Antimicrobial Resistance in Key Bloodstream Bacterial Isolates: Electronic Surveillance with The Surveillance Network Database—USA

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To assess the prevalence of antimicrobial-resistant pathogens among the most common bloodstream isolates, we examined antimicrobial susceptibility data from The Surveillance Network Database—USA, an electronic surveillance system that collects data from 118 clinical microbiology laboratories across the United States. Between 1995 and 1997, resistance to both vancomycin and ampicillin was much more prevalent among Enterococcus faecalis than Enterococcus faecium, suggesting the need for laboratories to identify to species. When staphylococcal isolates were examined for reduced susceptibility to vancomycin (minimum inhibitory concentration = 4 μg/mL), the frequency was highest in methicillin-resistant coagulase-negative staphylococci. We also learned that nonsusceptibility to ceftazidime in Klebsiella pneumoniae was more prevalent among isolates from blood (12.7%) than among isolates from urine (7.1%) or respiratory sources (9.3%). Although antimicrobial resistance is low overall for isolates of Escherichia coli from blood, the prevalence of ceftoxitin resistance among ceftazidime-resistant strains (61.9%) suggests the action of mechanisms other than extended-spectrum β-lactamase.

The most common pathogens isolated from cultures of blood are Staphylococcus aureus, Escherichia coli, coagulase-negative staphylococci, Klebsiella pneumoniae, and enterococci, and half of these bloodstream infections are thought to be nosocomial [1–3]. According to recent findings from the SCOPE (Surveillance and Control of Pathogens of Epidemiologic Importance) Program and NNIS (National Nosocomial Surveillance System), gram-positive bacteria currently account for approximately two-thirds of nosocomial bloodstream infections [2–4], and gram-negative organisms are responsible for 20% [2]. Ten years ago, NNIS determined that 57% of primary bloodstream infections were associated with gram-positive pathogens and 23% with gram-negative organisms [2].

Of particular concern is the rising prevalence of antimicrobial-resistant pathogens among bloodstream isolates [5, 6]. Of the nationwide surveillance studies, few reports focus solely on antibiotic resistance in organisms involved in bloodstream infections. We therefore undertook a study to determine the prevalence of antimicrobial resistance among bloodstream isolates obtained from patients across the United States. In particular, we examined resistance patterns among organisms most commonly associated with bacteremia, since these pathogens may present the most important threat to public health. Our study assessed antibiotic resistance among both gram-positive and gram-negative bloodstream isolates, including multiple resistance in enterococci, reduced vancomycin susceptibility in staphylococci, and extended-spectrum cephalosporin nonsusceptibility or resistance in K. pneumoniae and E. coli. All data were obtained and analyzed with The Surveillance Network (TSN) Database—USA, which collects antimicrobial susceptibility results from clinical microbiology laboratories distributed throughout the United States and enables users to perform analyses via the Internet.

Methods

Since 1994, TSN Database—USA has collected antimicrobial susceptibility data from clinical microbiology laboratories located within the United States. These data are used for surveillance of trends in antimicrobial resistance, to support both clinical and basic research, and as an aid in the education of laboratorians and physicians. The use of clinical laboratories as the data source ensures the collection of data on the most clinically relevant organisms, and the involvement of information technology enables access to these data much sooner than by conventional means.

At the time of this analysis, TSN Database—USA contained 11,123,472 test results from 118 laboratories, 785,558 strains, and 520 species. Each day, ~35,000 test results are transmitted automatically from the participating laboratories to the central database by use of certain electronic communication protocols. Both quantitative (disk diffusion zone diameters and MICs) and categorical (susceptible, intermediate, or resistant) test results are collected by TSN Database—USA, along with corresponding data, such as testing method and patient characteristics. The different names and codes for organisms, drugs, test methods, specimen sources, patient characteristics, and other variables are translated by software specific for each contrib-

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utating institution into common designations for the central database. Electronic transmissions of data are encrypted for security, and to ensure patient anonymity, laboratories rely on unique patient codes rather than on patient names or other information that could reveal the patient's identity. In addition, the identities of individual institutions cannot be revealed.

To control for the effects of selection bias, laboratories were chosen for participation on the basis of their geographic and demographic characteristics. To control for information bias, only laboratories that perform antimicrobial susceptibility testing according to interpretive standards established by the National Committee for Clinical Laboratory Standards (NCCLS) or approved by the U.S. Food and Drug Administration are included. Before enrollment, all participating laboratories undergo a site visit or pass an on-site inspection.

As an additional level of quality control, a series of quality assurance filters screen the test results before the data are merged from the central database into TSN Database—USA. These filters ensure that unusual antimicrobial susceptibility profiles are detected, appropriate testing methods have been used to generate the results, and appropriate NCCLS interpretive guidelines have been followed. If an unusual resistance profile is suspected, the real-time analysis of data enables microbiologists to obtain the suspicious isolate for confirmation testing. If a novel resistance profile is confirmed and is of public health importance, participating laboratories and the appropriate public health officials can be rapidly alerted. In addition, the isolate can be immediately procured and forwarded to basic research scientists for further study. If the unusual profile is due to error, the laboratory will take appropriate remedial actions.

Acceptable data pass through the series of filters into a screen for duplicate strains. If the same antibiogram is produced by the same bacterial species isolated from the same specimen source of the same patient within 5 days, the strain is considered a duplicate. Test results obtained with duplicate strains are prevented from entering TSN Database—USA.

We used proprietary software developed by MRL Pharmaceutical Services to query and analyze TSN Database—USA. Access to the online database is obtained with a password via the Internet. Query parameters include organism(s), drug(s) tested, susceptibility test method, data range (1994 through current year), specimen source, patient characteristics (location, age, sex, or race), institution type or bed size, and geographic region. Data may be arranged to present categories of antibiotic susceptibility (resistant, intermediate, and susceptible), trending analyses, data frequency distributions, disk diffusion zone size histograms, or MIC reports.

We evaluated antimicrobial nonsusceptibility and resistance in enterococci, staphylococci, *K. pneumoniae*, and *E. coli* for 1995–1997. Because TSN Database—USA contains both categorical and quantitative test results, we assigned strains with quantitative data to susceptible, intermediate, and resistant categories according to NCCLS interpretive standards [7]. Since data within TSN Database—USA are pooled from the participating laboratories, test results used in these analyses might have originated from subsets of the 118 laboratories. For example, a laboratory might not have contributed data for 1995, but the 1995–1997 analysis might include that laboratory’s data for successive years.

For 1995, 1996, and 1997, we analyzed vancomycin and ampicillin data from bloodstream isolates of the two most prevalent species of enterococci, *Enterococcus faecalis* and *Enterococcus faecium*. Susceptibility results were dichotomized on the basis of intensive care unit status of the patient source of the isolate. The electronic database can differentiate between strains isolated from outpatients, inpatients, and intensive care unit patients, yet the health care setting at the time of diagnosis does not necessarily correspond to status of the patient at the time of infection, making the distinction between nosocomial and community-acquired infections difficult.

Although no vancomycin-resistant staphylococci (MIC of \(\geq 32\, \mu g/mL\)) have been reported, recent studies have suggested that staphylococci currently considered susceptible by NCCLS standards but that have vancomycin MICs of 4 \(\mu g/mL\) may have the potential for developing a higher level of vancomycin resistance [8–10]. Strains with vancomycin MICs of 8 \(\mu g/mL\) are very uncommon. At the time of this analysis, the laboratories in our network had reported only two strains of coagulase-negative staphylococci with vancomycin MICs of 8 \(\mu g/mL\). We analyzed *S. aureus* and coagulase-negative staphylococci by year and oxacillin susceptibility status for strains with MICs of 4 \(\mu g/mL\). Because the value of disk diffusion for detecting reduced susceptibility to vancomycin is dubious [8, 11], only results from MIC-producing methods were considered for this analysis.

Since ceftazidine nonsusceptibility (i.e., NCCLS intermediate or resistant categories) may be used as a surrogate marker for extended-spectrum \(\beta\)-lactamas [7, 12–14], we estimated the frequency of extended-spectrum \(\beta\)-lactamas among *K. pneumoniae* isolates from blood, urine, and respiratory sources. For *E. coli* isolates from all specimen sources and from blood, we examined the prevalence of ceftazidine resistance as a function of cefoxitin resistance or susceptibility.

**Results**

**Vancomycin resistance among enterococci.** For 1995–1997, TSN Database—USA contained vancomycin susceptibility test results for 2,443 isolates of *E. faecalis* and 821 isolates of *E. faecium* from blood (figure 1). For all 3 years studied, vancomycin resistance (MIC of \(\geq 32\, \mu g/mL\) or zone diameter of \(\leq 14\, \text{mm}\)) remained <2% for *E. faecalis*, with no apparent increase. For *E. faecium*, the percentage of resistant strains steadily increased over the 3-year period, and by 1997, nearly one-half of *E. faecium* isolates were vancomycin resistant. When the two species were combined and analyzed as a
single group of vancomycin-resistant enterococci, the magnitude of the resistance problem was substantially lower than observed with *E. faecium* alone, because of the preponderance of *E. faecalis* in clinical specimens. When blood isolates from intensive care unit and non-intensive care unit patients were compared, we noted a similar pattern: Vancomycin resistance was much more common among *E. faecium* than *E. faecalis*.

Because resistance to both ampicillin (MIC of ≥32 μg/mL) and vancomycin significantly reduces or even nullifies the efficacy of any available cell wall–active agent, we examined species-specific resistance to both drugs (table 1). Only 0.1% of *E. faecalis* isolates from blood were resistant to both vancomycin and ampicillin, but 43.5% of *E. faecium* strains were resistant to both.

**Vancomycin activity in staphylococci.** By using a vancomycin MIC of 4 μg/mL to indicate reduced susceptibility among *S. aureus* and coagulase-negative staphylococci, we observed that methicillin-resistant coagulase-negative staphylococci were most likely to have vancomycin MICs of 4 μg/mL (figure 2). Increasing trends were detected for all but the methicillin-susceptible *S. aureus* group. Methicillin-resistant coagulase-negative staphylococci were then analyzed according to specimen source, either blood or nonblood sources, and we found that the percentage of strains with vancomycin MICs of 4 μg/mL ranged between 1.8% and 5.0% for isolates from blood (figure 3) and between 1.7% and 3.2% for isolates from sources other than blood for 1995–1997. For *S. aureus* isolated during the same study period, the percentage of strains with vancomycin MICs of 4 μg/mL ranged between 0 and 0.44% for isolates from blood (figure 3) and between 0.14% and 0.22% for strains from all specimen sources other than blood.

Because this analysis included all test methods, some of which may produce falsely low MICs [8], some strains with MICs of 8 μg/mL may be contained within this analysis. Currently, we collect strains with reduced glycopeptide susceptibility for repeat testing by the broth microdilution method.

**Table 1.** Vancomycin and ampicillin susceptibility profiles for enterococcal bloodstream isolates from 1995 through 1997.

<table>
<thead>
<tr>
<th>Profile</th>
<th><em>Enterococcus faecalis</em></th>
<th><em>Enterococcus faecium</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin-susceptible, ampicillin-susceptible</td>
<td>2,008 (94.5)</td>
<td>182 (25.4)</td>
</tr>
<tr>
<td>Vancomycin-susceptible, ampicillin-resistant</td>
<td>87 (4.1)</td>
<td>220 (30.8)</td>
</tr>
<tr>
<td>Vancomycin-resistant, ampicillin-susceptible</td>
<td>27 (1.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Vancomycin-resistant, ampicillin-resistant</td>
<td>3 (0.1)</td>
<td>311 (43.5)</td>
</tr>
<tr>
<td>Total</td>
<td>2,125 (100)</td>
<td>715 (100)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%).
Ceftazidime nonsusceptibility in K. pneumoniae and E. coli.

When ceftazidime nonsusceptibility (≤17 mm zone diameter or MIC of ≥16 μg/mL) was used as a surrogate marker for the presence of extended-spectrum β-lactamases in K. pneumoniae, 12.7% of 2,734 isolates from blood, 9.3% of 4,894 isolates from respiratory tract specimens, 7.1% of 10,398 isolates from urinary tract specimens, and 8.7% of 25,154 isolates from all sources were found to be putative producers of extended-spectrum β-lactamase during 1995 through 1997.

Of 71,800 E. coli strains, 850 (1.2%) were not susceptible to ceftazidime (≤17 mm zone diameter or MIC of ≥16 μg/mL), and 617 (0.9%) were resistant (≤14 mm zone diameter or MIC of ≥32 μg/mL). Of the 195 ceftazidime-resistant isolates from all specimen sources that were also tested against cefoxitin during 1995 through 1997, 112 (57.4%) were also resistant to cefoxitin (≤14 mm zone diameter or MIC of ≥32 μg/mL). For isolates cultured from blood, the proportion was similar. Of 21 ceftazidime-resistant blood isolates tested against cefoxitin, 13 (61.9%) were cefoxitin resistant.

Discussion

Consistent with earlier studies of isolates of enterococci from blood, E. faecalis was more commonly isolated and reported by participating laboratories than was E. faecium. We found that the frequency of vancomycin resistance among enterococci for 1995–1996 was 7.7%–10.9%, and similarly, NNIS reported a frequency of 10.5% [15] and Fridkin et al. [4] reported a frequency of 13% for vancomycin-resistant enterococcal strains isolated during 1995. However, when we examined the data by species, we noted that resistance was predominantly due to E. faecium. For 1997, the percentage of vancomycin-resistant E. faecium strains (48.8%) isolated and tested by our participating laboratories was comparable to the frequency reported for 1995–1997 (48%) by Edmond et al. [3] and that reported for 1995–1996 (45.8%) by the SCOPE Program [16]. Edmond et al. [3] also found that 3% of 502 E. faecalis were vancomycin-resistant, which is comparable to our finding of <2% for the same period.

Another concern is resistance to both vancomycin and ampicillin, a profile that is far more prevalent among E. faecium than E. faecalis. If vancomycin or multidrug resistance spreads to the more prevalent organism, E. faecalis, the public health threat posed by resistance in enterococci would acquire an even greater significance.

Our analyses demonstrate that unless laboratories pursue identification of resistant enterococci to species, surveillance will be limited. In fact, of 6,656 test results from enterococcal isolates from blood obtained from TSN Database—USA participating laboratories during 1995 through 1997, only 66% were identified to species. The rate of vancomycin resistance among Enterococcus species was ~19%.

For methicillin-resistant S. aureus and coagulase-negative staphylococci, our results indicate that presence of a vancomycin MIC of 4 μg/mL may be on the rise. When a vancomycin MIC of 4 μg/mL was used as a marker of potential reduced susceptibility, we observed that the organism group most likely to contain such strains was methicillin-resistant coagulase-negative staphylococci. Sieradzki et al. [10] recently reported that this organism group may have the greatest potential for developing vancomycin resistance. To better understand the clinical and scientific importance of this phenotype, strains with MICs of 4 μg/mL should be collected for species identification, characterization, and careful surveillance, which means that quantitative MIC data are critical for detecting changes in vancomycin susceptibility.

The emergence of resistance to extended-spectrum cephalosporins threatens the ability to treat infections caused by K. pneumoniae and E. coli, the most commonly encountered species of Enterobacteriaceae. In our analysis of K. pneumoniae by specimen source, we found that ceftazidime nonsusceptibility (≤17 mm zone diameter or MIC of ≥16 μg/mL) was notably higher among isolates from blood than among isolates from either urine or respiratory tract specimens, which suggests that the potent extended-spectrum β-lactamase resistance mechanism may be most significant among isolates from blood culture. Our finding that 8.7% of K. pneumoniae isolates from all specimen sources were not susceptible to ceftazidime is consistent with a report from the 1996 ASCP Susceptibility Testing Group [17], who found that ceftazidime nonsusceptibility ranged between 0 and 19% at their multiple sites in the United States, and with Jones et al. [18], who reported that ceftazidime resistance (≤14 mm zone diameter or MIC of ≥32 μg/mL) occurred in 7.1% of K. pneumoniae isolates. Similarly, our result for ceftazidime resistance among E. coli (0.9%) agrees with the recent report of the 1996 ASCP Susceptibility Testing Group [17], who found that ceftazidime resistance ranged between 0 and 3%.

In a recent study, Jacoby and Han [19] found that 52% of ceftazidime-resistant E. coli strains were also resistant to cefoxitin, and TSN Database—USA analysis revealed that 57.4% of strains had this profile. Although ceftazidime resistance in E. coli is thought to be a result of extended-spectrum β-lactamase production, extended-spectrum β-lactamases cannot hydrolyze cefoxitin. Therefore, the finding that ceftazidime resistance is correlated with cefoxitin resistance in the majority of ceftazidime-resistant E. coli isolates from blood may indicate that other mechanisms, such as AmpC enzyme production or altered drug uptake, might play an important role in ceftazidime resistance. In other words, whereas resistance in E. coli is uncommon, potent mechanisms, such as AmpC-mediated resistance, may be predominant among the cephalosporin-resistant strains that have emerged.

Our analyses indicate that antimicrobial resistance has clearly permeated the most commonly isolated bacteria from blood cultures. Of greatest concern is the potential for E. faecalis to acquire multidrug (i.e., vancomycin and ampi-
cillin) resistance, the decline in glycopeptide susceptibility among staphylococci, and the continued emergence of extended-spectrum cephalosporin resistance among the most prevalent species of Enterobacteriaceae. The antimicrobial-resistant pathogens analyzed in this study and those yet to emerge underscore the need for continued and timely surveillance. Careful monitoring of clinical laboratory data provides a key resource for this surveillance, and capitalizing on recent advances in information technology allows the rapid collection and analysis of these laboratory data.

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References