Microbiological Factors Influencing the Outcome of Nosocomial Bloodstream Infections: A 6-Year Validated, Population-Based Model

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All patients (n = 1,745) with nosocomial bloodstream infection identified between 1986 and 1991 at a single 900-bed tertiary care hospital were studied to identify microbiological factors independently associated with mortality due to the infection. Patients were identified by prospective, case-based surveillance and positive blood cultures. Mortality rates were examined for secular trends. Prognostic factors were determined with use of univariate and multivariate analyses, and both derivation and validation sets were used. A total of 1,745 patients developed nosocomial bloodstream infection. The 28-day crude mortality was 22%, and crude in-hospital mortality was 35%. Factors independently (all $P < .05$) associated with increased 28-day mortality rates were older age, longer length of hospital stay before bloodstream infection, and a diagnosis of cancer or disease of the digestive system. After adjustment for major confounders, *Candida* species were the only organisms independently influencing the outcome of nosocomial bloodstream infection (odds ratio [OR] for mortality = 1.84; 95% confidence interval [CI], 1.22–2.76; $P = .0035$). The two additional microbiological factors independently associated with increased mortality were pneumonia as a source of secondary infection (OR = 2.74; 95% CI, 1.87–4.00; $P < .0001$) and polymicrobial infection (OR = 1.68; 95% CI, 1.22–2.32; $P = .0014$). Our data suggest that microbiological factors independently affect the outcome of nosocomial bloodstream infection.

Each year, about 250,000 of the 35 million patients admitted to hospitals in the United States develop nosocomial bloodstream infections. According to vital statistics reports, the age-adjusted death rate due to septicemia has shown a linear increase over the past 4 decades [1]. Mortality rates associated with nosocomial bloodstream infections are higher than those associated with community-acquired infections [2–4]. In the largest community-based study published so far [4], 51% of the 2,978 episodes of bacteremia documented were hospital-acquired, and those were associated with a 50% higher risk of death than were community-acquired infections. Other studies have confirmed this observation [2, 3, 5–8].

The crude mortality associated with bloodstream infection approximates 35%, ranging from 12% to 80% [2–4, 6, 9]. The attributable mortality defines the mortality directly due to the infection after the underlying disease is controlled for. In six specifically designed studies, the attributable mortality due to nosocomial bloodstream infection averaged 26% [10] but varied with the organism causing the infection. For example, the attributable mortality associated with coagulase-negative staphylococci (CNS) was 14%; with *Candida* species, 38%; and with enterococci, 31%. We recently reported the attributable mortality of nosocomial bloodstream infections in critically ill surgical patients to be 35% (95% CI, 25%–45%) [11].

The primary objective of the study reported herein was to examine the importance of microbiological factors in the outcome of nosocomial bloodstream infection. We accounted for many important confounders and examined the secular trends in mortality rates.

Methods

Hospital Setting

The University of Iowa Hospitals and Clinics (UIHC) is a 902-bed institution serving Iowa and the bordering areas of surrounding states. The UIHC is a tertiary health care center admitting ~22,000 patients per year. During the study period, a maximum of 220 beds were designated for intensive care [12]. Continual prospective surveillance for nosocomial infections began in 1976, and recent studies using standard methods have estimated the sensitivity and specificity of this hospital-wide reporting of nosocomial infection to be 81% and 97%, respectively [13]. This surveillance system is case-based and utilizes clinically important criteria: all patients identified had received

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systemic antibiotic therapy directed at the organisms isolated in blood cultures.

Study Objective and Methods

The primary objective of the study was to determine the importance of microbiological factors per se for influencing mortality following nosocomial bloodstream infections.

All patients admitted to the UIHC who developed a nosocomial bloodstream infection between 1 July 1986 and 30 June 1991 were included in the study. The UIHC's definition of nosocomial bloodstream infection was based on that of the Centers for Disease Control and Prevention (CDC) [12, 14] and required one (unless the organism was judged to be a contaminant) or more positive cultures of blood drawn at least 72 hours after admission, in association with clinical signs of sepsis (based on standard definitions [12, 14]).

In cases in which the organisms could potentially be skin contaminants (e.g., *Bacillus* species, CNS, diphtheroids, micrococci, or *Propionibacterium* species), the definition of bloodstream infection required all of the following: (1) two or more positive cultures of blood drawn at least 72 hours after admission *or* at least one positive culture of blood from a patient with an intravascular line; (2) the presence of at least one of the following: temperature of >38°C, hypothermia (<36°C), chills, or hypotension (systolic blood pressure, <90 mm Hg); and (3) initiation of appropriate antimicrobial therapy.

Thus, all patients in the study presented clinical signs of sepsis associated with laboratory-proven bloodstream infection; in cases of potential skin contaminants, the infections were considered clinically important and were treated by the physician.

Bloodstream infection and corresponding crude mortality rates were calculated for the following pathogens: CNS, *Staphylococcus aureus*, streptococci, enterococci, *Escherichia coli*, *Klebsiella* species; *Enterobacter* species, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Candida* species; and others. Other analyses also included organisms considered as larger groups: gram-positive cocci, aerobic gram-negative bacilli, fungi, and others.

The primary outcome measure examined was 28-day mortality. In the event that the same patient had more than one episode of bloodstream infection, only the first episode was considered in the analysis of mortality, except when death occurred >28 days after bloodstream infection. In the latter situation, death due to the subsequent episode was considered [12]. We excluded from the analysis of mortality patients whose blood cultures were performed post-mortem. Total in-hospital mortality, regardless of length of stay, was used as a secondary outcome measure for descriptive purposes.

Definitions

Primary bloodstream infection refers to bacteremia (or fungemia) for which there was no documented distal source. According to the definitions proposed by the CDC, primary bloodstream infections include those resulting from intravenous or arterial line infections [14]. For descriptive and analytic purposes, however, the latter were stratified separately as previously defined [11, 12]. In brief, only microbiologically documented (by the semiquantitative culture technique described by Maki et al. [15]) line infections were subclassified as catheter-related bloodstream infections. Thus, infections that occurred in the presence of an intravascular catheter but without documentation of line infection by positive semiquantitative tip culture [15] were classified as primary bloodstream infection.

Secondary bloodstream infection was defined by infection that developed subsequent to a documented infection with the same microorganism at another body site [14]. *Polymicrobial bloodstream infection* refers to infections in which more than one microorganism was recovered from the blood within a 48-hour window after another had been isolated [16, 17].

Sources of secondary bloodstream infection included the following: lower respiratory tract infections, urinary tract infections, surgical wound infections, infections of gastrointestinal origin, intravenous or arterial line–related infections, and others (eye infections [$n = 2$]; skin infections [$n = 27$]; upper respiratory tract infections [$n = 21$]; oropharyngeal infections [$n = 8$]; and infections of gynecologic origin [$n = 21$]).

A diagnosis of nosocomial pneumonia required the finding on chest radiographic examination of a new or progressive infiltrate, consolidation, cavitation, or pleural effusion and at least one of the following [14]: (1) new onset of purulent sputum *or* change in the character of sputum, (2) organism(s) cultured from blood, (3) isolation of an etiologic agent from a specimen obtained by transtracheal aspiration, bronchial brushing, bronchoalveolar lavage, or biopsy, or (4) histopathologic evidence of pneumonia. Definitions for other sources of infection referred to recognized standards [14].

All patients who entered the operating unit were recorded as having had surgery. Only patients hospitalized for at least 24 hours in intensive care units (ICUs) before the occurrence of bloodstream infection were considered to have been exposed to a critical care unit. Neutropenia was defined as a total peripheral WBC count <1,000/mm^3 or a polymorphonuclear neutrophil count <500/mm^3 prior to the occurrence of bloodstream infection.

Underlying medical or surgical conditions were classified according to the primary diagnosis at admission and on the basis of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes [18]. There were 20 separate groups of diagnoses.

Changes over Study Period

As previously described [12], the following changes that occurred over the study period were examined: average length of stay, surveillance activities, definitions of nosocomial infection, and microbiological laboratory techniques. Between 1986

and 1991 the average length of stay remained stable for acute inpatients; the length of stay averaged 8.27 ± 0.16 days (median, 7 days; range, 7.98–8.48 days). Neither surveillance activities nor definitions of nosocomial bloodstream infection changed during the study period.

Between 1 January 1986 and 1 October 1987 the BACTEC 460 radiometric system (Johnston Laboratories, Towson, MD) was used, and a 5-mL blood culture inoculum was standard. After 1 October 1987 the BACTEC 660 nonradiometric system was used. After 1 April 1988 the standard blood culture inoculum doubled from 5 mL to 10 mL. It is estimated that an enhanced recovery of 33% occurred with use of the 10-mL inoculum and nonradiometric system [19].

Statistical Analysis

Trends in nosocomial bloodstream infection and mortality rates between 1980 and 1992 have recently been described in detail [12]. Factors associated with mortality due to bloodstream infection were initially analyzed by univariate analysis. The strength of the association between single prognostic variables and outcome (28-day or in-hospital mortality), odds ratios (ORs), and their corresponding 95% confidence intervals (95% CIs) were calculated. For continuous variables, mean values were compared with two sample *t*-tests for independent samples after correction for equality of variance (*F* test). Differences in proportions were compared with either the χ^2 test or Fisher's exact test (for expected cell frequencies less than five).

Independent prognostic variables were defined by multivariate logistic regression analysis. The 14 variables recorded at baseline for each individual in the analysis were as follows: age; admission to ICU before the time of bloodstream infection (yes or no); length of stay from admission to infection; neutropenia (yes or no); a diagnosis of cancer or disease of the digestive tract (yes or no); the year in which the infection occurred (1986, 1987, 1988, 1989, 1990, or 1991); and microbiological variables (primary infection; pneumonia; infections caused by gram-negative organisms, *P. aeruginosa,* CNS, or *Candida* species; bacteremic episodes lasting ⩾72 hours; and polymicrobial infection).

Microbiological variables were coded as yes or no. The two outcomes of interest were the 28-day and the total in-hospital mortality. In addition, whether the patient developed multiple episodes of bloodstream infection during the same hospital stay was tested when in-hospital mortality was the outcome measure. The model was built by the logistic regression procedure with SAS version 6.0 (SAS Institute, Cary, NC), with an entrance *P* value of ⩽.15 for inclusion. For descriptive purposes, independent variables associated with poor outcome were also identified, with use of 14-day as well as 21-day mortality as outcome measures. All tests were two-tailed, and *P* values <.05 were considered significant.

Results

Between 1986 and 1991, 120,841 patients were admitted to UIHC, averaging 21,140 patients a year and representing a total of 999,355 patient-days of care. Over the 6-year study period, a total of 1,745 patients were prospectively identified with clinically important, nosocomial bloodstream infections (1.44 per 1,000 discharges). Secular trends in bloodstream infection rates at UIHC and associated crude mortality rates have recently been described for the period 1980–1992 [12].

Study Population and Characteristics of Patients

The mean age of the study population was 49 years (median, 45 years). There were 995 males (57%) and 750 females (43%). A total of 534 patients (30%) had surgery, and 659 patients (38%) were admitted to an ICU prior to onset of bloodstream infection. A total of 366 patients (21%) had documented neutropenia before infection occurred. Sex, prior surgery, admission to an ICU, and documented neutropenia were not associated with an increased risk of death within 28 days following bloodstream infection (table 1).

The median length of hospital stay from admission to bloodstream infection was 12 days; it did not vary during the study period. The longer the patients stayed in the hospital before developing the infection, the poorer the outcome. A third of the study cohort (520 of 1,745) developed nosocomial bloodstream infection within 7 days following admission to the hospital; among those patients the 28-day and in-hospital mortality rates were 17% and 26%, respectively (table 1). Among patients who acquired the infection >14 days after admission ($n = 703$; 40%), 28-day and in-hospital mortality rates were significantly higher: 27% and 44%, respectively (χ^2 test for trends and *P* values for 28-day and in-hospital mortality: $\chi^2 = 22.8$ and 48.2, respectively; all *P* values <.0001).

Patients were admitted to the hospital for a variety of medical or surgical conditions. To account for the effect of underlying disease in the analysis, we stratified patients according to the primary diagnosis for admission (table 2). Cancer and diseases of the digestive system were the only underlying conditions associated with an increased risk of death within 28 days following bloodstream infection. A total of 524 patients (30%) had cancer. Both 28-day (25%) and in-hospital (40%) mortality rates following infection were significantly higher among cancer patients than among patients suffering from other medical conditions.

The odds ratio for death within 28 days following onset of infection in patients with cancer vs. that for patients without cancer was 1.31 (95% CI, 1.03–1.67; $P = .004$; table 2). Similarly, among 154 patients suffering from diseases of the digestive system, both 28-day (29%) and total in-hospital (44%) mortality rates were significantly higher ($P = .015$) than in the study population (table 2). Primary diagnosis groups associated with trends toward lower risk of death in the 28

Table 1. Characteristics associated with death within 28 days due to nosocomial bloodstream infection in patients at the University of Iowa Hospitals and Clinics, 1986–1991: univariate analysis.

Characteristic	No. of patients: Survivors (n = 1,364)	No. of patients: Nonsurvivors (n = 381)	28-d Mortality (%)	OR	95% CI
Age (mean, y)	43	56	...	1.017	1.012–1.021
Male	777 (57%)	218 (57%)	22	1.01	0.80–1.27
Female	587 (43%)	163 (43%)	22	...	...
Underwent surgery*	421	113	21	0.94	0.74–1.21
Admitted to ICU*	510	149	22	1.08	0.85–1.36
Neutropenic*[†]	280	86	23	1.13	0.86–1.48
Length of stay (d)*[‡]					
1–7	433	87	17	1.006	1.003–1.011
8–14	421	101	19	...	...
⩾15	510	193	27	...	...

NOTE. ICU = intensive care unit.
* Before the occurrence of bloodstream infection was considered.
[†] WBC count $<1{,}000/mm^3$ or polymorphonuclear neutrophil count $<500/mm^3$.
[‡] Exposure odds ratio for death assessed by univariate logistic regression (constant = 0.199; P = .036).

days following the onset of infection included complications of pregnancy (50 episodes, no deaths), liveborn infants (61 episodes, 8 deaths), and conditions originating in the perinatal period (26 episodes, no deaths) (table 2).

Crude 28-Day and In-Hospital Mortality Rates

Among 1,745 patients with bloodstream infection, 610 died; the crude in-hospital mortality was 35%. The 28-day crude mortality was 22% (381 of 1,745). The crude in-hospital mortality among patients with nosocomial bloodstream infections decreased significantly from 43% in 1986 to 27% in 1991 (r = 0.90; P = .014). Similarly, the 28-day mortality rates showed a trend toward a significant decrease, declining from 26% in 1986 to 16% in 1991 (r = 0.82; P = .047).

In an attempt to analyze reasons for the secular trend toward decreasing 28-day mortality (P = .047), we examined possible influences of infecting organisms. In fact, the increasing incidence of CNS had a profound influence on rates: after correction for the confounding variable (infections caused by CNS), the initially observed significant trend diseappeared (P = .42).

A total of 184 patients (10.5%) had multiple episodes of nosocomial bloodstream infection during their stay in the hospital; 23 (12%) had >2 episodes (range, 2–4 episodes). Patients with multiple episodes of infection did not differ from those with a single episode of infection (n = 1,561) in terms of age (mean age, 43 y vs. 42 y), gender (59% vs. 57% were male), prior exposure to surgery (30% vs. 31%), or admission to the ICU (37% vs. 38%).

The proportions of patients with cancer (85 of 184; 46%) and neutropenia (76 of 184; 41%) were significantly ($P < .05$) higher among patients who had multiple episodes than among those who had a single episode of bloodstream infection (439 of 1,561 [28%] and 291 of 1,561 [19%], respectively). Although 28-day mortality rates were similar among the two groups of patients (16% and 22%, respectively), in-hospital deaths were more frequent among those with multiple episodes of infection (95 of 184 [52%] vs. 515 of 1,561 [33%], respectively; OR for in-hospital death = 2.17; 95% CI, 1.58–2.98; $P < .001$).

Source of Bloodstream Infections

There were 1,090 episodes of primary bloodstream infections (1,090 of 1,745 = 62%). Among those, 212 infections (19%) were associated with a previous intravenous or arterial line–related infection (table 3). A large majority (157; 74%) of line-related bloodstream infections (proven by semiquantitative cultures) were caused by staphylococci (*S. aureus*, n = 79; and CNS, n = 78). Line-associated bloodstream infections developed an average of 15.6 days following admission; almost half (101 of 212; 48%) of the infections developed in patients who remained in or had been discharged from ICUs. A third (60) of these 212 patients had cancer or diseases of the digestive tract, and 16 (7.5%) had a subsequent episode of bloodstream infection during their hospital stay. Crude 28-day and in-hospital mortality rates among patients with CNS (17% and 28%, respectively) and *S. aureus* (15% and 23%, respectively) line-associated bloodstream infections were comparable.

A total of 655 bloodstream episodes were secondary to a previously documented nosocomial infection (655 of 1,745; 38%). Secondary bloodstream infections were associated with higher 28-day mortality (187 of 655; 29%) and in-hospital mortality (283 of 655; 43%) than were primary infections (194 of 1,090 [18%] and 327 of 1,090 [30%], respectively). The odds ratio for death within 28 days following infection for

Table 2. Primary diagnoses for admission and mortality rates associated with nosocomial bloodstream infection in patients at the University of Iowa Hospitals and Clinics, 1986–1991.

Primary diagnosis group	ICD-9-CM codes [18]	No. of patients		28-d Mortality (%)	OR*	95% CI
		Survivors	Nonsurvivors			
1: Infectious diseases	001–139	47	12	20	0.91	0.48–1.74
2: Neoplasms	140–239	392	132	25	1.31†	1.03–1.67
3: Endocrine disorders	240–279	30	8	21	0.95	0.43–2.10
4: Diseases of the blood	280–289	27	11	29	1.47	0.72–3.00
5: Mental disorders	290–319	3	1	25	1.19	0.12–11.5
6: Diseases of the nervous system	320–389	21	4	16	0.68	0.23–1.99
7: Diseases of the circulatory system	390–459	207	64	24	1.13	0.83–1.53
8: Diseases of the respiratory system	460–519	30	11	27	1.32	0.66–2.66
9: Diseases of the digestive system	520–579	110	44	29	1.49†	1.03–2.15
10: Diseases of the genitourinary system	580–629	48	13	21	0.97	0.52–1.81
11: Complications of pregnancy, childbirth, or puerperium	630–679	50	0	0	...	...
12: Skin and subcutaneous tissue diseases	680–709	6	4	40	2.40	0.67–8.55
13: Musculoskeletal system diseases	710–739	22	3	12	0.48	0.14–1.63
14: Congenital anomalies	740–759	32	6	16	0.67	0.28–1.60
15: Conditions originating in the perinatal period	760–779	26	0	0	...	...
16: Aspecific symptoms	780–799	21	6	22	1.02	0.41–2.55
17: Traumas or burns	800–989	130	29	18	0.78	0.51–1.19
18: Graft/surgery complications	990–999	62	19	23	1.10	0.65–1.87
19: Others (NEC)	V10–V29/V40–V80	47	6	11	0.45	0.19–1.06
20: Live-born infants	V30–V39	53	8	13	0.53	0.25–1.16
Total	...	1,364	381	22	...	...

NOTE. NEC = not elsewhere classified (ICD-9-CM codes V10–29 and V40–V80).

* The odds ratios (and 95% CIs) for developing a bloodstream infection were calculated for each primary diagnosis group (1–20) with use of all other diagnosis groups as baseline.

† For P values $<.05$.

patients with secondary bloodstream infection was 1.85 (95% CI, 1.47–2.32; $P < .001$). Polymicrobial infections had a poorer outcome, as reflected in higher crude 28-day mortality (75 of 247 [30%]; OR = 1.70; 95% CI, 1.26–2.29; $P < .001$) and in-hospital mortality (116 of 247 [47%]; OR = 1.83; 95% CI, 1.40–2.41; $P < .001$).

By univariate analysis, pneumonia as a source of secondary bloodstream infection was significantly associated with a poorer outcome, in comparison with the other sources (table 3). Both 28-day and in-hospital mortality following bloodstream infection episodes that complicated nosocomial pneumonia were associated with significantly higher exposure odds ratios for death (OR = 3.28; 95% CI, 2.39–4.45; $P < .001$; and OR = 3.56; 95% CI, 2.61–4.86; $P < .001$, respectively) than were those for infections of other origins. Among primary bloodstream infections, line-related infections were associated with a significantly lower risk for death in the study population (OR = 0.58; 95% CI, 0.39–0.86; $P < .009$).

Bloodstream Isolates and Pathogen-Specific Mortality Rates

A total of 2,046 isolates were recovered in 1,745 episodes of nosocomial bloodstream infection over the study period. Polymicrobial infections accounted for 14% (247) of the episodes.

Gram-positive cocci were the organisms most commonly responsible for nosocomial bloodstream infection in the study period; they were isolated from 55% (952) of the 1,745 infections. They were associated with lower 28-day mortality (18%) and in-hospital mortality (30%) than were aerobic gram-negative rods (24% and 37%, respectively). Fungal infections were associated with significantly higher 28-day mortality (35%) and in-hospital mortality (57%) than were infections due to other organisms; the odds ratio for death within 28 days due to fungemia was 2.07 (95% CI, 1.41–3.04; $P < .001$), in comparison with that for bloodstream infections caused by other organisms.

The 10 leading pathogens isolated in episodes of nosocomial bloodstream infection at UIHC from 1986 through 1991 are listed in table 4; 28-day as well as in-hospital mortality and estimated exposure odds ratios for death (28 days after infection) are shown in parallel. CNS were the most frequently isolated pathogens, involved in 25% of all episodes of bloodstream infection; they were associated with significantly lower 28-day mortality rates than were other organisms (OR = 0.63; 95% CI, 0.48–0.82; $P = .004$) (table 4).

Table 3. Sources of infection and associated mortality rates for 1,745 episodes of nosocomial bloodstream infection.

Type, source of infection	No. (%) of episodes	Percentage of total episodes	28-d Mortality (%)	OR	95% CI	*P* value	In-hospital mortality (%)	In-hospital:28-d mortality ratio
Primary bloodstream infection	1,090	62	18	...	...	...	30	1.69
Previous line-related infection[†]	212 (19)	...	15	0.58	0.39–0.86	.009	25	1.71
Secondary bloodstream infection	655	38	29	...	...	...	43	1.51
Pneumonia	193 (29)	...	44	3.28	2.39–4.45	<.001	69	1.59
Surgical wound	177 (27)	...	24	1.17	0.81–1.68	.46	33	1.36
Urinary tract infection[‡]	127 (19)	...	18	...	...	...	44	2.44
Gastrointestinal tract	27 (4)	...	22	1.02	0.41–2.55	.86	44	1.98
Other[§]	131 (20)	...	24	1.17	0.77–1.78	.52	37	1.52

NOTE. Only the leading sources of infections are listed; the odds ratios and 95% CIs for mortality were calculated for each leading source of infection with use of all other sources as baseline.

[†] Only microbiologically documented line-related infections were separated from the total number of primary bloodstream infections.

[‡] 109 of 127 (86%) were associated with the use of a urinary catheter.

[§] Includes infections at other sites (e.g., gynecologic tract, upper respiratory tract, eye, brain).

S. aureus was the second most important pathogen. *Candida* species were isolated in 134 infectious episodes and were the fourth leading pathogens responsible for bloodstream infection in the study period. By univariate analysis, *Candida* species and *P. aeruginosa* were associated with significantly higher 28-day mortality rates than were other organisms (OR = 1.98; 95% CI, 1.36–2.88; $P = .0002$; and OR = 1.58; 95% CI, 1.02–2.43; $P = .024$, respectively).

Independent Prognostic Factors

Factors independently influencing 28-day as well as in-hospital mortality due to nosocomial bloodstream infection were derived from multiple logistic regression procedures. The study population was divided into a derivation set and a validation set in order to assess specificity and sensitivity as well as consistency of the models derived. The models presented were derived from data regarding patients admitted in fiscal years 1986, 1987, 1988, 1989, and 1990 and were prospectively validated with data for patients admitted in 1991.

The analysis indicated that the best predictor of 28-day mortality in the study population was a model composed of six of the 14 variables tested (table 5); these included age (OR = 1.018 per year; 95% CI, 1.014–1.02; $P < .0001$), primary diagnosis of cancer or disease of the digestive tract (OR = 1.60; 95% CI, 1.23–2.08; $P = .0004$), and increased duration of hospital stay at the time of infection (OR = 1.009 per day in the hospital; 95% CI, 1.003–1.02; $P = .002$).

Microbiological factors that independently influenced the outcome were pneumonia as a source of secondary bloodstream infection (OR = 2.74; 95% CI, 1.87–4.00; $P < .0001$), infections due to *Candida* species (OR = 1.84; 95% CI, 1.22–2.76; $P = .0035$), and polymicrobial infections (OR = 1.68; 95% CI, 1.22–2.32; $P = .0014$). Although not statistically significant in

Table 4. Pathogens most commonly responsible in 1,745 episodes of nosocomial bloodstream infection, as related to mortality for patients at the University of Iowa Hospitals and Clinics, 1986–1991.

Organism	No. of isolates (%*)	28-d Mortality (%)	OR[†]	95% CI[†]	*P* value[†]	In-hospital mortality (%)	In-hospital:28-d mortality ratio
CNS	512 (25)	17	0.63	0.48–0.82	.004	29	1.71
S. aureus	303 (15)	22	0.97	0.72–1.31	.98	31	1.40
E. coli	163 (7.9)	26	1.22	0.84–1.77	.20	35	1.38
Candida species	134 (6.5)	35	1.98	1.36–2.88	.0002	57	1.62
Klebsiella species	127 (6.2)	19	0.79	0.50–1.25	.41	37	1.96
Streptococci	113 (5.5)	18	0.73	0.44–1.19	.42	36	2.05
P. aeruginosa	104 (5.1)	31	1.58	1.02–2.43	.024	47	1.53
Enterococci	100 (4.9)	25	1.16	0.73–1.85	.34	41	1.64
Enterobacter species	98 (4.8)	27	1.26	0.79–2.01	.28	40	1.50
S. marcescens	45 (2.2)	22	0.98	0.48–2.01	.95	40	1.80

* The proportion of all isolates ($n = 2,046$) recovered in the 1,745 episodes of bloodstream infections; only the 10 leading pathogens are listed.

[†] Values for increased risk of death 28 days after onset of bloodstream infection.

Table 5. Independent predictors of 28-day mortality due to nosocomial bloodstream infection: multiple logistic regression analysis.

Variable	Parameter estimate	Standard error	OR	95% CI	*P* value
Age	0.0175	0.002	1.018	1.014–1.02	.0001
Length of stay	0.0092	0.003	1.009	1.003–1.02	.0020
Cancer/disease of digestive system	0.0478	0.133	1.60	1.23–2.08	.0004
Microbiological factor					
Polymicrobial infection	0.5219	0.163	1.68	1.22–2.32	.0014
Pneumonia as a source	1.0068	0.193	2.74	1.87–4.00	.0001
Infection due to *Candida* species	0.6087	0.208	1.84	1.22–2.76	.0035

NOTE. The residual (goodness of fit) χ^2 value was 2.68 with 4 degrees of freedom ($P = .61$). For intercept: $B = -2.6607$; SE = 0.220. In terms of relative influencing importance, the percentages of χ^2 uniquely associated with each independent variable in the equation predicting 28-day mortality were as follows: age, 36%; pneumonia as a source of bloodstream infection, 23%; diagnosis of cancer or disease of the digestive tract, 11%; polymicrobial infection, 8.6%; length of hospital stay at time of bloodstream infection, 8%; and infection due to *Candida* species, 7.2%.

the model, bloodstream infections due to CNS tended to predict a favorable outcome and therefore relatively low mortality (OR = 0.79; 95% CI, 0.59–1.06; $P = .11$), and infections due to *P. aeruginosa* were associated with a poor outcome (OR for 28-day mortality = 1.04; 95% CI, 0.96–1.13; $P = .31$).

All variables independently associated with 28-day mortality due to nosocomial bloodstream infection also constituted independent factors influencing in-hospital death. Admission to an ICU and the occurrence of multiple episodes of bloodstream infection during the same hospital stay were additional independent predictors of in-hospital death (OR = 1.10; 95% CI, 1.05–1.16; $P < .0001$; and OR = 1.15; 95% CI, 1.07–1.23; $P < .0001$, respectively).

The occurrence of neutropenia either during or before the onset of infection was associated with an increased risk of in-hospital death (OR = 1.05; 95% CI, 0.99–1.12) but did not reach statistical significance ($P = .10$) in the in-hospital model. It constituted an additional independent factor influencing in-hospital mortality (OR = 1.44; 95% CI, 1.06–1.96; $P = .018$) when the occurrence of multiple episodes of infection was not included in the model.

The performance of the model was evaluated with use of receiver-operating-characteristics (ROC) curve analysis (figure 1). On the basis of the predicted 28-day outcome for each patient with bloodstream infection between 1986 and 1990 (derivation set), we evaluated the sensitivity and specificity of the model for classifying patients who developed the infection in 1991 (validation set) as dead or alive at 28 days. The main reason for validation was to test the model's stability and consistency. A threshold probability of 0.22 resulted in a sensitivity of 60% and a specificity of 67% (area under the ROC curve was 0.68).

Discussion

The primary objective of the study was to evaluate the impact of microbiological factors on mortality following nosocomial bloodstream infection. Special efforts were made to adjust for the confounding effect of underlying disease. In fact, microbiological factors profoundly influence the outcome of infection: independent factors in this study included pneumonia as a source of secondary bloodstream infection, polymicrobial infection, and *Candida* species as the etiologic cause. Multiple episodes of bloodstream infection also independently affected in-hospital mortality.

Earlier studies suggested that the source of bloodstream infection may predict death [2, 3, 20]. Roberts et al. [2] highlighted differences in mortality rates when the source of

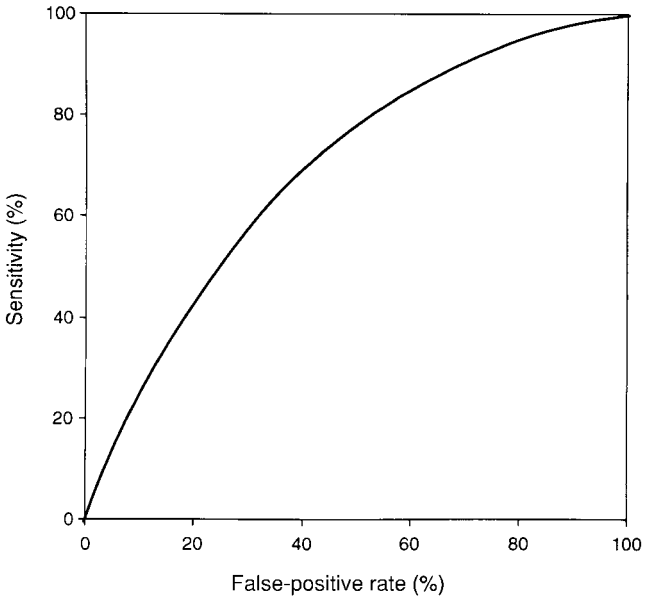

Figure 1. The performance of the prognostic model was evaluated by analysis of the receiver-operating characteristic (ROC) curve. On the basis of the predicted 28-day outcome for each patient with nosocomial bloodstream infection between 1986 and 1990 ($n = 1{,}439$), we evaluated the sensitivity and specificity of the model for classifying patients who developed the infection in 1991 ($n = 306$) as dead or alive at 28 days after onset. A threshold probability of 0.22 resulted in a sensitivity of 60% and a specificity of 67% (area under the ROC curve was 0.68).

secondary bloodstream infection was considered; pneumonia, the gastrointestinal tract, and multiple sources of infection were associated with the highest mortality rates (43%–55%). These authors also suggested that the risk of death due to bloodstream infection may extend well after 28 days following the onset of infection. Gatell et al. [20] showed that bacteremia arising from intraabdominal or lower respiratory tract sources or from an unknown origin constituted an independent predictor of death.

Nosocomial pneumonia is associated with a poor outcome, particularly in mechanically ventilated patients and in the elderly [21]. The attributable mortality of this infection was estimated to be 10%, or one-third of the total crude mortality in a hospital-based series [22] and 27%, or half of the total crude mortality among mechanically ventilated patients [23]. Mortality rates among patients with nosocomial pneumonia associated with bacteremia varied between 45% and 58% in hospital-wide series [24–26]. In a large cohort of critically ill patients ($n = 1,978$) admitted to a medical ICU, Fagon and collaborators recently demonstrated that both nosocomial pneumonia (OR = 2.08) and nosocomial bacteremia (OR = 2.5) independently contributed to death, in addition to the severity of underlying illness and number of dysfunctional organs [27].

The attributable mortality of bloodstream infection is ~27%, accounting for over two-thirds of the crude mortality. We now report that bloodstream infection arising from pneumonia is an important predictor of mortality. Previously we reported that secondary bloodstream infections were independently associated with mortality (OR = 2.46) [28], but that study was small, and the statistical power was inadequate to evaluate the impact of individual species or source of infection.

In the present study, we found that both the 28-day mortality (44%) and in-hospital mortality (69%) were higher than the mortality rates for bloodstream infections due to causes other than pneumonia (table 3). This observation suggests a possible relationship between both the primary infection and the bloodstream infection, as well as contributions from the underlying conditions. An entirely new study design would be required to understand the relative contributions (to outcome) of underlying disease, pneumonia, and bloodstream infection, alone or in combination.

Polymicrobial bateremia has been associated with higher mortality than has unimicrobial infection in almost all series [2, 28–32]. We previously demonstrated that polymicrobial infection was associated with poorer outcome than was unimicrobial infection, independently of the patient's underlying disease or the class of microorganism causing the infection [28]. Findings in the present study confirm the biological consistency of the phenomenon, after additional microbiological and other confounders were controlled for.

Appropriate antimicrobial therapy must cover all organisms identified in cases of polymicrobial infection. Since those infections independently contribute to a patient's death, clinical microbiology laboratories should consider more careful evaluation of blood cultures for additional organisms once one isolate has been recovered. Whether culture bottles could be removed from automated systems once they become positive without additional, as-yet-unidentified organisms being missed remains to be evaluated in prospective studies.

In specifically designed case-control studies, estimates of the attributable mortality due to the organism causing the infection have been given, after such confounding factors have been controlled for [10, 32–36]. The attributable mortality due to bloodstream infection caused by CNS was 14% (95% CI, 4%–21%); by *Bacteroides fragilis*, 19% (95% CI, 8%–30%); by enterococci, 31% (95% CI, 22%–41%); and by *Candida* species, 38% (95% CI, 26%–49%). Crude 28-day mortality rates associated with those pathogens were similar in our study: CNS, 17%; enterococci, 25%; and *Candida* species, 35%. *P. aeruginosa* is typically associated with high mortality rates in large series [2, 20, 37], and it was suggested as an independent predictor of death in one study [38]. Although significantly associated with an increased risk of death by univariate analysis (OR = 1.58 at day 28), it was not selected as an independent predictor of 28-day or in-hospital mortality in this study.

We confirmed the importance of candidal bloodstream infection. *Candida* species that were associated with the highest mortality rates (35% at 28 days and 69% at discharge) in our study cohort independently affected the outcome of infection, even after we controlled for other confounders. Given the high mortality attributable to candidemia, single positive cultures should not be regarded, as they have been in the past, as representing benign, transient colonization [39–41].

The difficulty of predicting which patients will develop disseminated candidiasis and the low sensitivity of blood cultures in such conditions, coupled with the availability of systemic antifungals with lower toxicity than amphotericin B, have led today to the consensus that all cases of candidemia should be treated [39, 41–44]. Because the yield of blood cultures depends on the volume of blood cultured and because the sensitivity of low-volume blood cultures for yeast is particularly low [45], it is recommended that physicians order repeated, high-volume (at least 10-mL) blood cultures for patients at high risk for candidemia.

The increasing importance of CNS as nosocomial bloodstream pathogens has recently been discussed by several authors [12, 46–49]; major reasons for such an increase have been discussed [12, 32, 50, 51] and include surveillance artefact, increased use of medical devices and broad-spectrum antibiotics, and an increase in the frequency of performing blood cultures. Recent studies have shown that the positivity of only a single blood culture for CNS is frequently associated with clinically relevant episodes of bloodstream infection [33, 52–54]. In the study by Herwaldt and colleagues [54], 50% of patients who met a stringent definition of CNS bacteremia had only one positive Isolator (DuPont Nem, Research Products, Boston) culture, and 28% had only one positive blood

culture set (BACTEC + Isolator); by multivariate analysis, the number of positive culture bottles was not associated with meeting the definition for infection, a finding confirming those of other investigators [33, 52, 53].

Therefore, results of recent investigations clearly indicate that the inclusion of patients in epidemiological study solely on the basis of the number of positive cultures would not be appropriate. Patients with bacteremia due to CNS in our study met prospectively defined criteria for infection that included more stringent criteria in cases of potential skin contaminants. CNS are considered to be of low virulence.

Consistent with the lower attributable mortality rate associated with bloodstream infection due to CNS [33], these infections were associated with a significantly reduced risk of death (OR = 0.63) in our study; although not statistically significant ($P = .11$), exposure odds ratios for death following bacteremia due to CNS were markedly decreased (OR = 0.79; 95% CI, 0.54–1.06) in the multivariate model predicting 28-day mortality. The secular trends in 28-day crude mortality indicated a progressive decline over the study period ($P = .047$); however, after correction for the confounding effect of CNS with lower crude mortality, the trend became nonsignificant ($P = .47$).

The consistency of data regarding the impact of microorganisms on outcome of bloodstream infection that have been obtained with different methodological approaches provides additional evidence of the association between microbiological factors and their impact on survival from such life-threatening conditions. Analytic approaches with both matched case-control studies and cohort studies employing multiple regression techniques to control for confounding variables have shown the importance of different species of microorganisms or the nature of the infection on outcome.

Our model predicted the 28-day mortality in 1991 based on data gathered in 1986–1991 with 60% sensitivity and 67% specificity and with use of a threshold probability of 22%. It is interesting that the model and its parameter estimates obtained with data from the periods of 1986–1990 and 1986–1991 were very similar. This observation mainly suggests that our model consistently shows those factors contributing to the mortality but also that additional factors should be included for further improvement.

Microbiological factors influencing 28-day mortality proved also to affect 14-day, 21-day (data not shown), and in-hospital mortality independently. It is noteworthy, however, that in terms of relative prognostic influence (expressed by unique χ^2 values for each independent variable—see table 5), microbiological factors explained only 38.8% of the 28-day mortality observed. Our findings need to be confirmed in large series from other facilities, including community hospitals.

Factors independently contributing to fatal outcome of nosocomial bloodstream infection were the same when 28-day and in-hospital mortality models were compared (not shown). Statistical parameters in the two models were very similar and within the confidence intervals of each respective parameter. The odds ratios for 28-day and total in-hospital death increased most markedly for the exposure to *Candida* species (OR = 1.84; 95% CI, 1.22–2.76; $P = .0035$; and OR = 2.37; 95% CI, 1.48–3.50; $P < .0001$, respectively) and to a primary infection with pneumonia (OR = 2.74; 95% CI, 1.87–4.00; $P < .0001$; and OR = 3.38; 95% CI, 2.42–4.72; $P < .0001$, respectively).

Only two additional factors independently influenced in-hospital mortality due to bloodstream infection: occurrence of multiple episodes of infection and admission to an ICU. Almost half (46%) of patients who suffered multiple episodes of infection had cancer. Although not statistically significant, neutropenia influenced in-hospital outcome (OR for death = 1.05; 95% CI, 0.99–1.12; $P = .10$); when occurrence of multiple episodes of infection was not considered in the model, neutropenia constituted an additional independent factor for in-hospital mortality (OR = 1.44).

Admission to an ICU is associated with an overall increased risk for nosocomial bloodstream infection [55]. Bloodstream infection has been reported to be 5–7 times as likely to occur in ICU patients as in ward patients. We recently estimated the attributable mortality associated with the infection as 35% (95% CI, 25%–45%) in a cohort of surgical critically ill patients at UIHC [11]. ICU-acquired bloodstream infection significantly and independently affected the in-hospital outcome in the present study population. These findings are consistent with those of our previous report [11] and those of recent multicenter studies [56, 57].

Refined outcome prediction would necessitate the inclusion of additional clinical and biological parameters, as well as accounting for the dynamics of the process of sepsis [58–60]. This study was designed to assess whether basic microbiological factors might independently influence the outcome of infection, with use of appropriate statistical analyses (that mandate large numbers). Additional variables should be included for better outcome prediction (i.e., severity of underlying illness, additional comorbidities, shock, and multiple organ dysfunction syndrome).

Because of the limitations of our data, we do not think that our model can be used currently in day-to-day clinical practices for outcome prediction. Additional microbiological factors of importance may include time to positive blood culture (faster detection would possibly indicate a larger inoculum), number of positive culture bottles per septic episode, time between identification and therapy, and appropriateness of antimicrobial treatment.

Because data about those variables were not available for the entire study cohort, we considered episodes of laboratory-proven infections that lasted 72 hours or more as a reasonable surrogate marker for those variables and tested it in the model; this parameter failed to show statistical significance. However, the proportion of patients who met the definition was relatively small (46 of 1,754; 2.6%); recent studies suggested that appropriate antimicrobial therapy is the rule in most circumstances today (84%–98%; see [61–63]). However, whether this could be considered as a reasonable surrogate should be further assessed.

Our study, with a very large sample size, clearly has sufficient statistical power to identify microbiological factors influencing the outcome of infection; however, use of additional variables would have enhanced the value of the model. Second, although pathogen-specific and infection site–specific mortality rates were similar to those reported in most series in the literature, crude 28-day and in-hospital mortality rates observed in this study do not represent attributable mortality estimates. Third, although all nosocomial bloodstream infections in this study met prospectively defined criteria, some infections may have been missed and others overreported.

Furthermore, misclassification of vascular catheter–related bloodstream infection is probable because only laboratory-proven (by semiquantitative culture) line infections were classified in this category; in contrast, non-laboratory-proven infections were included with primary bloodstream infections. Thus, the frequency of line-related bloodstream infections was underestimated in this study. Finally, the study population was heterogenous, and refined models are needed to assess the influence of currently identified microbiological factors in specific subpopulations.

In a recent national vital statistics report, age-adjusted death rates for septicemia demonstrated a progressive, linear increase from 0.3 deaths per 100,000 population in 1950 to 7.9 per 100,000 population in 1993 [64]. This analysis included community- as well as hospital-acquired bacteremias. Cases of nosocomial bloodstream infections comprise a large portion—perhaps 60% or more—of cases of septicemia and are associated with higher mortality rates [2–5]. To the best of our knowledge, our study involves the largest series of nosocomial bloodstream infections in which an attempt was made to measure the direct impact of microbiological factors on the outcome of the infection, after major confounders were controlled for.

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