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

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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*

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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 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]

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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

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.

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.

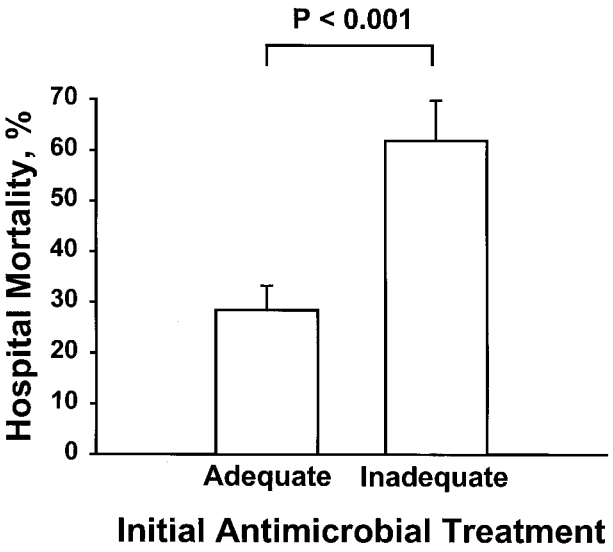

FIGURE 1. Hospital mortality according to the adequacy of the initial antimicrobial treatment prescribed for bloodstream infections. Upper 95% CIs are shown.

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).

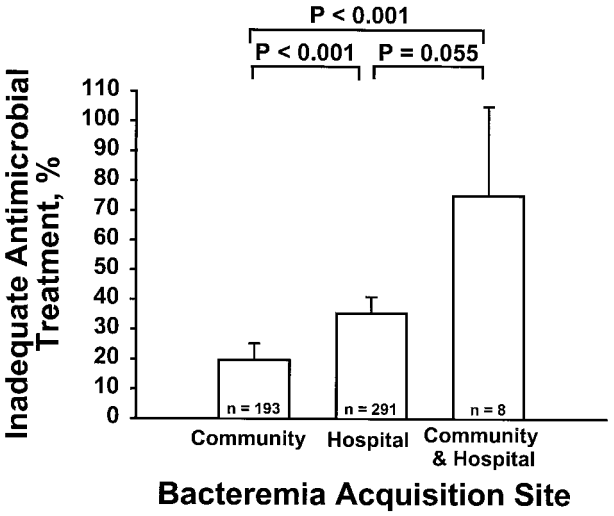

FIGURE 2. Rates of inadequate antimicrobial treatment according to the acquisition site for bloodstream infections. Upper 95% CIs are shown.

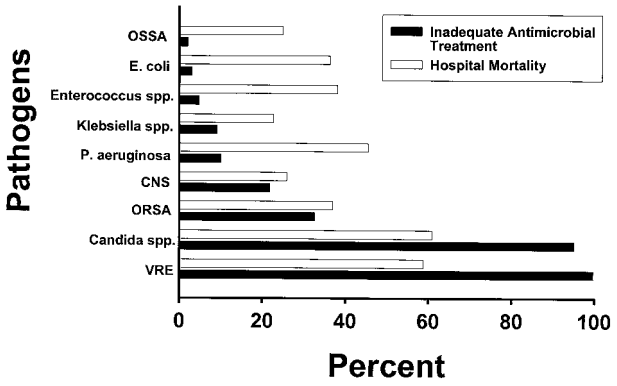

FIGURE 3. Hospital mortality and rates of inadequate antimicrobial treatment according to the most common pathogens associated with bloodstream infections. OSSA = oxacillin-sensitive *S aureus*; CNS = coagulase-negative staphylococci; VRE = vancomycin-resistant enterococci.

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

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

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

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

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