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 characteris-tics: 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.

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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 comorbid 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 pairwise 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-
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
ing highlights the importance of recognition of health
care–associated bloodstream infection. This find-
ness between the groups with health care–associated and
community-acquired bloodstream infection this finding is not
completely unexpected, but the magnitude of the differ-
ence between the groups with health care–associated and
community-acquired infection and the similarity be-
tween 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
infectious diseases specialist in the care of the pa-
tients.15 It is possible that inclusion of either of these vari-
able in our model could have altered our results. Fi-
tion,24 which we believe is reasonable based on available
limit generalizability to other regions. There is no con-
firmation in practice patterns and antimicrobial resistance may
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<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Demographic characteristics</td>
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<tr>
<td>Age (per decade)</td>
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<td>Men</td>
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<td>Renal disease</td>
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<td>Cancer</td>
<td>0.93 (0.63-1.36)</td>
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<td>Chronic obstructive pulmonary disease</td>
<td>1.12 (0.72-1.74)</td>
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<td>Source of bacteremia</td>
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<td>Intravascular device infection</td>
<td>1.65 (1.18-2.31)</td>
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<td>Urinary tract infection</td>
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<td>Pneumonia</td>
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<tr>
<td>Bacterial</td>
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<td>Methicillin-resistant</td>
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<td>Staphylococcus aureus</td>
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<td>Yeast</td>
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<tr>
<td>Polymicrobial</td>
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<td>Health care–acquired vs community-acquired</td>
<td>3.17 (1.67-5.99)</td>
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<td>Health care–acquired nosocomial vs community-acquired</td>
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<td>Nosocomial vs community-acquired</td>
<td>5.08 (2.48-10.42)</td>
<td>&lt;.001</td>
</tr>
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Abbreviations: CI, confidence interval; OR, odds ratio.
*Confounders of variables in the model: neutropenia, presence of an
intraocular device, methicillin-sensitive Staphylococcus aureus.
†Analysis of 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); hospital intravenous therapy, 1.8 (95% CI, 0.9-3.6;
P = .11); nursing home care, 1.3 (95% CI, 0.7-2.8; P = .42); nursing home resi-
dence, 1.0 (95% CI, 0.5-2.2; P = .97); and hemodialysis, 0.6 (95% CI, 0.3-1.3; P = .18).

There are several limitations to this study. All 3 hos-
pitals are within a 80-mile radius, and geographic vari-
ation in practice patterns and antimicrobial resistance may
limit generalizability to other regions. There is no con-
sensus definition of health care–associated status. We have
used the same definition used in a previous publica-
tion,25 which we believe is reasonable based on available
literature. Our study variables did not include 2 factors
that were shown by other investigators to be associated
with receipt of ineffective initial therapy: antibiotic treat-
ment in the previous month13 and clinical involvement
of an infectious diseases specialist in the care of the pa-
tient.15 It is possible that inclusion of either of these vari-
ables in our model could have altered our results. Fi-
nally, in order to analyze a large number of variables that
may impact the effectiveness of empirical antimicrobial
therapy, we performed multiple statistical comparisons.
Using a P value significance cutoff of .05, 1 of every 20
comparisons will be statistically significant by chance,
and it is therefore possible that false conclusions were
reached. For this reason, this and other similar studies
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 infec-
tions are a heterogeneous population of patients with dif-
ferent types of health care contact. Of the 5 defined sub-
sets of health care–associated status, only hospitalization
within the past 90 days was an independent predictor of
ineffective empirical therapy for bloodstream infection.
We speculate that colonization with resistant microor-
ganisms during the preceding hospital stay predisposed
this group to subsequent infection with resistant organ-
isms and that clinicians did not recognize prior hospi-
talization as a risk factor for ongoing colonization with
resistant organisms. This information suggests that re-
cent hospitalization is an underrecognized risk factor for
ineffective initial therapy and adverse outcomes.

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performed 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.

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REFERENCES