Nosocomial bloodstream infections are important causes of morbidity and mortality. In this study, concurrent surveillance for nosocomial bloodstream infections at 49 hospitals over a 3-year period detected >10,000 infections. Gram-positive organisms accounted for 64% of cases, gram-negative organisms accounted for 27%, and 8% were caused by fungi. The most common organisms were coagulase-negative staphylococci (32%), Staphylococcus aureus (16%), and enterococci (11%). Enterobacter, Serratia, coagulase-negative staphylococci, and Candida were more likely to cause infections in patients in critical care units. In patients with neutropenia, viridans streptococci were significantly more common. Coagulase-negative staphylococci were the most common pathogens on all clinical services except obstetrics, where Escherichia coli was most common. Methicillin resistance was detected in 29% of S. aureus isolates and 80% of coagulase-negative staphylococci. Vancomycin resistance in enterococci was species-dependent—3% of Enterococcus faecalis strains and 50% of Enterococcus faecium isolates displayed resistance. These data may allow clinicians to better target empirical therapy for hospital-acquired cases of bacteremia.

Bloodstream infections remain important causes of morbidity and mortality in the United States. Currently, such infections are the 13th leading cause of death, and over the past 2 decades the age-adjusted death rate from septicemia has risen by 78% [1]. It is estimated that 250,000 cases of bloodstream infections are acquired in hospitals annually [2]. Nosocomial bloodstream infections in patients in the intensive care unit are associated with an attributable mortality of 35%, an additional 24 days of hospital stay, and excess hospital costs of $40,000 per survivor [3].

Not only are nosocomial infections increasing in frequency, they are also more frequently caused by pathogens that are resistant to antimicrobials. In 1990, the cost of nosocomial infections caused by antibiotic-resistant bacteria in the United States was estimated at $4 billion [4]. In New York City alone in 1995, the direct costs attributable to infections with a single antibiotic-resistant pathogen, methicillin-resistant Staphylococcus aureus, were more than $400 million [4]. Despite the emergence of ever-increasingly antibiotic-resistant pathogens, the fraction of governmental funding for surveillance of these pathogens accounts for <1% of the total amount spent for surveillance of all infectious diseases [5]. A number of organizations, including the Institute of Medicine and the American Society for Microbiology, have recommended increased surveillance activities to monitor trends in infections due to antibiotic-resistant pathogens.

The SCOPE (Surveillance and Control of Pathogens of Epidemiologic Importance) Project was developed with the objective of monitoring nosocomial bloodstream infections via a nationwide surveillance network of hospitals. This project marked the first cooperative effort for surveillance among academia, the pharmaceutical industry, and multiple health care institutions and represents the first nongovernmental surveillance project for nosocomial infections.

**Methods**

Forty-nine hospitals across the United States were selected to participate in the project. Hospitals were chosen to maximize geographic diversity (figure 1), and the sample included hospitals of all sizes. Cases of nosocomial bloodstream infection were identified via concurrent surveillance at each hospital. Local infection-control practitioners were instructed to review the list of positive blood culture results in the microbiology laboratories of the collaborating institutions. Patient charts were then reviewed to establish whether the patients met the criteria for nosocomial bloodstream infection according to a standardized definition.

Each participating hospital laboratory detected positive blood culture results, identified organisms, and performed sus-
contaminant (e.g., diphtheroids, genic organism. If the bloodstream isolate was a potential skin blood drawn at least 48 hours after admission yielded a patho-
ring in a clinically ill patient when one or more cultures of where they were stored at 70°C. All isolates were saved on agar slants and submitted to the coordinating centers,

A nosocomial bloodstream infection was defined as occurring in a clinically ill patient when one or more cultures of blood drawn at least 48 hours after admission yielded a patho-
genic organism. If the bloodstream isolate was a potential skin contaminant (e.g., diphtheroids, Propionibacterium species, Bacillus species, coagulase-negative staphylococci, or micro-
cocci), all of the following additional criteria were required for diagnosis: the presence of an intravascular catheter, the initia-
tion of antimicrobial therapy, and at least one of the following—temperature of >38.0°C or <36.0°C, chills, or systolic blood pressure of <90 mm Hg. Multiple blood cultures yielding the same organism were considered a single infection.

Clinical information and microbiological data were recorded by the local infection-control practitioners on a standardized case report form and forwarded to the coordinating centers along with the microbiological isolate. Infections were strati-
ﬁed by location of patient (ward versus intensive care unit), by presence or absence of neutropenia in patients, and by clinical service. Infection-control practitioners also provided in-
hospital (crude) mortality data for patients with bloodstream infections stratified by offending pathogens. The study began in April 1995 and continues to the present.

Tests of statistical significance were two-tailed. The results presented represent data from the 3-year time period April 1995 through April 1998.

### Results

During the study period, 10,617 episodes of nosocomial bacteremia were detected at the study hospitals. Bacteremia due to a single organism was found in 9,214 cases (86.8%). Nearly two-thirds of the episodes (64.4%) were caused by gram-positive organisms, 27.0% were due to gram-negative bacteria, and the remaining 8.4% were caused by fungi. The rank order of major pathogens (table 1) shows that coagulase-
negative staphylococci accounted for nearly one-third of all nosocomial bacteremias (31.9%), followed by S. aureus (15.7%) and enterococci (11.1%). Candida species were the fourth most common cause, accounting for 7.6%. The most common gram-negative organisms were Escherichia coli (5.7%), Klebsiella species (5.4%), and Enterobacter species (4.5%). Crude mortality rates (table 1) ranged from 20.8% (for coagulase-negative staphylococci) to 39.9% (for Candida spec-
ies). The mean time from hospital admission to bacteremia for the major pathogens (figure 2) ranged from 12.7 days (viridans streptococci) to 23.9 days (Serratia species).

Overall, nosocomial bloodstream infections occurred with relatively equal frequency in the critical care and ward settings (51.5% vs. 48.5%), although the critical care settings account for the minority of beds in most hospitals. However, individual pathogens varied widely in this distribution (table 2). Of the 10 major pathogens, 4 were more likely to be isolated from patients in the critical care setting (Enterobacter species, Ser-
ratia species, coagulase-negative staphylococci, and Candida species), whereas S. aureus, Klebsiella species, E. coli, and viridans streptococci were more common in the ward setting. Pseudomonas species and enterococcal nosocomial blood-
stream infections occurred with equal frequencies in the two major inpatient settings.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Pathogen</th>
<th>No. of isolates</th>
<th>%</th>
<th>Crude mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Coagulase-negative staphylococci</td>
<td>3,908</td>
<td>31.9</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>Staphylococcus aureus</td>
<td>1,928</td>
<td>15.7</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>Enterococci</td>
<td>1,354</td>
<td>11.1</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>Candida species</td>
<td>934</td>
<td>7.6</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Escherichia coli</td>
<td>700</td>
<td>5.7</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>Klebsiella species</td>
<td>662</td>
<td>5.4</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>Enterobacter species</td>
<td>557</td>
<td>4.5</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>Pseudomonas species</td>
<td>542</td>
<td>4.4</td>
<td>33</td>
</tr>
<tr>
<td>9</td>
<td>Serratia species</td>
<td>177</td>
<td>1.4</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>Viridans streptococci</td>
<td>173</td>
<td>1.4</td>
<td>23</td>
</tr>
</tbody>
</table>
Serratia species 59.9 40.1 1.41 (1.04–1.90)
Enterobacter species 62.3 37.7 1.56 (1.32–1.85)
Staphylococcus aureus species 57.0 43.0 1.25 (1.10–1.41)
Candida species 54.1 56.9 0.94 (0.86–1.02)
Coagulase-negative staphylococci 58.9 41.1 1.34 (1.28–1.42)
Enterobacter 55.5 43.7 1.28 (1.17–1.42)
Pseudomonas aeruginosa 57.0 43.0 1.25 (1.10–1.41)
Klebsiella species 44.1 55.9 0.77 (0.68–0.86)
Staphylococcus aureus 43.7 56.3 0.75 (0.63–0.85)
Escherichia coli 33.0 67.0 0.47 (0.40–0.54)
Viridans streptococci 29.7 70.3 0.40 (0.29–0.55)

When patients were stratified into patients with neutropenia (absolute neutrophil count of <1,000/µL) and those without, two differences emerged. S. aureus infections were significantly less common in patients with neutropenia (9.8% vs. 16.2%; RR, 0.61; 95% CI, 0.49–0.75), and bacteremia due to viridans streptococci was significantly more common (3.6% vs. 16.2%; RR, 0.61; 95% CI, 0.49–0.75), and bacteremia due to S. aureus significantly less common in patients with neutropenia (9.8% vs. 21.1%; RR, 0.46; 95% CI, 0.36–0.58). In addition, patients with neutropenia on average developed nosocomial bloodstream infections 2 days earlier than did their counterparts without neutropenia (17.5 days vs. 19.3 days; P = .005).

When the pathogens were stratified by clinical service, several patterns emerged. On the pediatrics service, coagulase-negative staphylococci accounted for nearly half of the nosocomial bloodstream infections, with no other pathogens playing a prominent role (i.e., no other pathogen accounted for ≥10% of the cases). On general surgery, neurosurgery, internal medicine, and hematology/oncology services, the top-ranked pathogens were coagulase-negative staphylococci, S. aureus, and enterococci, which together accounted for 50%–60% of the cases of nosocomial bacteremia. Interestingly, on the hematology/oncology service, S. aureus accounted for only 11%, but the viridans streptococci were more prominent than on other services. On the obstetrics service, E. coli predominated (28.8%), and streptococci were also important (15.3%). On all services except obstetrics, coagulase-negative staphylococci were the most common bloodstream pathogens.

Candida species. Of the 934 Candida isolates causing nosocomial bloodstream infections, species other than Candida albicans accounted for 46.8% (table 3). Three species accounted for nearly 90% of the isolates other than C. albicans (Candida glabrata, 42.3%; Candida parapsilosis, 21.1%; and Candida tropicalis, 26.1%). The proportion of Candida isolates other than C. albicans varied with the geographic region and ranged from 30.2% in the Southwest to 54.5% in the Northeast (table 3). When stratified by clinical service, the proportion of Candida species other than C. albicans ranged from 35.6% among pediatrics patients to 58.7% among hematology/oncology patients. C. glabrata was the dominant Candida species other than C. albicans on all services except pediatrics, where C. parapsilosis accounted for two-thirds of the non–C. albicans isolates.

Staphylococci. Several gram-positive organisms exhibited significant rates of antibiotic resistance. Of the nearly 4,000 isolates of coagulase-negative staphylococci causing nosocomial bloodstream infections, 80.4% were resistant to methicillin. Vancomycin resistance was detected in eight coagulase-negative staphylococcal isolates (0.2%). Two hospitals each detected two nosocomial bloodstream infections with these organisms, while two others each had one such infection. No S. aureus isolates were detected that had reduced susceptibility to vancomycin.

The proportion of methicillin resistance among S. aureus isolates was 29.3%. The highest proportions of methicillin resistance in S. aureus isolates were seen in the eastern United States.
Geographic variation in enterococcal vancomycin resistance was significant and ranged from 10.3% in the Northwest to 21.5% in the Southeast States (Southeast, 38.5%; Northeast, 29.8%), with lower proportions observed in the Southwest (22.5%) and Northwest (14.5%). The general surgery and cardiothoracic services had the highest proportions of methicillin-resistant S. aureus (39.5% and 35.6%, respectively), intermediate rates were observed on internal medicine (29.8%) and hematology/oncology (24.7%) services, and low proportions were observed on pediatrics (11.3%) services.

Enterococci. Enterococcus faecalis accounted for 55.2% of the enterococcal isolates that were identified to the species level (20% of the enterococcal isolates were not speciated). Enterococcus faecium was the predominant species other than E. faecalis and accounted for 28% of the enterococci identified to the species level.

Ampicillin resistance in E. faecalis remained low (2.7%) but was markedly higher in E. faecium (81.1%). Overall, 17.7% of enterococcal isolates displayed resistance to vancomycin. Notably, the rates of vancomycin resistance were highly correlated with enterococcal species. The proportion of resistance to vancomycin was 16-fold higher (50.5%) in E. faecium isolates than in E. faecalis isolates (3.1%) (RR, 16.39; 95% CI, 10.70–25.12).

Figure 3. Rates of vancomycin resistance in enterococci by geographic region among 49 sentinel hospitals throughout the United States. Solid bars, Enterococcus faecalis; open bars, Enterococcus faecium.

Geographic variation in enterococcal vancomycin resistance was significant and ranged from 10.3% in the Northwest to 21.5% in the Southwest and 24.4% in the Northeast, with the Southeast having an intermediate level (13.2%). When species-specific vancomycin resistance levels were evaluated by geographic regions, the Northeast region stood out as the most problematic (figure 3).

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This ongoing surveillance project of nosocomial bloodstream infections underscores the important role of gram-positive organisms in the hospital setting. Coagulase-negative staphylococci, which emerged with the increasing use of intravascular catheters, continue to dominate as nosocomial bloodstream pathogens. At least in part, this is the likely reason for the bulk of these bloodstream infections occurring in the critical care setting. Unfortunately, some of these organisms may have been misclassified as pathogens, since they are common contaminants of blood cultures; however, the more stringent definition of bloodstream infection applied for these organisms should minimize this problem. Isolates from the intensive care unit vs. isolates from wards were significantly more likely to be methicillin-resistant (85% vs. 73%), but overall, only 20% of the isolates retained susceptibility to the penicillinase-resistant penicillins. It is not surprising then that the use of vancomycin has increased substantially in the last decade [15].

*S. aureus* remains an important cause of nosocomial bloodstream infection. Unlike coagulase-negative staphylococci, these organisms are significantly more likely to cause infections on the wards than in intensive care units. Overall, nearly 30% of isolates were resistant to methicillin, a rate 15-fold higher than that found in the United States 2 decades ago but only half that found currently in Japan [16]. In the dialysis population, levels of methicillin resistance are significantly higher. Interestingly, there are no currently approved, efficacious antibiotics to treat vancomycin-resistant *E. faecium*, and many different regimens are being tried in the United States. Although the Centers for Disease Control and Prevention found the proportion of vancomycin resistance among enterococci to be significantly higher in the critical care setting in the late 1980s and early 1990s [20], our data from a more recent time period show that this distinction is no longer seen (figure 4). The significantly higher level of vancomycin resistance seen in isolates from patients undergoing hemodialysis is likely to be associated with higher rates of vancomycin use in that population.

Yeasts continue to be important causes of nosocomial bloodstream infections. Importantly, in this study, they are associated with the highest crude mortality (40%). Of interest is the sizeable fraction of infections caused by *Candida* species other than *C. albicans* and the geographic variation in these species.

The gram-negative bacteria account for approximately one-quarter of nosocomial bloodstream infections, and no single genus accounts for >6% of the infections. This is a remarkable change from the late 1970s, when >75% of nosocomial bloodstream infections were caused by gram-negative rods. Interestingly, nosocomial bloodstream infections due to *Pseudomonas* species were not more prevalent in the patients with neutropenia, which may reflect changes in antimicrobial therapy for the empirical treatment of fever due to neutropenia. In general,
aminoglycosides, ciprofloxacin, and imipenem displayed good activity against the most common pathogens. Unfortunately, ampicillin no longer displays significant activity against any of the important hospital-acquired gram-negative organisms. Thus, it no longer has a role in the empirical treatment of gram-negative nosocomial bloodstream infections. Of note, *E. cloacae* appears to be the most problematic with regards to reduced levels of susceptibility to the third-generation cephalosporins. The 42% resistance to ceftazidime is not appreciably different from the 38% detected by the Centers for Disease Control and Prevention in 1991 [21]. Ciprofloxacin and imipenem continue to display good activity, however.

In summary, this ongoing surveillance project tracking nosocomial bloodstream infections at nearly 50 sentinel hospitals across the United States has provided timely data on the epidemiology of these infections and the emerging trends in antibiotic resistance. Plans are underway to evaluate the relationship between antibiotic use in these hospitals and the patterns of antimicrobial resistance observed.

Acknowledgments

The authors thank the infection-control practitioners and microbiology laboratory personnel at the participating hospitals for their active participation in and dedication to this project.

References