of the investigators made daily rounds on all study patients recording relevant data from the medical records, bedside flow sheets, and the hospital's main frame computer for reports of microbiologic studies (Gram's stains and cultures of sputum, blood, pleural fluid, urine, wound, tissue, and lower respiratory tract specimens). All chest radiographs were prospectively reviewed by one of the investigators (MHK), and the computerized radiographic reports were also reviewed 24 to 48 h later. In addition to recording the presence of community-acquired infections necessitating ICU admission, all identified nosocomial infections were also recorded prospectively. Patients were evaluated for the development of nosocomial infections only during their stay in the ICU. Antibiotic treatment administered in the ICU setting, both perioperative prophylactic antibiotics and antibiotic treatment of suspected infections, were evaluated using patients' medical records and the ICU computerized bedside workstations (EMTEK Health Care Systems Inc; Tempe, AZ).

Definitions

All definitions were selected prospectively as part of the original study design. Community-acquired infection (urinary tract, bloodstream, pneumonia, biliary tract, meningitis, and soft tissue infections) were defined according to the patient's admission diagnosis and the treating physician's orders in the medical record documenting the need for antibiotic treatment of a specific community-acquired infection. Additionally, all community-acquired infections were required to be established within 48 h of hospital admission. Similar temporal cutoffs for separating community-acquired infections from hospital-acquired infections have been proposed by other investigators.[21] Patients residing at a nursing home, skilled care facility, or rehabilitation center who developed an infection requiring hospital admission were classified as having community-acquired infections. Nosocomial infections (urinary tract, bloodstream, wound infection) were defined according to criteria established by the Centers for Disease Control and Prevention.[22]

The diagnostic criteria for ventilator-associated pneumonia (VAP) were modified from those established by the American College of Chest Physicians.[21] Ventilator-associated pneumonia was considered to be present when a new or progressive radiographic infiltrate developed in conjunction with one of the following: radiographic evidence of pulmonary abscess formation (*ie*, cavitation within pre-existing pulmonary infiltrates); histologic evidence of pneumonia in lung tissue; a positive blood or pleural fluid culture; or two of the following: fever (temperature $> 38.3°C$), leukocytosis (leukocyte count $> 10 \times 10^3/mm^3$), and purulent tracheal aspirate. Blood and pleural fluid cultures could not be related to another source and both had to be obtained within 48 h before or after the clinical suspicion of VAP. Microorganisms recovered from blood or pleural fluid cultures also had to be identical to the microorganisms recovered from cultures of respiratory secretions. VAP-complicating community-acquired pneumonia was considered to be present if new or progressive infiltrates developed at least 48 h after the start of mechanical ventilation and empiric antibiotic treatment. The previous infiltrates, attributed to the community-acquired pneumonia, were also required to be stable or improving in their radiographic appearance for at least 48 h prior to the development of these new or progressive infiltrates. Last, the criteria for VAP noted above also had to be met.

We calculated APACHE II scores on the basis of clinical data available from the first 24-h period of intensive care.[20] Acquired organ system derangements were defined using the modified criteria of Rubin and coworkers.[23] The definitions used for the systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock, were those proposed by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.[24] Mortality related to infection was predetermined to be present when a patient died during treatment for a community-acquired or nosocomial infection and the death could not be directly attributed to any other cause.

Prophylactic antimicrobial treatment was defined as any antimicrobial agent administered parenterally in the perioperative period for the prevention of infection resulting from the surgical procedure. All other antimicrobial administration in the ICU setting was classified as either empiric treatment or infection-directed treatment. Empiric treatment was considered to be present when antimicrobials were prescribed for fever or other systemic signs of infection (*eg*, hypothermia, leukocytosis) without identifying a specific localized source of infection. Infection-directed treatment was defined as the administration of antimicrobials for a specific clinically localized source of infection (*eg*, pneumonia, urinary tract, wound, bloodstream). The identified source of infection was required to be documented in the patient's medical record. Clinically localized sources of infection, excluding bloodstream infections, did not require microbiologic confirmation by Gram's stain or positive cultures in order to classify the associated antimicrobial therapy as infection-directed treatment. However, the classification of inadequate antimicrobial treatment required a microbiologically documented infection (*ie*, infection supported by positive culture results from an appropriate clinical specimen) to be present for the purpose of supporting this categorization. Last, antibiotic-resistant bacteria were defined as Gram-negative bacteria resistant to aminoglycosides; third-generation cephalosporins; extended-spectrum penicillins, quinolones, or imipenem; and Gram-positive bacteria resistant to oxacillin or vancomycin.

Statistical Analysis

All comparisons were unpaired and all tests of significance were two-tailed. Continuous variables were compared using the Student's *t* test for normally distributed variables and the Wilcoxon rank-sum test for non-normally distributed variables. The χ^2 or Fisher's exact test were used to compare categorical variables. The primary data analysis compared infected patients who received inadequate antimicrobial treatment to infected patients receiving adequate antimicrobial treatment. A second data analysis compared hospital nonsurvivors to hospital survivors. To determine the relationship between hospital mortality (dependent variable) and inadequate antimicrobial treatment of infection (independent variable), a multiple logistic regression model was used to control for the effects of confounding variables.[25,26] Multiple logistic regression analysis was also used to identify independent risk factors for the administration of inadequate antimicrobial treatment of infection.

A stepwise approach was used to enter new terms into the logistic regression models where 0.05 was set as the limit for the acceptance or removal of new terms. Model overfitting was examined by evaluating the ratio of outcome events to the total number of independent variables in the final models and specific testing for interactions between the independent variables was included in our analyses.[27] Results of the logistic regression analyses are reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Relative risks (RRs) and their 95% CIs

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were calculated using standard methods.[28] Values are expressed as the mean ± SD (continuous variables) or as a percentage of the group from which they were derived (categorical variables). All p values were two-tailed and p values of ≤ 0.05 were considered to indicate statistical significance.

Results

Patients

A total of 2,000 consecutive eligible patients were prospectively evaluated (Table 1). The mean age of the patients was 57.7 ± 18.1 years (range, 13 to 105 years), and the mean APACHE II score was 15.2 ± 7.8 (range, 0 to 53). Nine-hundred forty-four (47.2%) patients were women and 1,056 (52.8%) were men. One thousand two-hundred seven (60.3%) patients were admitted to the ICU for a medical diagnosis, whereas 793 (39.7%) patients were admitted to the ICU following a surgical procedure.

Inadequate Antimicrobial Treatment of Infection

One-hundred sixty-nine (8.5%) patients initially received inadequate treatment of an infection during their stay in the ICU (Tables 1 and 2). This represented 25.8% of the 655 patients assessed to have a clinically recognized infection present while in the ICU. Inadequate antimicrobial treatment of infection was most common among patients with nosocomial infections that developed after treatment of a community-acquired infection (45.2%), followed by patients with nosocomial infections alone (34.3%) and patients with community-acquired infections alone (17.1%) ($p < 0.001$). Infected patients who initially received inadequate antimicrobial treatment had statistically greater APACHE II scores, younger ages, were more likely to have undergone surgery prior to ICU admission, and had lower values for serum albumin than infected patients who initially received adequate antimicrobial treatment (Table 1). Differences in the processes of medical care between infected patients receiving inadequate antimicrobial treatment and infected patients receiving adequate antimicrobial treatment are shown in Table 2. Infected patients receiving inadequate antimicrobial treatment were statistically more likely to also receive antacids, histamine type-2 receptor antagonists, sucralfate, and vasopressors; to undergo tracheostomy, dialysis, central vein catheterization, and mechanical ventilation; and to have longer durations

Table 1—*Baseline Characteristics of the Study Cohort

Characteristic	Inadequate Antimicrobial Treatment (n = 169)	Adequate Antimicrobial Treatment (n = 486)	p Value	Nonsurvivors (n = 312)	Survivors (n = 1,688)	p Value
Age, yr	55.8 ± 17.1	60.1 ± 17.4	0.006	61.0 ± 17.6	57.0 ± 18.4	< 0.001
Gender, No.						
Male	90 (53.3)	232 (47.7)	0.216	172 (55.1)	884 (52.4)	0.370
Female	79 (46.7)	254 (52.3)		140 (44.9)	804 (47.6)	
Race, No.						
White	99 (58.6)	298 (61.3)	0.530	198 (63.5)	1,090 (64.6)	0.929
Black	70 (41.4)	184 (37.9)		111 (35.6)	583 (34.5)	
Other	0 (0.0)	4 (0.8)		3 (1.0)	15 (0.9)	
Congestive heart failure, No.	41 (24.3)	104 (21.4)	0.440	76 (24.4)	286 (16.9)	0.002
COPD, No.	37 (21.9)	102 (21.0)	0.804	57 (18.3)	247 (14.6)	0.100
Underlying malignancy, No.	27 (16.0)	58 (11.9)	0.178	65 (20.8)	214 (12.7)	< 0.001
HIV positive, No.	2 (1.2)	5 (1.0)	> 0.999	5 (1.6)	14 (0.8)	0.196
Albumin, g/dL	2.7 ± 0.8	2.9 ± 0.7	0.014	2.6 ± 0.7	3.1 ± 0.8	< 0.001
Pao_2/Fio_2	219 ± 126	237 ± 121	0.125	215 ± 130	277 ± 137	< 0.001
APACHE II score	20.7 ± 8.3	18.6 ± 7.1	0.004	24.2 ± 8.6	13.6 ± 7.3	< 0.001
Underwent surgery, No.	66 (39.1)	143 (29.4)	0.021	82 (26.3)	711 (42.1)	< 0.001
Surgery type, No.						
Vascular	7 (10.6)	17 (11.9)	0.787	9 (11.0)	148 (20.8)	0.034
Abdominal	32 (48.5)	73 (51.0)	0.730	44 (53.7)	329 (46.3)	0.205
Trauma	0 (0.0)	2 (1.4)	> 0.999	2 (2.4)	16 (2.3)	0.708
OB/GYN†	3 (4.5)	2 (1.4)	0.329	1 (1.2)	20 (2.8)	0.714
Thoracic	4 (6.1)	8 (5.6)	> 0.999	2 (2.4)	17 (2.4)	> 0.999
Orthopedic	4 (6.1)	15 (10.5)	0.438	4 (4.8)	100 (14.1)	0.015
Burn related	1 (1.5)	0 (0.0)	0.316	2 (2.4)	1 (0.1)	0.030
Other‡	15 (22.7)	26 (18.2)	0.442	18 (22.0)	80 (11.2)	0.005

*Values given as mean ± SD or No. (%).
†OB-GYN = obstetrics and gynecology.
‡Includes otolaryngologic surgery, plastic surgery, and wound debridements.

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Table 2—*Process of Care Variables

Variable	Inadequate Antimicrobial Treatment (n = 169)	Adequate Antimicrobial Treatment (n = 486)	p Value	Nonsurvivors (n = 312)	Survivors (n = 1,688)	p Value
Received corticosteroids, No.	52 (30.8)	140 (28.8)	0.629	90 (28.9)	356 (21.1)	0.002
Dialysis, No.	31 (18.3)	57 (11.7)	0.030	59 (18.9)	123 (7.3)	< 0.001
Reintubation, No.	15 (8.9)	37 (7.6)	0.601	12 (3.9)	47 (2.8)	0.309
Tracheostomy, No.	45 (26.6)	62 (12.8)	< 0.001	44 (14.1)	96 (5.7)	< 0.001
Antacids, No.	34 (20.1)	67 (13.8)	0.050	36 (11.5)	225 (13.3)	0.388
Histamine type-2 antagonists, No.	128 (75.7)	315 (64.8)	0.009	206 (66.0)	1,122 (66.5)	0.879
Sucralfate, No.	50 (29.6)	106 (21.8)	0.041	68 (21.8)	198 (11.7)	< 0.001
Vasopressors, No.	88 (52.1)	179 (36.8)	< 0.001	190 (60.9)	277 (16.4)	< 0.001
Urinary tract catheterization, No.	157 (92.9)	434 (89.3)	0.175	287 (92.0)	1,345 (79.7)	< 0.001
Duration of urinary tract catheterization, d	9.8 ± 10.1	7.1 ± 8.3	0.006	7.1 ± 8.6	4.1 ± 5.3	< 0.001
Central vein catheterization, No.	138 (81.7)	311 (64.0)	< 0.001	255 (81.7)	839 (49.7)	< 0.001
Duration of central vein catheterization, d	9.7 ± 10.0	7.2 ± 8.2	0.023	7.0 ± 8.3	4.4 ± 5.6	< 0.001
Mechanical ventilation, No.	128 (75.7)	318 (65.4)	0.013	237 (76.0)	744 (44.1)	< 0.001
Duration of mechanical ventilation, d	11.1 ± 10.6	7.6 ± 9.2	0.004	7.8 ± 9.2	4.4 ± 6.6	< 0.001
Antibiotic prophylaxis,† No.	7 (4.1)	34 (7.0)	0.187	10 (3.2)	452 (26.8)	< 0.001
Empiric antibiotic administration, No.	85 (50.3)	241 (49.6)	0.874	179 (57.4)	545 (32.3)	< 0.001
Infection directed antibiotic administration, No.	76 (45.0)	260 (53.5)	0.056	202 (64.7)	453 (26.8)	< 0.001

*Refers to processes of care occurring during patients' ICU stay. Values are given as mean ± SD or No. (%).
†Administered in the ICU.

of urinary tract catheterization, central vein catheterization, and mechanical ventilation. Infected patients receiving inadequate antimicrobial treatment were also statistically more likely to develop sepsis, severe sepsis, septic shock, and bloodstream infections than infected patients receiving adequate antimicrobial treatment (Table 3).

Multiple logistic regression analysis, using only the cohort of infected patients (n = 655), demonstrated that the prior administration of antibiotics (adjusted OR, 3.39; 95% CI, 2.88 to 4.23; $p < 0.001$), presence of a bloodstream infection (adjusted OR, 1.88; 95% CI, 1.52 to 2.32; $p = 0.003$), increasing APACHE II scores (1-point increments) (adjusted OR, 1.04; 95% CI, 1.03 to 1.05; $p = 0.002$), and decreasing patient age (1-year increments) (adjusted OR, 1.01; 95% CI, 1.01 to 1.02; $p = 0.012$) were independently associated with the administration of inadequate antimi-

Table 3—*Clinical Infections

Infection	Inadequate Antimicrobial Treatment (n = 169)	Adequate Antimicrobial Treatment (n = 486)	p Value	Nonsurvivors (n = 312)	Survivors (n = 1,688)	p Value
Sepsis classification, No. (%)						
SIRS†	166 (98.2)	477 (98.1)	> 0.999	311 (99.7)	1,499 (88.8)	< 0.001
Sepsis	131 (77.5)	292 (60.1)	< 0.001	173 (55.4)	312 (18.5)	< 0.001
Severe sepsis	68 (40.2)	117 (24.1)	< 0.001	112 (35.9)	86 (5.1)	< 0.001
Septic shock	60 (35.5)	92 (18.9)	< 0.001	100 (32.1)	63 (3.7)	< 0.001
Infection classification, No. (%)‡						
Nosocomial	73 (43.2)	140 (28.8)	< 0.001	80 (25.6)	133 (7.9)	< 0.001
Community-acquired	63 (37.3)	306 (63.0)	< 0.001	87 (27.9)	281 (16.7)	< 0.001
Both	33 (19.5)	40 (8.2)	< 0.001	35 (11.2)	38 (2.3)	< 0.001
Infection site, No. (%)						
Bloodstream	59 (34.9)	92 (18.9)	< 0.001	65 (20.8)	86 (5.1)	< 0.001
Lung	106 (62.7)	305 (62.8)	0.993	141 (45.2)	271 (16.6)	< 0.001
Wound	17 (10.1)	40 (8.2)	0.468	20 (6.4)	37 (2.2)	< 0.001
Gastrointestinal tract	27 (16.0)	62 (12.8)	0.293	44 (14.1)	76 (4.5)	< 0.001
Urinary tract	47 (27.8)	110 (22.6)	0.174	53 (17.0)	106 (6.3)	< 0.001
Miscellaneous§	17 (10.1)	55 (11.3)	0.647	18 (5.8)	54 (3.2)	0.024

*Values are given as No. (%).
†SIRS = systemic inflammatory response syndrome.
‡Patients having at least one infection.
§Includes peritoneal infection, meningitis, endocarditis, and infections of the skin and fascia.

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crobial treatment of infections. Similar results were obtained when the multiple logistic regression analysis was repeated for the entire patient cohort (n = 2,000) except that the presence of pneumonia was also identified as a variable independently associated with the administration of inadequate antimicrobial treatment. The distribution of the APACHE II scores for infected patients receiving adequate and inadequate antimicrobial treatment are shown in Figure 1.

Infection Classification

Among the 655 infected patients admitted to the ICU, 442 (67.5%) had a community-acquired infection, 286 (43.7%) developed a nosocomial infection, and 73 (11.1%) patients had both community-acquired and nosocomial infections. Overall, 527 (80.5%) of the clinically identified infections were supported by positive cultures. Among the infected patients, 162 (24.7%) were classified as having an antibiotic-resistant Gram-negative bacterial infection and 88 (13.4%) were classified as having an antibiotic-resistant Gram-positive bacterial infection. The likelihood of acquiring an antibiotic-resistant Gram-negative bacterial infection was greatest for patients with nosocomial infections, which occurred following treatment of a community-acquired infection (41.1%), and patients with nosocomial infections alone (43.2%) and least for patients with community-acquired infections alone (10.8%) ($p < 0.001$). Similar results were found for patients acquiring an antibiotic-resistant Gram-positive infection (30.1%, 15.0%, 9.2%; $p < 0.001$). Multiple logistic regression analysis demonstrated that the duration of mechanical ventilation (1-day increments) (adjusted OR, 1.13; 95% CI, 1.10 to 1.16; $p < 0.001$), the duration of central vein catheterization (adjusted OR, 1.10; 95% CI, 1.05 to 1.11; $p = 0.007$), presence of a tracheostomy (adjusted OR, 2.10; 95% CI, 1.54 to 2.85; $p = 0.016$), and the use of histamine type-2 receptor antagonists (adjusted OR, 1.52; 95% CI, 1.25 to 1.85; $p = 0.035$) were independently associated with the occurrence of a nosocomial infection.

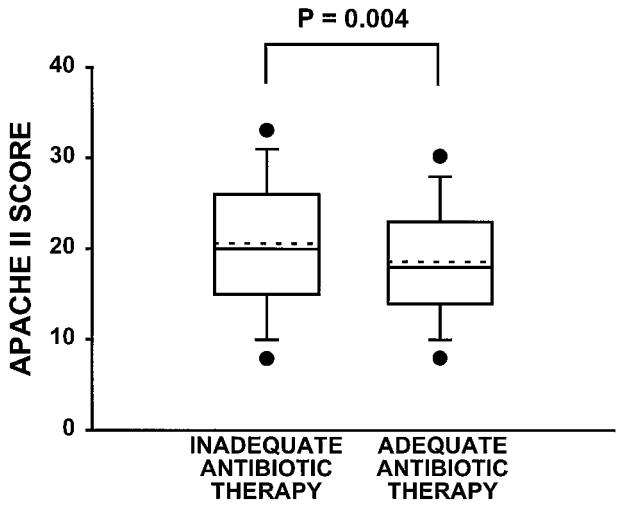

FIGURE 1. Box plots of APACHE II Scores for infected patients receiving either initially inadequate or adequate antimicrobial treatment. Boxes represent 25th to 75th percentiles with 50th percentile (solid line) and median (broken line) values shown with the boxes. The 10th and 90th percentiles are shown as capped bars, and symbols (solid circles) mark the 5th and 95th percentiles.

The distribution of the pathogens associated with clinically recognized community-acquired and nosocomial infections are shown in Table 4. *Pseudomonas aeruginosa* was the most common Gram-negative bacterial pathogen isolated from infected patients receiving inadequate antimicrobial treatment (n = 53), whereas ORSA was the most common Gram-positive bacterial pathogen isolated from such individuals (n = 45). Interestingly, vancomycin-resistant enterococci (VRE) was responsible for inadequate antimicrobial treatment in 13 individuals of which six (45.2%) were classified as community-acquired infections. *Escherichia coli* was the most common Gram-negative bacterial pathogen isolated from infected patients receiving adequate antimicrobial treatment (n = 76), whereas oxacillin-sensitive *S aureus* was the most common Gram-positive bacterial pathogen isolated from these patients (n = 88).

Reasons for the Administration of Inadequate Antimicrobial Treatment

The identified reasons for the initial administration of inadequate antimicrobial treatment of infections are shown in Table 5. The main reason for the administration of inadequate antimicrobial therapy was the presence of either antibiotic-resistant Gram-negative bacteria or antibiotic-resistant Gram-positive bacteria not appropriately treated by the prescribed antibiotic regimen. Among patients with community-acquired infections, the absence of adequate treatment for ORSA, Gram-negative bacteria resistant to third-generation cephalosporins (*eg*, ceftriaxone and ceftazidime) or other antibiotics, Candida spp, and VRE accounted for the majority of the inadequate antimicrobial treatments. For patients with nosocomial infections, the absence of adequate treatment for Gram-negative bacteria, resistant to the administered third-generation cephalosporins or some other class of antibiotics, accounted for most instances of inadequate antimicrobial treatment. Inadequate antimicrobial treatment for ORSA, Candida spp, and VRE were also relatively common among patients classified as having nosocomial infections.

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Table 4—*Microorganisms Associated With Infections

Pneumonia	Bloodstream	Urinary Tract	Other
I. Inadequate antimicrobial treatment			
A. Community-acquired infections			
P aeruginosa, 9	Candida spp, 9	Enterobacter spp, 5	*E coli*, 8
ORSA, 5	ORSA, 4	VRE, 2	Candida spp, 7
OSSA, 5	Enterococcus spp, 4	Enterococcus spp, 2	ORSA, 5
Aspergillus spp, 5	VRE, 4	Candida spp, 1	*K pneumoniae*, 3
Cytomegalovirus, 5	Acinetobacter spp, 3	Citrobacter spp, 1	*P mirabilis*, 3
Haemophilus influenzae, 3	Enterobacter spp, 3	*K species*, 1	OSSA, 2
Streptococcus pneumoniae, 2	*K pneumoniae*, 3	*P mirabilis*, 1	*P aeruginosa*, 2
Citrobacter freundii, 2	OSSA, 2		Enterobacter spp, 2
Pneumocystis carinii, 2	*P aeruginosa*, 2		Actinomyces spp, 1
Xanthomonas maltophilia, 1	CNS, 1		*Clostridium perfringens*, 1
Alcaligenes xylosoxidans, 1	*Providencia rettgeri*, 1		
Acinetobacter spp, 1	Cytomegalovirus, 1		
Klebsiella pneumoniae, 1	*Proteus mirabilis*, 1		
Adenovirus, 1	*S pneumoniae*, 1		
Mycobacterium kansasii, 1			
Mycobacterium avium-intracellulare, 1			
B. Nosocomial infections			
P aeruginosa, 33	Candida spp, 10	Candida spp, 4	*Clostridium difficile*, 9
ORSA, 18	ORSA, 8	VRE, 3	Candida spp, 6
Enterobacter spp, 14	Enterococcus spp, 6	Enterobacter spp, 2	ORSA, 4
X maltophilia, 13	Enterobacter spp, 5	*X maltophilia*, 1	Enterococcus spp, 3
K pneumoniae, 5	VRE, 3	*P aeruginosa*, 1	*P aeruginosa*, 3
OSSA, 3	*P aeruginosa*, 3	*P mirabilis*, 1	Citrobacter spp, 2
Cytomegalovirus, 3	Corynebacterium spp, 2	ORSA, 1	VRE, 1
Serratia marcescens, 3	CNS, 1	*K pneumoniae*, 1	OSSA, 1
Herpes simplex virus, 2	*Streptococcus viridans*, 1		*K pneumoniae*, 1
P carinii, 2	Peptostreptococcus spp, 1		Enterobacter spp, 1
P mirabilis, 1	*K pneumoniae*, 1		*Cryptococcus neoformans*, 1
E coli, 1	*X maltophilia*, 1		
Citrobacter spp, 1			
Rhinovirus, 1			
II. Adequate antimicrobial treatment			
A. Community-acquired infections			
OSSA, 34	OSSA, 11	*E coli*, 31	*E coli*, 11
Influenza virus, 14	*E coli*, 11	Enterococcus spp, 12	OSSA, 10
S pneumoniae, 10	*S pneumoniae*, 6	*P mirabilis*, 8	Enterococcus, 10
P aeruginosa, 10	Enterococcus spp, 5	*K pneumoniae*, 5	*C perfringens*, 5
H influenzae, 9	Group B streptococci, 5	Enterobacter spp, 4	*C difficile*, 5
ORSA, 7	ORSA, 4	*P aeruginosa*, 4	Bacteroides spp, 5
Moraxella catarrhalis, 5	*K pneumoniae*, 4	OSSA, 2	*K pneumoniae*, 5
Respiratory synctitial virus, 4	*P mirabilis*, 3	Citrobacter spp, 1	Group A streptococci, 4
P carinii, 4	Viridans group streptococci, 3		ORSA, 3
E coli, 3	Corynebacterium spp, 2		*H influenzae*, 2
K pneumoniae, 3	*P aeruginosa*, 2		*P aeruginosa*, 2
Cytomegalovirus, 3	Lactobacillus spp, 1		Enterobacter spp, 1
Legionella pneumophila, 2	*H influenzae*, 1		Fusobacterium spp, 1
Enterobacter spp, 2	Acinetobacter spp, 1		*Toxoplasma gondii*, 1
S marcescens, 1	Enterobacter spp, 1		*Histoplasma capsulatum*, 1
P mirabilis, 1	*M catarrhalis*, 1		*P mirabilis*, 1
			Candida spp, 1
			Bacillus cereus, 1
			Morganella spp, 1
			Lactobacillus spp, 1
B. Nosocomial infections			
P aeruginosa, 27	*E coli*, 7	Enterococcus spp, 9	*C difficile*, 13
OSSA, 21	OSSA, 7	*E coli*, 7	Enterococcus, 9
ORSA, 12	Enterococcus spp, 6	*P aeruginosa*, 5	*K pneumoniae*, 5
K pneumoniae, 10	*K pneumoniae*, 4	Citrobacter spp, 3	*P aeruginosa*, 4
Enterobacter spp, 8	ORSA, 3	*K pneumoniae*, 3	OSSA, 3
E coli, 5	*P aeruginosa*, 3	*S marcescens*, 2	*C perfringens*, 3
Cytomegalovirus, 5	*S marcescens*, 2	*P mirabilis*, 2	Candida spp, 2
X maltophilia, 3	Enterobacter spp, 1	*X maltophilia*, 1	Enterobacter spp, 2
H influenzae, 3	Viridans group streptococci, 1		*X maltophilia*, 1
S marcescens, 3	Corynebacterium spp, 1		Bacteroides spp, 1
Alcaligenes xylosoxidans, 3			*Hafia alvei*, 1
Acinetobacter spp, 3			*E coli*, 1
P mirabilis, 1			*P mirabilis*, 1
Citrobacter spp, 1			ORSA, 1

*The numbers represent the microbiologically documented infections within each category, some being polymicrobial. OSSA = oxacillin-sensitive *S aureus*; CNS = coagulase-negative Staphylococci.

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Table 5—*Classification of Inadequate Antimicrobial Treatment

Community-acquired infections (n = 442)
ORSA not treated (n = 14)
GNB resistant to the administered third-generation cephalosporins† (n = 13)
Candida spp not treated (n = 10)
GNB resistant to other noncephalosporin-administered antibiotics‡ (n = 7)
No antibiotic treatment initiated (n = 6)
VRE not treated (n = 6)
Inadequate treatment of other GPB (OSSA, Enterococcus spp) (n = 4)
Miscellaneous (n = 5)
Nosocomial infections (n = 286)
GNB resistant to the administered third-generation cephalosporins† (n = 39)
GNB resistant to other noncephalosporin-administered antibiotics§ (n = 21)
ORSA not treated (n = 17)
Candida species not treated (n = 15)
VRE not treated (n = 7)
No antibiotic treatment initiated (n = 5)
Inadequate treatment of other GPB (CNS, Enterococcus spp) (n = 3)
Clostridium difficile not treated (n = 2)
Miscellaneous (n = 7)

*GNB = Gram-negative bacteria; GPB = Gram-positive bacteria; OSSA = oxacillin-sensitive *S aureus*; CNS = coagulase-negative Staphylococci.

†Includes ceftriaxone and ceftazidime.

‡Other antibiotics included: ampicillin-sulbactam (n = 2), cefazolin (n = 2), ampicillin (n = 1), oxacillin (n = 1), and pipercillin-tazobactam (n = 1).

§Other antibiotics included: cefazolin (n = 6), pipercillin-tazobactam (n = 3), imipenem (n = 2), mezlocillin (n = 2), ciprofloxacin (n = 2), cefepime (n = 2), ampicillin (n = 1), oxacillin (n = 1), aminglycoside (n = 1), trimethoprim-sulfamethoxazole (n = 1).

Hospital Mortality

Three hundred twelve (15.6%) patients died during their hospitalization. The hospital mortality rate of infected patients receiving inadequate antimicrobial treatment (52.1%) was statistically greater than the mortality rate of patients without this risk factor (12.2%) (RR, 4.26; 95% CI, 3.52 to 5.15; $p < 0.001$). Among the 655 patients with a clinically recognized infection, the hospital mortality rate from all causes was statistically greater for infected patients receiving inadequate antimicrobial treatment (52.1%) than the same rate for infected patients receiving adequate antimicrobial treatment (23.5%) (RR, 2.22; 95% CI, 1.79 to 2.76; $p < 0.001$) (Fig 2). Similarly, the infection-related mortality rate was statistically greater among infected patients receiving inadequate antimicrobial treatment (42.0%) than infected patients receiving adequate antimicrobial treatment (17.7%) (RR, 2.37; 95% CI, 1.83 to 3.08; $p < 0.001$).

The hospital mortality rates for patients infected with antibiotic-resistant Gram-negative bacteria (n = 148; mortality, 41.2%), antibiotic-resistant Gram-positive bacteria (n = 74; mortality, 43.2%), and both antibiotic-resistant Gram-negative and antibiotic-resistant Gram-positive bacteria (n = 14; mortality, 35.7%) were statistically greater than the mortality rates for the remaining patients in the cohort (n = 1764; mortality, 12.1%; $p < 0.001$) and for the infected patients whose pathogens were not antibiotic-resistant bacteria (n = 419; mortality, 24.8%; $p < 0.001$). The mortality rate of infected patients who did not receive initial antibiotic therapy (n = 11; mortality, 45.5%) was not statistically different from the mortality rate of infected patients receiving initial antibiotic therapy (n = 644; mortality, 30.6%; $p = 0.328$).

Hospital nonsurvivors had statistically greater APACHE II scores, greater ages, lower PaO_2/FIO_2 ratios, lower serum albumin values, were more likely to have a diagnosis of congestive heart failure or underlying malignancy, and were less likely to have undergone surgery than patients who survived their hospitalization (Table 1). Differences in the processes of medical care for hospital nonsurvivors and survivors are shown in Table 2. Hospital nonsurvivors were statistically more likely to receive vasopressors, sucralfate, and corticosteroids; to undergo dialysis, tracheostomy, urinary tract catheterization, central vein catheterization, and mechanical ventilation than hospital survivors. Nonsurvivors also had statistically longer durations of urinary tract catheterization, central line catheterization, and mechanical ventilation; were less likely to receive antibiotic prophylaxis in the ICU; and were more likely to receive both empiric and infection-directed antibiotics during their stay in intensive care. Additionally,

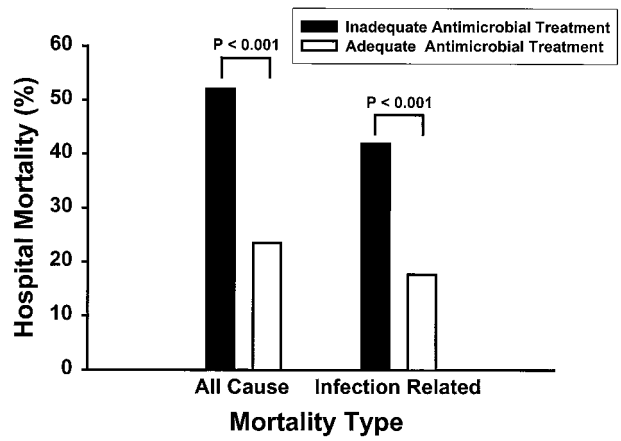

FIGURE 2. Hospital mortality and infection related mortality rates for infected patients from all causes (n = 655) receiving either initially inadequate or adequate antimicrobial treatment.

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hospital nonsurvivors were statistically more likely to meet clinical criteria for systemic inflammatory response syndrome, sepsis, severe sepsis, septic shock, and more likely to have developed community-acquired infections, nosocomial infections, or both types of infections than hospital survivors (Table 3).

Acquired Organ System Derangements and Lengths of Stay

Infected patients receiving inadequate antimicrobial treatment acquired a statistically greater number of organ system derangements than infected patients receiving adequate antimicrobial treatment (Table 6). Similarly, acquired derangements of lung, heart, bone marrow, and liver function occurred more commonly among infected patients receiving inadequate antimicrobial treatment. Hospital nonsurvivors also acquired a greater number of organ system derangements and derangements of each individual organ system examined than hospital survivors. The average ICU lengths of stay and the average durations of mechanical ventilation were statistically greater among patients receiving inadequate antimicrobial treatment and hospital nonsurvivors, respectively (Table 6).

Risk Factors for Hospital Mortality

Multivariate analysis demonstrated that inadequate antimicrobial treatment of infection was the most important risk factor for hospital mortality (Table 7). An increasing number of acquired organ system derangements, the administration of vasopressors, the presence of an underlying malignancy, increasing APACHE II scores, and increasing patient age were also identified as independent predictors of hospital mortality. Additionally, admission to the ICU following a surgical procedure was found to be an independent risk factor favoring hospital survival.

Table 7—*Independent Risk Factors for Hospital Mortality

Risk Factor	AOR†	95% CI	p Value
Inadequate antimicrobial therapy	4.26	3.35–5.44	< 0.001
Acquired organ system derangements (one-organ increments)	3.25	2.98–3.54	< 0.001
Use of vasopressors	2.20	1.81–2.66	< 0.001
Underlying malignancy	1.81	1.44–2.27	0.009
APACHE II score (one-point increments)	1.05	1.04–1.07	< 0.001
Increasing age (1-yr increments)	1.02	1.01–1.03	< 0.001
Surgical patient	0.40	0.33–0.49	< 0.001
Intercept	0.0013	0.0008–0.0021	

*Includes logistic regression model, where hospital mortality is the dependent outcome variable and the study population was the entire patient cohort (n = 2,000).
†AOR = adjusted odds ratio.

Discussion

We demonstrated a statistically significant association between the initial administration of inadequate antimicrobial treatment of infections and hospital mortality for adult patients requiring ICU admission. Multiple logistic regression analysis, controlling for potential confounding variables, demonstrated that the risk of hospital mortality was more than four times as great among infected patients receiving inadequate antimicrobial treatment compared with patients who did not possess this risk factor (adjusted OR, 4.26; Table 7). Similarly, when

Table 6—*Clinical Outcomes

Outcome	Inadequate Antimicrobial Treatment (n = 169)	Adequate Antimicrobial Treatment (n = 486)	p Value	Nonsurvivors (n = 312)	Survivors (n = 1,688)	p Value
Acquired organ system derangements, No.	2.5 ± 1.5	1.9 ± 1.4	< 0.001	3.2 ± 1.2	1.1 ± 1.0	< 0.001
Lung, No.	133 (78.7)	322 (66.3)	0.002	261 (83.7)	724 (42.9)	< 0.001
Kidney, No.	77 (45.6)	158 (32.5)	0.002	181 (58.0)	264 (15.6)	< 0.001
Bone marrow, No.	60 (35.5)	110 (22.6)	< 0.001	148 (47.4)	180 (10.7)	< 0.001
Gastrointestinal, No.	58 (34.3)	133 (27.4)	0.087	116 (37.2)	315 (18.7)	< 0.001
Heart, No.	22 (13.0)	61 (12.6)	0.875	110 (35.3)	96 (5.7)	< 0.001
Liver, No.	44 (26.0)	79 (16.3)	0.005	99 (31.7)	171 (10.1)	< 0.001
Brain, No.	27 (16.0)	54 (11.1)	0.098	99 (31.7)	39 (2.3)	< 0.001
Hospital length of stay, d	22.8 ± 25.7	20.0 ± 25.8	0.221	17.3 ± 25.4	12.8 ± 15.5	0.167
ICU length of stay, d	10.2 ± 10.2	7.1 ± 8.2	< 0.001	7.3 ± 8.8	3.9 ± 5.0	< 0.001
Duration of mechanical ventilation, d	11.1 ± 10.6 [n = 128]†	7.6 ± 9.2 [n = 318]	< 0.001	7.8 ± 9.2 [n = 237]	4.4 ± 6.6 [n = 744]	< 0.001

*Values are given as mean ± SD or No. (%).
†Numbers in brackets represent the number of patients receiving mechanical ventilation.

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only infected patients were examined, the risk of infection-related mortality was greater among individuals receiving inadequate antimicrobial treatment than patients receiving adequate antimicrobial treatment for their infections (Fig 2). We also identified potential risk factors for the administration of inadequate antimicrobial treatment of infections including the prior administration of antibiotics, presence of a bloodstream infection, severity of illness, and patient age. The significance of these findings are that they may help to explain, at least in part, the differences in hospital mortality observed between various groups of ICU patients. More importantly, these data could help to improve existing strategies for the treatment of suspected infection among critically ill patients. Last, our study results also support the observation that acquired infections, especially infections initially treated with inadequate antimicrobial treatment, are associated with an excess mortality above that attributable to patients' severity of illness at the time of ICU admission.[4]

Despite the widespread use of antimicrobial therapy in ICUs, few clinical studies have examined the influence of the adequacy of antimicrobial treatment on patient outcomes. The role of antimicrobial treatment as a determinant of outcome for critically ill patients is probably best documented for VAP and nosocomial bacteremia. Several epidemiologic studies have suggested that the administration of inadequate antibiotic treatment of VAP is an important determinant of hospital mortality.[29,30] Indeed, the initial administration of inadequate antibiotic therapy may partially explain the excess patient mortality associated with VAP, especially when it is attributed to antibiotic-resistant bacteria.[31–33] This hypothesis is further supported by other clinical investigations demonstrating a strong association between the initial administration of inadequate antimicrobial therapy and hospital mortality for patients with VAP.[8–11] These four investigations independently demonstrated that patients receiving inadequate empiric antimicrobial treatment, initiated before obtaining the results of cultures from respiratory secretions, blood, and pleural fluid, had greater hospital mortality rates than patients receiving empiric antimicrobial regimens that provided full coverage of all identified pathogens. More importantly, the study by Luna et al[9] found that subsequent changes in antimicrobial therapy based on the available culture results, for patients who initially received inadequate treatment, did not reduce their excess risk of hospital mortality. Therefore, it appears that the timing of the administration of adequate antimicrobial therapy is also an important determinant of outcome for patients with VAP.

Our study offers several potential explanations for the initial administration of inadequate antimicrobial treatment to infected patients. Prior antibiotic administration was found to be the most important risk factor associated with the occurrence of this undesirable medical practice. The prior administration of antibiotics to hospitalized patients, particularly to patients in ICUs, appears to predispose to colonization with bacteria that are often resistant to the previously prescribed classes of antibiotics.[33] More importantly, colonization with antibiotic-resistant pathogens predisposes to subsequent infection with these same highly virulent microorganisms.[18,33] Several groups of investigators have demonstrated an association between the prior administration of antibiotics and the occurrence of VAP due to antibiotic-resistant bacteria.[31–33] Most recently, Trovillet and coworkers[34] examined patients with VAP caused by potentially drug-resistant bacteria in hopes of identifying risk factors for this outcome. They identified a duration of mechanical ventilation of ≥ 7 days (OR, 6.0), prior antibiotic use (OR, 13.5), and the prior use of broad-spectrum antibiotics (OR, 4.1) as being independently associated with infection due to antibiotic-resistant bacteria. Additionally, these investigators demonstrated that patients with both prolonged durations of mechanical ventilation and prior antibiotic usage were more likely to acquire infection with antibiotic-resistant bacteria than patients having only one of these risk factors. Other investigators have also found an association between the duration of mechanical ventilation and the occurrence of VAP due to antibiotic-resistant bacteria.[35,36] An analogous situation has also been described for patients developing urinary tract infections and bloodstream infections. The longer urinary tract catheterization and central vein catheterization are employed, the more likely it is for patients to develop urinary tract and bloodstream infections with antibiotic-resistant pathogens.[37]

In addition to prior antibiotic administration, we found that increasing APACHE II scores, lower age, and bloodstream infections were independently associated with the administration of inadequate antimicrobial therapy. Greater severity of illness has previously been associated with longer lengths of stay in the hospital and ICU, the need for antibiotic administration, and increased susceptibility to nosocomial infections.[3–5] Therefore, it is not surprising that patients with a greater severity of illness are more likely to be at risk for receiving inadequate antimicrobial therapy. Similarly, patients with bloodstream infections, especially nosocomial bloodstream infections, often have received prior antibiotic therapy and have prolonged lengths of stay in the hospital, both factors predisposing to colonization and subsequent infection with antibiotic-resistant

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bacteria.[5] Additionally, several studies[13,14] suggest that nosocomial bacteremia due to antibiotic-resistant pathogens usually occur following previous antimicrobial treatment and are associated with worse patient outcomes. *S aureus*, antibiotic-resistant Gram-negative bacteria, and Candida spp are among the pathogens responsible for bloodstream infections, which are usually associated with the poorest outcomes.[38–41] Interestingly, these are the same pathogens most commonly associated with the initial administration of inadequate antimicrobial treatment in our study. Two of these earlier studies[39,41] also identified inadequate antimicrobial treatment of bloodstream infection as a risk factor for mortality. An explanation for the association of younger patient age with the administration of inadequate antimicrobial treatment of infections is less apparent from our study results. However, younger patients may be less likely to be suspected of having an infection, especially infection due to antibiotic-resistant bacteria, than older patients.

Recommendations for the Avoidance of Inadequate Antimicrobial Administration

Based on our experience from this investigation, and a review of the available medical literature, we have developed several initial recommendations aimed at the avoidance of inadequate antimicrobial treatment for infected ICU patients. First, it appears that antimicrobial therapy should be administered early in the course of infection to be most effective, especially prior to the development of severe sepsis and septic shock.[5,9] This will require a high index of suspicion on the part of practitioners caring for critically ill patients in order to consider the diagnosis of infection in a timely manner. To facilitate this procedure, recommendations for the systematic evaluation of fever among critically ill patients have been developed.[42] Additionally, guidelines for the administration of empiric antimicrobial therapy are available that can be used as a starting point for the selection of antimicrobial agents used for the treatment of suspected infections.[17,18] Due to the greater mortality associated with delays in treatment,[9] starting empiric antimicrobial treatment at the first suspicion of infection in critically ill patients seems prudent in most instances. However, in order to avoid increasing problems with drug-resistant infections, the antimicrobial regimen should subsequently be narrowed or discontinued altogether based on the patient's clinical course and culture results. This can usually be accomplished within 48 h of administrating the initial empiric antimicrobial regimen when culture results and bacterial antimicrobial sensitivity profiles become available. The recent application of computerized antimicrobial guidelines further supports such a practice by suggesting that more hospitalized patients can be successfully exposed to antimicrobial treatment without necessarily increasing the occurrence of antimicrobial-resistant infections.[43] Additionally, such guidelines can also help to curtail the unnecessary use of antimicrobials and may improve patient outcomes.[44]

For patients with suspected infection who have received prior antimicrobial therapy directed at Gram-negative bacteria, subsequent empiric antimicrobial treatment should include coverage of pathogens that may be potentially resistant to the earlier administered antibiotics. Methods of achieving this would include selecting a new class of antimicrobial agents for the empiric treatment of Gram-negative infections (*eg*, a quinolone or carbapenem antibiotic in a patient having received prior treatment with a third-generation cephalosporin), including a new class of antimicrobial agents for empiric treatment in combination with the previously administered agent in order to minimize the likelihood of inadequate treatment due to bacterial resistance (*eg*, treatment with an aminoglycoside or a quinolone antibiotic along with a previously administered broad spectrum cephalosporin), or the routine administration of combination antimicrobial therapy with agents to which the patient has not had previous exposure and to which antimicrobial resistance is thought to be unlikely (*eg*, combinations of broad spectrum antibiotics directed against Gram-negative bacteria). Although the routine use of combination antimicrobial therapy with dual agents directed against Gram-negative bacteria is controversial,[41,45] the administration of such therapy seems reasonable when attempting to avoid the occurrence of inadequate antimicrobial therapy due to antibiotic-resistant Gram-negative bacteria. Similar recommendations for the empiric treatment of Gram-positive bacteria cannot be made since the number of available antimicrobial agents for antibiotic-resistant Gram-positive cocci (*eg*, ORSA and VRE) is limited. Nevertheless, our study suggests that initial empiric treatment with vancomycin or quinupristin/dalfopristin for ORSA seems reasonable in patients at risk for infection with this specific pathogen.[6,37]

More sensitive and specific methods for the microbiologic diagnosis of certain infections may also be necessary in order to reduce the occurrence of inadequate antimicrobial treatment. However, this will require the development of new diagnostic probes and more rapid makers for the identification of specific classes of microorganisms in body fluids and tissues.[46–48] Our study suggests that such probes should be directed at specific antibiotic-resistant bacteria (VRE, ORSA, *P aeruginosa*) and nonbacte-

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rial pathogens (Candida spp). Additionally, improvements in our diagnostic capabilities for these pathogens, in order to exclude infection by them, may also result in decreasing the administration of unnecessary antimicrobial therapy. This offers the advantage of potentially reducing the occurrence of antimicrobial-resistant infections.[44] Finally, the more rapid diagnosis of infection due to these specific high-risk pathogens may allow for the earlier administration of adequate antimicrobial treatment and further improvement in clinical outcomes.[9] An alternative to such an approach would be to more routinely include empiric coverage for Candida spp and antibiotic-resistant Gram-positive bacteria in the initially prescribed empiric antibiotic regimens, especially for patients with suspected nosocomial infections. However, this may result in increased antimicrobial costs and potentially further increases in the occurrence of antimicrobial resistance among these pathogens. Future clinical investigation are needed to determine the best strategy for empiric antimicrobial administration in the ICU setting.

Conclusion

In summary, we demonstrated that the occurrence of inadequate antimicrobial treatment of infections among patients requiring intensive care is an independent determinant of hospital mortality. Clinicians caring for critically ill patients should be aware of these findings since they suggest that specific clinical practices should be adopted in order to avoid treating patients with inadequate antimicrobial regimens. Our study also suggests that clinicians must be aware of the prevailing pathogens accounting for community-acquired and nosocomial infections in their ICU as well as within the hospitals at which they practice. Additionally, the antibiotic-susceptibility profiles of these pathogens should be routinely available to physicians in order to guide their selection of antimicrobial agents. This implies that these antibiograms are updated on a regular basis in order to report and detect changes in the antimicrobial resistance patterns of these pathogens. The importance of prior antimicrobial administration, as a risk factor for subsequent administration of inadequate antimicrobial treatment, should also be recognized by clinicians prescribing antimicrobial treatment to critically ill patients. Last, consideration should be given to the empiric treatment of ICU patients with clinically suspected infection using an initially broad antimicrobial regimen, to include agents that were not previously administered especially for Gram-negative bacteria, in order to minimize the occurrence of inadequate antimicrobial treatment. Such broad treatment can usually be narrowed after a relatively short period of time (*ie*, 24 to 72 h) when the initial culture results become available usually without compromising patient outcomes.[44] Future studies of antibiotic guidelines and protocols aimed at the reduction of inadequate antimicrobial treatment are needed to assess their influence on patient outcomes. Until such data are available, clinicians should at least consider the possibility of inadequate antimicrobial treatment whenever prescribing antimicrobial agents in the ICU.

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The Influence of Inadequate Antimicrobial Treatment of Bloodstream Infections on Patient Outcomes in the ICU Setting*

Emad H. Ibrahim, MD; Glenda Sherman, RN; Suzanne Ward, RN; Victoria J. Fraser, MD; and Marin H. Kollef, MD, FCCP

Study objective: **To evaluate the relationship between the adequacy of antimicrobial treatment for bloodstream infections and clinical outcomes among patients requiring ICU admission.**
Design: **Prospective cohort study.**
Setting: **A medical ICU (19 beds) and a surgical ICU (18 beds) from a university-affiliated urban teaching hospital.**
Patients: **Between July 1997 and July 1999, 492 patients were prospectively evaluated.**
Intervention: **Prospective patient surveillance and data collection.**
Results: **One hundred forty-seven patients (29.9%) received inadequate antimicrobial treatment for their bloodstream infections. The hospital mortality rate of patients with a bloodstream infection receiving inadequate antimicrobial treatment (61.9%) was statistically greater than the hospital mortality rate of patients with a bloodstream infection who received adequate antimicrobial treatment (28.4%; relative risk, 2.18; 95% confidence interval [CI], 1.77 to 2.69; $p < 0.001$). Multiple logistic regression analysis identified the administration of inadequate antimicrobial treatment as an independent determinant of hospital mortality (adjusted odds ratio [AOR], 6.86; 95% CI, 5.09 to 9.24; $p < 0.001$). The most commonly identified bloodstream pathogens and their associated rates of inadequate antimicrobial treatment included vancomycin-resistant enterococci (n = 17; 100%), Candida species (n = 41; 95.1%), oxacillin-resistant *Staphylococcus aureus* (n = 46; 32.6%), coagulase-negative staphylococci (n = 96; 21.9%), and *Pseudomonas aeruginosa* (n = 22; 10.0%). A statistically significant relationship was found between the rates of inadequate antimicrobial treatment for individual microorganisms and their associated rates of hospital mortality (Spearman correlation coefficient = 0.8287; $p = 0.006$). Multiple logistic regression analysis also demonstrated that a bloodstream infection attributed to Candida species (AOR, 51.86; 95% CI, 24.57 to 109.49; $p < 0.001$), prior administration of antibiotics during the same hospitalization (AOR, 2.08; 95% CI, 1.58 to 2.74; $p = 0.008$), decreasing serum albumin concentrations (1-g/dL decrements) (AOR, 1.37; 95% CI, 1.21 to 1.56; $p = 0.014$), and increasing central catheter duration (1-day increments) (AOR, 1.03; 95% CI, 1.02 to 1.04; $p = 0.008$) were independently associated with the administration of inadequate antimicrobial treatment.**
Conclusions: **The administration of inadequate antimicrobial treatment to critically ill patients with bloodstream infections is associated with a greater hospital mortality compared with adequate antimicrobial treatment of bloodstream infections. These data suggest that clinical efforts should be aimed at reducing the administration of inadequate antimicrobial treatment to hospitalized patients with bloodstream infections, especially individuals infected with antibiotic-resistant bacteria and Candida species.** ***(CHEST 2000; 118:146–155)***

Key words: antibiotics; bacteremia; bloodstream infections; Candida species; enterococci; intensive care; outcomes; resistance; *Staphylococcus aureus*

Abbreviations: AOR = adjusted odds ratio; APACHE = acute physiology and chronic health evaluation; CI = confidence interval; ORSA = oxacillin-resistant *Staphylococcus aureus*

*From the Divisions of Pulmonary and Critical Care Medicine (Drs. Ibrahim and Kollef and Ms. Ward) and Infectious Diseases (Dr. Fraser), Department of Internal Medicine, Washington University School of Medicine, and the Department of Nursing (Ms. Sherman), Barnes-Jewish Hospital, Saint Louis, MO.
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Correspondence to: Marin H. Kollef, MD, FCCP, Pulmonary and Critical Care Medicine, Washington University School of Medicine, Campus Box 8052, 660 S. Euclid Ave., St. Louis, MO 63110; e-mail: mkollef@pulmonary.wustl.edu

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Bloodstream infections are among the most serious infections acquired by hospitalized patients requiring intensive care. The coexistence of a pathogen population with an ever-increasing resistance to

For editorial comment see page 9

many antibiotics and a patient population characterized by increasingly complex clinical problems has contributed to an increase in bloodstream infections, particularly those caused by antibiotic-resistant Gram-positive bacteria.[1] Antibiotic resistance appears to have contributed to increasing administration of inadequate antimicrobial therapy for bloodstream infections, particularly nosocomial acquired bloodstream infections, which is associated with greater hospital mortality rates.[2–8] However, some investigations have not found greater mortality rates with the presence of antibiotic-resistant bacteremia, particularly vancomycin-resistant enterococcal bacteremia compared with vancomycin-sensitive enterococcal bloodstream infections.[9,10] Nevertheless, the problem of antibiotic-resistant bacteremia is increasing in the hospital setting, as well as in the community.[11] Given the current trend of greater severity of illness for hospitalized patients, it can be expected that infections caused by antibiotic-resistant bacterial strains will be associated with greater morbidity and mortality, particularly when inadequate empiric antimicrobial treatment is administered.[12]

In addition to greater mortality rates, antibiotic-resistant bacterial infections are associated with prolonged hospitalization and increased health-care costs relative to antibiotic-sensitive bacterial infections.[13–16] Recently, a study from Beth Israel Deaconess Medical Center estimated that the emergence of antibiotic resistance among *Pseudomonas aeruginosa* increased hospital charges per patient by $11,981.[17] Other authors have also reported increased medical care costs associated with antibiotic-resistant infections, including oxacillin-resistant *Staphylococcus aureus* (ORSA).[18] The overall national costs of antimicrobial resistance have been estimated to be between $100 million and $30 billion annually for the control and treatment of infections caused by antibiotic-resistant bacteria.[15,19] The increased costs of infection caused by antibiotic-resistant bacteria have primarily been attributed to prolonged hospitalizations and greater antibiotic costs.[20] Additionally, the emergence of antibiotic resistance results in the need to develop new antimicrobial agents.[21,22] The costs required for the development of new antimicrobials, including the necessary clinical research to demonstrate their effectiveness and safety, have also increased in the last decade, possibly explaining the relatively slow development of new antibiotics.[23,24]

We performed a prospective cohort study that had two main goals: first, to determine the occurrence of bloodstream infections among patients requiring ICU admission, and second, to evaluate the relationship between the adequacy of the prescribed antimicrobial treatment for bloodstream infections and clinical outcomes. This study was performed to provide data that might improve the overall management of patients with bloodstream infections in the ICU setting.

Materials and Methods

Study Location and Patients

The study was conducted at a university-affiliated urban teaching hospital: Barnes-Jewish Hospital (1,200 beds), in St. Louis, MO. During a 2-year period (July 1997 to July 1999), all patients admitted to the medical ICU (19 beds) and surgical ICU (18 beds) were potentially eligible for this investigation. The medical and surgical ICUs are closed units with dedicated multidisciplinary health-care teams led by board-certified critical care specialists directing patient medical care. The requirement for antibiotic treatment and the selection of specific antimicrobial agents were determined by the patients' treating physicians. Patients were excluded if they were transferred to the medical or surgical ICUs temporarily because of a lack of available beds in one of the other hospital ICUs. The study was approved by the Washington University School of Medicine Human Studies Committee.

Study Design and Data Collection

A prospective cohort study design was used, segregating patients with a bloodstream infection according to hospital survival and the adequacy of their antimicrobial treatment. Hospital mortality was the main outcome variable evaluated. We also assessed secondary outcomes, including the durations of hospitalization, intensive care, and mechanical ventilation, and the occurrence of acquired organ system derangements. For purposes of this investigation, inadequate antimicrobial treatment of a bloodstream infection was defined as the microbiological documentation of infection (*ie*, a positive blood culture result) that was not effectively treated at the time the causative microorganism and its antibiotic susceptibility were known. Inadequate antimicrobial treatment included the absence of antimicrobial agents directed at a specific class of microorganisms (*eg*, absence of therapy for fungemia caused by Candida species) and the administration of an antimicrobial agent to which the microorganism responsible for the infection was resistant (*eg*, empiric treatment with oxacillin for bacteremia subsequently attributed to ORSA on the basis of blood culture results). All blood cultures for establishing the presence of a bloodstream infection were required to be obtained from percutaneously drawn sites using sterile technique and not drawn from indwelling vascular catheters.

For all study patients, the following characteristics were prospectively recorded: age; sex; race; serum albumin concentration (grams per deciliter); the ratio of PaO_2 to the concentration of inspired oxygen at the time of ICU admission; severity of illness

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based on APACHE (acute physiology and chronic health evaluation) II scores;[25] the presence of congestive heart failure requiring medical therapy with diuretics, inotropic agents, or vasodilators; COPD requiring medical therapy with inhaled bronchodilators or corticosteroids; underlying malignancy; positive serology for HIV; and the need for surgical intervention. Specific processes of medical care examined included the administration of corticosteroids, antacids, sucralfate, vasopressors, or histamine type-2 receptor antagonists; dialysis; presence of a tracheostomy; urinary tract catheterization and its duration; central vein catheterization and its duration; and the need for mechanical ventilation and its duration.

One of the investigators made daily rounds on all study patients, recording relevant data from the medical records, bedside flow sheets, and the mainframe computer of the hospital for reports of microbiological studies (Gram's stains and cultures of sputum, blood, pleural fluid, urine, wound, tissue, and lower respiratory tract specimens). All chest radiographs were prospectively reviewed by one of the investigators (M.H.K.), and the computerized radiographic reports were also reviewed 24 to 48 h later. Patients were evaluated for the development of bloodstream infections only during their stay in the ICU. Antibiotic treatment administered in the ICU setting, both perioperative prophylactic antibiotics and empiric antibiotic treatment of suspected infections, was evaluated using patients' medical records and the ICU computerized bedside workstations (EMTEK Health Care Systems Inc; Tempe, AZ).

Definitions

All definitions were selected prospectively as part of the original study design. Bacteremia was defined as the identification of a high-grade pathogen (*eg*, *P aeruginosa*, *S aureus*) in a blood culture specimen or the identification of a common skin contaminant or skin flora (*eg*, coagulase-negative staphylococci) in at least two separate blood culture specimens from the same patient drawn from different sites. Community-acquired bloodstream infections were required to be established within 48 h of hospital admission. Nosocomial bloodstream infections were required to be established after 48 h of hospitalization. Similar temporal cutoffs for separating community-acquired infections from hospital-acquired infections have been proposed by other investigators.[26] Patients residing at a nursing home, skilled-care facility, or rehabilitation center who had a bloodstream infection requiring hospital admission were classified as having community-acquired infections. Nosocomial bloodstream infections, as well as other nosocomial infections (urinary tract, wound infection), were defined according to criteria established by the Centers for Disease Control and Prevention.[27] The diagnostic criteria for ventilator-associated pneumonia were modified from those established by the American College of Chest Physicians, as previously described.[26,28]

Patients with catheter-related infection alone (*eg*, peripheral blood cultures are negative when the blood cultures drawn through the intravascular catheter are positive) are generally treated with removal of the intravascular catheter alone in our ICUs unless they appear clinically to have sepsis. Patients with catheter-related infections who also have positive peripheral blood cultures are usually treated with removal of the intravascular catheter and parenteral antibiotic therapy.

We calculated APACHE II scores on the basis of clinical data available from the first 24-h period of intensive care.[25] Acquired organ system derangements were defined using the modified criteria of Rubin and coworkers.[29] The definitions used for the systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock were those proposed by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.[30] Mortality related to a bloodstream infection was predetermined to be present when a patient died during treatment for a community-acquired or nosocomial bloodstream infection and the death could not be directly attributed to any other cause.

Statistical Analysis

All comparisons were unpaired, and all tests of significance were two-tailed. Continuous variables were compared using the Student's *t* test for normally distributed variables and the Wilcoxon rank-sum test for nonnormally distributed variables. The χ^2 test was used to compare categorical variables. The primary data analysis compared hospital nonsurvivors to hospital survivors. A second data analysis compared patients with bloodstream infections who received inadequate antimicrobial treatment with patients with bloodstream infections receiving adequate antimicrobial treatment. To determine the relationship between hospital mortality (dependent variable) and inadequate antimicrobial treatment of bloodstream infections (independent variable), a multiple logistic regression model was used to control for the effects of confounding variables.[31,32] Multiple logistic regression analysis was also used to identify independent risk factors for the administration of inadequate antimicrobial treatment of bloodstream infections.

A stepwise approach was used to enter new terms into the logistic regression models where 0.05 was set as the limit for the acceptance or removal of new terms. Variables entered into the logistic regression models were required *a priori* to have a plausible biological relationship to the dependent outcome variable to avoid spurious associations.[33] Model overfitting was examined by evaluating the ratio of outcome events to the total number of independent variables in the final models, and specific testing for interactions between the independent variables was included in our analyses.[32,33] Results of the logistic regression analyses are reported as adjusted odds ratios (AORs) with 95% confidence intervals (CIs). Relative risks and their 95% CIs were calculated using standard methods.[34] Values are expressed as the mean ± SD (continuous variables) or as a percentage of the group from which they were derived (categorical variables). All p values were two-tailed, and $p = 0.05$ was considered to indicate statistical significance.

Results

Patients

A total of 4,913 consecutive eligible patients were prospectively evaluated in the ICU. Among these, 492 patients (10.0%) were identified as having a bloodstream infection and were included in the study cohort (Table 1). The mean age of the patients was 57.8 ± 17.6 years (range, 15 to 102 years), and the mean APACHE II score was 23.4 ± 8.7 (range, 0 to 51). The mean APACHE II score of patients without bloodstream infection from these two ICUs during the same time period ($n = 3,299$) was 16.5 ± 8.2 (range, 1 to 48; $p \leq 0.001$ compared with patients with a bloodstream infection). Two hundred forty-four patients (49.6%) were women and 248 patients (50.4%) were men. One hundred forty-nine patients (30.3%) were admitted to the ICU after a surgical procedure, and 343 patients (69.7%) were admitted to the ICU for a medical diagnosis.

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Table 1—*Patient Characteristics

Characteristic*	Hospital Nonsurvivors (n = 189)	Hospital Survivors (n = 303)	p Value	Inadequate Antimicrobial Treatment (n = 147)	Adequate Antimicrobial Treatment (n = 345)	p Value
Age, yr	61.4 ± 17.1	55.6 ± 17.5	< 0.001	56.9 ± 17.3	58.2 ± 17.7	0.450
Sex, No. (%)						
Male	90 (47.6)	158 (52.2)	0.329	65 (44.2)	183 (53.0)	0.073
Female	99 (52.4)	145 (47.8)		82 (55.8)	162 (46.9)	
Race, No. (%)						
White	113 (59.8)	169 (55.8)	0.568	89 (60.5)	193 (55.9)	0.407
Black	74 (39.1)	128 (42.2)		57 (38.8)	145 (42.0)	
Other	2 (1.1)	6 (2.0)		1 (0.7)	7 (2.0)	
CHF, No. (%)	38 (20.1)	57 (18.8)	0.724	31 (21.1)	64 (18.6)	0.523
COPD, No. (%)	25 (13.2)	47 (15.5)	0.486	20 (13.6)	52 (15.0)	0.673
Underlying malignancy, No. (%)	37 (19.6)	42 (13.9)	0.093	30 (20.4)	49 (14.2)	0.086
HIV positive, No. (%)	3 (1.6)	6 (2.0)	> 0.999	4 (2.7)	5 (1.5)	0.335
Albumin, g/dL	2.6 ± 0.8	2.9 ± 1.5	0.003	2.5 ± 0.9	2.9 ± 1.4	0.001
Pao_2/Fio_2	212 ± 121	216 ± 138	0.627	214 ± 126	215 ± 134	0.982
APACHE II	27.7 ± 8.5	20.8 ± 7.7	< 0.001	23.7 ± 8.5	23.4 ± 8.8	0.701
Underwent surgery, No. (%)	54 (28.6)	95 (31.4)	0.514	50 (34.0)	99 (28.7)	0.240
Received corticosteroids, No. (%)	39 (20.6)	63 (20.8)	0.967	38 (25.9)	64 (18.6)	0.068
Dialysis, No. (%)	55 (29.1)	39 (12.9)	< 0.001	34 (23.1)	60 (17.4)	0.138
Vasopressors, No. (%)	150 (79.4)	113 (37.3)	< 0.001	93 (63.3)	170 (49.3)	0.004

*Values are given as mean ± SD unless otherwise indicated. CHF = congestive heart failure; Fio_2 = fraction of inspired oxygen.

Hospital Mortality

One hundred eighty-nine patients (38.4%) died during their hospitalization. Hospital nonsurvivors had statistically lower serum albumin concentrations, were older, had higher APACHE II scores, and were more likely to require dialysis and vasopressors compared with survivors (Table 1). Hospital nonsurvivors were also significantly more likely to require mechanical ventilation and central vein catheterization and to have longer durations of urinary tract catheterization and central vein catheterization (Table 2). The hospital mortality rate for patients receiving inadequate antimicrobial treatment for their bloodstream infections (61.9%) was statistically greater than the hospital mortality rate of patients receiving adequate antimicrobial therapy (28.4%; relative risk, 2.18; 95% CI, 1.77 to 2.69; $p < 0.001$) (Fig 1). Similarly, the bloodstream infection-related mortality rate for patients receiving inadequate antimicrobial treatment (29.9%) was significantly greater than the bloodstream infection-related mortality for patients receiving adequate antimicrobial treatment (11.9%; relative risk, 2.52; 95% CI, 1.73 to 3.67; $p < 0.001$). Hospital nonsurvivors were statistically more likely to have a bloodstream infection attributed to Candida species or multiple pathogens and statistically less likely to have a bloodstream infection attributed to coagulase-negative staphylococci and oxacillin-sensitive *S aureus* compared with hospital survivors (Table 3).

Multivariate analysis demonstrated that inadequate antimicrobial treatment was the most important risk factor for hospital mortality (AOR, 6.86; 95% CI, 5.09 to 9.24; $p < 0.001$). It explained 13.6%

Table 2—*Use of Invasive Medical Devices

Medical Devices	Hospital Nonsurvivors (n = 189)	Hospital Survivors (n = 303)	p Value	Inadequate Antimicrobial Treatment (n = 147)	Adequate Antimicrobial Treatment (n = 345)	p Value
Urinary tract catheter, No. (%)	165 (87.3)	248 (81.8)	0.109	124 (84.4)	289 (83.8)	0.871
Duration of urinary tract catheterization, d	12.7 ± 13.9	9.5 ± 9.9	0.022	12.4 ± 13.6	8.4 ± 10.4	0.003
Mechanical ventilation, No. (%)	162 (85.7)	179 (59.1)	< 0.001	119 (80.9)	222 (64.4)	< 0.001
Duration of mechanical ventilation, d	13.0 ± 13.5	10.7 ± 9.6	0.258	11.1 ± 12.6	6.9 ± 10.2	< 0.001
Central vein catheter, No. (%)	166 (87.8)	213 (70.3)	< 0.001	119 (80.9)	260 (75.4)	0.117
Duration of central vein catheterization, d	12.0 ± 13.9	9.5 ± 10.5	0.043	12.1 ± 13.6	7.0 ± 9.9	< 0.001

*Values are given as mean ± SD unless otherwise indicated.

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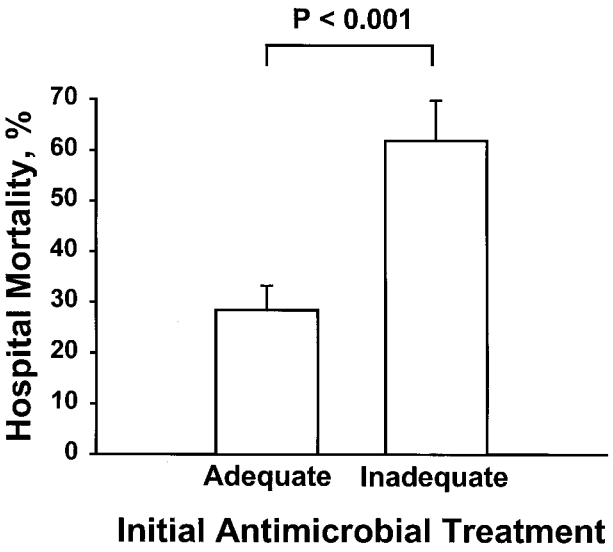

FIGURE 1. Hospital mortality according to the adequacy of the initial antimicrobial treatment prescribed for bloodstream infections. Upper 95% CIs are shown.

of the hospital mortality in our logistic regression model. The use of vasopressors (AOR, 2.99; 95% CI, 2.27 to 3.93; $p < 0.001$), an increasing number of acquired organ system derangements (one-organ increments; AOR, 2.32; 95% CI, 2.09 to 2.59; $p < 0.001$), increasing APACHE II scores (1-point increments; AOR, 1.04; 95% CI, 1.02 to 1.06; $p = 0.028$), and increasing age (1-year increments; AOR, 1.03; 95% CI, 1.02 to 1.04; $p = 0.001$) were also identified as independent predictors of hospital mortality. Life-sustaining therapies (*eg*, mechanical ventilation, vasopressors, or hemodialysis) were withdrawn before death in 29 of the nonsurvivors (31.9%) receiving inadequate antimicrobial treatment and in 24 of the nonsurvivors (24.5%) receiving adequate antibiotic treatment ($p = 0.259$).

Antimicrobial Treatment and Pathogens

One hundred forty-seven patients (29.9%) received inadequate antimicrobial treatment for their bloodstream infections. One hundred ninety-three patients (39.2%) had a community-acquired bloodstream infection, 291 patients (59.2%) had hospital-acquired bacteremia, and 8 patients (1.6%) had a community-acquired bloodstream infection followed by a hospital-acquired bloodstream infection. The administration of inadequate antimicrobial treatment was statistically greatest among patients with a hospital-acquired bloodstream infection after a community-acquired bloodstream infection, compared with patients having either community-acquired bacteremia or hospital-acquired bacteremia alone (Fig 2). Patients with hospital-acquired bloodstream infections were statistically more likely to receive inadequate antimicrobial treatment compared with patients with community-acquired bloodstream infections (Fig 2). Similarly, hospital mortality was statistically greatest for patients with a hospital-acquired bloodstream infection after a community-acquired bloodstream infection (75%) compared

Table 3—*Pathogens Associated With Bloodstream Infections**

Pathogens	Hospital Nonsurvivors (n = 189)	Hospital Survivors (n = 303)	p Value
Candida species	25 (13.2)	16 (5.6)	0.002
Coagulase-negative staphylococci	25 (13.2)	71 (23.4)	0.005
Multiple pathogens	38 (20.1)	35 (11.6)	0.009
OSSA	12 (6.4)	36 (11.9)	0.044
VRE	10 (5.3)	7 (2.3)	0.078
Klebsiella pneumoniae	5 (2.7)	17 (5.6)	0.122
P aeruginosa	10 (5.3)	12 (3.9)	0.487
Streptococcus pneumoniae	4 (2.1)	4 (1.3)	0.497
Enterobacter species	4 (2.1)	9 (2.9)	0.566
Escherichia coli	12 (6.4)	21 (6.9)	0.802
ORSA	17 (8.9)	29 (9.6)	0.831
Other pathogens	14 (7.4)†	23 (7.6)‡	0.940
Proteus mirabilis	2 (1.1)	3 (0.9)	0.942
Acinetobacter species	3 (1.6)	5 (1.7)	0.957
Enterococcus species	8 (4.2)	13 (4.3)	0.975

*Data are given as No. (%); OSSA = oxacillin-sensitive *S aureus*; VRE = vancomycin-resistant enterococci.

†Viridans group streptococci (n = 4), group B streptococci (n = 3), *Cryptococcus neoformans* (n = 2), Lactobacillus species (n = 1), *Haemophilus influenzae* (n = 1), *Serratia marcescens* (n = 1), *Stenotrophomonas maltophilia* (n = 1), *Providencia rettgeri* (n = 1).

‡Group B streptococci (n = 5), *Bacillus cereus* (n = 4), Viridans group streptococci (n = 2), *Serratia marcescens* (n = 2), Lactobacillus species (n = 1), *Haemophilus influenzae* (n = 1), Moraxella species (n = 1), Actinomyces species (n = 1), *Listeria monocytogenes* (n = 1), *Stenotrophomonas maltophilia* (n = 1), Morganella species (n = 1), *Cryptococcus neoformans* (n = 1), *Franciscella tularensis* (n = 1), *Mycobacterium kansasii* (n = 1).

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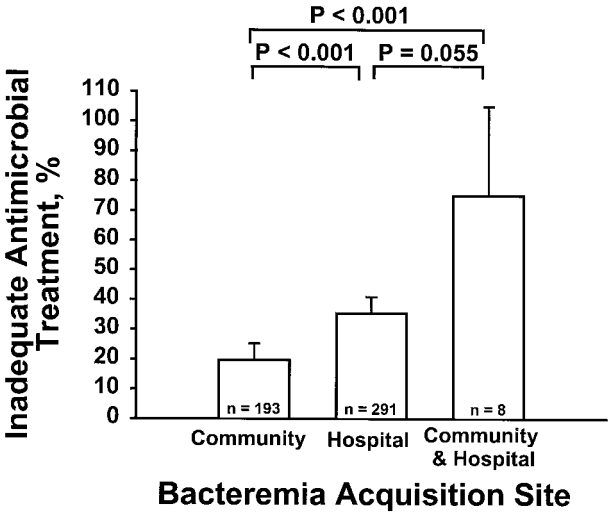

FIGURE 2. Rates of inadequate antimicrobial treatment according to the acquisition site for bloodstream infections. Upper 95% CIs are shown.

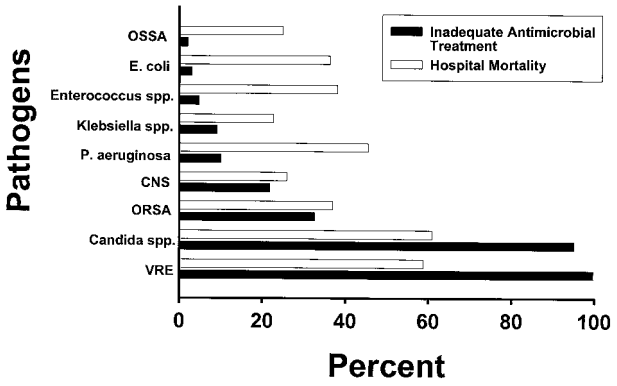

FIGURE 3. Hospital mortality and rates of inadequate antimicrobial treatment according to the most common pathogens associated with bloodstream infections. OSSA = oxacillin-sensitive *S aureus*; CNS = coagulase-negative staphylococci; VRE = vancomycin-resistant enterococci.

with patients with either community-acquired bacteremia (33.7%; p = 0.024) or nosocomial bacteremia (40.6%; p = 0.070). The source of bloodstream infections was most commonly classified as catheter-associated (24.4%) followed by pneumonia (18.5%), urinary tract infection (12.6%), GI tract infection/colonization (7.9%), mixed sources of infection (6.9%), biliary/pancreatic infection (2.6%), skin/soft tissue/wound infection (2.4%), peritonitis (2.0%), endocarditis (0.2%), and osteomyelitis (0.2%). In 22.2% of the bloodstream infections, a specific clinical source of infection was not identified.

Patients who received inadequate antimicrobial treatment for their bloodstream infections had statistically lower serum albumin concentrations, were more likely to require vasopressors and mechanical ventilation, and had significantly longer durations of urinary tract catheterization, mechanical ventilation, and central vein catheterization. Additionally, patients receiving inadequate antimicrobial treatment were statistically more likely to have received prior antimicrobial treatment during the same hospitalization compared with patients receiving adequate antimicrobial treatment (71.4% vs 48.1%; relative risk, 1.48; 95% CI, 1.26 to 1.75; p < 0.001).

The most commonly identified bloodstream pathogens and their associated rates of inadequate antimicrobial therapy included vancomycin-resistant enterococci (n = 17; 100%), Candida species (n = 41; 95.1%), ORSA (n = 46; 32.6%), coagulase-negative staphylococci (n = 96; 21.9%), and *P aeruginosa* (n = 22; 10.0%; Fig 3). A statistically significant relationship was found between the rates of inadequate antimicrobial treatment for individual microorganisms and their associated rates of hospital mortality (Spearman correlation coefficient = 0.8287; p = 0.006). Multiple logistic regression analysis demonstrated that a bloodstream infection attributed to Candida species (AOR, 51.86; 95% CI, 24.57 to 109.49; p < 0.001), prior administration of antibiotics during the same hospitalization (AOR, 2.08; 95% CI, 1.58 to 2.74; p = 0.008), decreasing serum albumin concentrations (1-g/dL decrements; AOR, 1.37; 95%CI, 1.21 to 1.56; p = 0.014), and increasing central catheter duration (1-day increments; AOR, 1.03; 95% CI, 1.02 to 1.04; p = 0.008) were independently associated with the administration of inadequate antimicrobial treatment. Prior administration of antibiotics during the same hospitalization was the only variable independently associated with infection caused by the most common microorganisms associated with inadequate treatment (Candida species, ORSA, vancomycin-resistant enterococci) compared with the other etiologic agents of bloodstream infection (AOR, 5.54; 95% CI, 4.33 to 7.09; p ≤ 0.001).

Secondary Outcomes

Hospital nonsurvivors were statistically more likely to develop sepsis, severe sepsis, and septic shock compared with hospital survivors (Table 4). Hospital nonsurvivors also acquired a statistically greater number of organ system derangements and had longer durations of mechanical ventilation and ICU stays but statistically shorter durations of stay in the hospital compared with hospital survivors. Patients receiving inadequate antimicrobial treatment had a statistically greater number of acquired organ system derangements compared with patients receiving adequate antimicrobial treatment (Table 4). Patients

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Table 4—*Secondary Clinical Outcomes

Outcomes	Hospital Nonsurvivors (n = 189)	Hospital Survivors (n = 303)	p Value	Inadequate Antimicrobial Treatment (n = 147)	Adequate Antimicrobial Treatment (n = 345)	p Value
Acquired organ system derangements, No. (%)	4.0 ± 1.3	2.2 ± 1.5	< 0.001	3.2 ± 1.7	2.8 ± 1.7	0.009
SIRS, No. (%)	189 (100.0)	297 (98.0)	0.087	146 (99.3)	340 (98.6)	0.674
Sepsis, No. (%)	174 (92.1)	256 (84.5)	0.014	124 (84.4)	306 (88.7)	0.184
Severe sepsis, No. (%)	140 (74.1)	100 (33.0)	< 0.001	76 (51.7)	164 (47.5)	0.431
Septic shock, No. (%)	132 (69.8)	82 (27.1)	< 0.001	72 (49.0)	142 (41.2)	0.109
Hospital length of stay, d	22.9 ± 27.4	24.8 ± 21.1	0.003	28.6 ± 29.3	22.2 ± 20.7	0.010
ICU length of stay, d	12.9 ± 13.8	9.0 ± 9.5	< 0.001	13.5 ± 13.4	9.2 ± 10.3	< 0.001
Duration of mechanical ventilation, d	11.2 ± 13.3	6.3 ± 9.1	0.001	11.1 ± 12.6	6.9 ± 10.2	< 0.001

*Values are given as mean ± SD unless otherwise indicated. SIRS = systemic inflammatory response syndrome.

receiving inadequate antimicrobial treatment also had significantly longer durations of mechanical ventilation and longer lengths of stay in the ICU and hospital.

Discussion

Our study demonstrated that critically ill patients with a bloodstream infection who received inadequate antimicrobial treatment were significantly more likely to die during their hospitalization compared with similar patients with bloodstream infections receiving adequate antimicrobial treatment. We also identified potential risk factors for the administration of inadequate antimicrobial treatment. These risk factors included the presence of a bloodstream infection caused by Candida species, prior antibiotic therapy during the same hospitalization, longer durations of central vein cannulation, and lower serum albumin concentrations at the time of ICU admission. Additionally, we found that bloodstream infections caused by antibiotic-resistant pathogens (Candida species, vancomycin-resistant enterococci, ORSA, and coagulase-negative staphylococci) were associated with the greatest rates of inadequate antimicrobial treatment. We further demonstrated a significant direct association between the administration of inadequate antimicrobial treatment for specific pathogens and their associated rates of hospital mortality (Fig 3). Nevertheless, some pathogens (*eg*, *E coli*, *P aeruginosa*) were found to be associated with relatively low rates of inadequate antimicrobial treatment yet had observed hospital mortality rates > 30%.

Previous studies have identified an important association between the administration of inadequate antimicrobial treatment of bloodstream infections and hospital mortality.[2–8] Leibovici and coworkers[2] found that the hospital mortality rate was significantly lower for patients with bloodstream infections who received adequate antimicrobial treatment as compared with inadequate treatment (20% vs 34%; $p < 0.001$). Similarly, Weinstein et al[4] showed that patients who received adequate antimicrobial treatment throughout the course of bloodstream infection had the lowest mortality. Our study results confirm these findings, as well as those demonstrated for nosocomial pneumonia, and also suggest potential strategies to reduce the administration of inadequate antimicrobial treatment.[35–38] However, the mortality rate of bloodstream infections is significant even when appropriate antimicrobial treatment is administered, especially for high-risk pathogens like *P aeruginosa*. This is most likely because of the virulence of these pathogens and the subsequent inflammatory response that occurs in the host, resulting in organ dysfunction and death.

The risk factors for the administration of inadequate antibiotic treatment identified in our study may explain, in part, the occurrence and potential prevalence of this problem. These risk factors appear to share a common characteristic, the presence of an antibiotic-resistance pathogen (Candida species) or predisposing to the development of antibiotic-resistant infections (prior antibiotic treatment, prolonged central vein catheterization). The role of low serum albumin concentrations is not entirely clear, although it may reflect poor nutritional status or greater severity of illness, which may predispose to infection with antibiotic-resistant pathogens. Bloodstream infection caused by Candida species, as well as other antibiotic-resistant pathogens (*eg*, ORSA, vancomycin-resistant enterococci, coagulase-negative staphylococci), requires treatment with specific antimicrobial agents that have activity against these microorganisms. Predicting the presence of an antibiotic-resistant bloodstream infection can be difficult. However, prior antibiotic exposure, prolonged

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hospitalization, and the presence of invasive devices have all been associated with their occurrence.[39] The increasing emergence of antibiotic-resistant pathogens as a source of infection, both in the community as well as in the hospital setting, makes it more likely that patients with bloodstream infections will receive inadequate treatment.

Prior treatment during the same hospitalization with antimicrobial agents appears to be one of the most important risk factors for the subsequent occurrence of an antibiotic-resistant infection. Additionally, the overuse of specific antimicrobial agents or classes of antibiotics can predispose to higher rates of resistance to those drugs among both community-acquired pathogens and hospital-acquired pathogens.[14] Similarly, the prolonged presence of invasive medical devices, especially intravascular catheters and devices, has been associated with the emergence of antibiotic resistance.[39] In addition to being a marker of greater severity of illness, these devices are frequently associated with the formation of biofilms on their surfaces. Antibiotic penetration into biofilms is usually diminished, allowing sequestered pathogens colonizing these devices within the biofilms to be exposed to subtherapeutic concentrations of antimicrobial agents. The presence of such an environment favors the emergence of antibiotic-resistant microorganisms.[40]

Our findings suggest that efforts aimed at reducing the administration of inadequate antimicrobial treatment could improve patient outcomes. Trouillet and coworkers[41] found that specific combinations of antimicrobial agents were more likely to provide adequate antimicrobial treatment of nosocomial pneumonia. Similar results have been demonstrated for bloodstream infections.[42,43] Rello and colleagues[44] demonstrated that the pathogens responsible for nosocomial infections among critically ill patients frequently vary among hospitals. These studies suggest that knowledge of the local microbial flora accounting for infections, and the risk factors predisposing to those infections, could reduce inadequate antimicrobial treatment by allowing for the selection of the most effective antimicrobial agents. LDS Hospital has used an automated antibiotic consulting service, which has been shown to increase the rates of adequate antimicrobial treatment compared with individual physician antibiotic practices.[45,46] Additionally, several clinical investigations suggest that scheduled antibiotic changes or cycling of antibiotics during specific periods may improve clinical outcomes, in part by reducing the administration of inadequate antimicrobial treatment.[47,48] Finally, the development of new technologies for the early identification of high-risk pathogens associated with the administration of inadequate antimicrobial treatment could reduce the occurrence of this problem.

Several limitations of this study should be noted. First, it was conducted at a single hospital. Therefore, these results may not be applicable to other hospitals with lower rates of bloodstream infection caused by Candida species and antibiotic-resistant bacteria. Second, we examined a mixed group of medical and surgical patients requiring intensive care. It is possible that other types of critically ill patients (*eg*, solid organ transplant recipients, cardiothoracic patients) may have different rates of inadequate antimicrobial treatment and different risk factors predisposing to the administration of inadequate treatment. Third, individual physician judgments guided the selection of antimicrobial treatment for our patients. Therefore, institutions using antibiotic guidelines or protocols for the administration of antimicrobial treatment may have different results.[45,46] Fourth, our empiric use of antibiotics may differ from that at other institutions. For example, $< 40\%$ of cases of ORSA and $< 25\%$ of cases of coagulase-negative staphylococci received inadequate antimicrobial treatment. This probably reflects our common empiric use of vancomycin for patients with suspected bloodstream infections or sepsis, which may not occur at other centers. Finally, the observational nature of this investigation does not allow us to draw an absolute causal relationship between the administration of inadequate antimicrobial treatment and specific clinical outcomes including hospital mortality.

Clinicians practicing in the ICU setting must be able to balance the need to provide adequate antimicrobial treatment to potentially infected patients with the risk that unnecessary antibiotic treatment carries (*ie*, predisposing to the subsequent emergence of antibiotic-resistant infections). A potential strategy for balancing these two competing issues would involve the early administration of broad-spectrum antimicrobial treatment to high-risk patients with suspected bloodstream infections. This should be followed by rapid tailoring of the antimicrobial regimen or discontinuation of antimicrobial treatment on the basis of culture results and the clinical course of the patient. Formal antibiotic use guidelines represent one tool for achieving such a balance.[45] Additionally, knowledge of local organisms (*eg*, hospital-specific or unit-specific) and their resistance patterns is of great importance for selecting appropriate antimicrobial treatment. Although we do not recommend routine empiric therapy for every cause of bloodstream infection (*eg*, vancomycin-resistant enterococci, Candida species) at the present time, there may be specific patient groups identified in the future that would benefit from such

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broader therapy. In our own practice, these study results have been used to select empiric antimicrobial regimens aimed at minimizing the initial administration of inadequate antimicrobial treatment to patients with suspected bloodstream infections. This usually means initial coverage with vancomycin for ORSA and coagulase-negative staphylococci (because of their prevalence at our institution) and two drugs for the treatment of *P aeruginosa* until the culture results become available.

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attacks. Unfortunately, quite a few referrals are asthmatic outliers with perennial asthma who do not respond well to any of the current approaches to therapy, alone or in combination.

It has been known for years that patients, patients' families, and patients' physicians frequently underestimate the severity of asthma.[1–3] Despite the widespread use of peak flowmeters in the home, I think the tendency is still to underestimate the severity of the disease in adults. Perhaps my view is skewed. Quite often, my first encounter with an individual asthmatic patient is in the medical ICU, and most of these patients require intubation and mechanical ventilatory support. Each patient seems to have a similar story: a failure to recognize the severity of the disease, leading to undertreatment.

Years ago, our therapeutic armamentarium was limited. Now long-acting β_2-agonists, supplemented with effective shorter-acting β_2-agonists as well as improved inhaled corticosteroids, are available. Newer drugs for preventing acute exacerbations include antagonists of metabolites of both lipooxygenase and cyclooxygenase arms of the arachidonic acid pathway. Leukotriene inhibitors have proven quite effective in some patients. In this issue of *CHEST* (see page 73), Tamaoki et al present data on the efficacy of a thromboxane α_2-receptor antagonist in reducing the quantity and viscosity of sputum in stable asthmatics. Theophylline, long out of favor as a therapy for adults, has an immunomodulatory effect at low doses and should be readdressed.[4] Manipulation of the variety of therapeutic modalities now available, in order to provide the most effective program for the individual patient with asthma, will undoubtedly be helpful in preventing acute exacerbations. However, our ongoing assessment of the severity and "brittleness" of a patient's disease must improve if we are to reduce morbidity and mortality.

As an intensivist who sees the morbidity and mortality of asthma almost daily, I remain convinced that regularly scheduled inhaled bronchodilators are the mainstay of maintenance therapy in all but the very mildest of asthmatic patients ("the open airway approach"). Both β_2-agonists and anticholinergic bronchodilators, alone or preferably in combination, are effective in patients with asthma (the dichotomy, β_2-agonists for asthma, anticholinergics for COPD, does not hold).

My major concern is that patients with the disease called asthma be treated individually and vigorously, that tapering doses of systemic corticosteroids be used early and liberally with exacerbations, and that the severity of the patient's disease not be underestimated. I would be happy never to admit another patient with status asthmaticus to my unit.

William A. Speir, Jr., MD, FCCP
Augusta, GA

Dr. Speir is Professor of Medicine, Section of Pulmonary and Critical Care Medicine, Medical Director, Medical Intensive Care Unit, Medical College of Georgia.
Correspondence to: William A. Speir, Jr., MD, FCCP, Section of Pulmonary and Critical Care Medicine, Medical Director, Medical Intensive Care Unit, Medical College of Georgia, Augusta, GA 30912-3135

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Empiric Antibiotic Use and Resistant Microbes

A "Catch-22" for the 21st Century

Over the past decade, clinicians have witnessed an unprecedented increase in the emergence and spread of antibiotic-resistant bacteria.[1–3] These include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), multiple drug-resistant Gram-negative rods, and resistant *Streptococcus pneumoniae*. ICUs are the leading incubators of many of these resistant organisms.[1–6]

In this issue of *CHEST* (see page 146), Kollef and colleagues demonstrate that ineffective therapy of resistant microorganisms is associated with increased mortality in critically ill patients. Clinicians at Barnes-Jewish Hospital used effective antibiotics empirically for the vast majority of patients with Gram-negative rod bacteremias. However, for patients with certain pathogens (MRSA, VRE, and Candida), the initial antibiotics used were not effective. Delays in instituting effective agents resulted in a higher mortality rate among these patients. Independent risk factors for development of resistant infections included previous treatment with antibiotics, presence of a central venous catheter (for longer duration), and low serum albumin levels.

These factors are likely to help identify "at-risk" patients at most institutions. Should we assume infections with antibiotic-resistant pathogens in every patient with one of these risk factors? If not, at what prevalence of antibiotic resistance should we include coverage of resistant organisms in empiric treatments? If we liberalize our use of the ever-decreasing list of effective antibiotics, aren't we promoting emergence of more multiresistant organisms, including the dreaded vancomycin-resistant staphylococci?

The emergence of antibiotic-resistant organisms is not new.[7] Microorganisms have always been endowed with genetic mechanisms for attaining resistance.[5,6] Clearly, our overuse of broad-spectrum antibiotics has accelerated the process of microbial resistance.[1,8,9] Resistance rates are highest in the ICUs of most institutions[1–5,10] due largely to overuse of antibiotics and cross-transmission. We can no longer assume that this is arcane "test-tube science" that can be ignored, counting on the pharmaceutical industry to stay one step ahead of resistant microbes through development of new antibiotics. We must lead in scrutinizing our (personal and aggregate) antibiotic prescribing patterns and in developing comprehensive institutional programs to minimize the emergence and further spread of these microbes. To the extent that patients move in and out of the ICU to various units of the hospital, our efforts will fail if control measures are limited only to the ICU. Solutions will necessarily require collaboration with other hospital personnel and integration of efforts, *ie*, a consistent, systematic, united front.

What should be our "first-line agents" in this era of resistant pathogens? Since the prevalence of resistant bacteria varies between and within institutions, the appropriate antibiotic choices for empiric therapy will necessarily vary between hospitals and will change with time. Interestingly, the problem of resistance had already impacted clinicians at Barnes-Jewish Hospital insofar as vancomycin was used "commonly" in their empiric cocktails of antibiotics. At many centers, where MRSA is not so prevalent, vancomycin is not used routinely. A prevalence of 15 to 20% resistance is, perhaps, a reasonable threshold to begin routine empiric coverage for resistant organisms in critically ill patients. The following general concepts are relevant to the discussion:

1. Initial Approach to Individual Patients: Clinicians should consider the balance between host (immunocompetence) and microbe (virulence) in determining the risks and benefits of immediate vs deferred and broad- vs narrow-spectrum treatment. The available clinical data (*ie*, the likely site of infection and organisms to which the host is susceptible) and the microbial resistance patterns at the institution should be considered in selecting antibiotics of adequate, but not unnecessarily broad, spectrum to cover the *probable* causes of infection.

2. Use Microbiology Antibiotic Susceptibility Results To Narrow the Attack: We must obtain culture/sensitivity results promptly, and modify the antibiotic(s) with the narrowest spectrum and/or lowest resistance potential[11] to which the isolated organism is sensitive.

3. Use Optimum Doses for a Full Course of Treatment: The optimum doses[12,13] of antibiotics should be continued for the full course to reduce the likelihood of selecting a resistant pathogen that will cause recurrent clinical disease. Unfortunately, for some sites of infection insufficient data exist to inform the optimal duration of therapy. Moreover, optimal duration could vary depending on the causative microbe, the severity of infection, and the immunocompetence of the host.

4. Avoid Antibiotic "Surfing": Clinicians should allow a reasonable time (which may vary for differing hosts/infections) for clinical improvement before declaring an antibiotic failure. In some severe infections, fevers may persist for up to a week. If the microbe is sensitive (in the laboratory) and the patient is otherwise improving, persistent fever should not, in itself, be considered treatment failure.

5. Hospital Infection Control: Resistant microbes will continue to emerge, but we can attenuate the rate of spread by implementing effective control measures. We must continually remind all staff who care for, or come in direct contact with, patients to adhere to standard precautions because we (healthcare workers) are vectors for nosocomial infections. The available data suggest that we are abysmal in both the frequency and quality with which we wash our hands between patient contacts.[14] Multiple drug-resistant nosocomial infections are unlikely to be reigned in unless this simple, yet difficult, step is taken. Physician-leaders should lead by example.

The risk of transmission is greatest while awaiting culture results. Extra precautions should be initiated when the admission data suggest the possibility of resistant, highly transmissible pathogens like VRE or MRSA. Waiting until cultures return unnecessarily increases risk of transmission to other patients. One approach is to place all patients with risk factors (history of MRSA or VRE infection, transfer from nursing homes, Gram's stain data indicating Gram-positive cocci in clusters, and/or long-term IV catheters) in contact isolation until infection/colonization has been ruled out. For example, in our critical care unit, patients are placed in precautionary contact

isolation if any Gram's stain of a body fluid reveals Gram-positive cocci in clusters, or cultures reveal staphylococcal infection and we are awaiting antibiotic sensitivities. But, this common-sense, preventative measure has not been proven to reduce the frequency of such infections and may not be cost-effective.

6. Institutional Restrictions on Antibiotic Use: Selective restriction, removal, or control of antimicrobial agents, particularly those with high resistance potential, may be important means of reducing the emergence of multiple drug resistance. Implementation of such measures in some institutions has resulted in reductions in the prevalence of resistant organisms.[15,16] Arbitrary rotation of classes or agents used in empiric cocktails may inadvertently increase the prevalence of multiple drug resistance. Such strategies are only likely to be helpful if they utilize microbial surveillance data to switch classes/agents when resistance emerges. Moreover, the use of centralized formulary restrictions and rotating crops of agents can only be successful if all stake-holders—intensivists, infectious disease specialists, hospital epidemiologists, pharmacists, and policy makers—coordinate their efforts (and staff physicians are convinced of the importance of such initiatives).

The emergence of multiple drug-resistant pathogens poses a new challenge to all. As intensivists, our critically ill patients will pay the heaviest price. Thus, we must lead the way in modifying clinicians' behaviors (*ie*, appropriate antibiotic selection and dosing, and hand washing) and formulate comprehensive strategies to contain resistant infections, thus reducing the risk to present and future patients. Increasing scientific attention to this problem will yield proven solutions that can be instituted in the future. In the meantime, let's make hand washing between patient contacts, one proven method of infection control, the 11th commandment in the ICU (and throughout the hospital).

Constantine A. Manthous, MD, FCCP
Yaw Amoateng-Adjepong, MD, PhD
Bridgeport, CT

Dr. Manthous is Assistant Clinical Professor of Medicine, and Dr. Yaw Amoateng-Adjepong is Instructor of Medicine, Division of Pulmonary and Critical Care, Bridgeport Hospital and Yale University School of Medicine.

Correspondence to: Constantine A. Manthous, MD, FCCP, Bridgeport Hospital, 267 Grant St, PO Box 5000, Bridgeport, CT 06610; e-mail: pcmant@bpthosp.org

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