Risk Factors for Ineffective Therapy in Patients With Bloodstream Infection

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Background: Infections occurring among outpatients having recent contact with the health care system have been termed health care–associated infections. The objective of this study was to analyze the impact of health care–associated status on effectiveness of initial therapy in hospitalized patients with bloodstream infections.

Methods: Prospective cohort study of adults with bloodstream infections at 3 North Carolina hospitals. Bloodstream infection was defined as health care–associated if it occurred within the first 48 hours after hospitalization and if patients had 1 of the following characteristics: had received home health services, outpatient intravenous therapy, or outpatient renal dialysis in the 30 days prior to hospital admission; had been hospitalized within 90 days prior to admission; or lived in a long-term care facility.

Results: Of 466 bloodstream infections, 132 (28%) were community-acquired, 178 (38%) were health care–associated, and 156 (33%) were nosocomial. Multivariable logistic regression using community-acquired status as a reference identified health care–associated status (odds ratio, 3.1; 95% confidence interval, 1.6-6.1) and nosocomial status (odds ratio, 4.3; 95% confidence interval, 2.2-8.3) as independent predictors of ineffective initial antibiotic therapy. Among health care–associated characteristics, hospitalization in the 90 days prior to admission was independently associated with ineffective initial therapy (odds ratio, 2.4; 95% confidence interval, 1.4-4.2).

Conclusions: Among patients treated in the hospital for bloodstream infection, health care–associated status was an independent predictor of ineffective initial antibiotic therapy. Hospitalization within 90 days prior to hospital admission was the component of health care–associated status most strongly associated with ineffective initial therapy.

Arch Intern Med. 2005;165:308-313
METHODS

This prospective cohort study was undertaken simultaneously at 3 medical centers: Duke University Medical Center (Durham, NC), Durham Regional Hospital (Durham), and Nash General Hospital (Rocky Mount, NC). The study protocol was approved by the institutional review boards at all 3 centers, and the requirement for informed consent was waived.

PATIENTS

Patients were identified by daily review of microbiology laboratory records from October 16, 2000, through February 28, 2001. Patients were included in the study if their blood cultures were drawn either in the hospital or in the clinic or emergency department immediately prior to admission and if the culture results were positive for fungus or bacteria. Patients with blood culture results positive for mycobacteria or viruses were excluded. Patients younger than 17 years and patients discharged from the emergency department without hospitalization were excluded. Only the first episode of bloodstream infection per patient was included.

DATA COLLECTION

Case report forms were completed by either a physician or an infection control practitioner. Mortality data were obtained from the patient’s medical record as well as from the Social Security Death Index. Data pertaining to mortality were collected at hospital discharge and 3 to 6 months after bloodstream infection. In some cases where data collection was incomplete, paper charts were reviewed to augment collected data.

DEFINITIONS

A candidate episode of bloodstream infection was defined as the first set of positive blood culture results during a period of hospitalization or in a clinic or emergency department visit immediately preceding hospitalization. Each candidate episode of bloodstream infection was prospectively followed up and was continuously assessed by 1 investigator in the manner previously described by Weinstein et al, using all available clinical data to classify episodes as contaminant, true positive, or of unknown clinical significance. Only candidate episodes of bloodstream infection classified as true positive were analyzed in this study.

Bloodstream infection was defined as nosocomial when it occurred more than 48 hours after the beginning of a period of hospitalization. If a patient was transferred from another hospital, the duration of inpatient stay was calculated from the date of admission to the first hospital.

Bloodstream infection was defined as a health care–associated when it occurred at the time of hospital admission or within 48 hours of admission and if the patient fulfilled any of the following criteria:

1. Received intravenous therapy at home or in an outpatient clinic in the previous 30 days; or
2. Received home health care such as wound care or specialized nursing care through a health care agency, family, or friends in the previous 30 days; or
3. Received renal dialysis in a hospital or clinic in the previous 30 days; or
4. Had been hospitalized in an acute care hospital for 2 or more days in the previous 90 days; or
5. Resided in a nursing home or long-term care facility for 2 or more days in the previous 90 days.

Bloodstream infection was defined as community-acquired when it occurred within the first 48 hours of hospital admission for patients who did not fit the criteria for health care–associated bloodstream infection.

Antibiotic therapy was defined as effective if the antimicrobial agent administered was active in vitro against the infecting organism and if the drug was given at adequate doses and by adequate route of administration. In the case of organisms for which antimicrobial susceptibilities are not routinely performed (eg, anaerobic organisms and Candida species), therapy was considered effective if the antibiotic administered was a recommended first-line or alternate agent for the infecting organism.

Initial therapy was defined as antibiotics received on the first day of therapy for bloodstream infection. Effective antibiotics administered on or before the same calendar day as the first blood culture were considered to have been started on day 0. If effective antibiotics were not administered by day 5 of antibiotic therapy, then time to effective therapy was censored at day 5, so as to dampen the impact of bloodstream infection episodes that were never effectively treated. Time to effective therapy was censored at day 5 in 3 patients.

Other definitions used for this cohort, including comorbidity conditions, predisposing factors, and primary source of infection, have been published previously.

STATISTICAL ANALYSIS

Statistical analysis was performed using SAS version 8.2 (SAS Institute Inc, Cary, NC). Differences between continuous variables by group were tested using the Wilcoxon rank-sum test. The χ² or Fisher exact test, as appropriate, were used to assess associations among categorical variables. Associations between epidemiologic categories of infection and other variables were analyzed by using conditional fixed-effects logistic regression to adjust for hospital site. Variables with a bivariate significance level of 0.20 or less were included in the initial multivariable models. Variables to be included in the final model were selected using a stepwise selection process. All predictors were checked for confounding. If the addition of a confounding variable affected the β-coefficient for the effect measure of a selected variable by greater than 10%, it was left in the model. Dummy variables were used to represent 2 of the 3 hospitals (the third hospital being the baseline) as well as 2 of the 3 epidemiological categories of infection, thereby adjusting for clustering of epidemiological factors and outcome by hospital site. All tests were 2-tailed, with a P value of .05 or less considered statistically significant.

RESULTS

Between October 16, 2000, and February 28, 2001, a total of 466 patients with bloodstream infection met criteria for inclusion in the study. The flow of cultures and patients considered for inclusion in the study is shown in the Figure. Of the 466 episodes of bloodstream infection, 132 (28%) were community-acquired, 178 (38%) were health care–associated, and 156 (33%) were nosocomial. Three hundred seven (65.9%) bloodstream infections occurred at Duke University Medical Center, 104 (22.3%) at Durham Regional Hospital, and 55 (11.8%) at Nash General Hospital.

POPULATION CHARACTERISTICS

Descriptive characteristics of this cohort are shown in Table 1. All comparisons between epidemiological cat-
egories were controlled for the effects of clustering by hospital. The mean age of the study patients was 60.4±18.2 years, and patients with health care–associated bloodstream infection were significantly younger than those with community-acquired infection (59.0 years vs 63.4 years, *P* = .04). Fifty-three percent of patients were men, and 56% were white. The most common comorbid conditions were vascular disease (192 patients [41%]), renal disease (144 [31%]), diabetes mellitus (135 [29%]), and cancer (126 [27%]). The most common sources of bloodstream infection were an intravascular device (138 patients [30%]), urinary tract infection (111 [24%]), and pneumonia (80 [17%]).

Of 178 patients with health care–associated bloodstream infection, 112 (63%) had been hospitalized in the past 90 days, 73 (41%) had received outpatient intravenous therapy or chemotherapy in the past 30 days, 60 (34%) had received home health services in the past 30 days, 57 (32%) had received hemodialysis in the past 30 days, and 36 (20%) were residents of long-term care facilities.

### ANTIMICROBIAL THERAPY

The microbiological characteristics of these bloodstream infections is shown in Table 2. The pathogens most frequently found in community-acquired bloodstream infection were *Escherichia coli* and *Streptococcus pneumoniae*. *Staphylococcus aureus* was the pathogen most frequently found among patients with nosocomial and health care–associated bloodstream infection.

Enterococci resistant to ampicillin and/or vancomycin were seen more frequently in patients with nosocomial bloodstream infection (8/156 [5%]) than in those with community-acquired bloodstream infection (0/132) (*P* = .009). Enterobacteriaceae of intermediate susceptibility or resistant to ciprofloxacin and/or ampicillin/sulbactam occurred at a similar rates in patients with community-acquired bloodstream infection (8%), health care–associated bloodstream infection (12%), and nosocomial bloodstream infection (12%) (*P* = .40 for each pair-wise comparison). Of 14 fungal bloodstream infections, 9 were due to *Candida* and 5 were due to *Cryptococcus*.

Nearly two thirds of patients (295/466 [63.3%]) received a single antimicrobial agent as their initial empirical therapy. More than a quarter of patients (127/466 [27.3%]) received 2 antimicrobial agents, 8.4% (39/466) received 3, and 1.1% (5/466) received 4 or more. The most commonly prescribed antimicrobial agents were vancomycin (37.6% of patients), quinolones (30.7%), third-generation cephalosporins (20.8%), β-lactam/β-lactamase inhibitor combinations (15.0%), and aminoglycosides (12.7%). All other classes of antimicrobials were used in less than 4% of patients.

### EFFECTIVENESS OF THERAPY

After controlling for hospital, the time from positive blood culture result to start of initial empirical therapy was similar for community-acquired, health care–associated, and nosocomial bloodstream infection (median for all groups, <1 day; *P* = .46). Among patients who received ineffective initial therapy, patients with community-acquired, health care–associated, and nosocomial bloodstream infection had similar durations of ineffective therapy (median, 2.0 days for all 3 groups; *P* = .98).

Patients with nosocomial bloodstream infection received ineffective initial therapy in 32.1% of episodes, compared with 8.3% of episodes for those with community-acquired bloodstream infection (odds ratio [OR], 5.1; 95% confidence interval [CI], 2.5-10.4; *P* = .001). Patients with health care–associated bloodstream infection received ineffective initial therapy 25.3% of the time compared with 8.3% for those with community-acquired bloodstream infection (OR, 3.2; 95% CI, 1.7-6.0; *P* < .001). There was no statistical difference between the proportion of patients receiving ineffective initial therapy for nosocomial bloodstream infection compared with those with health care–associated bloodstream infection (*P* = .13). Bivariate predictors of ineffective initial therapy, controlled for hospital, are shown in Table 3.

Multivariable analysis was performed to determine independent predictors of ineffective initial therapy. A multivariable model was constructed (Table 4) that considered all demographic characteristics, comorbid conditions, primary sites of infection, and pathogens for inclusion. Health care–associated status was a significant independent predictor of ineffective initial therapy (odds ratio, 2.4; 95% CI, 1.2-4.8), as was nosocomial status (odds ratio, 3.1; 95% CI, 1.5-6.5), using community-acquired status as the reference category. Methicillin-resistant *S aureus* (OR, 1.7; 95% CI, 1.0-2.8) and *Enterococcus* (OR, 2.3; 95% CI, 1.3-4.1) were associated with an increased likelihood of receiving inappropriate initial therapy, and infection due to *E coli* was associated with a decreased risk for ineffective therapy (OR, 0.3; 95% CI, 0.1-0.9). This model was controlled for the confounding effects of other pathogens (*S pneumoniae* and methicillin-resistant *S aureus*), the presence of neutropenia at the time of bloodstream infection, and the presence of an intravenous device. When health care–associated status was replaced in the model by its 5 individual defining features (dialysis, nursing home resi-
dence, receipt of home health care, receipt of home intravenous therapy, and hospitalization in the past 90 days), hospitalization in the 90 days preceding bloodstream infection (OR, 2.4; 95% confidence interval, 1.4-4.2) was identified as the only component of health care–associated status that predicted ineffective initial therapy.

MORTALITY OUTCOMES

The inpatient mortality rate for all patients included in the study was 21% (100/466 patients) (Table 1). There was no significant difference in inpatient mortality rates among the 3 study hospitals. The rate of inpatient mortality was similar in patients receiving effective empirical therapy (20.3%) compared with those receiving ineffective empirical therapy (25.5%) (P = .25).

Risk factors for health care–associated infection are becoming increasingly prevalent as medical care is deliv-
care–associated infections as an entity independent of receipt of ineffective initial antimicrobial therapy. This finding is notable. In multivariable analysis, health care–associated and nosocomial infection between rates of ineffective empirical therapy for patients community-acquired infection and the similarity between the groups with health care–associated and community-acquired bloodstream infection this finding is not the known differences between the group with health care–associated bloodstream infection than either nosocomial or community-acquired bloodstream infection. We examined the relationship between ineffective initial therapy and health care–associated status in this cohort. To our knowledge, no previously published study has examined this relationship.

In this study, patients with health care–associated bloodstream infection were 3 times more likely than patients with community-acquired bloodstream infection to receive ineffective initial antibiotic therapy. Based on the known differences between the group with health care–associated bloodstream infection and that with community-acquired bloodstream infection this finding is not completely unexpected, but the magnitude of the difference between the groups with health care–associated and community-acquired infection and the similarity between rates of ineffective empirical therapy for patients with health care–associated and nosocomial infection is notable. In multivariable analysis, health care–associated status was an independent risk factor for receipt of ineffective initial antimicrobial therapy. This finding highlights the importance of recognition of health care–associated infections as an entity independent of community-acquired infections and should serve as a warning to clinicians that this growing segment of the patient population is at risk for suboptimal treatment and poor outcomes.

Patients who acquire health care–associated infections are a heterogeneous population of patients with different types of health care contact. Of the 5 defined subsets of health care–acquired bloodstream infection in place of the health care–acquired epidemiological category resulted in the following hazard ratios: hospitalization for ≥2 d in the past 90 d, 1.8 (95% CI, 1.0-3.2; P = .04); home intravenous therapy, 1.8 (95% CI, 0.9-3.6; P = .11); home health care, 1.3 (95% CI, 0.7-2.6; P = .42); nursing home residence, 1.0 (95% CI, 0.5-2.2; P = .97); and hemodialysis, 0.6 (95% CI, 0.3-1.3; P = .18).
performing multiple comparisons should be viewed as exploratory and not absolutely conclusive.

Proper empirical antibiotic therapy for serious infections can be life saving. Empirical choices are based on the most likely and virulent possible pathogens for a given infection. In order make the best possible empirical antibiotic choices, clinicians must be aware of changes in health care delivery and associated antimicrobial resistance. Our data can be used by clinicians to more effectively prescribe antibiotics for patients with suspected bloodstream infection and may lead to improved clinical outcomes in these patients.

Accepted for Publication: November 16, 2004.
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Funding/Support: Dr McDonald was supported by a grant from the Agency for Healthcare Research and Quality. Dr Friedman was supported by an educational grant from Merck Pharmaceuticals. Dr Stout was supported by a K23 grant from the NIH/NIAID (AI051409). Dr Kaye was supported by a T. Franklin Williams Young Investigator Award from the Infectious Diseases Society of America, the Association of Subspecialty Professors, John A. Hartford Foundation, and Elan Pharmaceuticals.

Previous Presentation: This study was presented in part at the Society for Healthcare Epidemiology of America 14th Annual Meeting; April 17-20, 2004; Philadelphia, Pa.

REFERENCES