

REVIEW ARTICLE

## Bacteremias: A Leading Cause of Death

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Bloodstream infections (BSIs), recognized to be a major cause of morbidity and mortality globally, are increasing in incidence. The reported rates of crude and attributable mortality vary, possibly due to heterogeneity in patient populations and methodology. Few studies, however, have focused on pathogen-specific attributable mortality. These studies include *S. aureus*, coagulase-negative staphylococci and enterococcus. Other studies of attributable mortality have been conducted in select populations such as nosocomial and community-acquired cohorts, intensive care units, neutropenic patients, and HIV-positive patients. Regrettably, despite advances in treatment and intensive care facilities, mortality remains high. © 2005 IMSS. Published by Elsevier Inc.

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### Introduction

Approximately 250,000 cases of BSI occur in the U.S. per annum (1,2). Although studies on BSIs are diverse and include both non-selective and specific patient populations, several trends are apparent. These include an increasing incidence, a changing microbiology and a sustained, high mortality. On a national level, data from the National Center for Health Statistics for 2002 ranked septicemia as the 10th leading cause of death in the U.S. (3). A summary of studies investigating the crude and attributable mortalities of BSIs in different patient populations is found in Table 1.

### University Hospital-Based Case Series of Both Nosocomial and Community-Acquired Bloodstream Infections

Data from hospital-based case series, including both nosocomial and community-acquired BSIs, suggest that the incidence of bacteremia is on the rise. Martin et al. recently

summarized the epidemiology of sepsis in the U.S., having analyzed a representative sample of all non-federal hospitals from 1979 through 2000. Data were obtained from hospital discharge record ICD-9 codes and included both community- and hospital-acquired cases (4). In this 21-year analysis the incidence of sepsis rose from 164,000 cases (82.7 per 100,000 population) to nearly 660,000 cases (240.4 per 100,000 population).

Case series from university hospitals in Europe support the observation of an increasing BSI incidence. These series analyzed both nosocomial and community-acquired bacteremias. A Norwegian review of BSIs from both 1974 to 1979 and 1988 to 1989 highlights the changing nature of the etiology, clinical features and outcomes (5). A total of 1,447 BSIs were documented, of which 54% were nosocomial in origin. The authors observed a doubling of the incidence of BSIs between the two periods from 4.26 per 1000 admissions to 8.71 per 1,000 admissions.

In the Norwegian cohort analyzed by Haug et al., the microbiology of BSIs shifted between the two study time frames. Of note, the proportion of BSIs due to *Enterobacteriaceae* decreased from 48% in the first period of analysis to 34% in the second period. Additionally, there was a concurrent increase in coagulase-negative staphylococcal isolates from 6.5 to 16.9% of isolates. Among gram-positive organisms, by the second time period, coagulase-negative staphylococci surpassed *S. aureus* (16.9 vs. 12.5%). Given that 54%

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**Table 1.** Crude and attributable mortality

Author	Population	Study design	Crude mortality	Attributable mortality	Comment
Martin et al. (4)	Non-federal, acute care hospitals in the U.S.	Retrospective analysis of BSI cases captured by ICD-P coding	17.9–27.8%	Not available	Review of cases from a 21-year period. Crude mortality decreased in the last 5 years. Cases were both community and hospital acquired.
Haug et al. (5)	Norwegian University Hospital	Prospective analysis of BSI from 1974–1979 and 1988–1989	1974–1979: 27.6% 1988–1989: 18.8%	1974–1979: 12.3% 1988–1989: 6.9%	Cases were both community and hospital acquired
Esposito et al. (13)	Geriatric population from a suburban hospital in the U.S.	Retrospective analysis of 100 cases	26%	Not available	All cases were community acquired
Whitelaw et al. (12)	Geriatric population from a community-based teaching hospital, South Africa	Prospective analysis of 121 cases	38%	Not available	All cases were community acquired
Lark et al. (7)	Elderly veterans from the VA Hospital	Prospective analysis of 334 patients	14%	Not available	All cases were community acquired
Rayner and Willcox (14)	BSIs from a community-based teaching hospital, South Africa	Prospective analysis of 239 cases	29.2%	Not available	All cases were community acquired
Borer et al. (16)	BSIs from a rural region of Israel	Retrospective analysis of 187 Enterobacteriaceae bacteremias with a focus on ESBL-producing isolates	ESBL producer: 83.3%  Non-ESBL producer: 14.4%	Not available	Approximately 64% of cases were community acquired. All ESBL isolates occurred in elderly, debilitated patients Severity of illness matching was not performed
Elhanan et al.	Comparison of BSIs between teaching vs. non-teaching hospitals, UK	Prospective survey of 1048 bacteremic episodes	Community hospital: 22% Teaching hospital: 26.7%	Not available	63% of cases were community acquired Severity of illness matching was not performed.
Mylotte et al.	Comparison of BSIs between teaching vs. non-teaching hospitals, UK	Retrospective analysis of 248 BSIs	Community hospital: 16.7% Teaching hospital: 19.3%	Not available	All cases were community acquired Differences in age and APACHE score were noted between the two groups
Diekema et al.	Comparison of community onset BSI vs. nosocomial BSI in tertiary care medical centers, USA	Prospective analysis, 929 consecutive BSI episodes	Community onset: 14% Nosocomial: 34%	Community onset: 10% Nosocomial: 23%	All case matched for severity of illness Logistic regression model identified nosocomial BSI as independent predictor of death

(Continued)

**Table 1.** Continued

Author	Population	Study design	Crude mortality	Attributable mortality	Comment
Wisplinghoff et al. 2004	Nationwide, multicenter surveillance of nosocomial BSIs in U.S. Hospitals	24,179 cases analyzed from a prospective surveillance	27%	Not available	
DiGiovine et al.	Nosocomial BSIs in an ICU population	Prospective analysis	Cases: 35.3% Controls: 30.9%	No difference detected after strict matching	Matching performed based on age, race, length of stay, admission date, admitting diagnosis and chronic, co-morbid conditions
Pittet et al.	Nosocomial BSIs in a SICU, tertiary care medical center, USA	Pairwise-matched, case-control study	50%	35%	Matching performed by age, gender, admitting diagnosis, length of stay and total number of discharge diagnoses
Wey et al.	Nosocomial Candidemia in a tertiary care medical center, USA	88 closely matched pairs prospectively identified.	57%	47%	Matching performed by age, gender, comorbidities, date of admission, and surgical procedure
Rosenthal et al.	Central line associated BSIs in an ICU, Argentina	142 closely matched pairs prospectively identified	54.2%	24.6%	Matching performed by length of stay, gender, age, and severity of illness
Bertrand et al.	BSIs in a French hospital.	96 matched pairs in a case control study of patients hospitalized in 15 ICUs	CR-BSI: 38.5% Primary BSI: 50% Secondary BSI: 61.9% All BSI: 52.1%	CR-BSI: 11.5% Primary BSI: 28.6% Secondary BSI: 54.8% All BSI: 35.4%	Matching performed by admission diagnosis, hospital location and severity of illness.
Edmond et al.	VRE BSI in a tertiary care center, USA	Case-control study	67%	37%	Matching performed by time of hospitalization, duration of exposure, underlying disease, age, gender and surgical procedure
Pelz et al.	Comparison of VRE vs. VSE BSI	Prospective cohort study	VRE: 75% VSE: 45%	Not available	Using Cox proportional hazards modeling, VRE BSI was a significant predictor of death (HR 2.19)
Martin et al.	Nosocomial BSIs with coagulase-negative staphylococci	Matched historical cohort of 171 patients	30.5%	16.9%	Matching performed by age, gender, diagnosis, operative procedure and admission date.
Blot et al.	Comparison of BSIs between MRSA and MSSA isolates, Belgium	Retrospective cohort analysis	MRSA: 53.2% MSSA: 28.4 %	MRSA: 23.7 % MSSA: 1.3 %	Matching performed by APACHE II score and diagnosis
Tumbarello et al.	Nosocomial BSI in an HIV-positive cohort, Italy	Prospective case-control study	43%	27%	By multivariate analysis, CD4 <100 and APACHE score were predictors of death

(Continued)

Table 1. Continued

Author	Population	Study design	Crude mortality	Attributable mortality	Comment
Wang et al.	Nosocomial BSI in an HIV positive cohort, Taiwan	Retrospective case-control study	38.6%	26.1%	By multivariate analysis shock and hypoalbuminemia were predictors of death
Wisplinghoff et al. 2003;24, No. 12	BSI in a neutropenic cohort	Prospective, matched, case-control study	16%	12%	Matching performed by admission to the hematology/oncology unit, length of stay, gender, age, type and stage of malignancy, radiation therapy, and duration of neutropenia
Wagener et al.	BSIs in a solid organ transplant cohort	Prospective analysis of 125 bacteremic episodes	Heart: 33% Kidney: 11% Liver: 24%	Not available	
Wisplinghoff et al. 2003;36	BSIs in a cohort of hematologic and solid neoplasms	Prospective analysis with comparison between neutropenic and non-neutropenic patients	Neutropenic: 36% Non-neutropenic: 31%	Not available	

of the BSIs were nosocomial, the shifting microbiology was thought to be related to an increased use of intravascular devices, endocarditis and wound infections (5).

The growing predominance of gram-positive organisms has been noted also in a prospective analysis from Turkey (6). The study reviewed 567 episodes of BSIs of which 73% were hospital acquired and 27% were community acquired (6). Differences were noted in the microbiology between the hospital-acquired and the community-acquired cases. In the nosocomial cases, the most commonly isolated organisms were staphylococci (44%, of which 69% were methicillin resistant, enterococci (15%) and *E. coli* (12.5%). The community-acquired episodes were predominantly *Brucella* species (22%), *E. coli* (19%) and *S. aureus* (15%, of which 9% were methicillin resistant) (6).

Estimates of bloodstream infection mortality are varied and depend on the population studied. In studies that include both nosocomial and community acquired cases, the data suggest that the absolute number of BSIs has increased. However, the overall mortality may be decreasing. In the analysis by Martin et al., the investigators discovered an increase in the absolute numbers of death over a 21-year period (4). However, during the last 5 years of the study, the in-hospital mortality rate fell from a baseline of 28% in 1979 to 18%. The major predictor of mortality was organ failure, with greater survival seen in patients with fewer than three organ failures. Similarly, despite the increase in incidence observed by Norwegian investigators, mortality rates also decreased. Between 1974 and 1979, Haug et al. observed a crude and attributable mortality, respectively, of 28% and 12%. The following period of analysis between 1988 and 1989 revealed a crude and attributable mortality of 19 and 7%, respectively. Five patients with advanced age (>60 years of age) accounted for more than half of the bloodstream infections. Additionally, the mortality in this age group was greater than in patients <60 years of age, 31 vs. 14%. Clinical predictors of adverse outcome were septic shock, intensive care treatment, malignant disease and pulmonary source of infection (5).

### Community-Acquired Bacteremias in the Elderly

The epidemiology, microbiology and outcomes of community-acquired bacteremias in the elderly have been described. Lark et al. prospectively evaluated all patients admitted to the Veterans Affairs Medical Center over a 4-year period (7). Bacteremia was classified as community acquired if the positive cultures were drawn less than 48 h after admission to the hospital. A total of 387 BSIs were evaluated. The mean age at presentation was 62 years old. Comorbid conditions were commonly seen, including diabetes mellitus (22%), renal failure (21%), malignancy (21%), and COPD (13%) (7).

A large proportion of the bacteremias (40%) occurred in patients with indwelling urinary catheters. Additionally, 30%

of bacteremias were directly related to either an in-dwelling urinary or intravenous catheter. Microbiologically, 87% of all bacteremia were monomicrobial. The most common organisms identified were *S. aureus* (18%), *E. coli* (15%) and coagulase-negative staphylococci (12%). A study by Rayner et al. further supports the predominance of gram-positive organisms, specifically *S. pneumoniae*, as principal pathogens of bacteremia in the elderly. In this series, gram-positive organisms accounted for 51% of all isolates with *S. pneumoniae* as the principal gram-positive pathogen.

Other studies support the predominance of gram-negative organisms in the microbiology of bacteremias in the elderly. Whitelaw et al. prospectively studied 121 cases of bacteremia in elderly patients. Gram-negative organisms accounted for 65% of all cases, gram-positive 39% and polymicrobial 7% of cases. The most commonly identified organisms were *E. coli* (39%), *S. pneumoniae* (14%), *S. aureus* (12%) and *Klebsiella* species (8%). Similarly, Madden et al., in a review of 44 elderly patients with bacteremia, identified *E. coli* as the principal pathogen (8). Further, McCue et al. observed a preponderance of *E. coli* in a cohort of elderly patients with community-acquired BSI (9).

Data on mortality vary, and current evidence suggests that the overall mortality of bacteremia in elderly remains high. Studies from the early 1980s established a crude mortality rate of 22–37% (10–12). In a retrospective analysis of 100 geriatric patients with community acquired bacteremia admitted to a suburban hospital in the U.S., both a different microbiology and a higher crude mortality were documented (13). All cases occurred in patients >65 years of age. Community-acquired bacteremia was defined as a positive blood culture within 72 h of admission. A total of 100 cases were detected of which 62% were women. The crude mortality in this analysis was 26% (13).

The high mortality of BSIs in elderly patients is supported by data from the early 1990s. In a 2-year South African study, 121 consecutive episodes of community-acquired bacteremia were analyzed in a large, community based teaching hospital (12). All patients were between ages 65 and 89. Community-acquired bacteremia was defined as a positive blood culture within 48 h of admission. The crude mortality was 38%. Fifty one percent of all bacteremias occurred in women. A poor prognosis was associated with altered mental status on presentation, hypotension and inappropriate or delayed initial treatment.

More recently, Lark et al. prospectively evaluated outcomes of community-acquired bacteremia in a population of elderly veterans. Of the 334 patients described in their analysis, 45 deaths were reported for an overall in-hospital mortality rate of 14%. Logistic regression modeling identified several independent predictors of mortality: shock, renal failure, pneumonia, intra-abdominal infection or multiple sources of infection. Thus, for community-acquired bacteremia in a cohort of American veterans, a crude mortality of

14% was documented. These infections were monomicrobial, commonly associated comorbid conditions and urinary and intravenous catheters.

Current data therefore support the concepts that community-acquired bacteremia in the elderly is associated with high crude mortality ranging from 14–38%. Factors associated with a poor outcome include altered mental status on presentation, shock, multiorgan failure and inappropriate choice of antibiotic. The most commonly identified gram-positive organisms are *S. aureus*, *S. pneumoniae* and coagulase-negative staphylococci. Common portals of entry are the genitourinary tract, respiratory tract (pneumonia) and indwelling vascular catheters. Early diagnosis and appropriate treatment are likely critical to reduce mortality.

### **Community-Acquired Bacteremia: Experiences in Rural Settings, Comparisons between Teaching and Non-Teaching Hospitals and Comparisons between Community-Acquired and Nosocomial Cases**

Rural environments throughout the world are not immune to the pressures of a changing healthcare system. With the widespread use of empiric anti-infectives in the outpatient setting and the increased frequency of long-term, indwelling invasive devices such as urinary catheters, selective pressure for multi-drug resistant organisms has been introduced. Depending on their use, the local area antibiograms vary considerably. Additionally, evidence suggests that community acquired isolates are now increasingly resistant to antimicrobials and may be associated with greater morbidity and mortality.

In an early study of community-acquired bacteremia, Rayner and Willcox prospectively surveyed 239 cases of community-acquired bacteremia from the late 1980s (14). All cases presented to a large, community-based teaching hospital in South Africa. Fifty-one percent of isolates were gram-positive organisms, of which *S. pneumoniae* and *S. aureus* predominated. All pneumococcal strains were susceptible to penicillin, while 22% of *S. aureus* isolates were methicillin resistant. Of the gram-negative isolates, the most common were *E. coli* and *Klebsiella* species. Isolates of *E. coli* and *Klebsiella* species had a high rate of resistance to ampicillin, respectively, 60 and 95%. The overall mortality was 29%.

A case series from Jordan conducted in various rural health centers over an 18-month period revealed a mixed microbiology (15). Of the 215 patients evaluated for fever and presumed bacteremia, 126 blood cultures (59%) were positive. The most frequently recovered organisms were *S. aureus*, *Brucella melitensis* and *Streptococcus pneumoniae*. Widespread resistance to antimicrobials was reported, including multi-drug resistance in 44.4% of the isolates. The most commonly reported resistant organisms were *S. aureus* (62.5%), *S. pneumoniae* (57.1%) and *E. coli* (80%). The

most frequent sources of bacteremia were the urinary tract (15.9%), respiratory (14.3%), gastrointestinal (12.7%) and soft tissue infection (7.9%). The source of bacteremia was not identified in 13.5% (15). No mortality from bacteremia was reported in this cohort.

The emergence of community-acquired bacteremia with extended spectrum beta-lactamase (ESBL) producing organisms is of concern. A retrospective analysis of BSIs in a rural Israeli region analyzed 187 *Enterobacteriaceae* bacteremias, of which 64% were community acquired (16). Of the community-acquired cases, six were of the ESBL producing variety. Of these isolates, four were *K. pneumoniae*, one was *Enterobacter* species and one was *E. coli*. All ESBL cases occurred in the elderly, half of whom were debilitated, most had indwelling urinary catheters and all had received prior antibiotics. When compared to the cases without ESBL producing organisms, 50% were admitted to the ICU vs. 8% in the non-ESBL comparators. Furthermore, ESBL BSI were associated with a significantly higher complication rate (67 vs. 18%) and a higher mortality rate (83 and 14%) (16).

Differences may exist in the incidence, microbiology and outcome of community-acquired bacteremia between teaching and non-teaching hospitals. Elhanan et al. prospectively surveyed 1,048 episodes of bacteremia over an 18-month period in a 45-bed community hospital and a 900 bed tertiary care urban university hospital in the UK. The incidence of bacteremia in the teaching hospital was significantly greater than in the community hospital (2.64 vs. 2.18 per 1000 hospitalization days,  $p < 0.004$ ). In both institutions, the most commonly reported gram-positive organisms were *S. aureus*, *S. epidermidis* and *S. pneumoniae*. Although *E. coli* were the most commonly reported gram-negative isolates, a greater frequency of bacteremia by *Pseudomonas*, *Enterobacter* and *Acinetobacter* species was observed. Although the majority of bacteremias occurred in the medicine wards of both hospitals, differences in mortality were observed. The crude mortality was 22% in the community hospital and 27% in the academic institution. However, the populations were not matched for severity of illness.

Mylotte et al. compared community-acquired BSIs at teaching vs. non-teaching facilities with a focus on 30-day mortality. This retrospective analysis compared 174 episodes at a teaching hospital to 74 episodes at a non-teaching institution. Variables of interest included age, severity of illness (APACHE score), bacteriology and comorbid illnesses. Although the patients were older at the non-teaching hospital, the APACHE scores were lower for this cohort. *S. aureus* bacteremia occurred more frequently in the teaching hospital cohort while *E. coli* was more commonly seen in the non-teaching hospital group. There was no significant difference detected in 30-day mortality between the teaching and non-teaching cohorts (19 and 17%).

Data comparing the mortality of community-acquired bacteremia vs. nosocomial bacteremia are sparse. The results

from a Turkish case series suggest that differences in mortality may exist between nosocomial and community-acquired BSIs. Outcomes were both crude and attributable mortality, with attributable mortality defined as death occurring during the phase of active infection or antibiotic treatment. The investigators failed to match rigorously for confounders in the determination of attributable mortality. The overall mortality rate was 25.4%, whereas the attributable mortality rate for bloodstream infection was 16.6% in hospital-acquired episodes and 13.9% in community-acquired episodes (6). Predictors of mortality included co-morbid illnesses, severity of disease, indwelling urinary catheters, tracheal intubation and prior antibiotic use (6).

In a more recent study by Diekema et al., nosocomial BSIs were associated with excess mortality (17). In this prospective analysis, 929 consecutive BSI episodes from two tertiary care medical centers were studied for differences in outcome between community onset vs. nosocomial BSIs. Patient comparisons were adjusted for severity of illness. Crude mortality was 14% for community onset BSI and 34% for nosocomial BSI. Attributable mortality, respectively, was 10 and 23%. Using multivariate logistic regression analysis with in-hospital mortality as the outcome measure, nosocomial BSI was independently associated with death (OR 2.6).

### Nosocomial Bacteremias: Incidence and Microbiology

On a national level, nosocomial bacteremias are the 10th leading cause of death in the U.S. (18). Additionally, the age-adjusted death rate has increased by 78% over the last 20 years (19). Although the exact incidence of nosocomial bloodstream infections is unknown, it is believed that approximately 250,000 cases occur annually in the U.S. (1,2). Within the hospital setting, the incidence of nosocomial BSIs appears heterogeneous. Recent publications suggest that the incidence of nosocomial bacteremia ranges from 1% in intensive care unit populations to as high as 36% in bone marrow transplant recipients (20,21). In a recent study analyzing nosocomial BSIs caused by antibiotic resistant gram-negative bacteria in critically ill patients, the incidence of bacteremia was 11 cases per 1,000 ICU admissions (22). Finally, data from a 12 year retrospective review of nosocomial BSIs in a 900 bed, tertiary care hospital, documented a linear increase of crude infection rates from 6.7 to 188.4 per 1000 discharges (23). Thus, reports on the incidence of nosocomial bloodstream infection vary significantly, very likely reflecting differences in individual risk based on institution, co-morbid illnesses, length of stay, and hospital location.

The microbiology of nosocomial BSIs is similarly diverse. From the SCOPE database, at the end of a 7-year period, the majority of all BSIs were monomicrobial (2). Anaerobic bacteria accounted for only 1% of all BSIs. The

most common isolates were coagulase-negative staphylococci (31%), *S. aureus* (20%), enterococci (9%) and *Candida* species (9%). Enteric gram-negative pathogens figured lower on the ranks of organisms and included *E. coli* (2.8%), *Klebsiella* species (2.4%), *Pseudomonas aeruginosa* (2.1%) and *Enterobacter* species (1.9%) (2). Other studies confirm the emergence of gram-positive pathogens, specifically coagulase-negative staphylococci, and *S. aureus* and enterococci as the dominant organisms in nosocomial BSIs (4,19,20,24–26). This rise in the frequency of coagulase-negative staphylococci BSI isolates has occurred concurrently with the increased use of invasive intravascular catheters.

The distribution of nosocomial BSI organisms varies by clinical service. From the SCOPE database, the top ranked pathogens on general surgery, neurosurgery, internal medicine and hematology were coagulase-negative staphylococci, *S. aureus* and enterococci (2). On the obstetrics services, *E. coli* and streptococci were prominent. *Candida* species were preferentially seen in hematology and oncology patients (2). Infections with *Candida* species, enterococci and viridans group streptococci were more common in neutropenic patients. Bloodstream infections caused by coagulase-negative staphylococci, *Pseudomonas* species, *Enterobacter* species, *Serratia* species and *Acinetobacter* species were seen in the intensive care unit population (2).

An increase in antibiotic-resistant nosocomial BSI pathogens has been observed. Given the predominance of gram-positive organisms as bloodstream pathogens, the growing proportion of isolates exhibiting antimicrobial resistance is of concern. The proportion of *S. aureus* isolates resistant to methicillin ranges from 12.9–57% (2,26,27). From the SCOPE database, an increase in the rate of methicillin resistance was observed from 22% in 1995 to 57% in 2001 (2). Data from European centers confirms a similar increase of methicillin resistance albeit at a lower rate (27). In both the SCOPE and SENTRY databases, the proportion of coagulase-negative staphylococci resistant to methicillin was 75%. The proportion of enterococcal bloodstream isolates resistant to vancomycin was 2% of *E. faecalis* and 60% of *E. faecium* (2). Over a three-year time frame, the proportion of bloodstream isolates of enterococcal species reported as resistant to vancomycin in the SENTRY database was 14%. The management of BSIs will continue to challenge physicians as reports of pathogen resistance increase.

### Nosocomial Bacteremias: Attributable and Crude Mortality

Few studies have focused on the total impact of nosocomial BSIs, including attributable mortality, cost and length of stay. Data on attributable mortality are limited as the term attributable mortality is used to determine the mortality rate directly attributable to a specific risk factor (28). This type of

analysis requires robust matching so that the mortality in tightly matched controls can be subtracted from the overall mortality in infected cases (28). For attributable mortality related to nosocomial bloodstream infections, the controls are typically matched to cases based on age, gender, service, comorbidities, procedures, and length of stay in the control at least as long as the interval between admissions and infections is the case (28).

Mortality studies vary in both measures of outcomes and populations. In a nationwide case series, a crude mortality rate as high as 27% has been reported (2). However, only a modest number of matched case-control studies, or multivariable analyses have been performed to estimate the attributable mortality of nosocomial bloodstream infections. Data from early studies estimate the attributable mortality of nosocomial BSI from 21–31%. When the 95% confidence interval is applied, this estimate varies between 6 and 48% (28–32).

Recent studies of nosocomial BSI attributable mortality have been performed in heterogeneous patient populations. A study of intensive care unit patients with nosocomial BSIs focused on crude and attributable mortality (33). All cases were matched to a non-infected control by age, race, length of stay, admission date, admitting diagnosis and chronic, co-morbid conditions. There was no difference in crude mortality between cases (35.3%) and controls (30.9%). After matching, the investigators again were unable to detect a difference in attributable mortality (33). A prospective cohort study from Canada similarly addressed attributable mortality of nosocomial BSIs in intensive care unit patients (34). After controlling for severity of illness, age and post-surgical status via multivariate logistic regression modeling, ICU-acquired nosocomial BSI was not a significant predictor of mortality (34).

However, data from other investigations suggest that nosocomial BSIs are of significant attributable mortality. One series estimated the attributable mortality of hospital-acquired BSIs in a critically ill surgical cohort (23). This historical cohort study matched cases of hospital-acquired bacteremia occurring in a surgical intensive care unit by age, gender, admitting diagnosis, length of stay and total number of discharge diagnoses. The crude mortality rates from cases and controls were, respectively, 50 and 15% (23). The estimated attributable mortality was therefore 35% (95% confidence interval 25–45%).

Between 1977 and 1984, cases of hospital-acquired candidemia were analyzed in a major, tertiary care medical center (35). Eighty-eight cases of hospital-acquired candidemia were closely matched by age, gender, comorbidities, date of admission, and surgical procedure. The crude mortality of nosocomial candidemia in this case series was 57% and the reported attributable mortality was 48%. The corresponding risk ratio for mortality in this series was 2.94 with a 95% confidence interval of 1.95–4.43 (35). Rosenthal et al. studied nosocomial BSIs in critically ill patients from a medical-surgical intensive care unit. Data on nosocomial infections

were prospectively obtained, and the comparison was made between cases and non-cases in the intensive care units with matching based on length of stay. A catheter-related BSI rate of 44.61 per 1000 device days was reported with an attributable mortality of 25% (36). An excess length of stay of 5 days was reported in the analysis. In another series, the attributable mortality and excess length of central line-associated bloodstream infection was investigated with more rigorous matching (37). Cases and controls were matched for length of stay, gender, age, and severity of illness. In addition to an increased length of stay of 11.9 days, patients with catheter-related BSIs had an attributable mortality of 24.6% (37).

In a French study of nosocomial bacteremia, 2,201 patients hospitalized in intensive care units were analyzed for primary nosocomial bacteremias, catheter-related bacteremias and secondary nosocomial BSIs (38). For the purpose of this analysis, bacteremias were defined as catheter related, primary and secondary. In contrast to secondary bacteremias, primary bacteremias were without an identifiable source. Using a nested case-control study with logistic regression modeling, 111 episodes of nosocomial BSIs were identified. Bacteremias occurred in 5% of all patients with an ICU stay of >48 h duration (38). Of these, primary, catheter-related BSI and secondary BSI accounted for 29, 26 and 45% of all episodes. Values for attributable mortality varied based on the type of the nosocomial bloodstream infection. For all bacteremias, the attributable mortality was 35%. For catheter related, primary and secondary bacteremias the attributable mortality was, respectively, 12, 29, and 55%. These data suggest that within an intensive care setting, the excess mortality of nosocomial BSIs varies based on underlying pathophysiology of the bacteremia.

Other studies of attributable mortality are pathogen specific. Several studies have focused exclusively on the attributable mortality of nosocomial BSIs due to enterococci. Early studies of crude mortality showed that bacteremias due to vancomycin resistant enterococcus (VRE) were associated with a mortality of 17–100% (39–44). These studies failed to rigorously match for comorbid conditions. In a historical cohort study focusing on the attributable mortality of VRE bacteremia, all case patients were closely matched to controls by time of hospitalization, duration of exposure, underlying disease, age, gender and surgical procedure (45). A statistically significant difference in mortality was observed among cases (67%) and matched controls (37%). The mortality attributable to VRE bacteremia was 37%, and the risk ratio for death was 2.3. In this analysis, the VRE bacteremia was associated with a high attributable mortality and a risk of death twice that of controls (45).

Similarly, the clinical outcome of VRE bacteremia has been studied in a surgical-trauma population. To assess the degree of morbidity and mortality attributable to VRE, a matched case control was conducted comparing cases of

VRE to vancomycin-susceptible enterococcal (VSE) bacteremia (46). Patients were matched by a scoring system that factored age, APACHE II score, admitting service, hospital location and length of stay. VRE bacteremia was a statistically significant independent predictor of crude mortality (OR 4.0) and of infection-related mortality (OR 5.2) (46).

Other analyses of enterococcal bacteremia have not documented so high an attributable mortality. Data from a Spanish cohort reported an attributable mortality of 6% (47). The study design was a prospective matched case control in which all controls were matched by gender, age and hospital ward. The majority of isolates were *E. faecalis*, and only two cases of VRE were identified. The lower attributable mortality observed in this series may have been due to inadequate matching and to the predominance of VSE isolates.

Bacteremias with vancomycin-resistant enterococci (VRE) may have a greater attributable mortality than bacteremias with VSE. A recent analysis of the mortality of VRE vs. VSE infections prospectively studied in the intensive care unit examined 129 patients admitted to the surgical and medical intensive care units over a 3-month period (48). The authors considered multiple infection sites in the analysis and included specimens from blood, urine, wound and abscesses. Only 34 cases of VRE or VSE were identified, the most common being BSI (9 VRE and 12 VSE). For patients with VRE, the overall mortality was 75% compared to 45% in the VSE cohort (48). Using a Cox-proportional hazards model, VRE was associated with an increased relative hazard of in-hospital mortality (HR 2.18), while VSE was not a significant predictor of death (48).

Coagulase-negative staphylococci are major pathogens in nosocomial BSIs and their attributable mortality has been studied. In a matched-historical cohort of 171 patients with hospital-acquired coagulase-negative staphylococci the mortality rate of cases was 31% compared to 17% in controls (4). The attributable mortality was 14% and the risk ratio for death was 2%. All cases were matched to a control patient by age, gender, diagnosis, operative procedure and admission date.

Studies of *S. aureus* bacteremia have focused on attributable mortality and have compared outcomes between cases with methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) isolates. Owing to an increased incidence of MRSA, recent investigations have focused on the comparison of BSIs with methicillin-sensitive and methicillin-resistant isolates. Data from Belgium suggest that nosocomial MRSA bacteremia is associated with both a higher crude and attributable mortality (49). In a retrospective cohort analysis with matching based on APACHE II (Acute Physiology and Chronic Health Evaluation) score and diagnosis, 38 cases of MSSA bacteremia were compared with 47 cases of MRSA bacteremia in critically ill patients (49). In addition to an excess LOS and a greater frequency of renal

failure, patients with MRSA bacteremia had a greater 30-day mortality (53.2 vs. 18.4%). In addition, patients with MRSA bacteremia had a higher in-hospital mortality (63.8 vs. 23.7%) along with a higher attributable mortality (23.7 vs. 1.3%) (49).

Investigators in Canada have also compared the mortality between MRSA and MSSA bacteremia after controlling for age, gender and diagnosis (50). Attributable mortality was higher in the MRSA group (36 vs. 20%), but this failed to achieve statistical significance. A recent British study prospectively compared MRSA and MSSA nosocomial infections, including bacteremia. Over a 5-year period, all cases of nosocomial BSIs were prospectively analyzed with data collected for age, gender, service, disseminated infection, adequacy of treatment and outcome (51). The final analysis compared 433 cases of MSSA bacteremia to 382 cases of MRSA bacteremia. Although no statistically significant differences in mortality were observed between the MRSA and MSSA cohorts, a strong statistical trend was seen with MRSA bacteremia. The attributable mortality of MRSA bacteremia was 11.8 vs. 5.1% in MSSA. These data suggest that the attributable mortality of MRSA bacteremia exceeds that of bacteremia with MSSA.

The attributable mortality of *S. aureus* bacteremia may be greater in elderly populations. In a prospective cohort study of 385 patients with *S. aureus* bacteremia, 145 patients ages 66 and older were compared to 240 patients ages 18–60 years (52). After adjusting for confounding variables, a greater odds of death was seen in the older cohort (OR 2.30; 95% CI, 1.13–4.69). In a subset comparison of MRSA bacteremia between the young and old population, a greater odds of death was seen in the elderly (OR 2.59; 95% CI, 1.23–5.43) (52).

### Nosocomial Bacteremias: Socioeconomic Impact

Nosocomial BSIs are an important public health concern and have a significant direct socioeconomic impact. Estimates on cost and length of stay for nosocomial BSIs vary. Estimates on the attributable length of stay for nosocomial bacteremias range from 7 to 30 days (35,53,54). The costs of nosocomial bloodstream infections primarily reflect charges incurred due to excess length of stay and additional treatments. Estimates on excess costs per survivor vary from \$5,000 to \$40,000 (23,33,36).

An alternate measure of socioeconomic burden is years of potential life lost. This model of analysis has been applied to both nosocomial infections and to nosocomial BSIs. Analyses of years of potential life lost are based on several critical assumptions. If the mean age of death is 60 years and the life expectancy is 70 years age, then the years of potential life lost will be a function of both the nosocomial infection rate and the attributable mortality rate. Assuming a 5% total nosocomial infection rate, an attributable mortality rate of

20% with 35,000 resultant deaths, the years of potential life lost in the U.S. would be 350,000 annually (54). If the nosocomial infection rate is decreased to 2.5% with an attributable mortality rate of 10%, the years of potential life decreases to 87,500 annually (54). Applying this analysis in a fashion that the mortality rate and the nosocomial infection rate increase, a linear increase in the years of potential life lost would be expected. Conceivably, with a nosocomial infection rate of 10% and an attributable mortality rate of 30%, the annual years of potential life lost in the U.S. may be as high as 1,050,000 (54).

### Bloodstream Infections in the HIV Population

The Report on the Global HIV/AIDS Epidemic, UNAIDS, 2002 estimates that 40 million people worldwide are infected with HIV/AIDS. Patients with HIV/AIDS commonly present with community-acquired infections caused by bacteria, mycobacteria, parasites and fungi. The epidemiology of bacteremias in HIV-infected patients has been studied. The incidence of BSIs in HIV patients varies widely and is likely a reflection of heterogeneous populations studied. Investigations of BSIs in patients with AIDS originally focused on the microbiology of bacteremias with the goal of developing guidelines for empiric antibiotic therapy. Additionally, much of these data came from HIV-infected intravenous (IV) drug abusers. In one retrospective analysis of blood cultures from 200 AIDS patients performed in the early to mid-1980s, 75% of patients were IV drug users (55). A total of 1,120 sets of blood cultures were sent and 3.8% were positive. Of these, the most common isolates were *Salmonella* species, coagulase-negative staphylococci, *Cryptococcus neoformans* and *S. aureus*. When these data were compared to 2,013 positive blood cultures from non-AIDS patients, non-IV drug abusers, several statistically significant differences were observed. In contrast to AIDS patients, non-AIDS cases exhibited a higher rate of bacteremia with *S. pneumoniae*, *Candida* species and enteric gram-negative rods (exclusive of *Salmonella* species) (55).

In a 1980s analysis of 34 bacteremic episodes from 16 patients with HIV/AIDS, 25 episodes were community acquired whereas nine were nosocomial (56). Of the 25 community-acquired episodes, 19 were seen in IV drug abusers. The most common pathogens were *S. aureus* and *S. pneumoniae*, preferentially seen in the patients with a history of IV drug abuse. The remaining nine cases were nosocomial and included one each episode of *S. aureus*, *S. epidermidis*, *Fusobacterium*, *E. aerogenes*, *M. morgagnii* and two cases each of *K. pneumoniae* and *P. aeruginosa*. Thus, studies focusing on HIV/AIDS patients with concurrent IV drug abuse revealed a microbiologic pattern favoring gram-positive organisms such as coagulase-negative staphylococci, *S. aureus*, enteric gram negatives such as *Salmonella* species and opportunistic fungi such as *Cryptococcus neoformans*.

A more recent study from Taiwan focused on the incidence of bacteremia and fungemia in non-IV drug abuse patients with advanced HIV infection and highlights the importance of enteric gram-negative and fungal pathogens in this population. This prospective, 42-month study analyzed all HIV-infected patients with fever admitted to a university hospital (57). Of 210 patients, 41 (19.5%) had a total of 52 episodes of bacteremia or fungemia. All but one patient had AIDS, and the mean CD4+ count was 29/ $\mu$ L. Of the bacterial isolates, non-typhoidal *Salmonella* was the most common (80%). *S. aureus* was diagnosed in three episodes, whereas *S. pneumoniae* was seen in one. *C. neoformans* was the most common type of fungemia seen in 12 episodes.

Central venous catheters impact both the incidence and outcome of nosocomial BSI in HIV-positive patients. The incidence of catheter-related BSI among HIV-positive patients varies from 1.3 to 12 per 1,000 catheter days (58–64). The likelihood of infection is a function of catheter type and degree of immunosuppression. The most common type of central venous catheter is of the non-tunneled variety. This catheter type is implicated in 90% of all catheter-related bacteremias (58,65). In a study by Skiest et al., 142 HIV patients with non-tunneled central venous catheters showed 18.3% of the catheters were infected. The rate of infection was 2.8 per 1,000 device days. In different analyses, higher rates of infection were found (66). Two Italian surveys suggest a rate of catheter-related BSI of 8–12 per 1,000 device days (58,60,67). Data on BSIs with tunneled central venous catheters in HIV-positive patients are consistent with reports in the non-HIV-positive population. In a survey of tunneled-cuffed catheter-associated infections in HIV-positive hemodialysis patients, the reported BSI rate was 2.23 per 1,000 tunneled central venous catheters and was comparable to the rate of 2.5 per 1,000 tunneled central venous catheters observed in the HIV-negative controls. These data suggest that the incidence of catheter-related bloodstream infection in HIV-positive patients is in part a function of catheter type.

The microbiology of catheter-related BSIs in HIV-positive patients consists predominantly of gram-positive organisms. Multiple studies support the prominence of *S. aureus* and coagulase-negative staphylococci as pathogens in catheter-related BSIs in HIV-positive patients (61,64,66). Hospital-acquired gram-negative rods such as *Acinetobacter* species, *Pseudomonas* species and *Stenotrophomonas* species have also been implicated in the pathogenesis of catheter-related BSIs in the HIV-positive population (68). Unlike fungemic episodes reported in case series of community-acquired BSIs, yeasts (not molds) are the principal pathogens. Data from non-HIV patient cohorts have shown an increase in the secular trend of BSIs with *Candida* species over the decades (2,69). This too has been observed in cohorts of HIV-positive patients (58).

The mortality associated with bacteremia in HIV disease is varied and depends largely upon the population studied. In one retrospective analysis over a 16-month period, 44 cases of community-acquired bacteremias were identified in HIV-positive patients, 70 with the diagnosis of AIDS. All cases had positive blood cultures within 24 h of admission. The most commonly identified sources of bacteremia were pneumonia, indwelling central venous catheters, and cellulitis. Fourteen patients had no identifiable source. In this series, only 4 of the 44 patients died during the course of hospitalization resulting in a crude mortality of 9% (70).

In contrast, nosocomial BSI in HIV-positive patients are associated with a much higher mortality. Additionally, mortality is associated with both low CD4 counts and severity of illness. In a series from Italy, a 3-year prospective matched case-control study method was employed to study the risk factors, prognostic indicators, impact on length of stay, and crude and attributable mortality of bacteremia in HIV-infected patients (63). Eighty four cases were matched with 168 controls for age, gender, CD4+ lymphocyte count, diagnosis upon admission, hospital location and length of stay preceding the BSI. After logistic regression analysis, the independent predictors of bacteremia were severity of illness by APACHE II score and the presence of a central venous catheter. The crude mortality was 43% with an attributable mortality of 27% (95% CI, 13–48). By multivariate analysis, the investigators identified CD4+ count  $<100/\text{mm}^3$  and APACHE II score  $>15$  as independent predictors of mortality. The risk ratio for death in this analysis was 3.91 (95% CI, 2.06–7.44) (63).

A large, retrospective analysis of nosocomial BSIs in HIV patients further supports the high crude and attributable mortality elsewhere reported. In Taiwan, the medical records of all HIV-positive patients with nosocomial BSIs were reviewed (71). Fifty seven episodes of nosocomial BSI were identified, and data were collected on CD4+ count, HIV classification by CDC criteria, white blood cell count, serum albumin, severity of systemic inflammatory response, presence of CVCs, active opportunistic infection, organ failure and outcome. Logistic regression modeling was employed to determine predictors of mortality. The incidence of nosocomial BSI in HIV-infected patients was 2.3 per 1,000 patient days of hospitalization. Of all nosocomial BSI, 77% were classified as primary. The crude and attributable mortality were 39 and 26%, respectively. Multivariate analysis via logistic regression modeling revealed shock and hypoalbuminemia as independent predictors of mortality.

### Bacteremia in Neutropenic Patients

Infection in the immunocompromised, neutropenic host continues to be a major clinical dilemma. Data from multiple studies suggest that the attack rate for nosocomial bacteremia in neutropenic patients ranges from 11 to 39% (72–75).

The microbiology of neutropenic BSIs is summarized in a comprehensive review of bacteremia spanning two decades. Elting et al. summarized data on bacteremia from 10 consecutive randomized clinical trials of antibiotic therapy in febrile, neutropenic cancer patients (76). In total, 909 bacteremia episodes were reviewed. Gram-positive organisms caused 46% of bacteremias, gram-negative organisms caused 42% of bacteremias, and 12% of episodes were polymicrobial (76). Additionally, data from this series suggest that the distribution of bacteria has changed over time as the initial predominance of gram-negative organisms shifted to gram positive (76). The most common gram-positive organisms identified were coagulase-negative *Staphylococcus* (17%),  $\alpha$ -hemolytic *Streptococcus* (13%), and *S. aureus* (8%). The most common gram-negative pathogens identified were *Escherichia coli* (12%), *Pseudomonas* species (10%) and *Klebsiella* species (9%). Data from a prospective cohort study of nosocomial BSIs in adult neutropenic patients further support this microbiologic picture. In this series of bacteremic episodes, the microbiology of the BSIs consisted of coagulase-negative *Staphylococcus* (16.7%), *Viridans streptococci* (16.7%), *E. coli* (16.7%), *P. aeruginosa* (7.1%) and *S. aureus* (6%) (72). These data are consistent with other studies finding coagulase-negative staphylococci, *E. coli*, viridans group streptococci, *P. aeruginosa* and *S. aureus* as major pathogens in neutropenic BSIs (77–79).

A comprehensive analysis of nosocomial BSIs in the U.S. reported increased drug resistance, particularly in gram-positive organisms. The proportion of *S. aureus* isolates with methicillin resistance increased from 22% in 1995 to 57% in 2001 (2). The emergence of drug-resistant BSI pathogens applies to the neutropenic population as well. A Pakistani study of microbiologic spectrum and susceptibility of bloodstream isolates from febrile neutropenic patients supports this trend. Eighty three organisms were isolated from 60 patients, with 43% gram-positive cocci and 57% gram-negative rods. Forty percent of the *S. aureus* and 55% of the coagulase-negative *Staphylococcus* were resistant to methicillin yet sensitive to vancomycin. These authors concluded that the spectrum of bacterial isolates was shifting to towards resistant, gram-positive organisms (80).

Several studies have focused on crude and attributable mortality of BSIs in neutropenic patients. The estimated attributable mortality of BSI in cancer patients is between 7.5 and 30% (74,75). These studies failed to match patients on multiple factors and did not employ a case-control analysis. A more accurate estimate is available. One recent study of bacteremia in neutropenic patients focused on attributable mortality and employed a prospective cohort and matched case-control analysis of 81 matched pairs. Matching was based on admission to the hematology–oncology unit, length of stay, gender, age, type and stage of malignancy, radiation therapy, and duration of neutropenia. The crude mortality rates of cases and control were 16 and 4%, respectively (72). The attributable mortality was 12% (72).

## Bacteremia in Patients with Solid Organ and Bone Marrow Transplant

Infections in solid organ and bone marrow transplant recipients remain problematic. Data on incidence vary by both type of bone marrow and solid organ transplantation. Neutropenia is an additional risk factor for bacteremia in transplant populations. The incidence of bacteremia in bone marrow transplant patients is as high as 360 BSIs per 1,000 neutropenic episodes (21). Another series defined the incidence of infectious complications within 30 days in a cohort of 219 autologous bone marrow transplant recipients (81). In this series, the incidence of bacteremia was 7.8%.

In solid organ transplant populations, the rate of bacteremia differs by transplantation type. One study reviewed 277 consecutive admissions of solid organ transplant patients. The rates of BSIs in solid organ transplants were 28% for liver, 10% for heart or heart–lung, and 5% for kidney transplants (82). For the total cohort, the rate of bacteremia was 10%. Another prospective study of solid organ transplants documented a bloodstream infection rate of 24% in liver transplants, 11% in heart transplants, and 6% in kidney transplants (83).

The microbial spectrum of bacteremias in bone marrow and solid organ transplants varies. As in other populations, a shift favoring the predominance of gram-positive pathogens has been documented. In one large series of patients with both hematological malignancies and solid neoplasms, gram-positive organisms accounted for 62% of all bacteremias in 1995 and 76% of bacteremias in 2000 (72). Other investigators have reported proportions of gram-positive infections between 70 and 81% (84,85). Of these gram-positive pathogens, the most commonly reported were coagulase-negative staphylococci, *Viridans streptococci*, *S. aureus*, and *Enterococcus* species (21,72,73,81,84,86,87). The most commonly reported gram-negative pathogens, in various orders of rank, were *E. coli*, *Enterobacter* species, *Klebsiella* species, and *Pseudomonas* species (21,72,73,81,84,86,87). Like incidence, the mortality of bacteremia in the solid organ transplantation population varies based on transplant type. In one prospective analysis of 125 bacteremic episodes in recipients of heart, kidney or liver transplants, the 14-day mortality following bacteremia was, respectively, 33, 11 and 24% (83). In a different analysis of 53 liver transplant recipients, a lower incidence of bacteremia (21%) was observed (88). Likewise, the reported mortality was lower. Five deaths (9%) were reported in this series with only two from septicemia (88). Another analysis of 101 consecutive liver transplantations reported an overall mortality of 26% (26/101). Of these, 23 were due to infection (89%) and 5 were due to bacteremia (88).

Data on the crude mortality of bacteremia in bone marrow transplant recipients vary widely. In one analysis of BSIs in 519 bone marrow transplant recipients, mortality varied largely by pathogen. Although gram-positive pathogens

were the predominant isolates, not a single death was recorded in patients with *S. aureus*, enterococci, or *Streptococcus* species. A high mortality in bacteremia was observed with *B. fragilis* (50%), *P. aeruginosa* (40%) and *Enterobacter/Citrobacter/Serratia* species (25%). The mortality of nosocomial bacteremia in hematologic and solid neoplasms is affected by neutropenia. In a large prospective study of 2,340 patients with underlying malignancy, mortality was compared between neutropenic and non-neutropenic patients (72). The overall mortality rate was 32% and ranged from 16% in patients with bacteremia due to viridans group streptococci to 45% with *Candida fungemia* (72). When the analysis was stratified by neutropenia, the crude mortality was 36% for neutropenic patients and 31% for non-neutropenic patients.

### Conclusions

Bacteremias are significant causes of morbidity and mortality worldwide. Studies suggest that the incidence of BSIs is on the rise. Whereas gram-negative organisms were more common in the 1970s, gram-positive organisms are now the predominant pathogens and include coagulase-negative staphylococci, *S. aureus* and enterococci. This has been observed in diverse patient populations including both community-acquired and nosocomial cases. Of the gram-negative isolates, the enterobacteriaceae are the most common. *E. coli* is prominent among elderly patients with community-acquired BSIs. Furthermore, increases in antimicrobial resistance have been reported for *S. aureus* and enterococci. In the outpatient setting, resistant isolates have been observed with increased frequency and include organisms such as *S. pneumoniae*, *S. aureus* and ESBL-producing gram-negative rods.

The results of studies focusing on crude and attributable mortality are varied, in part related to the heterogeneous populations observed. It should be understood that obtaining reliable data on attributable mortality is challenging due to rigorous matching requirements. Few studies have focused on pathogen-specific attributable mortality. They include studies on *S. aureus*, coagulase-negative staphylococci and enterococci. Other studies of attributable mortality have been conducted in select populations including patients in intensive care units, neutropenic patients, and HIV-positive patients. Despite advances in medical care, BSIs remain a leading cause of death worldwide.

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