Age- and Sex-Associated Trends in Bloodstream Infection

A Population-Based Study in Olmsted County, Minnesota

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Background: Despite increasing concerns about antimicrobial resistance and emerging pathogens among blood culture isolates, contemporary population-based data on the age- and sex-specific incidence of bloodstream infections (BSIs) are limited.

Methods: Retrospective, population-based, cohort study of all residents of Olmsted County, Minnesota, with a BSI between January 1, 2003, and December 31, 2005. The medical record linkage system of the Rochester Epidemiology Project and microbiology records were used to identify incident cases.

Results: A total of 1051 unique patients with positive blood culture results were identified; 401 (38.2%) were classified as contaminated. Of 650 patients with cultures deemed clinically relevant, the mean ± SD age was 63.1 ± 23.1 years, and 52.5% were male. The most common organisms identified were Escherichia coli (in 163 patients with BSIs [25.1%]) and Staphylococcus aureus (in 108 patients with BSIs [16.6%]). Nosocomial BSIs were more common in males than females (23.8% vs 13.9%; P = .002). The age-adjusted incidence rate of BSI was 156 per 100 000 person-years for females and 237 per 100 000 person-years for males (P < .001), with an age- and sex-adjusted rate of 189 per 100 000 person-years. Rates of BSI due to gram-positive cocci were 64 per 100 000 person-years for females and 133 per 100 000 person-years for males (P < .001); gram-negative bacillus BSI rates (85/100 000 person-years for females and 79/100 000 person-years for males) were not significantly different between sexes (P = .79). The rate of S aureus BSI was 23 per 100 000 person-years for females and 46 per 100 000 person-years for males (P = .005).

Conclusions: There are significant differences in the age and sex distribution of organisms among patients with BSIs. The incidence of BSI increases sharply with increasing age and is significantly higher in males, mainly because of nosocomial organisms, including S aureus.

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MORTALITY FROM BLOODSTREAM INFECTIONS (BSIs) remains high, with a case-fatality rate as high as 20% to 30%, despite significant advances in antimicrobial therapy and automated blood culture techniques. Concerns about increasing antimicrobial resistance among blood isolates have been noted, especially due to organisms with limited available treatment options, such as extended-spectrum β-lactamase–producing gram-negative bacilli or methicillin-resistant Staphylococcus aureus. Recent data suggest that rates of BSI due to S aureus have been increasing, with the rate of nosocomial primary S aureus BSI more than doubling. Previous European observations of BSIs from the 1980s and 1990s have estimated incidence rates of BSI to be between 76.5 and 153 per 100 000. There has been speculation that as rates of BSI increase, complications of BSIs, such as infective endocarditis (IE) and vertebral osteomyelitis, also will increase. However, there have been minimal recent population-based data evaluating trends in BSI, and it is unclear which populations are at highest risk for BSI due to different organisms. Such data are necessary for targeting treatment and prevention efforts. We, therefore, conducted a retrospective, population-based, cohort study to evaluate age- and sex-associated trends in the incidence of BSI in a geographically defined population.

STUDY SETTING

Olmsted County is located in southeastern Minnesota and has population characteristics similar to those of US non-Hispanic whites. The population according to the 2000 census was 124 277. There is a low prevalence of intravenous drug abuse. The Rochester Epidemiology Project is a medical record linkage system that indexes medical records from all individuals.
als seen by a health care provider and residing in Olmsted County. A single dossier exists for each patient, into which medical diagnoses, surgical interventions, and other key information from medical records are regularly abstracted and entered into computerized indexes using the International Classification of Diseases, Ninth Revision, Clinical Modification. The Rochester Epidemiology Project provides access to all inpatient, outpatient, emergency department, and nursing home records of county residents, regardless of provider, allowing for accurate population-based incidence studies of disease causes and outcomes.13

CASE ASCERTAINMENT

Cases of BSI were identified via computerized databases from both microbiology laboratories in Olmsted County: Mayo Clinic and Olmsted Medical Center. All positive blood culture results identified between January 1, 2003, and December 31, 2005, were included. The BSIs were classified as nosocomial, health care associated, or community acquired.6 The Mayo Clinic uses an automated blood culture system (BACTEC 9240) and aerobic (Plus/10 Aerobic/F) and anaerobic (Lytic/10 Anaerobic/F) culture vials, and Olmsted Medical Center also uses an automated blood culture system (BACTEC 9050) and aerobic (Standard/10 Aerobic/F) and anaerobic (Anaerobic/F) culture vials (BD Biosciences, San Jose, Calif). Blood cultures were identified using standard microbiology techniques according to the Clinical Laboratory Standards Institute. Both laboratories are certified by the College of American Pathologists. There were no significant changes in culture techniques during the study period. The medical records of all cases of BSI were manually reviewed by the primary investigator (D.Z.U.) to confirm the diagnosis and residency status. Any cases of BSI judged problematic were reviewed with an experienced infectious diseases investigator (L.M.B.). Nonresidency in Olmsted County at the time of BSI was an exclusion criterion. Patients were followed up from the date of BSI through their most recent health care encounter, as documented in the Rochester Epidemiology Project database.

Given that contaminated blood cultures may represent up to half of all positive blood culture results,12,15 we used the definition of contamination as previously described by Bekersis et al.12 A blood culture was considered to be “contaminated” if 1 or more of the following were identified in only 1 bottle: coagulase-negative staphylococci species, Propionibacterium acnes, Micrococcus species, viridans group streptococci, Corynebacterium species, or Bacillus species.

DATA ANALYSIS

Incidence rates of BSI were derived using cases of BSI as the numerator and assuming that the entire Olmsted County population between 2003 and 2005 was at risk of infection. The denominator was interpolated from the 2000 Olmsted County census figures, using an annual projected population growth rate of 1.9% per year. Incidence rates were directly adjusted to the age distribution of the US white 2000 population.25 Only initial episodes of BSI were included as incident cases. For patients with multiple events, incidence rates were calculated based on the first event only. Deaths were confirmed via Minnesota electronic death certificate data, and 95% confidence intervals (CIs) around the point estimates were calculated assuming that incident cases followed a Poisson error distribution. Differences in means between multiple groups were tested with 1-way analysis of variance. Cox proportional hazards modeling was used to examine the association between organism and survival while adjusting for age and sex. The level of significance for all statistical tests was 2-sided, with α<.05. All analyses were conducted using computer software (JMP software, version 6.0.0; SAS Institute Inc, Cary, NC). The institutional review boards of Mayo Clinic and Olmsted Medical Center approved the study.

RESULTS

A total of 1051 unique patients with positive blood culture results between January 1, 2003, and December 31, 2005, were identified. Of these patients, 401 (38.2%) had positive blood culture results that met the definition of contamination. Of the contaminants, 286 (71.3%) were coagulase-negative staphylococci, 29 (7.2%) were Corynebacterium species, 18 (4.5%) were Micrococcus species, and 12 (3.0%) were Propionibacterium acnes. A total of 650 patients had positive blood culture results that were deemed clinically relevant, and were included as incident cases. Multiple BSIs were noted in 29 patients (4.5%). The mean±SD age of the cases was 63.1±23.1 years, and 52.5% were male. Of the cases, 64 (9.8%) were nonwhite, reflecting the general demographic characteristics of southeastern Minnesota. A total of 188 cases (28.9%) occurred in patients older than 80 years. Causative organisms by epidemiologic category are shown in Table 1. The 2 most common causative organisms overall were Escherichia coli (163 BSIs [25.1%]) and S aureus (108 BSIs [16.6%]).

Of the BSIs, 124 (19.1%) were nosocomial, 237 (36.5%) were health care associated, and 289 (44.5%) were community acquired. Males were more likely to have nosocomial BSIs than females (Figure 1). Females had 43 nosocomial BSIs (13.9%), 112 health care–associated BSIs (36.2%), and 154 community-acquired BSIs (49.8%), compared with 81 nosocomial BSIs (23.8%), 125 health care–associated BSIs (36.7%), and 135 community-acquired BSIs (39.6%) for males (P=.002).

Age- and sex-specific incidence rates are shown in Table 2. The annual incidence of BSIs during the study period, age and sex adjusted to the US white 2000 census, was 189 (95% CI, 174-204) per 100 000 person-years. The age-adjusted incidence rates were 156 for females (95% CI, 146-167) and 214 for males (95% CI, 197-234) (P<.001). The incidence rate of BSIs in the eldest patients (≥80 years) was 1455 (95% CI, 1268-1691) per 100 000 person-years—more than 3 times greater than the incidence rate among the next oldest age group (60-79 year olds). In addition, the incidence rate in males in this group (rate, 2149; 95% CI, 1695-2603) was almost twice that of females (rate, 1143; 95% CI, 922-1366) (P<.001). Incidence rates increased with age across both sexes, but males had substantially higher incidence rates in the older age groups (≥70 years) (Figure 2).

To further investigate sex-associated differences in patients with BSIs, we compared rates of BSI due to gram-positive cocci vs those due to gram-negative bacilli. There were 321 total gram-positive BSIs (49.8%), 281 gram-negative BSIs (43.6%), and 43 polymicrobial BSIs (6.7%). The mean age among those with polymicrobial BSIs (71.5 years; 95% CI, 64.6-78.5 years) was greater than among those with gram-positive BSIs (61.8 years; 95% CI, 59.3-64.4 years) or gram-negative BSIs (63.1 years; 95% CI, 60.1-66.0 years).
### Table 1. Rank Order of Microorganisms in 650 BSIs, 2003 to 2005, in Olmsted County, Minnesota

<table>
<thead>
<tr>
<th>Rank</th>
<th>Total (N = 650)</th>
<th>Nosocomial (n = 124)</th>
<th>Health Care Associated (n = 237)</th>
<th>Community Acquired (n = 299)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Escherichia coli</em></td>
<td><em>S aureus</em></td>
<td><em>E coli</em></td>
<td><em>E coli</em></td>
</tr>
<tr>
<td>2</td>
<td><em>Staphylococcus aureus</em></td>
<td>Coagulase-negative staphylococci</td>
<td><em>S aureus</em></td>
<td><em>S aureus</em></td>
</tr>
<tr>
<td>3</td>
<td><em>Coagulase-negative staphylococci</em></td>
<td><em>E coli</em></td>
<td><em>β-Hemolytic streptococci</em></td>
<td>Krebsiella species</td>
</tr>
<tr>
<td>4</td>
<td><em>Klebsiella species</em></td>
<td>Enterococcus species</td>
<td><em>Coagulase-negative staphylococci</em></td>
<td>Krebsiella species</td>
</tr>
<tr>
<td>5</td>
<td><em>β-Hemolytic streptococci</em></td>
<td><em>Klebsiella species</em></td>
<td><em>β-Hemolytic streptococci</em></td>
<td>Krebsiella species</td>
</tr>
<tr>
<td>6</td>
<td>Polymicrobial (≥2 organisms)*</td>
<td><em>Pseudomonas species</em></td>
<td>Polymicrobial</td>
<td><em>S pneumoniae</em></td>
</tr>
<tr>
<td>7</td>
<td>Viridans group streptococci</td>
<td>Candida species</td>
<td>Viridans group streptococci</td>
<td>Enterococcus species</td>
</tr>
<tr>
<td>8</td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Anaerobe</td>
<td><em>S pneumoniae</em></td>
<td>Anaerobe</td>
</tr>
<tr>
<td>9</td>
<td>Enterococcus species</td>
<td>Polymicrobial</td>
<td><em>Pseudomonas species</em></td>
<td>Enterococcus species</td>
</tr>
<tr>
<td>10</td>
<td>Anaerobe</td>
<td><em>β-Hemolytic streptococci</em></td>
<td>Anaerobe</td>
<td><em>Pseudomonas species</em></td>
</tr>
<tr>
<td>11</td>
<td><em>Pseudomonas species</em></td>
<td>Viridans group streptococci</td>
<td>Candida species</td>
<td>Candida species</td>
</tr>
<tr>
<td>12</td>
<td><em>Candida species</em></td>
<td><em>S pneumoniae</em></td>
<td>Other</td>
<td>Candida species</td>
</tr>
<tr>
<td>13</td>
<td>Other†</td>
<td>Other</td>
<td>Other</td>
<td>Other</td>
</tr>
</tbody>
</table>

Abbreviation: BSI, bloodstream infection.

*Polymicrobial BSIs are counted with their respective organisms.

There was a similar difference in rates of BSIs due to viridans group streptococci, 25 (of 35, or 71.4%) of which were in males (incidence, 16/100,000 person-years for males and 5/100,000 person-years for females; *P* = .01). Comparisons of incidence rates by sex for the 6 most common organisms are shown in Figure 4.

The median duration of follow-up after BSI was 329 days (interquartile range, 94-668 days). Eighty-eight individuals died during the initial hospitalization (crude mortality, 13.5%). There was no overall difference in mortality by sex (hazard ratio for males, 1.07; 95% CI, 0.68-1.70; *P* = .76). The hazard ratio for death corresponding to a 10-year increase in age was 1.18 (95% CI, 1.06-1.32; *P* = .002). The age-adjusted hazard ratio for death due to nosocomial BSI was 4.64 (95% CI, 2.52-8.80; *P* < .001).

In our geographically defined population, the incidence of BSI increased sharply with age. Bloodstream infection due to *E coli* was far more common in females, likely reflecting the propensity for urinary tract infections, including pyelonephritis, in females. There were marked differences in the rates of *S aureus* BSI between males and females, with rates in males almost double those in females in some age groups. A similar difference was noted with viridans group streptococci.

The difference in sex-specific incidence rates is striking. Reasons for the increased frequency of BSI due to gram-positive cocci in males seem directly related to the increased number of nosocomial BSIs in males. Increased intravenous drug abuse among males seems an unlikely explanation, given that most cases were in elderly persons and given the low prevalence of intravenous drug abuse in Olmsted County. It is tempting to speculate that this proclivity among older males for BSIs due to gram-positive cocci may explain, in part, the ob-

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Figure 1. Distribution of the 650 bloodstream infections (BSIs) by health care exposure category. CA indicates community acquired, and HCA, health care associated. Percentages may not total 100 due to rounding.

60.4-65.8 years) (*P* = .03). The overall incidence of gram-positive BSIs was 64 (95% CI, 53-75) per 100,000 person-years for females and 133 (95% CI, 112-153) per 100,000 person-years for males (*P* < .001). Gram-negative BSI incidence was 85 (95% CI, 72-98) per 100,000 person-years for females and 79 (95% CI, 64-95) per 100,000 person-years for males (*P* = .79). Age- and sex-associated trends in the incidence of gram-positive vs gram-negative BSI are shown in Figure 3. For *E coli*, the age-adjusted incidence rate was 61 (95% CI, 50-72) per 100,000 person-years for females and 32 (95% CI, 22-42) per 100,000 person-years for males (*P* = .002); the age- and sex-adjusted rate was 48 (95% CI, 41-55) per 100,000. The overall age-adjusted incidence rate (per 100,000 person-years) for *S aureus* was 23 (95% CI, 16-30) for females and 46 (95% CI, 34-57) for males (*P* = .005); the age- and sex-adjusted rate was 32 (95% CI, 26-39) per 100,000 person-years.

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**COMMENT**
The incidence rates of IE in a population-based setting have been previously described, with an age- and sex-adjusted rate of 4.9 per 100,000 person-years. The incidence rate ratio for male vs female sex was 2.5:1.0. Recent series of patients, from the International Collaboration on Endocarditis, with IE due to \textit{S. aureus} reported that 60% to 70% were male.28,29 In our study, the rate of \textit{S. aureus} BSIs in males was twice that in females. The sex discrepancy in IE cases could be explained by differences in underlying rates of BSI. This is a novel observation that deserves further investigation.

Data derived from population-based studies for BSI in the United States were not previously available. The incidence of BSI in our study (190 per 100,000 person-years) exceeds that of prior estimated incidence rates of BSI from Europe from the 1980s and 1990s (76.5 and 153 per 100,000). It is unclear if this is because of a true increase in the rates of BSI overall, changes in blood culture techniques resulting in detection bias, or differing population demographics in the varying regions studied.

The rank order of microorganisms defined in our study was similar to that reported previously. In our population-based study, \textit{E. coli} remained the most common causative organism, followed by \textit{S. aureus}. These trends for organisms isolated are similar to a recent large series of BSIs from the United Kingdom, which also reported \textit{E. coli} and \textit{S. aureus} as the most common organisms isolated. A recent analysis of 24,179 cases of nosocomial BSIs in US hospitals found that the most common organisms were coagulase-negative staphylococci, \textit{S. aureus}, enterococci, and \textit{Candida} species. We speculate that the difference in rank order of microorganisms seen in our study is because of the inclusion of community-acquired and health care–associated BSIs.

Our study has several limitations. We used a set definition of blood culture contamination to avoid ascertainment bias in retrospectively identifying incident cases. However, as noted by Bekeris et al., isolates classified as contaminants using this study definition could still be reflective of clinical infection. Prior studies of BSIs with coagulase-negative staphylococci have suggested that approximately 25% to 30% of isolates were considered to be pathogens. In our study, there were 58 clinically significant coagulase-negative staphylococcal BSIs (16.9%)
of 344 positive blood culture results for this organism. Our results may, therefore, underestimate the true incidence of BSIs due to this organism.

Another limitation is that Olmsted County is a relatively homogeneous population in regard to racial and ethnic composition, with a low prevalence of intravenous drug abuse. Therefore, the generalizability of our study’s findings to groups underrepresented in the population could be limited. However, as previously noted, the characteristics of the Olmsted County population are similar to those of other US whites, with the exception of slightly higher income and education levels, and studies in Olmsted County can be extrapolated to a large part of the general population. Presumably, an increased prevalence of intravenous drug abuse would result in an increase in the incidence of BSI in younger age groups.

Last, it is possible that residents of the population could have been examined and diagnosed as having BSI at an institution outside of Olmsted County, although the geographic isolation of Olmsted County from other urban centers makes this unlikely. Only patients with BSI detected via positive blood culture result were included as incident cases; therefore, patients with BSIs who did not have blood cultures drawn (ie, did not seek medical attention or were treated empirically without cultures) would have been missed. Patients who received antimicrobial therapy prior to cultures being obtained may have falsely negative cultures. Our results, then, would be an underestimate of the true incidence of BSIs. It is difficult to know what impact, if any, this would have on age- and sex-specific incidence rates.

The primary strength of the study is that through use of the Rochester Epidemiology Project we were able to study incidence of BSI in a large population without the referral bias seen with single-institution studies of BSI. The essentially complete ascertainment of all BSI cases in our study for a population of known size, age, and sex distribution allows an unbiased and accurate estimation of incidence rates.

In conclusion, our data indicate that there are striking sex-associated differences in organism distribution among patients with BSI. Escherichia coli BSI was more common in females, and BSI due to Staphylococcus aureus and viridans group streptococci was more common in males. The epidemiologic and pathogenic factors associated with these sex differences deserve further investigation. In addition, sex-specific BSI trends may have implications for empirical antimicrobial therapy in patients with pre-
sumed BSI, especially as rates of antimicrobial resistance increase. Further research on specific sex-associated risk factors for BSI is needed to clarify these trends.

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Author Contributions: Dr Uslan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Uslan, Crane, Steckelberg, Cockerill, St. Sauver, and Baddour. Acquisition of data: Uslan and Cockerill. Analysis and interpretation of data: Uslan, Steckelberg, Cockerill, St. Sauver, Wilson, and Baddour. Drafting of the manuscript: Uslan and St. Sauver.

Critical revision of the manuscript for important intellectual content: Uslan, Crane, Steckelberg, Cockerill, St. Sauver, Wilson, and Baddour. Statistical analysis: Uslan. Obtained funding: Steckelberg and Baddour. Administrative, technical, and material support: Crane, Steckelberg, Wilson, and Baddour. Study supervision: Steckelberg, Cockerill, Wilson, and Baddour. Epidemiologic expertise: St. Sauver.

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